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Guest Editor:

Carmine Pinto
Director, Medical Oncology, IRCCS - S.Maria Nuova Hospital, Reggio Emilia, Italy

President, Italian Association of Medical Oncology (AIOM)

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Please, note that abstracts marked with an asterisk (*) are oral communications.

The Scientific Committee has chosen the papers on the basis of the originality of the research and the originality of the results. The authors are responsible for the text and the translation.

17th National Congress of Medical Oncology
October, 23-25, 2015: Rome Italy

Guest Editor
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Dear Collegues,

On behalf of the Board of Directors and of the Scientific Committee, it is a great pleasure for me to introduce the proceedings of the XVII National Congress of our Association.

As usually, the abstracts have been published in a special issue of "Annals of Oncology", the official Journal of ESMO.

We continue to observe an increasing number of abstracts suggesting, once again, the presence of a widespread research activity in spite of the shortage of public funds and lack of interest of public authorities. We are pleased with the role of young oncologists. Many and many young oncologists are coauthors of the abstracts and several are first authors. This should be an encouragement for all of us: there is a present and also a future for AIOM.

As you can realize by reading this issue, all topics of medical oncology have been covered, including prevention, screening, trasnslational research, simultaneous care, ethics and mutidisciplinary approaches. They will be debated in several educational and scientific sessions co-organized with several other scientific societies. We would like to highlight as the multidiciplinary approach, including supportive and simultaneous care, is a relevant part of the program of the meeting. As medical oncologists, clinicians involved in the care of the patients, we have to keep in our mind that "research" does not mind to forget the daily activity in the ward as well as the ability to answer the patients' daily needs. Nevertheless, at the same time, we must remember that a research activity improves the care of cancer patients in our units. The ability to coniugate these two aspects is the only way to improve the chance of cure for our patients.

Finally, I'd like to thank the Scientific Committee and all the reviewers for the inevaluable work along last months and I hope that all of you can enjoy the meeting and it could be the occasion of sharing knowledge, and experiences by providing an enrichment in our skills.

The Board of Directors for the years 2013–2015 includes:

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We are looking forward to seeing you in Rome.

Dr Carmine Pinto
(President of the Congress)

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Plenary session

1* Long-term outcome results of the phase III PROMISE-GIM6 study evaluating the role of LHRH analog (LHRHa) during chemotherapy as a strategy to reduce ovarian failure in early breast cancer patients

M. Lambertini[1], L. Boni[2], A. Michelotti[3], T. Gamucci[4], T. Scotto[5], S. Gori[6], M. Giordano[7], O. Garrone[8], A. Levaggi[1], F. Poggio[1], S. Giraudi[1], C. Bighin[1], C. Vecchio[1], M.R. Sertoli[1], S. Pastorino[1], P. Pronzato[1], L. Del Mastro[1]

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Background: The administration of LHRHa during chemotherapy (CT) is still considered an experimental strategy to preserve ovarian function and fertility mainly due to the lack of data on long-term ovarian function and pregnancy rate, and because of the concerns about the safety of the procedure in hormone-receptor positive breast cancer. The present analysis reports long-term outcome results of the phase 3 PROMISE-GIM6 study aiming to evaluate the role of LHRHa as a strategy to protect ovarian function during CT.

Material and methods: In this multicenter, randomized, phase 3 study, premenopausal women with stage I to III breast cancer candidates for (neo)adjuvant CT were randomly allocated (1:1) with a centralized system to receive CT alone or combined with LHRHa triptorelin. The primary aim was to compare the incidence of CT-induced early menopause between treatment arms (Del Mastro et al. JAMA 2011). The present analysis focuses on long-term ovarian function, pregnancies, and disease-free survival (DFS) events.

Results: From October 24, 2003 through January 14, 2008, 281 patients entered the study. Median follow-up was 7.3 years (6.3-8.2 years). A total of 226 patients (80.4%) had hormone receptor positive disease. The 5-year cumulative incidence estimate of menstrual resumption was 72.6% (95% Confidence Intervals [CI] 65.7-80.3) in the CT plus LHRHa arm and 64.0% (95% CI 56.2-72.8) in the control group (hazard ratio [HR] 1.28, 95% CI 0.98-1.68; p = 0.071). The age-adjusted estimate of HR was 1.48 (95% CI 1.12-1.95; p = 0.006). A total of 8 pregnancies occurred in the CT plus triptorelin group and 3 pregnancies in the CT alone group (HR 2.56, 95% CI 0.68-9.6; p = 0.142; age-adjusted HR 2.40, 95% CI 0.62-9.22; p = 0.204). Thirty-six DFS events were observed among the 148 patients allocated to CT plus triptorelin and 29 among the 133 patients allocated to CT alone. The estimated rates of DFS at 5 years were 80.5% (95% CI 73.1-86.1) and 83.7% (95% CI 76.1-89.1) in the CT plus triptorelin and CT alone arms, respectively (HR 1.17, 95% CI 0.72-1.92; p = 0.519).

Conclusions: In premenopausal, young breast cancer patients, the concurrent administration of LHRHa triptorelin and CT increases the probability of long-term ovarian function maintenance, with no negative effect on prognosis. The higher number of pregnancies in the CT plus triptorelin arm as compared to the CT alone arm suggests a possible benefit in terms of fertility preservation (ClinicalTrial.gov: NCT00311636).

2* FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as initial treatment for metastatic colorectal cancer (TRIBE study): updated survival results and final molecular subgroups analyses

A. Falcone[1], C. Cremolini[1], C. Antoniotti[1], S. Lonardi[2], M. Ronzoni[3], A. Zaniboni[4], G. Tonini[5], L. Salvatore[1], G. Masi[1], S. Mezi[6], G. Tomasello[7], C. Carlomagno[8], G. Allegrini[9], S. Chiara[10], M. D'Amico[11], C. Granetto[12], C. Lupi[13], E. Sensi[13], G. Fontanini[13], L. Boni[14], F. Loupakis[1]

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Background: The phase III TRIBE study met its primary endpoint by demonstrating that first-line FOLFOXIRI plus bev significantly prolongs PFS, as compared to FOLFIRI plus bev (*Loupakis et al, N Eng J Med 2014*). At a median follow-up of 32.2 months a preliminary OS analysis indicated a borderline OS improvement with FOLFOXIRI plus bev (HR:0.79, p = 0.054) with a consistent effect across *RAS* (*KRAS* and *NRAS* codons 12, 13, 61) and *BRAF* V600E molecular subgroups.

Patients and methods: 508 patients were randomized to either FOLFIRI plus bev (Arm A, N = 256) or FOLFOXIRI plus bev (Arm B, N = 252). On available samples from *RAS* and *BRAF* wild-type (wt) patients (N = 129), also *KRAS* and *NRAS* codons 59, 117 and 146 were analysed by means of Sequenom® MassArray, identifying a new "all wt" population (N = 93).

Results: At a median follow-up of 48.1 months, in the intention-to-treat population, updated median OS for Arm B vs Arm A was 29.8 vs 25.8 months (HR = 0.80, 95% CI, 0.65-0.98, p = 0.030). Notably an estimated 5-years OS rate for Arm B of 24.9% vs 12.4% in Arm A. Molecular results were informative for 357 patients (70.3%). All wt patients had significantly longer OS as compared to *RAS* mutant (HR = 0.70, p = 0.006) and to *BRAF* mutant (HR = 0.24, p < 0.001). The benefit from FOLFOXIRI plus bev was consistent across all molecular subgroups (Table 1). All wt patients treated with FOLFOXIRI plus bev reported a median OS of 41.7 months as compared to 33.5 months in the FOLFIRI plus bev group (HR = 0.75, 95% CI, 0.45-1.24).

Conclusions: FOLFOXIRI plus bev significantly improves survival of metastatic colorectal cancer patients and the OS advantage increases over time. Benefit from FOLFOXIRI plus bev is independent of *RAS* and *BRAF* mutational status. All wt patients have a better outcome independently from the treatment arm. Notable results with FOLFOXIRI plus bev are achieved in all wt patients.

Table: 2*

	Arm A FOLFIRI + Bev	Arm B FOLFOXIRI + Bev	HR [95%CI]	Arm A FOLFIRI + Bev	Arm B FOLFOXIRI + Bev	HR [95%CI]
	Median PFS (mos)	Median PFS (mos)		Median OS (mos)	Median OS (mos)	
All wt (N = 93)	12.2	13.7	0.82 [0.53-1.26]	33.5	41.7	0.75 [0.45-1.24]
***RAS* mut (N = 236)**	9.5	12.0	0.82 [0.63-1.07]	23.9	27.3	0.95 [0.71-1.27]
***BRAF* mut (N = 28)**	5.5	7.5	0.56 [0.20-1.14]	10.8	19.1	0.60 [0.27-1.33]

3* A phase III multicenter trial comparing two different sequences of second/third line therapy (irinotecan/cetuximab followed by FOLFOX-4 vs. FOLFOX-4 followed by irinotecan/cetuximab in K-RAS wt metastatic colorectal cancer (mCC) patients refractory to FOLFIRI/Bevacizumab

G. Rosati[1], G. Nasti[2], S. Lonardi[3], A. Zaniboni[4], A. Romiti[5], M. Aglietta[6], D. Bilancia[1], V. Iaffaioli[2], V. Marsico[3], M. Giordano[7], D. Corsi[8], F. Ferraù[9], R. Labianca[10], R. Berardi[11], F. Galli[12], L. Frontini[13], S. Cascinu[11]

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Background: Impressive improvements in survival have been reported in mCC with the addition of bevacizumab or cetuximab to chemotherapy. Nevertheless, their efficacy in different therapy lines and the optimal sequence are still controversial. While bevacizumab seems to loose its efficacy along the course of treatment lines, cetuximab is active even in 2° and 3° line therapy. Therefore, we designed a multicentre randomised, phase III study to compare efficacy and safety of two different sequences of Cetuximab or FOLFOX to optimize the treatment of mCC pts refractory to FOLFIRI/bevacizumab.

Methods: Pts were randomised in a 1:1 ratio to receive as 2° or 3° line cetuximab/irinotecan followed by FOLFOX-4 (Arm A) or FOLFOX-4 followed by cetuximab/irinotecan (Arm B). Primary end point was progression free survival (PFS); secondary end points were overall survival and toxicity.

Results: 110 mCC patients were enrolled in this trial and 108 were evaluable for analysis (two early). 63 patients were males and 45 females, with a median age of 61 years. Efficacy results are reported in the table. Treatments were well tolerated with a low number of serious adverse reactions in both arms (8 and 4, respectively), even if grade 3-4 toxicity was overall higher in cetuximab treatment.

Conclusions: While PFS (primary end point) was not met, FOLFOX seems to be more effective than cetuximab (overall survival: 18.6 months vs 12.4 months) as 2° line treatment in patients receiving bevacizumab/FOLFIRI. This seems to confirm preclinical and clinical (FIRE-3) data suggesting that a prior anti-VEGF therapy may determine a lower sensitivity to a subsequent anti-EGFR treatment.

Eudract number 2007-006254-26/Clinicaltrials.gov: NCT01030042
Research Funding Source: AIFA (Agenzia Italiana del Farmaco) Code FARM 6XB38F

Table: 3*

Evaluable patients	Arm A (54 patients)	Arm B (54 patients)	Hazard Ratio (Arm B vs. Arm A) (95% confidence interval)
ORR			
II line	**15/52 (29%)**	**21/52 (40%)**	
III line	**7/30 (23%)**	**8/36 (22%)**	
PFS (median) (months)	**9.9**	**11.3**	HR = 0.85 (0.56-1.28); p = 0.42
OS (median) (months)	**12.4**	**18.6**	HR = 0.79 (0.52-1.22); p = 0.28
Treatment compliance Completed			
II line	**66.7%**	**70.3%**	
III line	**80%**	**71%**	

Arm A: CETUXIMAB followed by FOLFOX; **Arm B**: FOLFOX followed by CETUXIMAB

4* Ovarian suppression with luteinizing hormone-releasing hormone agonists during chemotherapy as a strategy to preserve ovarian function and fertility in breast cancer patients: a systematic review and meta-analysis of randomized studies

F. Poggio, M. Lambertini, M. Ceppi, D. Ugolini, A. Levaggi, S. Giraudi, A. D'Alonzo, C. Bighin, M. Vaglica, G. Rossi, E. Blondeaux, S. Pastorino, A. Abate, G. Iacono, P. Pronzato, L. Del Mastro

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Background: The role of temporary ovarian suppression with luteinizing hormone-releasing hormone agonists (LHRHa) in the prevention of chemotherapy-induced premature ovarian failure (POF) is still controversial and considered an experimental strategy to preserve ovarian function and fertility in cancer patients. Recently, new data suggest the potential efficacy of this strategy in breast cancer patients. Our systematic review and meta-analysis of randomized trials aims to evaluate the role of LHRHa during chemotherapy in the prevention of POF and fertility in premenopausal breast cancer patients.

Material and methods: A literature search using PubMed, Embase and the Cochrane Library was conducted; furthermore, the proceedings of major conferenceswere screened to identify relevant unpublished studies. We calculated Odds Ratios (OR) and 95% confidence intervals (CIs) for POF from each trial and obtained pooled estimates through the random effects model as suggested by DerSimonian and Laird.

Results: A total of 12 eligible studies with 1,231 breast cancer patients were included. A statistically significant reduction in the risk of chemotherapy-induced POF with the use of LHRHa was observed (OR = 0.36; 95% CI 0.23–0.58, p < 0.001). However, the heterogeneity among studies was also statistically significant (I-squared = 47.1%, p = 0.026): this is probably due to the fact that the definition of POF was not homogeneous in the different studies and was evaluated at different time points after the end of chemotherapy. For trying to overcome this limitation, we evaluated the benefit of the technique restricting the analysis to the 8 studies with available information on the rate of amenorrhea one year after the end of chemotherapy. The benefit of the use of LHRHa was confirmed (OR = 0.55; 95% CI 0.41–0.73, p < 0.001). Five studies reported the number of pregnancies after breast cancer treatment: 33 and 19 pregnancies occurred in patients receiving chemotherapy concurrently with LHRHa and those undergoing chemotherapy alone, respectively (OR = 1.83; 95% CI 1.02–3.28, p = 0.041).

Conclusions: Temporary ovarian suppression with LHRHa significantly reduces the risk of chemotherapy-induced POF and increase the pregnancies rate in young breast cancer patients. Current guidelines on fertility preservation should consider the use of LHRHa during chemotherapy as a reliable strategy to preserve ovarian function and fertility in breast cancer patients.

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Session A. Breast cancer

A01* Genomic hallmarks of invasive lobular breast carcinoma and their clinical relevance

G. Zoppoli[1], G. Gundem[2], G. Pruneri[3], D. Larsimon[4], M. Fornili[5], D. Fumagalli[6], D. Brown[7], R. Salgado[6], T. Van Brussel[8], D. Lambrechts[8], R. Bose[9], O. Metzger[10], C. Galant[11], F. Bertucci[12], M. Piccart[13], E. Biganzoli[5], G. Viale[3], P.J. Campbell[2], C. Sotiriou[7], C. Desmedt[7]

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Background: Invasive lobular breast carcinoma (ILBC) is the second most frequent histological type of breast cancer after invasive ductal breast carcinoma (IDBC). From a clinical point of view, ILBC more often presents with multiple foci, may show increased sensitivity to aromatase inhibitors, tends to relapse later in time, and metastasizes to unusual anatomic sites compared to IDBC. At present, no specific treatment recommendations are available for ILBC. Here we performed an extensive genomic characterization of the largest cohort of primary ILBC cases collected so far to this purpose, with the aim of identifying genetic determinants of such disease with potential clinical implications.

Patients and methods: Starting from 630 well annotated primary ILBC cases with a 10-year median follow up, we performed targeted sequencing of mutations and indels in 360 cancer-genes and genome-wide assessment of copy number aberrations in 413 and 170 samples respectively. We correlated our findings with the clinical, pathological, and outcome features of our set, and compared alteration frequencies with IDBC data from The Cancer Genome Atlas publicly available database.

Results: Genes belonging to the PI3K pathway, namely, *PIK3CA*, *AKT1*, and *PTEN* were mutated in more than 50% of ILBC cases, whereas *ERBB2* and *ERBB3*, part of the ERBB receptor tyrosine kinase family, globally showed alterations in 8.7% of samples. Mutations in the *ESR1* transcriptional regulator *FOXA1* were identified in 9% of cases, and focal gains in the *ESR1* locus (chr6 q25.1), with transcriptional evidence of activation, were found in 25% of samples. All the described alterations showed higher frequency in ILBC than IDBC. The phenotypic variability of ILBC was reflected by *ERBB2* mutational enrichment in the mixed-non-classic ILBC subtype, while the solid ILBC subtype was characterized by a higher frequency of *ARID1A* mutations and *ESR1* locus gains. Chromosome 1q gains were independently associated with longer breast cancer free interval (BCFI), while the opposite was observed for chr17q12 and 11p gains. Finally, *AKT1* and *ERBB2* mutations appeared to confer an increased short-term relapse risk.

Conclusions: Several alterations with immediate therapeutic relevance show high frequency in ILBC (e.g., *ERBB2*, *ERBB3*, and *AKT1* mutations), or urgently deserve dedicated clinical investigation (e.g., *FOXA1* mutations and *ESR1* gains).

A02* Clinical and pathological predictors of Advanced Breast Carcinoma with Luminal subtype (ABC-Lum) identifying prognostic 'outliers': multicenter retrospective analysis in the 'real-world' scenario

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Background: In order to identify prognostic 'outliers' affected by ABC-Lum to be further analyzed with molecular and genomic tools, a multicenter retrospective analysis was accomplished.

Methods: Clinical-pathological data were correlated to OS and PFS according to a Cox model. A continuous score based on the multivariate Cox model was derived, and dichotomized according to prognosis (Maximally selected log-rank statistics).

Results: Data from 302 pts were gathered; median age 60 years (range 30-91), Verona/Lecce/Roma: 59.6/23.5/16.9%. At a median follow-up of 26 months (range 1-300), median PFS and OS were 13 (95% CI 11-15) and 39 months (95% CI 31-46). Objective Response (HR 1.86, 95% CI 1.21-2.86, p = 0.0004), HT for advanced disease (HR 2.96, 95% CI 1.91-4.58, p < 0.0001), number of metastatic sites (HR 1.85, 95% CI 1.21-2.82, p = 0.004), number of treatment lines ≥4 (HR 1.48, 95% CI 0.98-2.28, p = 0.07) and adjuvant HT (HR 1.46, 95% CI 0.95-2.25, p = 0.08) were significant independent predictors for OS at the multivariate analysis. Number of metastatic sites (HR 1.78, 95% CI 1.31-2.43, p < 0.0001), PS (HR 1.54, 95% CI 1.12-2.13, p = 0.007), and Ki67 (HR 1.36, 95% CI 0.99-1.87, p = 0.058) were independent predictors for PFS. No significant differences between Luminal A and B were found. A 3-class model significantly (p < 0.0001) differentiated low-, intermediate-, and high-risk, for PFS (AUC 0.54, SE 0.05) and OS (AUC 0.51, SE 0.04) as follows:

Table: A02*

Outcome	Risk Classes [Score]	Median (months, 95% CI)	2-yrs (%)
OS	**Low [1-3]**	61 (44-78)	72.9
	Intermediate [4-7]	34 (24-43)	46.6
	High [>7]	13 (12-14)	23.6
PFS	**Low [0]**	17 (14-20)	33.6
	Intermediate [1-2]	10 (9-11)	14.5
	High [3]	5 (2-8)	5

Accordingly, the 2-class model, differentiated low-, and high-risk pts for PFS (AUC 0.52, SE 0.05) and OS (AUC 0.51, SE 0.05), respectively (p < 0.0001).

Conclusions: The commonly adopted clinical and pathological parameters may help to identity prognostic 'outliers' affected by ABC-Lum pts to be addressed to molecular analyses.

A03* Luminal-like metastatic breast cancer: which is the room of endocrine maintenance therapy after first line chemotherapy?

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Background: Endocrine therapy (ET) is appropriate first line option for patients (pts) with hormone receptor-positive metastatic breast cancer (Luminal MBC). Chemotherapy (CT) is generally preferred for symptomatic pts with heavy tumor burden involving visceral organs. Maintenance therapy with ET (CT- > ET) is a valid

strategy after initial CT regimen in absence of progressive disease. The optimal duration of CT and the role of maintenance therapy for MBC are still matter of debate. The aim of this study was to explore differences between cohorts of pts treated at first line with CT or CT- > ET.

Methods: The study included 604 consecutive pts with Luminal MBC treated at the University Hospitals of Udine and Naples, Italy, from 2004 to 2014. The analysis focused on 252 pts treated with first line CT. Namely, 129 pts received CT whereas 123 received CT- > ET. We estimated overall survival (OS), progression free survival (PFS) and post progression survival (PPS). Clinicopathological data were analyzed to investigate the association with first-line treatment strategy.

Results: Median OS in CT and CT- > ET cohorts was 31.2 and 52 months respectively (log-rank test, P < 0.0001). Median PFS was 6.1 months for CT cohort and 17.2 months for CT->ET cohort (log-rank test, P < 0.0001). Median PPS of CT and CT->ET cohort was 21.1 and 27.5 months respectively (log-rank test, P = 0.0502). BC immunophenotype, metastatic sites, body mass index, age and ECOG performance status were not associated with treatment choice. On multivariate analysis, patients with *de novo* metastatic disease were more likely to receive an ET maintenance treatment (OR 2.87, 95%CI 1.66-4.5; P = 0.0002), while a distant involvement of two or more sites was associated with a CT only treatment (OR 0.51, 95%CI 0.3-0.88; P = 0.0147).

Conclusions: Patients who received ET maintenance showed a better prognosis in terms of PFS and OS. No differences in clinicopathological characteristics between the two therapy groups were observed. A *de novo* diagnosis of metastatic disease predicted ET maintenance after CT therapy while a high tumor burden predicted a CT-only treatment. However, the study design does not allow to answer the question if the choice of first line treatment influences the outcome or *vice versa*.

A04* PDL1 and PD1 expression by tumor infiltrating lymphocytes in primary breast cancer

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Background: A high extent of tumor infiltrating lymphocytes (TIL) has been linked with good clinical outcomes in HER2+ and triple negative (TN) breast cancers (BC). Some patients further mount an anti-tumor immune response organized in tertiary lymphoid structures (TLS). The development of escape mechanisms allows the growth and metastatic spread of the tumor. Programmed death-1 (PD1) and its ligand (PDL1) are checkpoint molecules whose interaction dampens the activation of the immune response. The purpose of this study was to characterize PD1 and PDL1 expression in primary BC.

Material and methods: To evaluate the extent and organization of TIL infiltration, 146 untreated BC tumors from patients who underwent surgery between 2001 and 2013 at the Institut Jules Bordet were stained with a double immunohistochemical (IHC) labeling protocol using antibodies against CD3 and CD20, pan T and B cell surface markers, respectively. PDL1 and PD1 expression were assessed on the same cases with a second IHC staining. The stained sections were scored by two independent pathologists blinded to clinical data. PDL1 and PD1 positivity were defined as ≥1% positive cells.

Results: Triple negative breast cancer (TNBCs) patients had the greatest extent of TIL ($p < 0.0001$) and together with HER2+ the highest presence of TLS compared to luminal subtypes. PDL1 expression was detected in 23% of our tumor samples (mostly TNBCs, $p < 0.0001$) and more frequently on TIL (21%) than tumor (5%) or stromal cells (3%) ($p = 0.0002$). A positive association was observed between lymphocytic PDL1 expression and TIL ($p < 0.0001$), TLS presence ($p < 0.0001$) (both evaluated by anti-CD3 and anti-CD20) and PD1 ($p < 0.0001$). 19% of the cases were PD1+ (mostly TNBCs; $p = 0.0004$) and expression was associated to TIL ($p < 0.0001$) and TLS ($p < 0.0001$). Lymphocytic PDL1 and PD1 co-expression in the same tissue section was found in 11% of our cases (28% TNBCs). However, morphologically their presence was rarely co-localized. Our results reveal that, at the protein level, PDL1 is chiefly expressed on lymphocytes in TNBCs, and as well as PD1, its presence is associated with high levels of TIL and TLS presence. In the majority of cases PDL1 or PD1 positive, expression was mutually exclusive, with only a few samples co-expressing these molecules. This indicates that these targetable molecules reflect immune activation, in relation to the various lymphocyte subpopulations present, which we are currently investigating.

A05 Effect of Mediterranean Diet on the prevalence of breast cancer relapse: preliminary results of the "SETA PROJECT"

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Background: Breast cancer is a multifactorial disease and diet is one of the factors affecting cancer initiation. Recent studies suggest that Mediterranean Diet can be used as a tool to prevent cancer occurrence. Aim of this case-control study was to compare the recurrence of women treated for breast cancer and assigned to one of 2 groups: 1) free-diet with dietary advice for cancer prevention; 2) Mediterranean Diet.

Material and methods: 307 women with diagnosis of breast cancer and treated at the Department of Oncology-hematology, Hospital of Piacenza (Italy) have been enrolled in the study. After surgical and/or medical treatment and/or radiotherapy, women have been asked if they wanted to follow a normal diet with dietary advice to reduce the occurrence of cancer relapse (Std-Diet) or a Mediterranean Diet (Med-Diet). The adherence to the Mediterranean diet was determined with the Med Score (range 0-55) proposed by Trichopoulou. 199 women were included in the Std-Diet group and 108 patients in the Med-Diet group. Body mass index was recorded for each subjects. In addition a blood sample was taken, in the morning while fasting, for the determination of: glucose, cholesterol, insulin, vitamins A-D-E, sexual hormones, Ca, P, Mg, plant pigments (lycopene, β-carotene, lutein, zeaxanthin and cryptoxanthin), TNF-α, IL-1, IL-6, Reactive Oxygen Metabolites (ROM). The women received a questionnaire about quality of life sf-36 and physical activity. The comparison of cancer relapse between the 2 diets groups was carried out with the chi-squaremethod, while the correlation of data was performed with the PROC CORR of SAS 9.2. All participants gave theirs written informed consensus and the research was approved by the Ethical Committee of the Hospital.

Results: During the follow-up, (3 years) 11 patients relapsed in the cohort with normal diet plus nutritional advice (Std-Diet), while no recurrence was observed in the Med-diet group. This difference is significant: $\chi 26.19$; $P < 0.05$. The Med-Score resulted significantly correlated ($r = 0.51$; $P < 0.01$) with the β-carotene level in blood, while no significant relationship was observed with other pigments. According to this data the compliance of patients to Mediterranean diet could be estimated according to the level of pro-vitamin A.

Conclusions: The adoption of a Mediterranean Diet has reduced the risk of cancer recurrence. The levels of β-carotene can provide a good estimation of compliance to Mediterranean Diet

A06 Impact of time to surgery after neoadjuvant chemotherapy in patients with operable breast cancer

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Background: Some studies of adjuvant chemotherapy (CT) suggested that a shorter interval before the start of therapies may improve survival outcomes in many groups of patients. Time to surgery (TTS) after neoadjuvant CT and survival outcomes have not been established yet. The aim of this study is to evaluate the impact of TTS after neoadjuvant CT in terms of Overall Survival (OS) and Disease Free Survival (DFS).

Patients and methods: A retrospective analysis was conducted in 295 patients receiving neoadjuvant CT for stage I-IIIc breast cancer between 1991 and 2013. 56 pts underwent surgery within 21 days (group A) from last CT cycle, 148 pts within 22-35 days (group B) and 91 pts after 36 days (group C). The majority were infiltrating ductal carcinoma, stage IIA (37.6%) and IIB (33.9%), with nodal involvement in 51.6% of the cases. LumA 18.3%, LumB/HER2- 28.2%, LumB/Her2+ 20.7%, HER2+ 9.8%, TNBC

21%. All patients were treated with neoadjuvant CT: 70.5% with anthra-taxanes based regimen, 18% with anthra- alone, 10.9% with taxanes alone, 0.3% with CMF; plus Trastuzumab in 70% of HER2+ diseases.

Results: After a median follow up of 4.6 years, it was observed that patients in group A showed a significant better OS than group B (HR 4.22; 95% CI, 1.27–14.00, p = 0.018) and group C (HR 3.61; 95% CI, 1.01–12.86, p = 0.048). Moreover group A showed a significant better DFS than group B (HR 3.41; 95% CI 1.34 to 8.65, p = 0.010) and group C (HR 3.77; 95% CI 1.42 to 9.95, p = 0.007). No correlations with OS were found in pts who achieved pCR (20.7%); pCR was predictive of better 5- and 10-years DFS independently from TTS (95.4% in the pCR-group vs 75.4% of non-pCR group, HR 0.16; 95% CI 0.04 to 0.66, p = 0.011). TTS may influence DFS in non-pCR group: indeed 5-years DFS is 97.3% in group A, 72.7% in group B (HR 2.89; 95% CI 1.14 to 7.36, p = 0.026), and 68.5% in group C (HR 3.44; 95% CI 1.3 to 9.1, p = 0.013). No significant correlations with regard of stage at diagnosis or molecular subtypes were found.

Conclusions: These results suggest that TTS after primary CT may influence patients' survival, regardless of stage at diagnosis and tumor subtype, so that a shorter interval between that last cycle of neoadjuvant chemotherapy and breast surgery should be addressed whenever possible.

A07 Last-line treatment of advanced breast cancer: outcome measures and prognostic factors

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Background: An increasing number of patients (pts) receive several sequential lines of treatment for metastatic breast cancer (MBC). Therefore, there is a crucial need to identify prognostic factors in heavily treated pts, which could help medical oncologists in the decision about continuation of active treatment versus best supportive care (BSC). The aim of this study is to identify patients' characteristics and clinical factors that can predict outcome in pts with MBC with specific focus on last-line of treatment.

Patients and methods: The study analyzed a series of 593 consecutive pts with MBC treated at the Department of Oncology of Udine, between January 2004 and June 2014. Unconditional logistic regression analysis tested the association between clinical factors and death within 30 and 90 days from the start of last-line treatment.

Results: The event "death" occurred in 409 pts. Median number of therapeutic lines was 3. On multivariate analysis, worse ECOG performance status (PS) was significantly associated with a survival shorter than 30 days from last-line treatment (ECOG 2/3 vs 0/1: OR 4.48, 95%C.I. 1.89-10.63). Similar results were observed for death within 90 days (ECOG 2/3 vs 0/1: OR 1.88, 95%C.I. 1.03-3.43). On the other hand, a shorter than 30 days interval between last-line treatment and death was observed in presence of liver function impairment (OR 4.04, 95%C.I. 1.26-12.995), but no significant association was found when the interval considered was 90 days. Conversely, death within 90 days from last-line prescription was more frequent if progression-free survival (PFS) after previous therapy was shorter than 3 months (shorter PFS vs longer: OR 2.43, 95%C.I. 1.36-4.33). Among pts who have already received a third-line therapy, multivariate analysis showed that only ECOG PS was significantly associated to death within 30 days (ECOG 2/3 vs 0/1: OR 5.38, 95%C.I. 2.03-14.26). Of note, no other variables in multivariate analysis were found to be related with outcome (age, presence of dyspnea or pleural effusion, jaundice, edema, anorexia and weight loss).

Conclusions: This study analyzed clinical factors influencing the survival after last-line treatment prescription in pts with MBC. ECOG PS confirmed its prognostic role whether liver function impairment seems to be relevant only in predicting outcome within 1 month. Notably, age was not found to be associated with outcome when adjusted for clinical symptoms.

A08 A meta-analysis on impact of age at first pregnancy on the risk of developing breast cancer according to subtype

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Background: Breast cancer (BC) is a heterogeneous disease with at least three subtypes defined based on the expression of hormone receptors (HR) and HER2. Previously, it was shown that delaying first pregnancy is associated with an increased risk of developing BC. However, it remains unclear whether the protective effect is more relevant in one subtype over another. The aim of ourmeta-analysis is to better elucidate the association of age at first pregnancy (AFP) with the risk of developing BC according to subtype.

Material and methods: Epidemiologic studies (case-control and cohort studies) were identified by searching the PUBMED and EMBASE databases with no date restriction up to October 2014. Eligible studies were those that evaluated the impact of AFP on BC risk with available information on HR and HER2. The PRISMA criteria were used to select the studies.Tumor subtypes were defined as: Luminal (HR + /HER2- and HR + / HER2+), HER2+ (HR-/HER2+) and triple negative (TNBC: HR-/HER2-). The summary risk estimates (pooled odds ratio [OR]) and 95% confidence intervals (CI) were calculated using random effects models (DerSimonian-Laird method) for the association between AFP and risk of BC by tumor subtype.

Results: A total of 14 eligible studies (11 case-control and 3 cohort studies) were identified, including 17,528 BC patients (13,922 luminal, 939 HER2+ and 2,667 TNBC) and 664,489 controls (i.e. women who did not develop BC). Most studies defined "young" AFP as ≤ 24 years and "old" AFP as > 24 years. "Old" AFP was associated with a 15% higher risk of developing luminal BC (OR = 1.15; 95% CI 1.00-1.32; p = 0.05), with high heterogeneity (I2 = 86.9%) mainly due to one study which showed a significant reduction in risk in the "old" group. No impact of AFP was shown on the risk of developing HER2 (OR = 0.85; 95% CI 0.70-1.04; p = 0.10; I2 = 19.8%) and TNBC (OR = 0.94; 95% CI 0.80-1.11; p = 0.45; I2 = 64.5%).

Conclusions: The association between AFP and BC risk varies according to BC subtype suggesting possible etiologic differences. We found that AFP only impacts the risk of developing luminal BC. This information would be helpful to better counsel women on their risk to develop BC and could have relavant implications on preventive strategy.

A09 Self-evaluation subjective toxicity according to the Common Toxicity Criteria in breast cancer patients undergoing adjuvant chemotherapy: final results of an Italian prospective study

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Background: For patients (pts) enrolled in cancer clinical trials, chemotherapy-related side effects (CSE) are collected by an interview and by assigning a grade of severity according to conventional systems like the Common Toxicity Criteria (CTC) for adverse events. This process is time consuming and it is hardly feasible in the clinical practice. We tried to evaluated a CTC v4.02-based, self-administered questionnaire to collect 10 common CSE in pts undergoing standard adjuvant chemotherapy (ACT) for operable breast cancer.

Methods: Our questionnaire was administered to 604 pts from 11 Italian sites, after the 1st and the 3r^{d} cycle of ACT. For each item (nausea, vomiting, constipation, anorexia, taste alterations, diarrhea, fatigue, pain, neuropathy and dyspnea) the CTC v4.02 definitions of severity grade were translated into Italian and rephrased into statements. Pts were asked to choose the statement that best represented the worst CSE experienced after ACT. At each time-point, information on CSE was extracted from the medical charts to compare pts versus physicians (MD) reported side effects.

Results: Overall 1177 questionnaires were collected, 596 after cycle 1 and 581 after cycle 3 of ACT. A median of 82% of the fields was completely filled-in. 594 and 573 pts-questionnaires had a corresponding MD-questionnaire. The frequency of CSE (any grade) was systematically higher in pts than in MD questionnaires at both time-points, resulting in low concordance rates (concordance regarding the first time-point is summarized in Table 1, Cohen's K statistics are reported in the last column). We found that the magnitude of the discrepancy in the frequency of CSE was linearly correlated with the number of pts enrolled at each specific site.

Conclusion: Self-evaluation of adjuvant CSE according to the CTC system is feasible in the clinical practice and potentially time saving. Whether the observed discrepancy is due to pts over- or MD underreporting CSE needs to be clarified, but our results suggest a potential effect of local workloads on this phenomenon.

Table: A09 Concordance between pts and MD questionnaires (missing data excluded)

Toxicity	N	Reported by pts and MD	(%)	Reported by pts but not by MD	(%)	Reported by MD but not by pts	(%)	Not reported by pts and MD	(%)	K Statistics	95% CI
Nause	539	191	(35)	169	(31)	25	(5)	154	(29)	0.32	0.26-0.39
Vomiting	565	58	(10)	70	(13)	4	(1)	440	(78)	0.54	0.46-0.63
Constipation	546	57	(10)	211	(39)	8	(1)	270	(49)	0.20	0.13-0.24
Anorexia	563	36	(6)	261	(46)	5	(1)	261	(46)	0.10	0.06-0.14
Dysgeusia	556	43	(8)	234	(42)	3	(1)	276	(50)	0.14	0.10-0.19
Diarrhea	567	21	(4)	60	(11)	4	(1)	482	(85)	0.35	0.24-0.47
Fatigue	532	124	(23)	276	(52)	8	(2)	124	(23)	0.15	0.11-0.19
Pain	517	31	(6)	134	(26)	21	(4)	331	(64)	0.16	0.08-0.23
Paresthesia	582	13	(2)	119	(20)	4	(1)	446	(77)	0.13	0.06-0.20
Dyspnea	574	11	(2)	131	(23)	2	(<1)	430	(75)	0.11	0.05-0.17

A10 Risk of unplanned presentations and hospital admission of metastatic breast cancer outpatients

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Background: Overall survival for metastatic breast cancer (MBC) patients (pts) has improved but treatment-related toxicities can lead to unscheduled visits and/or to unplanned hospital admissions. We describe the magnitude of this underreported phenomenon identifying its risk factors.

Materials and methods: We retrospectively analyzed a consecutive series of MBC pts who had an unplanned visit to the Oncology Department or Emergency Department (ED) of the University Hospital of Udine, Italy, from June 2013 to Dec 2014. Demographical data, tumor characteristics and treatment history were recorded. Cross-tables, $\chi 2$ test, and univariable logistic regression were used.

Results: 194 unplanned visits (100 MBC pts) were observed. Median age was 64 years (range 33-84); 95.4% of pts had a hormone receptor-positive disease and 20.6% a HER2-positive disease. ECOG PS was 0-1 in 76.7%. Overall, 44.3% pts had more than 1 access within 30 days and 11.9% of visits led to hospitalization. Median number of metastatic sites was 3 (1-6): 78.4% bone, 46.9% liver, 36.1% lung, and 17.0% central nervous system (CNS) involvement. Lung (HR 4.0; 95%CI 1.6-9.9; p = 0.003) and CNS (HR 3.1; 95%CI 1.2-8.1; p = 0.020) metastases were significantly related with hospital admission. Pts attending the ED (8.2%) had a higher risk of hospitalization (HR 5.7; 95%CI 1.8-17.6; p = 0.003). We recorded 139 visits (71.6%) in pts on chemotherapy (median time from last treatment: 11 days, range 0-405). Median number of prior chemotherapy lines was 3 (0-12). The most frequent reasons for unscheduled presentations are shown in table 1. Concomitant use of NSAIDs (HR 2.5; 95%CI 1.1-6.0; p = 0.042) and opioids (HR 2.9; 95%CI 1.1-7.5; p = 0.025) significantly linked with hospitalization.

Conclusions: Grade 3-4 anemia and pain NRS > 4 are linked with a higher risk of repeated unscheduled visits, while grade 3-4 liver impairment, lung and CNS metastases, and concomitant NSAIDs and opioids with unplanned hospitalization. Identifying risk factors for multiple unplanned visits of MBC outpatients is critical to improve quality of cancer care.

Table: A10 Reasons for unscheduled visits and risk for multiple accesses within 30 days and hospitalization

		MULTIPLE ACCESSES			HOSPITALIZATION		
FACTORS	**%**	OR	95%CI	P-value	OR	95%CI	P -value
Pain NRS >4	23.7	9.6	2.2-42.4	0.003			
Thromboembolic event	5.2	–	–	NS	–	–	NS
Grade 3-4							
Anemia	11.9	3.5	1.1-11.1	0.031	–	–	NS
Fever	11.9	–	–	NS	–	–	NS
Neutropenia	6.2	–	–	NS	–	–	NS
Febrile neutropenia	0.5	–	–	NS	–	–	NS
Liver impairment	4.6	–	–	NS	3.9	1.4-10.9	0.008

A11 Unplanned hospital admission of early breast cancer outpatients treated with adjuvant chemotherapy

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Background: Although curative therapy for early breast cancer (EBC) patients (pts) has lead to an improved survival rate, it is also associated with treatment-related toxicities that may increase the need of unscheduled visits to the oncology clinic and/or to unplanned hospital admissions.

Materials and methods: We retrospectively analyzed a consecutive series of EBC pts who completed at least 1 cycle of adjuvant chemotherapy and who had an unplanned visit to the Oncology Department and to the First Aid Department of the University Hospital of Udine, Italy, from June 2013 to Dec 2014. Demographical data, tumour characteristics, and treatments information were recorded. Cross-tables, $\chi 2$ test, and univariable logistic regression were used to identify potential predictors for repeated presentations and hospitalization.

Results: A total of 106 unplanned visits were recorded. Median age was 51.4 years (range 26.9-77.0). In our series, 60.7% of EBC pts were diagnosed with pT1a-c tumours, 39.3% with pN0, 91.6% with an invasive ductal carcinoma, 84.1% with hormone receptor-positive disease, and 30.8% with HER2-positive. By the time of the presentation, the median Karnofsky PS was 90 (60-100). Overall, 66.2% of pts were receiving an anthracycline-based regimen and 33.8% a taxane-based regimen, median number of cycles was 6 (3-8). Median time from last treatment administration was 9 days (95%CI 6.9-20.8). Overall, 57.2% of pts had more than 1 access within 90 days, 44.3% within 30 days, and 11.9% of visits led to hospitalisation. Most frequent reasons for unscheduled presentations were: fever 29.9%, grade 3-4 neutropenia 21.5%, mucositis 8.5%, febrile neutropenia 7.5%, and grade 3-4 gastrointestinal toxicity 6.9%. Four pts (4.7%) experienced a thromboembolic event and 4 pts (4.7%) an allergic reaction during paclitaxel infusion. Fever (OR 13.7; p = 0.019), neutropenia (OR 11.8, p = 0.027), and febrile neutropenia (OR 48.5, p < 0.001) strongly correlated with an increased risk of hospitalization. However, they did not increase the risk of repeated unscheduled visits within a cut off time of 30 days.

Conclusions: Our analysis outlines the major toxicity that may lead to repeated unplanned presentation and/or hospitalization. We believe that a better understanding of the risk factors related to unplanned hospitalization of EBC outpatients is crucial to improve quality of oncology services and pts quality of life.

A12 First line trastuzumab- or lapatinib-based therapy in her2-positive metastatic breast cancer patients after prior (NEO)adjuvant trastuzumab

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Background: Approximately 15-20% of patients (pts) with HER2-positive early breast cancer relapse during or after (neo)adjuvant trastuzumab. The optimal first-line

treatment in this setting has been poorly investigated so far. We evaluated the clinical outcomes of HER2-positive metastatic breast cancer (MBC) pts with prior exposure to (neo)adjuvant trastuzumab who underwent first-line trastuzumab- or lapatinib-based therapy.

Materials and methods: This is an ancillary study within a retrospective cohort study conducted in 14 Italian centres of the GIM (Gruppo Italiano Mammella) group. Consecutive pts undergoing first-line trastuzumab or lapatinib-based therapy after prior exposure to (neo)adjuvant trastuzumab were included. Analyses were performed according to the type of first-line therapy for metastatic disease (trastuzumab or lapatinib). Dichotomous clinical outcomes were analyzed using logistic regression and time-to-event outcomes using Cox proportional hazards models controlling for relevant demographic, clinicopathologic and therapy characteristics. All data were analyzed using Stata 12.3 (StataCorp LP).

Results: Out of 450 MBC pts included in the study, 416 (92%) received trastuzumab and 34 (7.5%) lapatinib. A total of 128 pts relapsed after prior (neo)adjuvant trastuzumab and were included in the present analysis: 101 (24.3%) received first-line trastuzumab and 27 (79.4%) lapatinib. As compared to the trastuzumab cohort, more pts in the lapatinib group had a trastuzumab-free interval < 1 month (37% vs 14%) and brain metastasis as first site of relapse (38.2% vs 9.4%). In pts receiving first-line trastuzumab or lapatinib, the following outcomes were observed, respectively: overall response rate (ORR) 61.3% vs 45.5% (p = 0.184), clinical benefit rate (CBR) 72.5% vs 68.2% (p = 0.691), median progression-free survival (PFS) 12 vs 11.4 months (p = 0.814) and median overall survival (OS) 48.2 vs 34.7 months (p = 0.722). In pts who had brain metastasis as first site of relapse receiving first-line trastuzumab or lapatinib, PFS was 9.9 vs 12.2 months (p = 0.093) and OS 28.5 vs 33.7 months (p = 0.280), respectively.

Conclusions: In HER2-positive MBC pts relapsing after prior (neo)adjuvant trastuzumab and receiving first-line trastuzumab or lapatinib, no significant differences in their clinical outcomes were observed. Although not significant, atrend favouring the use of lapatinib was observed in pts with brain metastases as first site of relapse.

A13 Predictive factors of response to neoadjuvant chemotherapy (NAT) in triple negative breast (TNBC) cancer patients: a restrospective multicenter observational study

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Background: This is a multicenter observational study with the aim to evaluate predictive factors of response to NAT in TNBC pts

Methods: 196 TNBC pts treated with NAT were enrolled from 7 Italian cancer centres and retrospectively evaluated for % of pCR, ki67 pre and postNAT and treatment duration. Pts receiving NAT regimens were divided in 2 groups: longer (TAC and anthra-taxane sequences) and shorter (< 6 cycles) therapy duration and in 3 groups as a function of Ki67 levels (low (LL) ≤15 %, intermediate(IL) 15.1–35% and high(HL) >35%) OS and PFS were calculated by the Kaplan-Meier product-limit method. Log-rank and Tarone-Ware tests were used to assess differences between groups. A multivariate logistic regression model was developed using stepwise regression (forward selection) to compare the predictive power of different factors.

Results: pts median age was 47 yrs (25-77), cT1-T2 62%and cT3-cT4 38%, 79% of pts had clinical axillary disease, 41% of pts received longer NAT and 59% shorter. PreNAT ki67 levels were: LL 20%, IL 12% and HL 68%.PostNAT ki67: LL 22%, IL 6% and HL 42% and 52 pts (26.5%) achieved pCR (95%CI 20-33). In the group of pts that received longer NAT pCR was significantly more frequent compared to the group that received shorter NAT (38% vs 19% p = 0.005). Moreover pCR was more frequent in pts HL of ki67 (34%) compared to those with LL/IL (20%)(p = 0.05). In multivariate analysis HL of preNAT ki67 (OR 1.2 CI 95%1-1.3, p = 0.02) and longer duration of NAT response (OR 2.1 CI95% 1-4.3, p = 0.04) were significant predictive factors for. Conversely, cT and cN didn't appear predictive. At a median follow-up of 42 months (2-190) overall PFS at 3yrs was 65% and 5yrs OS 76%. Pts with pCR had higher DFS and OS than pts with NopCR. DFS and OS gradually worsened with increasing postNAT ki67 level Table 1.

Table: A13

	DFS 3yrs (%)	OS 5yrs (%)
Ki67 HL >35%	56.3	62.2
PCR	92.9	92.9
No pCR	56.4	70.7

Conclusions: Our analysis suggests that in TNBC treated with pre-NAT high ki67 levels and "adeguate" chemotherapy regimen are predictive factors of response and that post-NAT high ki67 levels and no pCR are negative predictors of survival. Data collection is ongoing and update results will be presented.

A14 CTC subpopulations in metastatic breast cancer

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Background: Circulating Tumor Cells (CTC) are rare cells shed into the bloodstream from primary and metastatic tumor. Integrating CTC-derived biomarkers with traditional patient data may enhance our understanding of metastatic cancer disease. Aim of this study is to explore the association between clinicopathological features of metastatic breast cancer (MBC), CTC number, and distribution of CTC subpopulations.

Materials and methods: The study enrolled 56 MBC patients treated at the University Hospital of Udine, from 2013 to 2015, regardless line of treatment. Among them, 53 were eligible for the CTC molecular analysis. DEPArray® system was used to identify and sort single, viable CTC through a multiparametric fluorescence analysis. Blood samples were depleted from the CD45 and glycophorin positive fractions and stained with an antibody cocktail. Cells presenting epithelial (EP), mesenchymal (ME) and transitional (EMT) immunophenotype but negative CD45, were counted and sorted for the molecular characterization. CTC subpopulations numerosity was considered both by absolute cell count and as a percentage of total CTC. The association between clinicopathological features and CTC distributions was explored through Wilcoxon-Mann-Whitney test.

Results: Patients affected by HER2 positive disease had a significantly lower number of ME CTC in comparison with HER2 negative (P = 0.006), triple negative, and luminal disease (P = 0.02). In presence of bone metastasis, EP and EMT cells were significantly higher both in percentage (P = 0.01, P = 0.03 respectively) and in absolute terms (P = 0.01, P = 0.05), whereas a lower number of ME cells was observed (P = 0.04). Furthermore, patients with liver involvement showed a higher percentage of EP CTC (P = 0.02). Of note, patients with more than one localization site seem to have a marginally higher number of EP CTC and in presence of liver localizations tended to have a lower percentage of ME subpopulation. Having received more than 2 therapeutic lines was marginally associated with higher number of cells negative for both EP and ME markers.

Conclusions: This study suggests the importance of dissecting the heterogeneity of CTC in MBC. Precise characterization of CTC could help in estimating metastatization pattern and outcome, driving clinical decision-making and surveillance strategies. Results need to be confirmed through larger trials.

A15 Development of a risk model to identity prognostic 'outliers' underwent surgery for early-stage invasive lobular breast carcinoma (ILBC) according to clinical and pathological factors

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Background: The aim of this analysis was to define a risk model for early-stage ILBC by combining clinical and pathological predictors.

Methods: Clinical-pathological data were retrospectively correlated to disease-free survival, and overall-survival (DFS/OS) (Cox model). A continuous score was derived according to Hazard Ratios (HR) at multivariate analysis, and dichotomized according to prognosis (ROC analysis) in order to identify risk classes.

Results: 405 pts were gathered: median age: 60 years (range 35-96); menopausal status pre/post: 28.4%/71.6%; mastectomy/quadrantectomy/tumorectomy: 36.8%/20.5%/47.5%; pT1/pT2/pT3/pT4: 58.0%/31.6%/7.7%/2.7%; pN0/pN + /unknown (unk) 57.8%/38.3%/4.0%; lobular/ductal-lobular/other: 71.6%/25.9%/2.5%; Ki67 (cut-off 25%) high/low/unk 19.8%/71.2%/9.1%; Grading 1/2/3/unk: 16.5%/38.3%/13.%/31.4%; ER and PgR positive/negative/unk: 93.5%/3.0%/3.5% and 82.7%/9.9%/7.4%, respectively; HER2 positive/negative/unknown: 4.9%/64.0%/31.1%; hormonal therapy yes/no: 85.4%/14.6%; radiotherapy: yes/no/unk: 64.0%/32.6%/3.5%. Median follow-up was 67 months (range 1-396). Nodal involvement (HR 4.57, 95% CI 2.14-9.75,

p < 0.0001), histology (HR 2.30, 95% CI 0.92-5.77, p = 0.075), Ki67 (HR 3.61, 95% CI 1.35-9.63, p = 0.010) and radiotherapy (HR 2.27, 95% CI 1.10-4.69, p = 0.026) were independent predictors for DFS at the multivariate analysis. Nodal involvement (HR 5.38, 95% CI 2.26-12.79, p < 0.0001), age (HR 3.74, 95% CI 1.53-9.13, p = 0.004), Ki67 (HR 12.57, 95% CI 4.13-38.23, p < 0.0001), and radiotherapy (HR 2.10, 95% CI 0.89-4.91, p = 0.087) were independent predictors for OS at the multivariate analysis. The 2-class model significantly (Log-rank p < 0.0001) differentiated low- and high-risk, as follows:

Table: A15

Outcome	Risk Classes [Score]	5-yrs (%)	10-yrs (%)
DFS	**Low [0-2]**	91.8	82.4
	High [>2]	64.4	50.2
OS	**Low [0-2]**	97.2	88.4
	High [>2]	82.2	67.4

Accordingly, the 3-class model derived by ROC analysis, differentiated low-, intermediate- and high-risk pts for both outcomes (Log-rank p < 0.0001). The 2-class model predicted DFS and OS with a prognostic accuracy of 0.68 (SE 0.03) and 0.70 (SE 0.03); the 3-class model with a prognostic accuracy of 0.68 (SE 0.03) and 0.67 (SE 0.03), respectively.

Conclusions: A risk classification system comprising the commonly adopted clinical and pathological parameters (nodal involvement, Ki67, age, and radiotherapy) accurately separates ILBC pts into different risk classes, allowing to identity prognostic 'outliers'.

A16 Does body mass index impact on clinical outcomes in her-2 positive metastatic breast cancer?

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Background: The available evidence suggests that increased body mass index (BMI) is associated with a worse prognosis in patients (pts) with HER2 positive early breast cancer (EBC). However, the effect of BMI on the clinical outcomes of HER2 positive metastatic breast cancer (MBC) pts has not been explored so far.

Material and methods: We conducted a multicenter retrospective analysis of 329 consecutive pts with HER-2 positive MBC treated with first-line trastuzumab-based regimens. World Health Organization BMI categories were used: normal 18.5-24.9 Kg/m2, overweight 25-29.9 Kg/m2, and obese ≥30 kg/m2. Given the limited sample size, we carried out the analyses using two categories: BMI <25 (normal/underweight) and BMI ≥25 (overweight/obese). Univariate Progression Free Survival (PFS) and Overall Survival (OS) curves were estimated using Kaplan-Meier method. Multivariate survival analysis was performed using the Cox proportional hazards model controlling for relevant clinical and pathologic characteristics. Response to trastuzumab was evaluated using multivariate logistic regression analysis.

Results: Median age was 53 years (range 22-84). Overall, 176 (53.5%) pts were normal or underweight, 109 (33%) pts were overweight, and 44 (13.4%) pts were obese. No differences in hormonal receptor expression (p = 0.452) and in first site of relapse (p = 0.820) were seen between BMI < 25 and BMI ≥ 25 group. Median PFS was 14.8 months in BMI < 25 group and 15.7 months in BMI ≥ 25 group (adjusted-HR 0.88; 95%CI 0.66-1.17; p = 0.387). Median OS was 58.6 months in BMI < 25 group and 52.6 in BMI ≥ 25 group (adjusted-HR 0.88; 95%CI 0.59-1.31; p = 0.525). The multivariate analysis showed no statistically significant association between BMI categories and OS. The Overall Response Rate (ORR) was 71.7% and 65.9 % (p = 0.296) and Clinical Benefit Rate was 82.1% and 83.3% (p = 0.781) in BMI < 25 and BMI ≥ 25 group respectively.

Conclusion: This analysis suggests that the presence of overweight or obesity at MBC diagnosis is not an adverse prognostic factor in pts with HER2-positive disease treated with first-line trastuzumab-based regimens. In contrast with the EBC stage, in the metastatic setting we hypothesize that the mechanisms by which BMI may affect prognosis are less important than tumor biology per se.

A17 First line treatment in patients with luminal-like metastatic breast cancer: a propensity score-matched analysis

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Background: Even if endocrine therapy (ET) is generally the most suitable option for patients (pts) with luminal-like metastatic breast cancer (l-MBC), chemotherapy (CT) is preferred in some cases. Aims of this study are to investigate potential prognostic factors for pts with l-MBC, to explore clinico-biological factors influencing treatment decision, and to analyze the impact of the treatment strategies on pts' outcome.

Methods: We included 604 pts with l-MBC treated at University Hospitals of Naples and Udine, Italy, from 2004 to 2014. Clinico-pathological factors were evaluated to test the association with 1st line treatment choice (ET vs CT) and with outcome measures. The influence of treatment choice on outcome was estimated by a propensity score matching (PSM).

Results: On multivariate analysis, Luminal B profile (HR 1.82, 95%CI 1.21-2.75), age ≥70 years (HR 1.79, 95%CI 1.25-2.57), and >1 site of metastases (HR 2.15, 95%CI 1.41-3.29) showed independent prognostic value in predicting OS. *De novo* MBC was associated with better OS. First line CT was chosen for 41.7% of pts. On multivariate analysis, HER2 positivity (OR 4.16, 95%CI 1.56-11.06) and presence of liver metastases (OR 2.75, 95%CI 1.02-7.39) were associated with higher CT use. Conversely, age =70 years (OR 0.24, 95%CI 0.12-0.49), and bone only disease (OR 0.19, 95%CI 0.08-0.44) were associated with ET. There was no statistically significant difference between ET and CT as 1st line therapy for both PFS (HR 0.80, 95%CI 0.60-1.06) and OS (HR 0.82, 95%CI 0.57-1.20). A subgroup of 340 pts was analyzed by PSM to correct for unbalanced characteristics (pts' age, tumor phenotype, number and sites of metastases). No statistically significant differences were observed for both PFS (8.8 vs 12.6 months with ET and CT respectively, HR 0.83, 95%CI 0.66-1.04) and OS (36 vs 44.9 months respectively, HR 0.86, 95%CI 0.66-1.14).

Conclusions: Luminal B-like profile, old age and number of site of metastases are unfavourable prognostic factors in pts with l-MBC whereas *de novo* MBC is associated with better outcome. Choice of 1st line treatment of l-MBC is mainly driven by age, HER2 status and presence of bone or liver metastases. Although the study was not powered to detect potentially relevant differences between treatments, there were no statistically significant differences in outcome according to treatment choice.

A18 Whole-exome sequencing of HER-2 positive human breast cancers: potential molecular mechanisms of response to neoadjuvant chemotherapy plus trastuzumab

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Background: Despite relevant advances in the field of HER2+ breast cancer (BC) treatment, a consistent number of patients (pts) present primary or secondary resistance. Up today no biomarkers of trastuzumab activity are available in clinical practice.

Material and methods: Consecutive pts treated with neoadjuvant anthra/taxane-based chemotherapy plus trastuzumab were enrolled in this study. We defined pathological complete response (PCR) to study treatment the complete disappearance of infiltrating tumour in breast and nodes (ypT0/isN0). Whole-exome sequencing (Ion Proton Sequencer®) of genomic DNA from FFPE of the diagnostic biopsy and residual tumour after treatment was performed. Gene mutations were characterized using COSMIC,

HER2 Resitance and Driver Cancer databases. Differences in gene mutations were reported between pts with PCR or not.

Results: Between 2010 and 2014 we retrospectively identified 65 HER2 positive BC pts treated with neoadjuvant chemotherapy plus trastuzumab at our institution. Median age at diagnosis was 50 years (range 26-76); 39 (60%) pts had hormonal receptor (HR) positive disease. Stage III BC was diagnosed in 38 (59%) pts. We observed a PCR rate of 48% with an overall conversion rate from mastectomy to conservative surgery of 29%. Up today we analyzed 3 pts with PCR (2 pts stage IIIB; 1 pt stage IIIC) and 2 pts with nonPCR (all pts stage IIIB). All pts had HR negative disease. Mutations were found in NOTCH2NL, IGQAP2, FUCA2, OR6C74, UGT2B7and CAPN2genes in the biopsy of nonPCR pts. Interestingly these mutations rise in the post therapy samples while are nearly absent in PCR pts. On the other side we found some variants in MACC1and MAPK1genes present in PCR pts and absent in non responding one.

Conclusions: Our preliminary results if confirmed in additional patients samples deserve further evaluation in functional studies and in prospective clinical trial. All the analyses have been performed at the Pisa Science Foundation - ONLUS, Pisa, Italy.

A19 The value of hormone serum concentration to predict the gonadotoxic effect of chemotherapy and the efficacy of LHRH analogs as a strategy to reduce treatment-related premature ovarian failure in breast cancer

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Background: Temporary ovarian suppression induced by LHRH analogs (LHRHa) is a promising strategy to preserve ovarian function. During chemotherapy (CT) limited evidence exists on the impact of LHRHa on hormone serum concentration (follicle-stimulating hormone[FSH], estradiol [E2]and anti-Mullerian hormone [AMH]). We assessed ovarian function using FSH, E2 and AMH in a cohort of pts of the PROMISE-GIM 6 study.

Material and methods: The PROMISE-GIM 6 study is a phase III randomized study aiming to evaluate the role of LHRHa as a strategy to protect ovarian function in breast cancer (BC) pts undergoing (neo)adjuvant CT. We assessed FSH, E2 and AMH, as potential markers of the gonadotoxic effect of CT, and the short- and long-term efficacy of ovarian suppression with LHRHa. FSH, E2 and AMH were evaluated at baseline (before CT initiation), at the end of CT and at the end of endocrine therapy (ET: = 6 years from diagnosis). Median values of AMH, FSH and E2 were compared with the Wilcoxon two sample test.

Results: Out of 88 premenopausal BC pts, 44 received CT alone and 44 received CT + LHRHa triptorelin (T). In pts treated with CT alone or CT + T, respectively, median age was 40 and 38 years at study entry and 43 and 44 years at the end of ET. The median serum concentration of FSH increased significantly after CT, from 5 to 21.2 mIU/ml ($P < 0.001$), whereas E2 decreased from 70 to 20 pg/ml ($P < 0.001$). AMH levels did not change significantly during chemotherapy. As compared to baseline evaluation, at the end of ET, FSH increased from 5 to 11.26 mIU/ml ($P < 0.001$); no significant difference in E2 levels was observed (70 at baseline and 74 pg/ml; $P = 0.73$), while AMH decreased from 3.15 to 0.61 ng/ml ($P < 0.001$). At the end of CT, in patients in the CT alone and the CT + T arms, respectively, median values of FSH were 43 and 17.15 mIU/ml ($P = 0.02$), median values of E2 were 34 and 52.45 pg/ml ($P = 0.02$), whereas median values of AMH were 3.88 and 4.16 ng/ml ($P = 0.8$). At the end of ET, in patients in the CT alone and the CT + T arms, respectively, median values of FSH were 28.3 and 7.6 mIU/ml ($P = 0.02$), median values of E2 were 114.5 and 68 pg/ml ($P = 0.3$) and median values of AMH were 0.5 and 0.75 ng/mL ($P = 1.00$).

Conclusions: In BC patients, FSH, E2 and AMH could be consider potential markers of CT-induced gonadotoxicity; moreover, they seem to predict the short-term efficacy and FSH seems to predict also the long-term efficacy of ovarian suppression with LHRHa.

A20 FDG-PET/CT as a predictor of pathological complete response (pCR) in breast cancer (BC) patients (pts) treated with neoadjuvant chemotherapy (NAC): a single center retrospective study

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Background: FDG-PET/CT represents a promising method to assess response to NAC in BC. We conducted a retrospective study in BC pts receiving NAC to investigate: the correlation of clinical and pathological characteristics with baseline tumor SUVmax; the correlation of metabolic response assessed by FDG-PET/CT with pathologic complete response (pCR).

Patients and methods: From 2010 to 2014, 59 stage II-III BC pts were treated at our institution with anthacycline and/or taxane based NAC, also with trastuzumab if HER2 +. Pts underwent FDG-PET/CT at baseline and after NAC completion. The metabolic response (ΔSUV) was defined as follows: [(tumor SUVmax after NAC – tumor SUVmax before NAC) / tumor SUVmax before NAC]. Pathologic response was evaluated by Pinder score; pCR was defined as absence of invasive cancer in the primary tumor. The association between continuous variables was investigated using Spearman's Rho correlation analysis. The comparison between median ΔSUV and pathologic response was analyzed using Mann-Whitney test.

Results: Among the 59 pts, we observed 15 pCR (13 with no residual BC, 2 with residual in situ BC), 10 partial response (PR) with ≤ 10% residual invasive BC and 34 PR with >10% residual invasive BC. At baseline, median Ki67 in the whole population was 30% (3%-70%), and Ki67 was directly correlated with baseline SUVmax (Rho = 0. 51; $p < 0.0001$). Median ΔSUV (mΔSUV) was -82% in pts with no residual BC, -24% in pts with residual in situ BC, -82% in pts with ≤ 10% residual invasive BC and -36.5% in pts with >10% residual invasive BC. mΔSUV was significantly different among pts who achieved pCR compared with no pCR (-82% vs -48%, $p = 0.01$).

Conclusions: In our study, SUVmax of BC before NAC was positively correlated with Ki67. mΔSUV was significantly different among pts who achieved pCR compared with no pCR. FDG-PET/CT represents an interesting tool for assessment of response to NAC.

A21 A Network Meta-Analysis of Everolimus plus Exemestane versus Chemotherapy in the First and Second Line Treatment of Estrogen Receptor Positive Metastatic Breast Cancer

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Background: The goal of study was to compare the efficacy and toxicity of chemotherapy to exemestane plus everolimus (EXE/EVE) through a Network Meta-Analysis (NMA) of randomized controlled trials (RCTs).

Method: NMA methods extend standard pairwise meta-analysis to allow simultaneous comparison of multiple treatments while maintaining randomization of individual studies. The method enables "direct" evidence (i.e. evidence from studies directly comparing two interventions) and "indirect" evidence (i.e. evidence from studies that do not compare the two interventions directly) to be pooled under the assumption of evidence consistency. We used NMA to evaluate progression-free survival (PFS) and time to progression (TTP) curves in 34 studies, and response rate (RR) and the hazard ratios (HR) of the PFS/TTP in 36 studies. A number needed to treat (NNT) analysis was also performed as well as descriptive comparison of reported toxicities.

Results: The NMA for PFS/TTP curves and HR project EXE/EVE to be more efficacious than capecitabine plus sunitinib, CMF, megestrol acetate and tamoxifen, with an average expected PFS/TTP difference ranging from about 2.1 months for capecitabine plus sunitinib to more than 6 months for tamoxifen. The NMA for overall RR shows that EXE/EVE provides a better response rate than bevacizumab plus capecitabine or taxane, capecitabine, capecitabine plus sorafenib, capecitabine plus sunitinib, CMF, gemcitabine plus epirubicin plus paclitaxel, everolimus plus tamoxifen, exemestane, FEC, megestrol acetate, mitoxantrone and tamoxifen. Finally, the NMA for NNT shows that EXE/EVE is more beneficial as compared to BMF, capecitabine, capecitabine plus sunitinib, CMF, FEC, megestrol acetate, mitoxantrone and tamoxifen.

Conclusions: The combination of EXE/EVE as first or second line therapy for ER positive /HER2 negative metastatic breast cancer is more efficacious than several chemotherapy regimens that were reported in the literature. Toxicities also favored EXE/EVE in most instances.

A22 Neoadjuvant Chemotherapy (NC) with or without Anthracyclines in different Invasive Breast Cancer (IBC) subtypes: outcomes according to pathological complete response (pCR) and proliferation index (PI) of residual tumor (RT)

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Background: The outcomes of IBC pts who received NC could be different by Subtypes.

Methods: We retrospectively reviewed the clinical records of 228 pts treated with NC for stage II-III IBC from 2000 to 2014. For each pt we recorded baseline tumor size, type of NC, type of surgery (S), pathological response (pCR defined as the absence of invasive cells in the breast and the lymph nodes regardless of DCIS). IHC subtypes were defined according to ER and PgR expression, Ki-67 level, and HER2 status: Luminal A (LA): ER and PR + ,HER2-ve and Ki67< 20%(4.8%) Luminal B (LB): ER and/or PR + ,HER2-ve and Ki67 = 20%(27.2%) Luminal HER2 (LHER2): ER and/or PR + ,HER2+ and any Ki67(25.4%) HER2 positive (HER2+): neg ER and PR, HER2+ and any Ki67(11.4%) TN: ER-and PR-ve, HER2-ve and any Ki67(17.5%) Unknown in 33 cases(13.6%) pCR and OS outcomes also on the basis of both pre- and post- NC Ki67 levels were assessed

Results: Median age was 50 yrs (r. 25-75). The NC consisted of an anthracyclines (A)? taxanes (T) in all HER2- (151 pts), associated with weekly carboplatin (C) in a few cases (9) of TN and of T + trastuzumab (H) ± A (32) or C (36 pts) in HER2+ disease. Only 8 pts did not receive S: 5 for distant progression disease (PD) and 3 because still on NC. Quadrantectomy was performed in 127 pts (56%) pCR was achieved in 52 pts (23%) with further 4 pts showing a RT =1 mm

Table: A22 Relationship between pCR and Sub, ki67 and PD

	LA (%)	LB (%)	LHER2 (%)	HER2 +	TN (%)	Median Ki67	PD (%)
pCR	0	8.2	31.0	52.0	36.4	47.4	5.8
No pCR	100	91.8	69.0	48.0	63.6	38.1	34.3
p Value	<0.0001					< 0.0001	<0.0001

All but 21 HER2+ pts (89) received H obtaining pCR in 39.7% of cases regardless chemotherapy type (A-based 35.5% vs C- 43.7%). Seven of 9 pts receiving C addition underwent S with pCR in all but 2 cases. The median Fup was 52 ms (r.1-182 ms). The 5y-RFS and OS were higher in whom achieved pCR than those did no (RFS 93.8 vs 67.8%;p = 0.001 and OS 95.8 vs 76.0%;p = 0.007). Median Ki67 in pretreated core biopsy was 40 compared to 30% in post-NC RT. Pts with high (>30%) post-NC PI showed significantly higher risk for relapse (5y-RFS 49.3%;p = 0.001) and death (5yOS 56.4%;p = 0.007) compared with pts with <15% (RFS 93.6 and OS 89.6%) or >15-30 Ki67 levels (RFS 73.0 and OS 82.6%) .

Conclusions: The pCR rate was significantly higher in aggressive subtypes HER2+ and TN than luminals. Pts achieving pCR showed better RFS and OS compared to no pCR pts. Interestingly high pre-NC PI seems to predict the possibility obtaing pCR, while post-NC PI seem to be of prognostic value in pts who do not receive pCR.

A23 Correlation between treatment with aromatase inhibitors and carotid intima-media thickness, carotid stenosis and abdominal aortic diameter. A prospective cohort study

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Background: Aromatase inhibitors (AIs) are standard adjuvant treatment of post-menopausal women with hormone receptor positive breast cancer (BC). AIs inhibit the production of estrogens, known to have a key protective role on the risk of developing cardiovascular (CV) diseases. However, the impact of AIs on the risk of CV diseases is still controversial. This is a prospective cohort study aiming to evaluate the role of estrogen deprivation induced by AIs on the development of CV diseases, assessed using surrogate markers such as carotid intima-media thickness (CIMT), carotid stenosis and abdominal aortic diameter.

Material and methods: A total of 410 post-menopausal women were enrolled, 210 healthy controls and 200 BC patients previously treated with AIs for at least 36 months. Every woman attended an ultrasound examination of both carotids and abdominal aorta. CIMT, presence of stenosis and abdominal aortic diameter were measured. Differences in CIMT measurements, carotid stenosis and abdominal aortic diameter were compared between the two cohorts by $\chi 2$ test.

Results: Median age was 71 and 72 years for the BC cohort and healthy women cohort, respectively. CIMT was measured in common carotid artery, 1 cm before bifurcation. Average CIMT was 1.01 ± 0.04 mm and 1.08 ± 0.02 mm for BC cohort and healthy women cohort, respectively (p = 0.069). With older age, a statistically significant increase in the CIMT was reported within the healthy women cohort ($p \leq 0.005$), while no effect was observed within the BC cohort (p = 0.13). The incidence of carotid stenosis in the two cohorts was similar: 24.2% in the BC cohort and 28.6% in the healthy women cohort (AIs vs controls: OR = 0.80; 95% CI 0.51-1.25; p = 0.32). Hypertension was associated with a statistically significant higher risk of developing carotid stenosis (OR = 0.58 95% CI 0.37-0.91; p = 0.02). No aneurismatic dilatation of the aorta were recorded in the two cohorts. Only 2 (1.1%) cases of abdominal aortic ectasia were reported in the BC cohort.

Conclusions: The use of AIs is not associated with a higher incidence of increased CIMT, presence of stenosis or abnormal aortic diameter. Although evaluated with the use of surrogate markers, AIs seem not to appreciably increase the risk of CV diseases.

A24 First line trastuzumab-based therapy in her2-positive metastatic breast cancer patients presenting with de novo or recurrent disease

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Background: Approximately 5-10% of breast cancer (BC) patients (pts) have metastases at the time of diagnosis (de novostage IV), suggesting distinct biological and clinical implications as compared to those relapsing after prior treatment for early stage BC (recurrent disease). We evaluated the patterns of care and clinical outcomes of HER2-positive metastatic breast cancer (MBC) pts receiving first line trastuzumab-based therapy, according to the type of metastatic presentation.

Materials and methods: This is an ancillary study of a retrospective cohort study conducted in 14 Italian centers within the GIM (Gruppo Italiano Mammella) group. Consecutive pts undergoing first-line trastuzumab-based therapy were eligible for the study. Analyses were performed according to the type of presentation of metastatic disease (de novoor recurrent). Dichotomous clinical outcomes were analyzed using logistic regression and time-to-event outcomes using Cox proportional hazards models controlling for relevant demographic, clinicopathologic and therapy characteristics. All data were analyzed using Stata 12.3 (StataCorp LP).

Results: A total of 416 MBC pts (median age, range 42–63 years) were included, 113 (27.2%) with de novo stage IV and 303 (72.8%) with recurrent disease: 64 (56.6%) and 186 pts (61.4) had hormone-receptor positive disease, respectively. Among pts with recurrent disease 101 (33.3%) received prior trastuzumab-based therapy in the (neo) adjuvant setting. Overall survival (OS) and progression-free survival (PFS) median follow-up were 2.59 years (1.56–4.41) and 1.11 years (0.63–2.17), respectively. In pts with de novo stage IV disease and in those with recurrent disease the following outcomes were observed, respectively: objective response rate (complete response + partial response), 163 pts (67.1%) vs 72 pts (72.0%) (adjusted OR = 0.90; 95% CI 0.34–2.38; p = .833); clinical benefit rate (complete response + partial response + stable disease), 76 pts (76.0%) vs 187 pts (77.0%) (adjusted OR = 1.21; 95% CI 0.40–3.64; p = .731); median PFS, 14.4 months vs 14.7 months (adjusted HR = 1.21; 95% CI 0.79–1.86;p = .380);median OS, 55.9 months vs 49.0 months (adjusted HR = 1.26; 95% CI 0.71–2.23; p = .439).

Conclusions: The study shows that clinical outcomes of HER2-positive MBC pts with de novo stage IV disease do not differ significantly from those of pts with recurrent disease.

A25 Prospective study of fertility preservation strategies in young early breast cancer patients: the PREFER (PREgnancy and FERtility) trial

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Background: Anticancer treatments may impair ovarian function and fertility in young cancer patients. All patients should receive an assessment and communication about risk of treatment-related infertility. We evaluated feasibility and patients' preferences of 3 different strategies attempt to preserve ovarian function and fertility: oocyte cryopreservation, ovarian tissue cryopreservation and temporary ovarian suppression with LHRH analogues (LHRHa) during chemotherapy.

Methods: From March 2010 to March 2015, 87 breast cancer patients younger than 45 years (median age: 39, range: 25–45), referred to our Institution and consented to be enrolled in the PREFER study. They were offered the possibility to reduce the chance of treatment-related infertility before the initiation of chemotherapy: the oncologists proposed both the administration of LHRHa during chemotherapy, and a reproductive counselling performed by the gynecologist, where oocyte cryopreservation and ovarian tissue cryopreservation were discussed.

Results: The majority of young women (78 patients, 89.7%) showed concerns about the possible loss of ovarian function and fertility due to anticancer therapies. A total of 75 patients (86.2%) accepted the treatment with LHRHa, started at least 1 week before chemotherapy; only 20 patients (23%) accepted the reproductive counselling by fertility specialist. The main reason for refusal was previous pregnancies (28 pts, 48.3%). Out of 20 patients who accepted the reproductive counselling, 6 patients (30%) were not eligible for comorbidities, only 4 (20%) accepted to undergo oocyte cryopreservation and 1 (5%) ovarian tissue cryopreservation. The reasons for refusal were: fear of delaying cancer treatment (2 patients, 10%), fear of the ovarian stimulation required (1 patient, 5%), low successful rate of the technique (1 patient, 5%) and other reasons (2 patients, 10%). In the 4 patients undergoing oocyte cryopreservation a median number of 11.5 oocytes were retrieved and 9.0 oocytes cryopreserved per patient.

Conclusions: This preliminary analysis suggests that fertility issues are of great importance in young early breast cancer patients; the majority of them (89.7%) accept the use of LHRHa during chemotherapy. A total of 20 patients (23%) were referred to fertility specialists and 5 women (5.7%) undergoes oocyte cryopreservation and ovarian tissue cryopreservation.

A26 Outcomes of hormone-responsive (HR+) HER2 negative (HER2-) metastatic breast cancer (MBC) patients (P) according to their starting first-line (1st) treatment (T): chemotherapy (CT) or hormonal therapy (HT)

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Background: Most of HR + /HER2- MBC P received both HT and CT as T of their disease. HT is the preferred 1st T but no data from clinical trials support that the sequence 1st HT and CT thereafter, is the best. Outcomes of P treated with 1st HT or 1st CT were retrospectively evaluated.

Methods: P were split into 2 groups according to the 1st T: CT or HT. Clinical benefit (CB) at the 1st T and median overall survival (OS) were evaluated in the 2 groups using Pearson Chi Square and Kruskal-Wallis tests, Kaplan-Meier (KM) curves and log-rank tests. For every day of follow-up (FU), the proportion of P in CT relative to those present at the time (t) in the 2 groups was computed. The weighted averages of the proportion of P in CT was calculated, using as weights the KM OS functions in the 2 groups, and these proportions (with 95% CI) were cumulated along t to achieve the average percentage of t spent in CT at different t.

Results: From 2007 to 2013, 119 P started with HT and 100 with CT. Median FU was 37.8 months (m). P treated with CT as 1st T were younger and with poorer prognostic factors (number and type of metastatic sites) compared to P starting with HT. CB (77 vs 81%, p = .537) and median OS (50.7 vs 51.1 m, p = .548) were similar for the 2 groups. Table 1 shows the proportions of t spent in CT at different t in the 2 groups. Time spent in CT, as proportion of the OS t, was significantly longer during the first 3 years (Y) in P starting with CT (54-34%) as compared to P starting with HT (11-18%). This difference decreased after the 3rd Y and overall was 28% in 1st CT and 18% in 1st HT.

Conclusions: The sequence 1st CT followed by HT, as compared with the opposite sequence, is associated with a longer t of OS spent in CT. However, despite the poorer prognostic factors, P starting with CT had an OS superimposable to that of P starting with HT.

Table: A26

	1st HT			1st CT			
Time of FU (Y)	P in CT	P evaluable at different t	Time spent in CT (95% CI)	P in CT	P evaluable at different t	Time spent in CT (95% CI)	p-value*
1	22	107	0.11 (0.07-0.18)	17	78	0.54 (0.46-0.60)	<0.05
2	16	88	0.16 (0.10-0.24)	8	60	0.38 (0.30-0.47)	<0.05
3	10	67	0.18 (0.11-0.26)	15	45	0.34 (0.26-0.44)	<0.05
4	8	39	0.18 (0.10-0.27)	4	31	0.32 (0.23-0.43)	ns
5	8	29	0.18 (0.10-0.29)	4	16	0.30 (0.20-0.43)	ns
6	2	22	0.18 (0.10-0.30)	3	14	0.30 (0.19-0.45)	ns
7	2	15	0.18 (0.09-0.31)	2	11	0.29 (0.18-0.45)	ns
8	0	11	0.18 (0.09-0.31)	2	7	0.29 (0.17-0.45)	ns

*estimated by means of a Monte Carlo simulation method

A27 Bevacizumab maintenance (BM) in first line treatment for metastatic breast cancer (MBC): a multicenter retrospective observational study

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Background: Bevacizumab (B) combined with Paclitaxel (P) is a treatment option in MBC patients (pts). This multicenter observational study was performed in order to evaluate activity of both B-P association and BM after P discontinuation in real world MBC pts.

Methods: 280 MBC pts treated with weekly dose of P with B, with or without BM after P discontinuation were enrolled from 11 Italian cancer centres and retrospectively evaluated. Firstly, the RR for B-P was calculated, and secondly the PFS and OS were evaluated for all pts and separately for pts with/without BM. Chi-square and Fisher Exact tests were used to evaluate possible associations. OS and PFS were calculated by the Kaplan-Meier product-limit method. The log-rank and Tarone-Ware tests were used to assess differences between subgroups.

Results: pts median age was 56 yrs (range 27-82), ECOG PS 0/1-2 66/44%, ER/PgR positive 83%, TNBC 17%, prior neo/adjuvant taxanes 73%, visceral involvement 60% and bone metastasis alone 11.4%. The median administrations of P and B per pts were respectively 18 (1–39) and 14 (1-52). 14.6% of pts are still receiving B-P and 16.8% pts having PD during B-P are not evaluable for BM. Of the remaining 192 pts, 51.7% received BM after P interruption (withBM). At a median follow-up of 20 mo (range 2-90) 10% pts achieved CR, 54% PR, 18% SD and 12% PD. Disease control rate (CR + PR + SD ≥ 6 m) occurred in 74% pts. The RR was significantly different between ER/PgR pos and TNBC (p = 0.03), which had RR respectively of 71% and 52%. No significant difference was found between pts with or without P pretreatment, nor between different P schedules. Overall, median PFS was 14 mo (95% CI, 12-16) and median OS was 41mo (95% CI 30-51). The median duration of BM was 6 mo (range 2-40). A significant difference was highlighted when comparing median PFS among pts withBM (18 mo, 95%CI 16-20) and withoutBM (13 mo 95% CI 7-18). The median OS was 55mo (95% CI 41-69) in pts withBM and 40 mo (95% CI 29-51) in pts without BM: the two groups did not differ significantly.

Conclusions: Our analysis showed that the pts withBM after B-P combination had statistically and clinical significant improvement in PFS. Data collection is ongoing and update results will be presented.

A28 Endocrine therapy is not effective in BRCA2 mutated breast cancers even when they express hormonal receptors

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Background: BRCA germ-lines mutations increased Breast Cancer (BC) risk and may contribute to different clinical and biological features. However, their impact on prognosis and treatment choice has not completely defined. Aim of our study was to compare breast cancer features in BRCA1 and BRCA2 mutation carriers with that in patients with sporadic disease and to assess their impact on prognosis.

Patients and methods: Tumor pathologic features and clinical characteristics were examined in 287 patients (269 female and 18 male) with invasive breast cancer eligible for a genetic testing for BRCA mutations between 1996 and 2013 at our Institution. Subgroups differences were analysed using Chi Square Test. The Cox univariate and multivariate proportional hazard regression model was used to evaluate the prognostic factors on overall survival (OS).

Results: Of the 287 assessed breast cancer patients, 90 (31.4%) hosted a BRCA pathogenic mutation: 46.7% were BRCA1 and 53.3% BRCA2 carriers. BRCA1 carriers developed more often triple negative tumors (64.3%) than the other two groups (14.5% and 18.7% in BRCA2 and sporadic tumors, respectively; $p < 0.0001$). Conversely, BRCA2-tumors showed a higher frequency of luminal phenotype (75%), in comparison with BRCA1-tumors (21.4%) and sporadic tumors (63.9%; $p < 0.0001$); BRCA2-tumors had a higher incidence of lymphovascular invasion (LVI, 35.4%) than the other two groups (14.3% and 23.4% in BRCA1 and sporadic tumors, respectively; $p = 0.02$). At multivariate analysis a better OS was correlated to a positive estrogen receptor expression ($p = 0.002$) and to the absence of BRCA2 mutation ($p = 0.03$) and lympho-vascular invasion ($p = 0.007$).

Conclusions: Outcomes in carriers of BRCA1 mutations, were similar to outcomes in patients with sporadic disease. Conversely, risk of distant recurrence and death was significantly higher in BRCA2 mutation carriers when compared with those with sporadic disease, although they develop more often luminal BC. Thus, our observations may suggest a more intensive adjuvant approach in this subset of patients, even when they have an high expression of hormone-receptors.

A29 Multigene prognostic and predictive tests in Luminal breast cancer patients: relation between Mammaprint® results and nodal status in a retrospectively monocentric analysis

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Background: Breast cancer prognosis and predictive biomarkers development would allow sparing some patients from chemotherapy or identifying patients for whom chemotherapy would be indicated. Mammaprint® can discriminate patients with good or poor prognosis and could help us to decide for using chemotherapy, especially in intermediate risk patients with Luminal subtypes.

Material and methods: We evaluated with MP 81 consecutive patients (pts) with invasive operable Luminal A or Luminal B breast cancer (pT1-4pN1-3M0) diagnosed from 2008 to December 2009 at Ferrara University Hospital. Treatment decisions were based on clinical-pathological features, regardless of the MP results. Then we retrospectively evaluated the patients clinic-pathological characteristics, focusing especially on nodal status, and their progression free survival in relation to the MP results.

Results: Forty-two pts (51.9%) were Luminal A (LA) (ER = 10%, PR = 20% and Mib1 < 20%) and 39 pts (48.1%) were Luminal B (LB) (ER = 10%, PR < 20% or Mib1 = 20%), MP indicated a good prognosis in 27 (64.3%) LA and 14 (35.9%) LB pts and poor prognosis in 15 (35.7%) LA and 25 (64.1%) LB pts. MP results were significantly correlated with proliferative activity ($p = 0.002$), histological grade ($p = 0.002$), but not significantly correlated with nodal involvement ($p = 0.220$) and tumor size ($p = 0.426$). Between Luminal A pts, 22 (52.4%) were pN0 (15 MP low and 7 MP high risk), 15 (35.7%) with 1 to 3 node metastases (7 MP low and 8 MP high risk) and 5 (11.9%) with more than 3 lymph node metastases (all MP low risk). Considering instead LB pts 15 (38.5%) were pN0 (7 MP low and 8 MP high risk), 15 (38.5%) with 1 to 3 node metastases (7 MP low and 8 MP high risk) and 9 (23.1%) with more tha 3 lymph node metastases (all MP high risk). At a median follow-up of 70.5 months, 6 pts experienced disease recurrence: 1 (2.4%) between 42 LA pts with MP high risk and pN1 stage and 5 (12.8%) between 39 LB pts, 1 with MP low and pN0, and 3 with MP high (1 pN0, 1 pN1 and 1 with more than 3 lymph node metastases).

Conclusions: Accurate prediction of recurrence risk is of vital importancefor tailoring adjuvant chemotherapy for each breast cancer patient, but our data confirm the unclear utility of Mammaprint® in our clinical practice in comparison to classical prognostic parameters.

A30 Genetic and epigenetic factors affect RET gene expression in breast cancer cell lines and influence survival in patients

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Background: The RET proto-oncogene encodes for a transmembrane tyrosine kinase receptor whose signalling pathway is activated by the binding with one of its ligands and coreceptors. Aberrant RET signaling is oncogenic, as demonstrated by its involvement in different human cancers. In recent years, a large body of evidence has demonstrated that RET is overexpressed in a subset of breast cancer (BC). In particular, in Estrogen Receptor-positive (ER+) breast tumors, overexpression of RET resulted to be involved in endocrine resistance.

Materials and methods: We investigated the molecular mechanisms (either genomic, transcriptional or post transcriptional) which underlie RET overexpression, and its possible modulation in BC, in two ER+ cell lines, MCF7 and T47D, known to express high e low levels of RET mRNA. Looking for genetic variants responsible of variable RET expression, we have also carried out a pilot association study in 93 ER+ BC patients.

Results: We noticed that RETexpression is similarly modulated by estrogens in MCF7 and T47D while treatments with TNF, IL-8 and deacetylase inhibitors differently affect RET expression in BC cell lines. After sequencing ER-responding regions and a known enhancer in intron 1 at RET locus, we identified two single nucleotide variants rs12247450 and rs2435357, whose genotype is different between MCF7 and T47D, possibly accounting for the opposite RET expression pattern. In particular, SNP rs2435357 is associated with reduced expression of the gene. T47D cells carry the genotype associated with lower expression and this data can explain both the reduced expression of the RET gene and the different response to Sodium Butyrate. We carried out a pilot study genotyping for rs2435357 a cohort of 93 ER + early BC patients. We observed a statistically significant increased OS in patients with one of the variant alleles (CT or TT) in comparison to those carrying the CC wild type allele. The association was confirmed in multivariate analysis, where nodal status, grading, HER2 status and Ki67 were adjusted for (HR = 0.243, 95%; CI = 0.088-0.675; P = 0,007).

Conclusions: Our data are consistent with the observation that RET overexpression is associated to poor prognosis in ER+ BC and strongly candidate this SNP as prognostic factor. These findings might deepen into the role played by RET in breast tumorigenesis and stand RET as a potential candidate molecular target for BC treatment.

A31 Clinical benefit of fulvestrant in postmenopausal women with advanced breast cancer according to body mass index

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Background: Obesity is a risk factor for the development of breast cancer in postmenopausal women and has been linked to an increased risk of recurrence and death. Endocrine therapy is widely implicated for advanced breast cancer (ABC) treatment worldwide. This study aims to examine the association of baseline body mass index (BMI) with the clinical benefit derived by fulvestrant in postmenopausal women with ABC.

Methods: Consecutive patients treated with fulvestrant for ABC were investigated. The selection criteria were as follows: postmenopausal status; estrogen and /or progesterone receptor expression in primary or metastatic tumor; at least one tumor assessment after initiating fulvestrant. BMI was calculated according to WHO formula. Patients were categorized as normal (BMI 18.5 - 24.9 kg/m2), overweight (BMI 25 - 29 kg/m2) and obese (BMI> 30 kg/m2). The activity of fulvestrant was evaluated in terms of clinical benefit rate (CBR) defined as the proportion of partial or complete responses or stable disease lasting at least 6 months.

Results: A total of 250 patients were treated with fulvestrant between January 2009 and March 2015. We reviewed the first 105 consecutive cases and selected 75 matching eligibility criteria. Median age at diagnosis was 54 (range 28-81) years old. Metastatic

sites were: bone and visceral 57 (76%) cases, visceral 10 (13%) bone 6 (9%), and skin metastases 2 (2%) . Fulvestrant was administered as first line therapy in 4 cases, second line in 27, third line in 27, and over the third line in 17 cases. Median duration of hormonal therapy with fulvestrant was 6.1 months (range 3.4 - 71.9) According to BMI, 44 (59%) patients were classified as normal weighted, 19 (25%) as overweight and 12 (16%) patients obese. No difference in estrogen receptor expression was found according to BMI. The clinical benefit rate was 53%; of note, CBR raised to 70.5% among normal weigh patients and dropped to 31.6% and 25% among overweight and obese patients, respectively (p= 0.001).

Conclusion: Fulvestrant is active in patients with ABC even in late lines of treatment. Increased BMI has a negative influence on treatment outcome. Even with a limited number of cases, it appears that normal weighted patients are (2.5 fold) more likely to achieve benefit from fulvestrant as compared to over-weighted and obese patients. The analysis will be extended to additional cases and the final analysis will be presented at the meeting.

A32 Clinical and pathological factors predicting long-term disease control with lapatinib and capecitabine for patients with HER2 positive metastatic breast cancer: results from a multicenter retrospective study

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Background: The combination of the dual HER1/HER2 inhibitor lapatinib and capecitabine (LC) is a therapeutic option for patients (pts) with HER2-positive metastatic breast cancer (HER2 + MBC) after failure of trastuzumab-based therapy. No clinical and/or pathological factors have been identified as predictive markers of efficacy for LC. We conducted this retrospective analysis to investigate factors associated with progression-free survival (PFS) in pts with HER2 + MBC receiving LC.

Patients and methods: Clinical and pathological data of 148 pts with HER2 + MBC treated from March 2007 to December 2013 with LC after failure of at least one prior trastuzumab-based treatment (given either in adjuvant or metastatic setting) were collected from 13 Italian institutions. PFS and overall survival (OS) were estimated by Kaplan Meier method and compared with log-rank test. A Cox multivariate analysis was performed to evaluate the association between clinical/pathological characteristics and risk of disease progression with LC.

Results: At a median follow-up of 41 months (IQR 23-62), median PFS and OS were 7 and 21 months, respectively. Pts with PFS > 7 months had a significantly longer OS compared to those with PFS ≤ 7 months (36 vs 15 months; p < 0.001). In the multivariate analysis for PFS, HER2 luminal subtype (HR 0.53; C.I. 95% 0.29-0.95, p< 0.03) and progressive disease to prior trastuzumab at the first tumor assessment (HR 0.30; C.I. 95% 0.10-0.89, p< 0.03) were significantly associated with reduced risk of disease progression on LC, whereas visceral metastases before starting trastuzumab-based therapy were associated with higher risk of progression on LC (HR 2.11; CI 95% 1.08-4.12, p = 0.03). Stage at diagnosis, tumor grading, proliferation index, metastatic sites before starting LC, PFS after primary treatment for early breast cancer, PFS achieved with first-line trastuzumab and treatment with trastuzumab beyond progression were not associated with PFS on LC.

Conclusion: Pts treated with LC who achieved PFS > 7 months had significantly longer OS. HER2 luminal subtype and rapid disease progression with prior trastuzumab were associated with a longer PFS with LC. The latter finding suggests that the underlying mechanisms of primary resistance are different for trastuzumab and lapatinib. Additional biological studies are needed to investigate predictive markers of sensitivity and resistance to LC.

A33 Impact of Body Mass Index (BMI) on outcome of metastatic breast cancer (MBC) patients (pts) treated with Eribulin in a real-world population: a multicenter retrospective study

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Background: The relationship between BMI and prognosis was observed mostly in early breast cancer pts. Even though an analogous association seems to be conceivable also in women with MBC, modest direct data is available to sustain or rebut it. We evaluated the prognostic impact of BMI in MBC pts treated with Eribulin chemotherapy.

Patients and methods: The relationship between BMI (kg/m2) and clinical benefit rate (complete or partial response and stable disease, CBR) progression-free survival (PFS) and overall survival (OS) was assessed in 101 pts with MBC treated with Eribulin as third or subsequent-line in 6 Italian Oncologic Centers. WHO BMI categories were used: under and normal weight, 18.5-24.9 kg/m2, and overweight, =25 kg/m2. The association was tested by the Chi-Square test. Survival curves were estimated by the Kaplan-Meier method. Regression Cox model was applied.

Results: Median age was 61 years (range 31-79). Overall, 57.4% of the pts were normal or underweight and 42.6% were overweight. Regarding HR status, 79.2% of the pts had ER and/or PgR positive disease. 51.5% of the pts received Eribulin as third line treatment for MBC. The median follow-up was 12 months (range, 2-32). CBR was 67.2% in normal or underweight pts, whereas it was 51.2% in overweight pts (p = 0.1). Among pts receiving Eribulin as third line treatment we observed a CBR of 63.5%, while in pts treated in more advanced lines it was 57.1% (p = 0.52). CBR was 42.9% in HR negative tumors and 65% in ER and/or PgR tumors (p = 0.06). When analyzing ER and PgR separately CBR was statistically significantly higher in expressing tumors (p = 0.03 and p = 0.01, respectively). Stratifying pts according to treatment lines, we observed 77.8% and 48% of CBR in under or normal weight and overweight pts when treated in third line, respectively (p = 0.03). No significant findings emerged in subsequent lines. Median PFS was 4 months (95% CI,3-5) in under or normal weight and 3 months (95% CI, 2.1-4) in overweight pts, p = 0.002. Median OS was 13 months (95% CI, 11-15) and 12 months (95% CI, 6-18) in under or normal and overweight, respectively p = 0.96. In multivariate analyses, statistically significant association between BMI category (p = 0.009), ER status (p = 0.004) and PFS was observed.

Conclusions: This study suggests a prognostic role of BMI even in heavily pretreated MBC pts, even if results are restricted to a specific chemotherapeutic agent. Further studies are warranted to confirm this novel findings.

A34 Safety analysis, correlation with response and previous treatments of the association of everolimus (EVE) and exemestane (EXE) in 181 metastatic breast cancer patients (MBC)

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The toxicity profile of EVE EXE combination was reported in the Bolero 2 trial in the selected pts population. In order to evaluate the safety in the clinical practice and to evaluate a possible correlation of toxicities with previous treatments, clinical data from 181 pts were retrospectively collected. The hypothesis of a correlation of toxicities with response was also evaluated. Characteristics of pts: median age 65 ys (range 37-83), 1 site of disease in 27%, 2 or more sites in 73%. Bone was involved in 81%, lymph node 34%, liver 38%, lung 23%, skin 7%, brain 3%, soft tissues 21% of the pts. Overall, median number of previous treatments for advanced disease was 3 (range 0-9): median number of previous chemotherapy (CT) and hormone therapy (HT) was 2 (range 0-9). 96% of the pts started the treatment at 10 mg daily dose, 4% at 5 mg for physician choice. Median time of treatment was 4 months (range 1-48). Results: Distributions of

toxicities were: grade (G) 1-3 stomatitis in 65% of pts, G 1-4 hepatic 21%, G 1-4 non-infectious polmonitis 15%, G 1-3 skin 35%, G 1-3 glucose alteration 25%, G 1-2 lipid alterations 28%, G 1-3 nausea 13%, G 1-2 vomiting 5%, G 1-2 limbs edema in 9%, G 1-2 pleural effusion 4,5%, G 1-2 pericardial effusion 1,2%, G 1-2 diarrohea 7%, G 1-3 asthenia 51%, G 1-2 arthralgia 21%, G 1-2 myalgia 4%, G 1-2 infections 7%. Treatment was discontinued in 15 pts (8,2%; 11 toxicity, 4 refusal). Due to toxic events, EVE was reduced to 5 mg in 27% of pts. The response rate was as follow: CR 1,8%, PR 24,9%, SD 33,1% PD 34,9%, not evaluable 5,3%, 6% of pts are too early to evaluate. No correlation was found in the analysis between toxicity and number of prior therapies, neither between toxicity and response. In the multivariate analysis, previous exposure to anthracycline for advanced disease represents the only predictive factor of grade ≥ 2 toxicity (OR = 2.85 CI95% 1.07-7.59, p = 0.036).Conclusions: The association of everolimus and exemestane has confirmed to be a safe and effective treatment for endocrine sensitive MBC pts even in routine clinical practice. The rate of treatment discontinuation due to toxicity is low and none correlation between previous number of treatments and response or between toxicity and response was found. Previous anthracycline exposure may represent a predictive factor for developing a higher grade of toxicity and should be taken in account when the EVE EXE combination is chosen in the setting of CT pretreated patients.

A35 Cancer with BRCA mutations in high-risk families

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Background: Deleterious mutations in *BRCA1/BRCA2* are associated with a life time risk of breast cancer from 60 to 80% and an ovarian cancer risk from 10 to 40%. Although the association of *BRCA1*/2 mutations with breast and ovarian cancer is well defined, the potential association of these mutations with other cancers is inconsistent. We would like to investigate the relationship between *BRCA* mutations and the distribution of other familial cancers.

Patients and methods: In the program of Genetic Counseling in Oncology of Mantova, in 10 years, approximately 1000 families were selected for risk of hereditary breast and/or ovarian cancer. The members of the family, included first-and second-degree relatives, and the information collected were organised in a family pedigree. We selected 286 patients with breast cancer who had at one of the following risk factors: reported family history of breast or ovarian cancer at any age; 40 years or younger at diagnosis; bilateral breast cancer; breast and ovarian cancer; male gender. Genetic counselling was also focused on personal and family history of all cancers.

Results: From January 2004 to December 2014 we have selected 286 index cases (ICs) eligible for genetic testing (SIGU guidelines were used). Among ICs, *BRCA* mutation was detected in 68 (23,8%) patients: 44 (64,7%) had a deleterious mutation and 24 (35.3%) a Variant of Uncertain Significance. We observed that *BRCA*-positive group had a higher frequency of family history and a younger age of diagnosis (≤40). There were 23 members of 68 families who had histories of cancer other than breast or ovary. The most common site of other primary cancer was the stomach and colon-rectal, 21,7% and 17% respectively. We can report two example:

1. the BRCA1 mutation p.Leu1306Aspfsx23 was detected in a proband with breast cancer at 39 and, six years afterwards, we diagnosed stomach cancer in her positive-sister;
2. the delection of exon24, which caused the loss of all amino acid residues of the BRCA1-MLH1 interaction site, was detected in a proband with breast cancer at 36 and a family history of colon-rectal cancer.

Conclusion: In our small mutated and affected population, we observed that *BRCA* mutations in high-risk breast patients were associated with family members with other primary cancer. Genetic counselling based on accurate information should be provided to families with *BRCA* mutation carriers. Future directions require a focus on providing optimal genetic counselling and testing for family members.

A36 Relationship between levels of HER-2 amplification and pathologic complete response to trastuzumab-based neoadjuvant treatment

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Background: Fluorescence in situ hybridization (FISH) is used to determine human epidermal growth factor receptor-2 (HER-2) status and patient eligibility for trastuzumab therapy. Using FISH we analyzed the relationship between pathologic complete response (pCR) to trastuzumab-based neoadjuvant therapy and levels of HER-2 amplification in locally advanced breast cancer treated in our institution.

Material and methods: We retrospectively reviewed the data of 68 HER-2 positive breast cancer patients (pts) treated from January 2009 to June 2014 with trastuzumab based neoadjuvant therapy. Biopsies or citological samples were analyzed by dual-color FISH using a HER-2 gene–specific probe and a centromeric probe for chromosome 17 (PathVysion HER-2 DNA Probe kit, Vysis-Abbott) to determine HER-2 amplification. Tumors were classified by FISH as follow: low amplification (Gene Copy Number < 6 and Ratio = 2), intermediate amplification (6 = Gene copy number = 10), and high amplification (gene copy number > 10 or uncountable due to clusters of signals). This cut-off were raccomended by American Society of Clinical Oncology/ College of American Pathologists 2013. The repeated measure ANOVA and Student' s test were used to compare continuous variables. The $\chi 2$ test was used to compare discrete variables. The observed data are presented as means ± Standard Deviation (SD) when showed. A bivariate correlation was used in order to evaluate significant association between factor. Multivariate logistic regression analysis was used to estimate odds ratios and two-sided 95% confidence interval. A p value of 0,05 or less was considered statistically significant. All the analyses were performed using IBM-SPSS (V21.0).

Results: HER-2 status of tumor samples as assessed by FISH correlated: 12 low amplification (LA), 17 intermediate amplification (IA) and 39 high amplification (HA). Trastuzumab-based neoadjuvant therapy achieved pCR in 20 of 68 (29%) tumors. Patient age, T or N stage, tumor grade, hormone receptor status, were not significantly related to pCR. The only variable related to pCR was the level of HER-2 amplification, with 17 of 39 (44%) in HA tumors, compared with 1 of 17 (6%) in IA and 2 of 12 (17%) in LA tumors ($p < 0.01$).

Conclusions: Although the number of cases included in this study is not large, our analysis shows that high levels of HER-2 amplification assessed by FISH are positive correlated to higher rate of pCR to trastuzumab-based neoadjuvant treatment.

A37 Metastatic breast cancer and circulating exosomes. Hints from an exploratory analysis

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Background: Exosomes are nanovesicles secreted by living cells. Depending on their origin, exosomes could carry different biological molecules capable of influencing tumor microenvironment. Aim of the study is to characterize circulating exosomes and to explore their possible association with clinicopathological features of metastatic breast cancer (MBC).

Patients and methods: The study enrolled 56 MBC patients (pts) treated at the University Hospital of Udine between 2013 and 2015, regardless line of treatment. Exosomes were isolated from plasma by ExoQuick® solution. After this enrichment step, exosomes were conjugated with anti-CD63 coated beads to assess their protein expression profiles by flow cytometry. The fluorescence intensities of different antibodies were tested on single bead-exosomes decorated with CD63 and CD9 antibodies. The differences in exosomal subpopulation distribution between controls and MBC patients and their association with clinicopathological features were analyzed through Wilcoxon-Mann-Whitney test.

Results: MBC pts differed significantly in specific exosomes subpopulations. In particular, compared to controls, a higher expression of CD44 (P = 0.0372), HGFR (P = 0.0311), CXCR4 (P = 0.0094), CD49d (P = 0.0441), E-cadherin (P = 0.0003) and HER2 (P < 0.0001) was observed. Exosomes positive for CXCR4 characterized pts affected by luminal or HER2 positive disease (P = 0.0199 and P = 0.0227, respectively), and among the latter subgroup a lower expression of E-cadherin (P = 0.0137) was also observed. A disease with KI67 >14% was associated with higher expression of CD49D (P = 0.0487). Pts with multiple metastatic sites had a higher fraction of HER2 (P = 0.0376) and marginally of KDR-positive exosomes. Visceral localizations were associated with higher expression of KDR (P = 0.041) and, in particular, lung involvement was associated with a lower expression of CD49d (P = 0.0438). Of note, liver localizations were marginally associated with higher expression of CXCR4 and KDR. Pts beyond 1st line of treatment showed a higher proportion of CD44 positive exosomes (P = 0.0379), whereas a marginally lower expression of EGFR was observed in pts beyond the 3rd line.

Conclusions: In pts with MBC, distinct subpopulations of exosomes were observed according to tumor biology, disease burden and therapeutic history. The capability of exosomes to be a proxy of disease characteristics and a potential predictor of metastatization spread warrants further investigation through larger trials.

A38 BRCA1/2 mutations and hereditary breast cancer: clinical phenotype, type of mutation and founder effect

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Background: Many different mutations involve BRCA1/2 genes and their incidence differs across several populations. The aims of our study were to describe incidence and type of mutation in breast cancer (BC) BRCA-carriers of our region and to correlate type of mutation with clinical phenotypes.

Methods: 256 consecutive patients were included, selected according to breast cancer familiarity and clinical characteristics, for genetic testing who tested positive for BRCA 1/2 mutations. All tests were performed at the Oncology Genetics Center of the Marche region between years 1999 and 2014.

Results: BRCA1 mutations occurred in 114 women and 2 men, BRCA2 mutations occurred in 114 women and 16 men, respectively. Approximately 64% of BRCA1 and 59% of BRCA2 mutations were pathogenetic, the others were of unknown clinical significance. We found a great heterogeneity in our population, more than half were subject-specific mutations (no other patient had the same alteration). Only 2 pathogenetic mutations were identified in more than 10 patients: the BRCA1 pathogenetic missense 300T > G, that was highlighted in different Italian regions, and the BRCA2 non sense mutation 9106C > T, which has a possible founder effect in the Italian country. Twelve patients from 10 families and 12 patients from 9 families showed the BRCA1 300T > G mutation and the BRCA2 9106C > T mutation, respectively. That BRCA2 mutation was observed in one of male breast cancer cases. The most frequent pathogenetic mutations were frameshift type (52.1% of BRCA1 and 64.3% of BRCA2 pathogenetic mutations). Pathogenic missense mutations and rearrangements were more frequent in BRCA1 than in BRCA2 (17.8% vs 4.3%, $p = 0.01$; 17.8% vs 0%, $p < 0.001$) and nonsense mutations showed an opposite distribution (5.5 vs 28.6%, $p < 0.001$). Within the pathogenetic mutation group the "triple negative" phenotype was observed more frequently in BRCA1 carriers ($p < 0.001$) while the "luminal B Her2"-one in BRCA2 carriers ($p < 0.001$).

Conclusion: The BRCA1 pathogenetic missense 300T > G mutation has been already described in Italy and in Europe (Poland and Czech Republic). The BRCA2 9106C > T mutation is recurrent in male breast cancer cases from the North-East of Italy. Thanks to its frequency in our study, we support the possibility of its founder effect in our population Concerning the mutation types, we confirmed the known lower frequency of rearrangements in BRCA2 gene than in BRCA1 one.

A39 Dose-finding study on a continuous dose of oral vinorelbine (VNR) in heavily pre-treated metastatic breast cancer (MBC) patients (pts)

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Background: Pts with metastatic cancer need palliation and safe regimens that can be given for a long time. Low and continuous dose of antineoplastic drugs has been shown to have antiangiogenic activity. The rapid absorption, and relatively short half-life of the oral formulation of VNR represent favourable pharmacokinetic feature to test a continuous dose schedule, in order to optimise its use as metronomic therapy.

Methods: Pts with measurable MBC were treated with an escalating dose of oral VNR from 50 mg/m2 to 90 mg/m2 per week fractionated on days 1, 3 and 5 until progressive disease or unacceptable toxicity.

Results: Among 36 pts included in the study, 3 were treated at 50 mg/m2/w (level 1), 6 at 60 mg/m2/w (level 2), 4 at 70 mg/m2/w (level 3), 8 at 80 mg/m2/w (level 4), and 15 at 90 mg/m2/w (level 5). No dose-limiting toxicity has been observed. The median age was 54 years (range 23-75), 31 pts had visceral metastasis, and 30 had positive receptors. The median number of prior lines of hormonal-therapy was 3 (range 1-6) and of chemotherapy (CT) was 2 (range 1-5); 28 pts received adjuvant or neoadjuvant CT, 26 (72.2%) received antra-based and 22 (61.1%) taxane-based CT. The main toxicities were: asymptomatic neutropenia grade 3-4 in 6 pts (1 in level 4 and 5 in level 5), asthenia grade 3 in 9 pts (1 at level 1, 2 at level 2, 1 at level 3, 3 at level 4, 2 at level 5), neurotoxicity grade 3 in 2 patients (one at level 2 and one at level 4). One pt experienced an intestinal sub-occlusion and hospitalization was required with no permanent side effect; 2 pts discontinued treatment after 7 cycles for G 3 neurotoxicity, and 1 patient after 4 cycles for gastotroenteritis. Three responses were observed only in fist-line chemotherapy (1 CR and 2 PR), 27 pts showed SD, while 6 women experienced PD. Clinical benefit at 3 months was 55.6% and at 6 months 19.4%. Median PFS was 3.3 months (95% c.i.: 2.8-3.8) and median OS was 13.3 months (95% c.i.: 8.4-18.1).

Conclusions: The administration of continuous oral VNR 3 times per week is feasible, with a low toxicity profile. The maximum tolerated dose was not reached at 90 mg/m2/w. Further studies in fist- and second-line are needed in order to confirm that metronomic VNR could be represent an effective and safe step forward in cancer control.

A40 Albumin-bounded Paclitaxel (nab-Paclitaxel) in metastatic breast cancer: new insights from a real life multicenter Italian experience

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Background: Nab-paclitaxel (*nab*-PTX) has been shown to improve outcome of patients with metastatic breast cancer (MBC) when compared to conventional taxanes. Aiming to determine how the clinical practice treatment results compare with the evidence-based data, we analyzed patterns of treatment and outcome of women receiving *nab*-PTX in different chemotherapy (CT) lines for their MBC.

Patients and methods: From February 2011 to June 2014, 215 consecutive MBC patients were treated with *nab*-PTX at 9 Italian Centers: 145 (cohort A) received the 260 mg/m^2 q3w schedule (78 in 2nd line, 46 in 3rd line, 21 in $\geq$ 4th line) and 70 (cohort B) were treated with the 125 mg/m^2 weekly regimen (25 in 2nd line, 18 in 3rd line, 27 in $\geq$ 4th line). Median number of given cycles: 8 (range 3-26). Median age: 54 years (range 31-83; ≥65 years 49%); median ECOG performance status ≤1: 82%; visceral dominant disease: 74%; ≥3 metastatic sites: 62%; median disease-free-interval (DFI) ≤24 months: 41%; taxane-based CT in the adjuvant or metastatic setting: 68% and 65%, respectively.

Results: The objective response rate (ORR) in the whole population was 51% (18 CR, 91 PR, 67 SD ≥ 16 weeks), for an overall CB rate of 82%. At a median follow-up of 18 months (range 6-30) median PFS was 7.8 months (range 3-23+), median OS has not yet been reached. Major toxicities: WHO gr.1-2 fatigue: 38%-27%; gr.3-4 neutropenia: 32%-18%; gr.3 sensory neuropathy: 18%. In the subgroup analysis age <65 years, DFI ≤ 24 months, triple negative subtype and predominant visceral disease were significantly correlated with higher ORR and PFS in cohort A, while in cohort B older patients with no visceral involvement and ≤ 2 metastatic sites had the better outcome ($p = 0.04$). The line of CT treatment significantly affected both the probability of response (61% ORR in 2nd line *versus* 38% in ≥3 lines, $p < 0.05$) and outcome (PFS value of 12.6 months *versus* 4.9 months, respectively, $p = 0.03$).

Conclusions: Our real word experience confirm that *nab*-PTX can safely be offered to most women with MBC, with reasonable expectations of CB and without concern of significant toxicity, also in those 'difficult-to-treat' settings as taxane-pretreated women, triple negative disease and elderly patients. For the daily clinical practice, the chance of a flexible schedule of administration allows a better targeted therapeutic approach to each woman at different points of her history, basing on both disease-related factors and patient attitudes.

A41 Evaluation of safety and activity of everolimus plus exemestane in metastatic breast cancer: a single institution experience

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Background: Everolimus (EV) is an oral inhibitor of mammalian target of rapamicin (mTOR), recently approved in combination with exemestane (EX) for the treatment of hormonal positive metastatic breast cancer (MBC) progressed to a non steroideal aromatase inhibitor.

Patients and method: We retrospectively evaluated 63 consecutive patients (pts) treated with EV plus EX in our institution from July 2012 to April 2015. At the beginning of EV's therapy median age was 63 years (range 45-80); pts older than 70 were 15. Visceral metastases were present in 35 pts (56%) and 18 pts (28.6%) had more than two sites of metastasis. 19 pts (30%) and 18 (28.5%) had liver and lung involvement respectively. Pts received previous hormonal therapy for metastatic disease for a median number lines of 1 (range 0-4) and chemotherapy for a median line

of 1 (range 0-5) respectively. EV plus EX was administered as first line in 10 pts (15.8%).

Results: Oral mucositis, observed in 45 pts (71%), was the most common toxicity: it presented with a grade 3 appearance in 10 pts (16%). Then in order of frequency: skin toxicity in 22 pts (35%), fatigue in 19 pts (30%) and transaminase increase in 18 pts (28.5%). Non-infectious pneumonitis was reported in 11 pts (17%) with only 1 case of grade 3; diarrhea in 12 pts (19%), in all cases of grade 1 or 2; hyperglycemia and hypercholesterolemia respectively in 15 (23.8%) and 10 pts (16%) respectively with a case of grade 3 in both. Other relevant observed toxicity were, anemia in 10 pts (16%) and piastrinopenia in 5 pts (7.9%). Overall, 27 pts (43%) reduced EV dosage to 5 mg per day. 15 pts (23.8%) were 70 years or older and among them 6 (43%) stopped treatment for toxicity and 8 (53%) decreased EV dosage. Furthermore, we admitted 2 pts for enteritis. The incidence of toxicity was similar in elderly patients, except for fatigue observed in 7 pts (46.6%). In the overall population median duration of treatment was 7.6 months (m) (range 1-25 m) and median progression free survival (PFS) was 7.9 m (1-23 m).

Conclusion: In our real life experience the activity and toxicity of EV plus EX treatment was comparable to BOLERO-2 study except for oral mucositis and metabolic disorder. A careful patient's proactive monitoring is strictly necessary in order to minimize the toxicity and obtained the best results of combination.

A42 Incremental value of 3D echocardiography and two-dimensional speckle tracking in the early detection of cardiotoxicity linked to chemotherapy and trastuzumab in patients with HER-2 positive breast cancer

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Background: Chemotherapy (CT) induced cardiotoxicity is a potentially lethal complication that frequently affects patients (pts) treated with anthracyclines and targeted agents such as trastuzumab (Tr).

Patients and methods: From November 2013 to April 2015 we enrolled 30 patients; median age 51 years (range 40-62) with HER2 positive breast cancer. All pts received the same schedule of CT (17 in neoadiuvant and 13 in adiuvant setting): 4 cycles of EC (Epirubicin 90 mg/mq ev q21, Cyclophosphamide 600 mg/mq ev q21), followed by Paclitaxel 80 mg/mq ev q7 for 12 weeks and Tr 6 mg/Kg ev q21, (loading dose 8 mg/Kg) given concomitantly up to a year of treatment. Echo-cardiogram with two-dimensional and with three-dimensional approach were performed before starting CT, after anthracyclines and then every 3 months after the start of Tr, up to one year of completion. Several parameters of ventricular remodeling and function were evaluated: two-dimensional EF ejection fraction (EF) (EF 2D), three-dimensional EF (EF 3D), Global Longitudinal Strain (GLS), systolic s' wave at TDI of the annulus (s'TDI), Ventricular Elastance and Ventricular-Arterial Coupling.

Results: According to the latest data of the literature, 4 (13,3%) pts had a cardiac event linked to the toxicity by EC and Tr: 2 pts had an important reduction of LVEF under 50% and 2 pts had an event of ACS (Acute Coronary Syndrome) so discontinued treatment with tr; EF 3D and GLS were able to identify early on a significant reduction in left ventricular function, even after the first cycle of EC and before the start of Tr ; while EF 2D decreasead significantly only after the start of Tr. Neither the assessment of systolic tissue speed at the level of annulus nor the ratio E/e' (ratio between E wave of transmitral flow and wave e' of TDI) significantly change during treatment. From baseline whether Ventricular Elastance or Ventricular-Arterial Coupling worsened progressively during the treatment.

Conclusions: The evaluation of left ventricular function with new echocardiographic methods with three-dimensional approach allows early identification of cardiac-toxicity linked to CT and targeted agents, than the ventricular ejection fraction evaluated two-dimensionally and tissue indices derived from TDI. This could allow a prompt treatment of cardiac demage and the completion of antineoplastic therapy.

A43 Effectiveness of Bevacizumab maintenance therapy associated with metronomic chemotherapy and hormone therapy after treatment with taxanes in patients with HER-2 negative metastatic breast cancer (mBC)

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Background: it is known that the continuation of Bevacizumab after therapy with taxanes is a strategy recommended in HER-2 negative metastatic breast cancer. Currently, it is not well defined yet if and which treatment bind to the anti-VEGF antibody. However, considering the undoubted antiangiogenic effect of metronomic chemotherapy, we evaluated if the triple combination Bevacizumab, hormone therapy and chemotherapy may be an option for maintenance therapy in these type of patients.

Material and methods: Our study aims to evaluate the effectiveness of the association between Bevacizumab, metronomic chemotherapy and hormone therapy, by measuring the PFS, as primary endpoint and OS and RR as secondary endpoints. We enrolled 22 patients with HER2-negative mBC, who received at least six cycles of treatment with Bevacizumab + taxanes. Progression-free patients, at the suspension of the taxane, continued treatment with the antibody, combined with oral metronomic chemotherapy and hormone therapy if receptor-positive.

Results: From April 2009 to January 2015 were evaluated 22 patients who received treatment with taxanes + Bevacizumab, followed by maintenance Bevacizumab, associated to Capecitabine (45.5%), Cyclophosphamide (45.5%) or Etoposide (9%) in metronomic schedule. 17 patients (77.3%) also received hormone therapy. At a median follow-up of 19 months, 5 patients have not relapsed yet. The median PFS from beginning of maintenance was 22 months (95% CI: 6.9-37.1). The median OS was 51 months (95% CI 7.1-94.9), whereas at the time of data analysis, only 10 patients have died. CR and PR were achieved/maintained in 2 (9.1%) and 5 (22.7%) patients, respectively, for an overall response rate of 31.8%; 11 (50%) women experienced SD and 4 (18.2%) patients had a PD at first control. The treatment appears to be well tolerated.

Conclusions: From our study results, the continuation of Bevacizumab, combined with chemotherapy and hormone therapy, appears to improve the chance of disease control.

A44 Metastatic breast cancer outcome in real life: a single institution experience. Preliminary results

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Background: Many treatments are available for metastatic breast cancer (MBC) and the choice should be based on specific characteristics such as hormone receptor and human epidermal growth factor receptor 2 (HER2), tumor involvement and prior treatments. Gene profiling studies have underlined the heterogeneity of BC and have distinguished subtypes based on molecular characteristics. In daily clinical practice patients (pts) are classified based on immunohistochemistry. The present study correlates progression free survival (PFS), overall survival (OS) and survival postprogression (SPP) of MBC pts to biological characteristics. Hereby we present data on PFS and OS.

Material and methods: We retrieved medical records of 346 MBC pts treated at our institution. 325 were analysed (15 pts never started therapy, 1 received RT only and 5 not already evaluated). We collected data on primary and advanced disease, and defined the subgroups according to S. Gallen criteria: Luminal A (LA), Luminal B (LB), HER2 positive and triple negative (TN).

Results: Median age at diagnosis was 58 y (range 26-87), median age at diagnosis of MBC was 63 y (28-87), F/M: 320/5, most common metastatic site: bone 180 pts (55.4%), soft tissues 167 pts (51.4%), liver 71 pts (21.8%), lung 70 pts (21.5%) and CNS 16 pts (4.9%). 97 pts (29.8%) presented de novo MBC. Median time to MBC from initial diagnosis of BC was 45.6 m (3.2-281). Immunophenotypes were: LA 28 (8.6%), LB 155 (47.7%), HER2 52 (16%), TN 24 (7.4%) missing 66 (20.3%). 181 pts (55.7%) received neo/adjuvant chemotherapy, 159 pts (48.9 %) received adjuvant endocrine therapy. Pts were exposed to a median of 3 (1-16) lines of therapy. All pts were exposed to 1st line, 225 (69.2%) to 2nd, 155 (47.7%) to 3rd, 108 (33.2%) to 4th, 78 (24%) received 5 or more lines. Median PFS at 1st line was 11,1+ months (m) (0.2-153.8), 6.5+ m (0.4-85.4) at 2nd, 4.7+ m (0.2-50.6) at 3rd, and 5 m (0.4-92.5+) at 4th. Median OS was 27.3+ m (0.3-199.2). LA, LB, HER2 and TN pts received a median of 2.5 (1-11), 2 (1-16), 3 (1-13) and 2 (1-6) lines respectively. Median OS in LA, LB, HER2 and TN was 36.3+ m (2.2-96.1), 26.6+ m (0.3-193.1), 25.6+ m (1.1-193.5) and 12.1 m (2.2-94.3 +) respectively.

Conclusions: Our results are in line with other similar reports. Interestingly the median PFS decreases from the 1st to the 3rd line of therapy, but, does not between 3rd and 4th line. Data on SPP will be presented.

A45 Chemotherapy-induced changes of CD8+ T-cells in patients with advanced breast cancer

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Background: Cytotoxic chemotherapy (CT) has traditionally been thought to be immunosuppressive but increasing evidences suggest concept of "immunogenic" CT, indicating that some cytotoxic drugs (such as anthracyclines) can also stimulate a tumor-specific immune response. The immunomodulation via CT (and targeted therapy) opens potential clinical applications in breast cancer (BC) but the variability in both immune and CT responses require a careful pt selection.Changes in sub-populations of cytotoxic (CD8+) T-cells, which are observed in aging (immunosenescence) and in conditions of chronic immune stimulation, are not well documented in pts with advanced BC undergoing CT.

Patients and methods: To explore shifts in CD8+ T-cells and the effect of CT and of age on different T-cell sub-populations, using high-resolution multicolor flow cytometry, CD8+ T-cell subsets were analyzed in 18 pts (median age 59, range 44 - 70 yrs) with advanced BC undergoing anthracycline-based CT. An older group of 10 healty women was utilized as a, during a 6-month longitudinal study

Results: As expected, there was a consistent decrease in absolute numbers of leukocytes, lymphocytes, T-cells and CD8+ T-cells during CT in BC pts. Among the T-cells, there was a lower CD8-/CD8+ ratio, persisting over the 6 months, in pts compared to controls. The proportion of CD28-CD57+ cells also remained higher among pts with cancer throughout the study duration. The number of CD28 + CD57- and CD28-CD5- cells decreased faster during CT than CD28 + CD57+ and CD28-CD57+ cells, while only CD28-CD57- cells showed a significant reconstitutive capacity after 6 months.

Conclusion: Anthracycline-based CT elicit several changes in immune-related parameters including the composition and phenotype of immune cells. The immune system is weakened by age-related changes in immune responses and these changes appeared to be more pronounced in BC pts during CT, with senescent CD8+ T-cells playing a role. The normal condition was not restored after 6 months of CT.

A46 Lapatinib and continuous metronomic capecitabine in HER2 positive advanced breast cancer (ABC): a single center experience

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Background: The efficacy of lapatinib (Lap) plus capecitabine (Cap) in HER2 amplified advanced breast cancer (ABC) has been widely reported in literature. However, cutaneous and gastro-intestinal toxicity may interfere with the optimal treatment delivery.

Methods: In this observational cohort study, 24 patients (pts) with HER2 amplified ABC from a single Institution who received Lap/continuous metronomic Cap modified schedule (Lap, 1250 mg/daily, plus Cap, 1500 mg/daily) were enrolled from November 2009 to December 2014. We report data on efficacy and tolerability .

Results: In our analysis, 23 pts were evaluable for toxicity and 20 pts for response. Median age was 51 years (range 34-70). Median follow-up was 25 months (range 1-53). The majority of pts (84%) had visceral metastases and about half of pts (52.5%) received $\geq$ 3 previous lines for advanced disease. The overall response rate (ORR) was 40%, with 2 complete responses (CR) and 6 partial response (PR). Four pts had prolonged stable disease (SD) (21%). The clinical benefit rate (CBR= partial response PR + complete response CR + prolonged stable disease SD $\geq$ 24 weeks) was achieved in 60% of pts. Four progressive disease (PD) were observed (20%). Median progression free survival (PFS) was 4.8 months, median overall survival (OS) 27 months. Treatment was well tolerated, mainly in terms of photosensitivity reaction during sun exposure. Main toxicities were grade 2 (G2): hand-foot syndrome (HFS) in 7 pts (30%), diarrhea in 5 pts (21%), ungueal alterations in 3 pts (13%), rash in 2 pts (8%). No grade 3 or 4 specific Lap/continuous metronomic Cap induced toxicities were reported. Three pts had dose reduction for gastrointestinal toxicity and 2 treatment discontinuations for persistent diarrhea G2.

Conclusions: Our analysis showed that Lap/continuous metronomic Cap modifies schedule is active as treatment in HER2 positive ABC and minimally toxic. This combination might be considered when low toxicity burden is advisable and could allow sun exposure contrary to literature data.

A47 Inherited mutations in breast cancer susceptibility genes among a triple negative breast cancer cohort unselected for family history of breast cancer

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TNBC defined by a lack of ER, PgR and Her 2 expression in tumor cells occurs most frequently in young or pre-menopausal women and often have a worst outcome than patients with other breast cancer subtype. Recent studies have suggested a link between BRCA mutations and TNBC. BRCA1 and BRCA2 mutations are present in 8-14% and 5% of TNBC unselected for family history of breast cancer respectively. Recent advances in DNA sequencing have led to the development of breast cancer susceptibility genes panel to germline genetic testing of patients. We assessed the frequency of mutations in predisposition gene (BRCA1 -2) and in 7 predictor genes (BARD1, PALB2, BRIP1, CDH1, PTEN, CH£CK2 and TP53) and the clinical outcome in a cohort of patients with TNBC unselected for family history of breast and ovarian cancer in order to evaluate the clinical utility of germline testing in these subset of TNBC. 36/140 frozen samples of TNBC from patients unselected for family history of BC and OC were enrolled and germline DNA was sequenced to identify mutations. Mutations were identified in 13/36 pts (36.1%), of these 7 (19.5%) in BRCA1 and BRCA2 genes. Mutations in other predisposition genes were detected in 7/36 pts, with the majority observed in genes involved in homologous recombination including PALB2 3/36 (8.3%), BARD1 2/36 5.6%), CDH! 1/36 (2.8%), BRIP1 1/36 (2.8%) associated with BRCA1 mutation, no mutations were discovered in PTEN and CHEK2. Pts with TNBC and germline mutations treated with adjuvant/neoadjuvant chemotherapy have a better outcome in term of DFS and OS than pts with TNBC without germline mutations, only 4/13 pts with mutation experienced progressive disease. Due to the restricted number of pts of our cohort is not possible to generalized our results but we can suggest that germline genetic testing BRCA1 and BRCA2 in TNBC unselected for family history of BC and OC should be considered. Although Mutations in other predisposition genes have been observed among patients with TNBC more data from large trials are needed before to translate the use of these genes in clinical practice.

A48 A possible prognostic significance of c-Kit receptor expression and angiogenesis in early breast cancer patients: a pilot study

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Background: C-KitR is a transmembrane tyrosine kinase (TK) receptor, which is expressed both on mast cells (MCs) and stromal and epithelial breast cancer (BC) cells playing a role in tumor angiogenesis. This study aims to evaluate a correlation between the immunohistochemical staining of c-KitR expressed both on stromal and epithelial BC cells, mast cell density positive to tryptase (MCDPT) and microvascular density (MVD) to each other in 105 female early BC patients.

Material and methods: Tumor sections were immunostained with primary anti-tryptase, anti-CD117 and anti-CD34 antibodies by means of immunohistochemistry. Slides were evaluated by means of an image analysis system at x 400 and x 1000 magnifications. Adjacent sections were evaluated in terms of MCDPT, MCD positive to c-KitR, and percentage of malignant cells positive to c-KitR. In the last evaluation only a pattern of membrane immunostaining was considered to be positive.

Results: The mean ± s.d. of MCDPT, MVD, c-KitR staining of stromal and epithelial BC cells was 8.35 ± 2.99, 30.11 ± 8.24, 9.18 ± 3.36, 28.73 ± 15.45, respectively. It has

been found a strong correlation between MVD and c-Kit staining of stromal cells (r = 0.71, p = 0.0002), MVD and MCDPT (r = 0.77, p = 0.000), and c-Kit staining of stromal cells and MCDPT (r = 0.84, p = 0.000) by Pearson correlation.

Conclusions: Results demonstrated a strong and significant correlation between MVD, c-KitR staining of stromal cells and MCDPT. These evidences indicate an involvement both of MC tryptase and c-KitR in BC tumor angiogenesis. Based on the lack of correlation between increased MVD and high percentage of c-KitR staining of epithelial BC cells, we suggest that clones of malignant epithelial BC cells positive to c-KitR probably don't stimulate tumor angiogenesis. Therefore, c-KitR expression could represent a novel surrogate angiogenic marker with prognostic significance in BC patients. In this patients setting, it's intriguing to hypothesize that c-KitR TK inhibitors (e.g. imatinib, masitinib) might be investigated in clinical trials.

A49 Phase I of weekly nab-paclitaxel in combination with weekly liposomal encapsulated doxorubicin as first-line treatment for HER2 negative metastatic breast cancer patients: preliminary results

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Background: Taxanes and anthracyclines (A) remain among the most active and widely used chemotherapy (CT) agents in breast cancer (BC) patients. Despite their optimal antitumor activity, the re-treatment of this agent in metastatic settings is limited by main myelosuppression, cumulative cardiotoxicity and allergic reactions. Encapsulation of A within liposomes (LDox) result in new formulation designed to minimize distribution of the drug to healthy tissues with an increase distribution to tumor site. Nab-paclitaxel is a novel nanoparticle, albumin bound paclitaxel (NP) and it was developed to reduce toxicities from paclitaxel and improve its efficacy. The aim of this study is to define the feasibility of the new combination of weekly (w) (1,8,15, every 28 days) NP and LDox, coupling tolerability profile and efficacy.

Methods: Patients (pts) untreated for HER2 negative MBC entered the study. Overall, 3 escalating dose level (DL) were evaluated (I: wNP 100 mg/m^2 + wLDox 20 mg/m^2; II: wNP 125 mg/m^2 + wLDox 20 mg/m^2; III: wNP 125 mg/m^2 + wLDox 25 mg/m^2). Before escalating to the next DL, 3 pts will receive at least one cycle of CT. If none of the 3 pts experience a dose limiting toxicity (DLT) within 2 wks, another 3 pts will be accrued at the next DL; otherwise, 3 additional pts will be treated at the same DL. The maximum tolerated dose (MTD) will be defined as the DL below the DLT reached.

Results: 6 women [m age 59, median metastatic site: 2 (1-3]) were enrolled. A total of 26 cycles (64 administrations) were given. To date no DLT was reached and in the table are showed haematological and no-haematological side effects encountered.

Table: A49

Reported event(s)	Cohort I (3 pts)		Cohort II (3 pts)	
	Any Grade	Grade3-4	Any Grade	Grade3-4
Anaemia	2	–	–	–
Neutropenia	3	2	3	2
Piastrinopenia	–	–	1	–
Nails micosys	1	–	–	–
Stomatitis	2	–	–	–
Nausea	–	–	1	–
Diarrhea	1	–	1	–
Asthenia	–	–	1	–
Alopecia	2	2	2	2

Conclusions: Combination wNP/wLDOX affords treatment with two active drugs in women with MBC. At doses of wNP 125 mg/m^2 + wLDox 20 mg/m^2 DLT is not yet reached to date and appears to have a favorable toxicity profile. Final results of phase I study to define MTD will be presented to the meeting. Phase II will be started at the recommended dose of both drugs.

A50 Prevention of cardiotoxicity in adjuvant breast cancer (BC) therapy

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Background: A fearsome long-term toxicity of BC adjuvant chemotherapy (adj-CT) is left ventricular dysfunction and heart failure. Low-dose (LD) angiotensin converting enzyme (ACE) inhibitors showed efficacy in the treatment of some forms of cardiomyopathy and heart failure. Our study evaluated LD-ACE inhibitor administration to BC patients (pts) undergoing adj-CT with anthracyclines (ANTHs) +/- Trastuzumab to prevent left ventricular ejection fraction (LVEF) reduction.

Patients and methods: From June 2013 to March 2015 47 women (median age 56 years: range 30-77) affected by BC undergoing adj-CT either with ANTHs (30 pts) or ANTHs followed by Trastuzumab (17 pts) were enrolled. All pts had an echocardiography (ECO) performed at baseline and then every 3 months (mts) during therapy and six mts after the end of treatment; median LVEF baseline value was 64% (range 58%-76%). We checked troponin T (Tn-T) and brain natriuretic peptide (BNP) at baseline (median values respectively 6,5 ng/L, range 3-24 ng/L, and 24 pg/ml, range 7-110 pg/ml), after each cycle of treatment and, in the absence of clinical suspicion, 6 mts after the completion of adj-CT. Pts showing an increase in Tn-T and BNP greater than or equal to twice the basal values started Enalapril 2.5 mg/day (therapeutic range 5-20 mg/day) and repeated ECO every three mts until six mts after the end of adj-CT.

Results: Six pts (12 %) started Enalapril during ANTHs therapy after significant increase of Tn-T (median peak 17; range 8-31) and BNP (median peak 53; range 38-89); BNP and Tn-T level increased in 3 pts, Tn-T in 2 pts, BNP in 1 pts. In all cases there was a quick reduction of Tn-T and BNP already by the next cycle of adj-CT; the following ECO control showed a LVEF value almost identical to baseline. No pts discontinued adj-CT neither the only one who underwent following one year Trastuzumab treatment. LD-ACE inhibitor was well tolerated and administered for at least six mts after the end of adj-CT.

Conclusions: Starting LD-ACE inhibitor treatment before ECO evidence of LVEF reduction confirms to prevent myocardial damage by adj-CT in the short-medium period. Although in a small number of pts, our study shows that a clinical prevention approach is feasible and effective also in General Hospitals where the Oncology and Cardiology Units are present and cooperate. A longer follow-up is needed to confirm our data in the long term cardiotoxicity prevention setting.

A51 Vitamin D pathway modulation in Caucasian case series of healthy women and breast cancer patients

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Background: The debate on the association between Vit D deficiency and breast cancer risk is still open. Moreover, single nucleotide polymorphisms (SNPs) in the Vit D receptor (VDR) have been associated with various types of cancer. This study evaluates Vit D and Binding Protein (DBP) levels, VDR and DBP polymorphisms in healthy donors (HD) and breast cancer patients (BCP) in a Caucasian case series.

Material and methods: The study provides 77 adult women enrolled at IRST-IRCCS Meldola: 50 donors, and 27 breast cancer patients untreated with Vit D supplementation. The following markers were analyzed on blood samples: Vit D and DBP serum protein levels by ELISA, and the polymorphisms Fok1, A1012 G, dcx2 (SNPs of VDR) and rs4588 (SNP of DBP) by qPCR. The association among markers, and osteoporosis risk factors was evaluated in the 2 groups.

Results: From Sept to Dec 2014, 77 Caucasian women were enrolled. HD presented less osteoporosis risk factors respect to BCP 8 ($p<0.0001$). Vit D and DBP levels were not significantly different between HD and BCP (vit D: 28.32, 11,26-60.70 ng/ml vs 26.74,11.02-52.00 ng/ml in HD and BCP respectively; DBP: 301.17, 105.00-797.48 ug/ml vs 316.31,128.09-467.76 ug/ml in HD and BCP respectively). However, deficiency of Vit D concentration was observed in 8% of HD respect to 14 % of BCP; furthermore, Vit D suboptimal and upper normal concentrations were observed in 38% of HD and 30% of BCP. Lower VIT D levels were significantly associated (P=0.035) with rs4588 SNP of DBP (A>C) in BCP but not in HD.

Conclusions: This study on a Caucasian case series highlights other parameters of Vit D pathway should be evaluated to understand the VIT D activity pathway. In particular, we found SNP analyses of VDR and DBP could have a role as markers to evaluate bone health and breast cancer risk together with Vit D and DBP levels. The enrolment of a similar case series of HD and BCP is ongoing in Tanzania, Africa, in order to analyze the same markers in this population.

A52 Everolimus activity on breast cancer and bone cell cocultures

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Metastatic bone disease has a major impact on both morbidity and mortality of breast cancer patients. Alterations in mTOR signaling are involved both in cancer progression and in osteoclasts differentiation. The aim of this study is to highlight the role of the mtor inhibitor Everolimus on osteoclastogenesis induced by growth factors or by cancer cells. To this end, we have developed an in vitro human model of osteoclastogenesis from peripheral blood monocytes. We used the conditioned media of the osteotropic human breast cancer cell line SCP2 to induce osteoclast differentiation. Everolimus was tested at an early step of osteoclastogenesis (5°-7° days) and later at 10°-12° days of differentiation. Osteoclastogenesis was detected by trap assay at day 14. SCP2 conditioned media (CM) was found to significantly induce osteoclastogenesis respect to control media. Furthermore the osteoclast number observed were similar to that obtained with growth factors RANKL and MCSF (differential medium: DM). Everolimus significantly decreased osteoclastogenenis in the presence of both CM and DM. Interestingly, the effect of Everolimus was much higher if administered to cells early. In this case the inhibition of osteoclastogenesis reached almost the 70%. In conclusion, with this study we develop an in vitro model that reproduce the interactions between breast cancer cells and the bone microenvironment. In particular we found a different effect on breast cancer-induced osteoclastogenesis according to the timing of Everolimus administration. Our model may represent a valid platform for preclinical trials of bone targeted drugs and for the study of the molecular mechanisms beyond breast cancer interplay with bone cells. In the future great importance will be also given to test drugs combinations.

A53 Neuroendocrine-immune response and mood changes in early breast cancer patients following surgery and adjuvant chemotherapy

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Background: Confrontation with cancer is emotionally challenging in patients and there is now clear evidence that the psychological state of the individual can influence progression of the disease. About 15-50% of breast cancer (BC) pts meet diagnostic criteria for anxiety and depression. Depressed metastatic BC pts show blunted cortisol awakening responses and reduced respiratory sinus arrhythmia, reflecting a physiologic profile often associated with chronic stress. These endocrine changes could alter immune defense mechanisms or act directly on tumor metabolism affecting cancer progression.

Material and methods: Pts with newly diagnosed early BC (age > 18 years) and eligible for adjuvant (Ad) chemotherapy (CT) were included and assessed after 30-40 days from surgery of primary tumor. Pts were followed prospectively by oncologist and psycologist throughout the period of treatment 1 week before the start of CT after 3 or 4 cycle and 1 month after 6 or 8 cycle of CT; after the end of CT all the pts were assessed at 6, 12, 18 and 24 months. The Ad CT included mainly anthracycline and taxanes regimens. The Ad hormonal therapy consisted of tamoxifen or aromatase inhibitors in premenopausal or postmenopausal ormonoresponsive pts, respectively. Cortisol was assessed in the saliva 30 days after surgery and at months 6 and 12 after CT. On the same days serum Brain-derived Neurotrophic Factor (BDNF) levels, anti and pro-inflammatory cytokines, leptin, adiponectin, were measured and psychological tests administered to assess depressive symptoms, coping style and anxiety.

Results: Preliminary results from 30 pts showed increased levels of cortisol and serum chemokine MIP-1b LFA-IV- after six months of CT. As concern psychological tests, the average scores detected using the Beck Depression Inventory (BDI) indicates mild depression. Interestingly, we found increased levels of BDNF associated to decreased anxiety and depression levels at 12 months follow-up.

Conclusions: Overall, data indicate that psychological factors can affect physiological responses in BC pts. This is especially relevant since stressful events and negative affective states can amplify the consequences of the pathology, precipitating disease progression and promoting recurrence. Further analyses and results on the longest follow up are in progress in order to increase the strength of the data. Funding: Ministry of Health Ricerca Finalizzata-2009 and Fondazione Veronesi 2012 to F.C.

A54 Pertuzumab in metastatic breast cancer (MBT) HER-2 +: Experience of the Department of Medical Oncology, Ospedale Oncologico Regionale "A. Businco", Cagliari, Italy

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Background: Pertuzumab (P), a humanized monoclonal antibody (Ab) that inhibits the dimerization of HER receptors, has a mechanism of action complementary to trastuzumab (H). Recent phase II-III clinical studies of patients (pts) with MBC HER-2 + treated with a combination therapy of the two Abs with taxanes (T) have shown promising results for efficacy with an acceptable toxicity profile.

Materials and methods: From May 2014 to April 2015, we treated in first line 17 pts with MBC HER-2 + with P in combination with H and T-based chemotherapy (CT). Pts median age: at observation 48 y (35-65), at diagnosis 45 y (29-60); 2/17 pts breast cancer familiarity; 3/17 pts de novo metastatic; 14/17 pts prior adjuvant CT and 9/14 pts prior (neo)adjuvant H; 5/17 pts primary CT; 2/14 pts relapsed early (6-12 mos) after adjuvant CT and 1/14 during adjuvant CT (3 mos). Hormone Receptor positive pts were 52.9% (8/17 received OT for adjuvant and 4/17 OT for metastatic disease) Mean disease event free survival: 51 mos (median 36 mos, range 5-173) and mean H-free interval 32.6 mos (median 24 mos, range 3-84). Metastatic sites in 14/17 pts: 9/14 lymph node, 7/14 pleural-lung, 6/14 bone, 4/14 liver, 3/14 soft tissue, 3/14 pleural and/or peritoneal effusion, 2/14 brain. De novo stage IV pts had multi-site metastases.

Results: Pts received treatment for a mean of 6.7 mos (from 1 to 11 mos), mean cycles 9.4 (from 2 to 16 cycles): 11/17 pts received P + H +docetaxel (75mg/m^2 d1 q21) and 6/17 pts paclitaxel weekly (80 mg/m^2) for a total of 6-9 cycles. Treatment response: 15/16 pts had Objective Response in all sites including 3/15 Complete Response in liver, lung and breast; 2/17 are SD. 5/17 pts currently receiving maintenance therapy with P + H after CT. All pts have maintained response. No cardiac toxicity or LFEV reduction was observed. Grade 3-4 neutropenia (1 febrile) was observed in association with docetaxel in 6/17 pts and 8/17 pts received G-CSF. Diarrhea and asthenia was reported by 7 to 12 pts.

Conclusions: In our real-life experience 64.3 % pts had received (neo)adjuvant H; in 16/17 pts evaluable after 4-9 cycles of P + H + Taxanes Overall Response Rate to treatment was high, 93.7% (OR 15, of which 3 CR + 1 SD). Our results confirm that P in association with H + T can yield optimal results in terms of response, maintenance of PS of 0-1 in all pts, significant clinical benefit in symptomatic pts, with good manageability and tolerability.

A55 Prognostic relevance of Hormonal Receptor positive Status in HER2-positive Metastatic Breast Cancer Patients: Retrospective Analysis in Real Life

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Background: Hormonal Receptor (HR) co-expression occurs in approximately one half of Her2-positive metastatic breast cancers and it has been considered a potential prognostic factor.

Material and methods: We performed a retrospective analysis of 80 patients treated with at least first-line treatment for Her2 positive metastatic breast cancer (MBC) over the last fourteen years at Medical Oncology, San Salvatore Hospital, University of L'Aquila. Progression Free Survival (PFS), Global Overall Survival from the first diagnosis of breast cancer (Global OS) and Overall Survival from diagnosis of metastatic disease (MBC OS), were evaluated according to HR status in overall 80 patients and in those receiving Anti-Her2 therapies: 41 (51%) HR+ and 39 (49%) HR-. 65 patients (81%) received anti-Her2 first-line regimens: 31 (48%) HR+ and 34 (52%) HR-.

Results: overall, PFS was 13 months: HR + , 17 months; HR-, 10 months. PFS was not significantly different according to HR status. Global OS was 102 months: HR + , 130 months; HR-, 75 months. MBC OS was 52 months: HR + , 64 months; HR-, 43 months. Both Global OS (p .002) and MBC OS (p .047) were significantly favourable in HR+ subgroup. In patients receiving anti-Her2 therapies Global OS was 92 months: HR + , 105 months; HR-, 75 months. Median PFS was 12 months: HR + , 17 months; HR-, 9 months. MBC OS was 52 months: HR + , 64 months; HR-, 43 months. Global OS was significantly better in HR+ subgroup (p .028), while PFS (p .306) and MBC OS (p .15) were not significantly different.

Conclusions: the present retrospective analysis in real life suggests a favourable prognostic relevance of HR status in Her2 positive MBC patients and it was confirmed in patients who received anti-Her2 regimens (median Global OS). Clinical outcome of Her2-positive MBC patients treated with anti-Her2 first-line regimens (PFS, MBC OS) was not significantly different.

A56 Neuregulin1ß and galectin3: novel biomarkers in breast cancer

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Introduction: Neuregulins (NRGs) are proteins that activate the ErbB2 receptors in human breast tumors. NRGs have cardioprotective effects. The cerbB2 positive breast cancer patients are treated with Trastuzumab, a monoclonal antibody that can induce a clinically significant cardiomyopathy. Galectin 3 (Gal-3) expression is implicated in a variety of processes associated with heart failure, including myofibroblast proliferation, fibrogenesis, tissue repair, inflammation, and ventricular remodeling. We have measured serum NRGs and Gal-3 and correlated them to cardiac biomarkers in patients with breast cancer undergoing chemotherapy.

Methods: We have evaluated circulating NRG-1β and Gal-3 in 30 breast cancer patients without cardiovascular risk factor (median age 60 years) in treatment with Anthraciclyne and Taxanes, with or without Trastuzumab (15 cerbB2 positive and 15 cerbB2 negative) correlating these data with NT-proBNP, CK-MB and Troponine before every course of chemotherapy and in 30 healthy controls.

Results: At baseline, circulating NRG-1β and Gal-3 were significantly elevated either in cerbB2 negative or in cerbB2 positive patients with respect to healthy volunteers: in cerbB2 positive NRG mean (SD) 1,21 (1,0) ng/ml, GAL-3 mean (SD) 15,09 (3,13) ng/ml; in cerbB2 negative NRG mean (SD) 3,36 (30) ng/ml, GAL-3 mean (SD) 23,81 (9,675) ng/ml; in controls: 0 ng/ml. Plasma NRG-1β and GAL-3 concentration remained elevated without any significant modification after each cycle of chemotherapy in both cohorts of patients: in cerbB2 positive NRG mean (SD) 2,42 (1,2) ng/ml, GAL-3 mean (SD) 16,43 (3,40) ng/ml; in cerbB2 negative NRG mean (SD) 4,5 (3,12) ng/ml, GAL-3 mean (SD) 25,13 (9,607). NT-proBNP in cerbB2 positive mean 180 pg/ml; in cerbB2 negative mean 270 pg/ml, above the upper limit of 130 pg/ml. CK-MB levels in cerbB2 positive mean 5 ng/ml; in cerbB2 negative mean 10 ng/ml, above the upper limit of 3,6 ng/ml, resulting significantly higher in cerbB2 negative then in cerbB2 positive patients. Troponine levels remained below the cutoff of 0.08 ng/ml in both groups.

Conclusions: Serum NRG and GAL-3 together with cardiac biomarkers measurements could be a useful tool for the early detection of patients at high risk of developing cardiotoxicity.

A57 Multicenter study of the eValuation of Eribulin (E) use in Sicily in metastatic breast cancer (MBC): A Prospective RegistrY (VESPRY trial)

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Background: Eribulin mesylate is a non taxane microtubule dynamics inhibitor that represents a firmly established therapeutic option for the treatment of MBC.

Methods: This is an ongoing, open-label, multi-institutional, prospective, post-marketing observational, single arm study of the use of E for the treatment of third line of patients (pts) with pretreated locally advanced or metastatic breast cancer. This study is being conducted in 14 oncology centers in Sicily. The estimated enrollment is 120 pts who will receive, after two lines of chemotherapy for MBC, at least one dose of E at 1.23 mg/m^2 on days 1 and 8 of every 21-day cycle. Pts will receive E until progression. A population analysis of 120 patients will ensure a precision deemed sufficient for the estimation of the confidence interval at 95% of the percentage of pts with severe neutropenia (grade 3-4), expected to be around 45% in this population. Primary Endpoints: safety profile of the Eribulin and response according to the site of metastases. Secondary Endpoint: evaluation of response according to different subtypes of breast cancer.

Results: At the time of this analysis 69 pts were collected. Median age was 60.5 (range 30-79). All pts received previously anthracycline and taxane based therapies. Subtypes: Luminal A 78%, Luminal B 6%, HER2 enriched 6% and Triple Negative 10%. The main site of metastases was: lung 45%, bone 38% and liver 27%. A median of 5 cycles of Eribulin (range 1-21) was administrated. Acceptable and manageable safety toxicity profile was recorded (G2 diarrhea 23%, asthenia G1 23%, G1-G2 neutropenia 18%, G1 neurotoxicity 18%). We reported only one case G4 mucositis, leading to treatment interruption. Overall response rate was 23% (all Partial Response) and Stable Disease 60%. We performed an organ-specific analysis that revealed an higher rate of stabilization in the lung lesions compared to other site of metastases (lung 82%, liver 65% and brain 63%). The estimated median Time to Progression was 4 months (range 1-9).

Conclusions: This preliminary analysis showed that Eribulin in third line setting has a favorable safety profile and a comparable efficacy to that reported in the pivotal trial (Cortes J, 2011).

A58 Everolimus in ER + /HER-2 negative metastatic breast cancer (MBC): what we have learned from two years of clinical practice. A single Institution experience

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Background: The everolimus–exemestane pair was approved by the US Food and Drug Administration (FDA) in 2012 to treat women with hormone receptor-positive (ER+), HER2-negative metastatic breast cancer (MBC) that got worse after treatment with aromatase inhibitor alone. The main benefit of this regimen is that it is less toxic than chemotherapy and offers patients a better quality of life.

Patients and method: We have evaluated the efficacy and safety of exemestane and everolimus in post-menopausal patients with ER + /HER-2 negative MBC after progression with aromatase inhibitors. Patients were evaluated for adverse events (AEs) and serious adverse events (SAEs) graded according to NCI-CTC for AEs (version 3).

Results: Between September 2012 and April 2015, in our Institution, 30 consecutive patients with MBC were treated with the daily combination of everolimus and exemestane. 63.4% of patients received everolimus and exemestane within the first three lines of treatment. The median age was 66 years (51-82). 43.3% of patients had asymptomatic visceral metastases. Of all patients, 3.3% had a complete response (CR) and 13.3% a partial response (PR); 30% had a stable disease (SD) while 36.7% had a progressive disease (PD). 5 patients were not evaluable because it is too early. Median PFS was 7.1 months (1.57-26.8). 4 patients have continued the treatment for more than 20 months. The most common toxicities were stomatitis (56.6%), asthenia (23.3%), neutropenia (20%) and rash (16.6%). However only 4 cases of G3 adverse events require a reduction of everolimus administration to 5 mg every day.

Conclusions: Our experience, although with a small number of patients, demonstrates that oral mTOR inhibitor everolimus in ER + /HER2-negative post-menopausal MBC has a similar efficacy and safety profile compared to the BOLERO-2 trial. In this patient population, everolimus is generally well tolerated and the appropriate management of treatment-related AEs is fundamental to improving patient quality of life and treatment outcomes.

A59 T-DM1 for HER2 positive advanced breast cancer: a single institution, "real life" experience

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Background: Ado-trastuzumab emtansine (T-DM1) is a novel antibody drug conjugate effective for HER2-positive metastatic breast cancer (MBC) patients (pts) previously treated with trastuzumab and taxanes.

Patients and method: Consecutive HER2 positive MBC pts treated at our institution with T-DM1 3.6 mg/kg iv every 21 days were eligible for the study. Clinicopathologic and treatment characteristics were reported. Adverse events (AEs) and severe adverse

events (SAEs) were graded according to National Cancer Institute Common Terminology Criteria.

Results: Between July 2013 and May 2015, we identified 24 consecutive pts. Median age 57.5 years (range 36-80); <65 yrs 16 pts (67%), >65 yrs 8 pts (33%). Histology: ductal carcinoma 23 pts (95%), other 1 pt (5%). 17 pts (71%) had hormonal receptor (HR) positive disease and 7 (29%) HR-negative cancer; 6 pts (25%) showed an HER2 negative primary tumor, but HER2 positive on metastatic site. 6 pts (25%) showed bone metastases (mts), 8 pts (33%) visceral mts, and 10 pts (42%) both bone and visceral mts. 14 pts (58%) received a neadjuvant/adjuvant treatment. All pts were previously treated with trastuzumab and taxanes. T-DM1 was administred as first line in 1 pt (4%), as second line in 7 pts (30%), as third line in 8 pts (33%) and in 8 pts (33%) in subsequent lines. Pts received T-DM1 for a median time of 5.2 months. mPFS was 6.3 months (range 2.7-12.6). 7 pts (33%) showed a progressive disease (PD) as best response, 4 (19%) stable disease (SD), 8 (38%) partial response (PR) and 2 (10%) complete response (CR); among the 6 pts with an HER2 negative primary tumor 4 (67%) showed a PD and 2 (33%) a SD as best response. The most common toxicities reported were elevated serum concentrations of transaminases (G1-2), observed in 11 pts (46%); asthenia (G1-3) in 12 pts (50%) and nausea (G1-3) in 10 pts (42%). Thrombocytopenia (G1) was observed in 5 pts (21%). No SAEs neither cardiac events were observed. T-DM1 dose reduction due to AEs was necessary in 2 pts (8%) and no drug interruption due to toxicity was observed. No difference in AEs rate was noticed in elderly patients.

Conclusions: Our single intitution "real life" experience confirmed the very favorable toxicity profile of T-DM1, even in elderly pts. However, with the limitations of the retrospective nature of the study and the small sample size, we observed an inferior mPFS than reported previously. Interestingly the higher rate of PD in pts who showed an HER2 negative primary tumor.

A60 Next Generation Sequencing mutational analysis in "Triple Positive" breast cancer

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Background: Breast cancer is a heterogeneous disease, for histological types and molecular classifications. HER2 protein overexpression or gene amplification is reported in 15-20% of primary breast carcinoma and 50% of these are also hormonal receptors positive. The co-expression of these receptors could activate different transduction pathways and molecular characterization of these tumors has not yet been widely explored.

Material and methods: We retrospectively analyzed biologic and clinical data of 15 patients (pts) with primary triple positive (Estrogen = 1%, Progesterone = 1% and HER2 IHC 3+ or SISH amplified) breast cancer, diagnosed from 2005 to 2008 at Ferrara University Hospital. Tumor sample were analyzed with nex generation sequencing (NGS) and the results were correlated with the pts clinical parameters. The gene analyzed with NGS were: ABL1, ALK, CDH1, CDKN2A, ErbB2, FBXW7, FGFR3, GNAQ, JAK3, KDR, KIT, MET, mTOR, TP53, PIK3CA, PTEN STK11. We considered significant the mutations present in more than 15% of reads, and used computer prediction programs (PolyPhen2 algorithm) and information in literature and mutations databases (Cosmic) to define the clinical significance of mutations.

Results: We have found 14 significant mutations in 10 pts: 7 in PIK3CA, 2 in TP53, 1 in ABL1, 1 in CDKN2A, 1 in ErbB2, 1 in KDR and 1 in MET. One pts had 3 different mutations, 2 pts showed 2 mutations and 7 pts had a single mutation. The PIK3CA mutation (6 pts, 40%) was numerically the most frequent in pts with postmenopausal status (83.4% vs 16.6%), with stage II or III (83.4% vs 16.6%), with high proliferative activity (83.4% MIB1 = 20% vs 16.6% < 20%) and with high estrogen receptor positivity (= 50%) (83.4% vs 16.6%). All pts were treated according to guidelines of the period. At a median follow-up of 85.4 months, only 3 pts relapsed, one with single TP53 mutation (PFS 14.3 months), one with ABL1 single mutation (PFS 48.2 months) and one without significant mutation (PFS 24.6 months).

Conclusions: As reported in Genoma Cancer Atlas, PIK3CA and TP53 mutations are the most frequent in our Luminal B HER2 enriched breast cancer pts. In our series PIK3CA mutations were more frequent compared to literature, probably due to the particular characteristics of triple positive pts. No clear relationship between recurrence and type of mutation can be confirmed.

A61 Tumor-stroma cross-talk in the study of the osteoclastogenic potential of a metastatic breast cancer cell line: a coculture system

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Bone metastases represent a major challenge in the treatment of breast cancer, but the complex interactions involved have hampered the development of robust in vitro models. The aim of this work is to investigate the osteoclastogenic potential of the osteotropic, human breast cancer cell line SCP2, evaluating its modulation by bone marrow-derived mesenchymal stromal cells (MSC) in presence or absence of the EGFR-blocking compound gefitinib. While conditioned medium (CM) from SCP2 monocultures did not induce significant osteoclastogenesis in human peripheral blood mononuclear cells (PBMC), we showed that CM from SCP2-MSC coculture increased the osteoclastogenesis of PBMC, as evidenced by TRAP staining, and the effect was abrogated upon pre-treatment of SCP2-MSC coculture with gefitinib. Coculture of SCP2 with MSC increased the expression of the bone-related marker RANK in the breast cancer cells and increased EGFR expression. Comparable upregulations were observed after treatment of SCP2 with gefitinib. In conclusion, we have developed an in vitro human model of coculture of cancer cells, MSCs and osteoclasts, reporting the modulation of the osteoclastogenic potential of SCP2 and applying it also in the context of advanced breast cancer drug testing.

A62 Effectiveness and resulting surgical behavior after neoadjuvant chemotherapy in locally advanced breast cancer: our experience

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Background: The aim of our study was to evaluate how neoadjuvant chemotherapy is able to produce a downstaging in locally advanced breast cancer.

Patients and methods: We evaluated all patients, over the last four years, who have undergone neoadjuvant treatment for locally advanced breast cancer, considering the clinical TNM at the time of diagnosis and pathological TNM on the surgical specimen. The baseline assessment was performed with MRI, CT scan and physical examination.

Results: We enroled 29 patients treated with neoadjuvant chemotherapy from 2011 to 2014. The mean tumor size was 41.6 mm and median 42 mm (range, 17-86 mm). 8 patients had a multifocal tumor. 10 patients had a clinical nodal staging ≥2a. 12 patients were HER-2 positive; estrogen receptor positivity was in 18 cases, of which 11 were also positive for progesterone receptors. All patients received a sequential scheme with EC ± 5FU, followed by treatment with taxanes ± Trastuzumab. After medical treatment 13 patients had a radiological complete response, 13 patients a partial response and 3 experienced a stabilization disease. The mean tumor size was 11.5 mm and median 3.7 mm (range 0-86). 23 patients were treated with mastectomy anyway, and 6 patients with quadrantectomy. The postoperative staging identified a tumor regression in all patients but two, with a regression to pT0 or pTis in 8 patients; only two patients presented stability compared to diagnosis; only two patients maintained pN = 2a. After surgery, all HER-2 positive patients continued treatment with Trastuzumab till 12 months; 14 patients received hormone therapy, 2 patients were treated with adjuvant chemotherapy. 17 patients underwent radiotherapy. At the time of data only 6 patients had recurrence, including 3 local and 3 remote.

Conclusions: Neoadjuvant chemotherapy in locally advanced breast cancer seems to have a major reductive effect on the primary disease and regressive on lymph node involvement. These results do not always entail a change of attitude surgery, despite the confirmation of good pathologic response. There are still cases in which disease control occurs only through a stabilization disease, but predictors of this type of response are not yet clear.

A63 A retrospective analysis of consecutive patients series in first line treatment for metastatic luminal HER2- breast cancer

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Background: The luminal subtype takes shape in hormone receptors expression, has a favorable prognosis and is sensitive to endocrine therapy (OT), which is recommended as first-line treatment in asymptomatic patients. Material and methods. A single institution retrospective analysis on 48 women with metastatic HER2-asymptomatic or mildly symptomatic luminal breast cancer to assess the efficacy of our first line treatment was performed. Thirteen patients (9 visceral metastases and 4 bone metastases) were treated with OT. Thirtyfive patients underwent to chemotherapy (CT) (31 with taxanes) without or with (15 patients) bevacizumab. After a median of 8 months, 16 of these patients interrupted CT without progressive disease and started maintainance OT.

Results: Median age was 51.5 years. Progression free survival (PFS) was significantly higher in OT arm (median 8 months; 95% CI 6.1-29.6) versus CT only arm (4 months; 95% CI 3.9-7.6) (p = 0.04; HR 0.50; 95% CI 0.15-0.98). When we added to CT group (19 patients) those patients treated with OT after CT (CT + OT, 16 patients), PFS was 11 months (95% CI 9.7-17.2), with no difference compared to OT only (p = 0.47; HR 0,80; 95% CI 0.34-1.65). Overall survival (OS) was improved in OT arm (39 months; 95% CI 22.6-52.2) versus CT (11 months; 95% CI 9.3-27.9) (p = 0.01; HR 0.27; 95% CI 0.08-0.73). OS in CT + OT was 23 months (95% CI 18.4-36.3), with a significant difference compared to OT only group (p = 0.04; HR 0.37; 95% CI 0.16-0.99). Response

rates (RR) were 23% in OT group (3/13) and 15.7% in CT group (3/19) (p = 0.38), 34.2% in CT + OT (12/35) (OT versus CT + OT: p = 0.46). Disease control rates (DCR) were 84.6% in OT (11/13) and 47.3% in CT (9/19) (p = 0.03), 71.4% in CT + OT (25/35) (OT versus CT + OT: p = 0.35). At multivariate analysis, ki67 value resulted an indipendent prognostic factor for PFS (p = 0.006).

Conclusions: Our retrospective analysis showed a non inferior efficacy of OT versus CT in first line treatment. OT appears to maintain a key role in prolonging survival and in obtaining long stabilization, as resulted by differences in survival and in disease control rate in favor of OT as compared to CT. Advantages of OT were maintained even in those patients who delayed OT due to the first line CT. Finally, the prognostic role of ki67 can narrow the benefits of chemotherapy to a small subgroup of patients with aggressive disease.

A64 Fast Walking And Resistance Exercise Program In Breast Cancer Survivors

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Background: Physical Exercise is normally suggested in preventing metabolic risk factors especially in cancer patients. Despite aerobic exercise has been well studied, few data are available in case of combination with resistance exercise, particularly unsupervised. The study aims to assess the cardiovascular and metabolic impact of mixed exercises at moderate level, in cancer survivors.

Methods: 15 survived breast cancer women (without evidence of disease at the time of enrollment and with median age 55.51 year) were submitted to an unsupervised exercise program consisting on three sessions/ week for 6 months. The resistance exercises included a maximum of 20 strength repetitions, calculated from Hand Grip and Chair Test for strength for the upper and lower limbs. Aerobic training included 30 minutes of "fast walking" at 70% of own maximum Heart Rate (HR) calculated at 6 minute Walking Test (6MWT). Body Mass Index (BMI) and circumferences of waist/hip were measured at the beginning and after 6 months, as well as HR, respiratory rate, Systolic and Diastolic Blood pressure and perceived exertion from CR10 scale, calculated at the 6MWT test.

Results: Anthropometric parameters showed a trend toward an improvement: BMI (Kg/m2) T0: 28.90 ± 7.70 T6:28.84 ± 7.05. Waist (cm) T0: 91.33 ± 16.97; T6 91.87 ± 17.10; Hip (cm) T0: 108.13 ± 16.37; T9 108.17 ± 15.04, body composition and hydration data showed on the contrary a significant improvement (Fat Mass (FM)% T0: 38.44 ±5.04 %, T6: 37.65 ± 5.00 %, p < 0.03; Fatty Free Mass (FFM) % T0: 61.56 ± 5.04, T6: 62.35 ± 5.00 %, p< 0.03, Total Body Water (TBW) % T0: 49.26 ± 7.22 %, T6: 47.94 ± 5.97 % p < 0.05). The respiratory rate is significantly reduced (T0: 31.15 ± 4.61 pm, T6: 29.42 ± 3.34 pm p < 0.04).The functional parameters also showed a significant improvement of the number of repetitions at Chair Test (T0: 13.20 ± 4.84 rip, T6: 15.31 ±3.54 rip, p< 0.01).

Conclusions: Combination aerobic and resistance exercise produces, in a short time, a significant improvement of those parameters associated to some cardiovascular risk factors involved on the overall quality of life. This effect is possible by using a program of "unsupervised " exercise.

A65 Primary prophylaxis of neutropenia in women affected by breast cancer undergoing adjuvant chemotherapy with fec 100 +/- docetaxel: comparison of efficacy and tolerability between lenograstim and pegfilgrastim

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Introduction: myelosuppression is primary toxicity of many chemotherapy regimens and limits their applicability. Use of G-CSF is important to reduce incidence of febrile neutropenia, but is burdened with bone pain.

Objectives: evaluate safety and toxicity of a single injection of pegfilgrastim compared to daily administration of lenograstim in breast cancer patient undergoing adjuvant chemotherapy.

Methods: single injection of Pegfilgrastim compared to 5 daily administrations of Lenograstim in a population of 56 women undergoing chemotherapy with FEC-100 for 6 cycles (Group A) or 3 FEC-100 followed by 3 DOCETAXEL-100 (Group B).

Results: In Group A, 40% of patients showed Neutropenia-G4, 35,3% of those treated with Lenograstim, while 44,4% of those treated with Pegfilgrastim. in Goup B, 57,1% of patients showed Neutropenia-G4: 75,0% of those treated with Lenograstim and 33,3% of patients treated with Pegfilgrastim (p = 0,005). Overall, 30,4% of all patients developed BP with intensity of 7-10 second Numeric Rating Scale. Bone Pain incidence was significantly higher in Group B than in Group A (52,4% vs 17,1%, p = 0,005), with no significant differences between Lenograstim and Pegfilgrastim. In both groups, the average duration of Bone Pain was 4-6 days.

Conclusions: Both G-CSFs showed efficacy in reduction of Neutropenia, but Pegfilgrastim showed a better action with similar side effects in Group B. Moreover, Pegfilgrastim could be a better choice for patient's compliance because of single injection in front of 5 necessary for L. Overall, Bone Pain incidence was significantly higher in Group B than in Group A (p = 0,005), with no significant differences between Lenograstim and Pegfilgrastim.

A66 (R)-a-Lipoic acid reduces sensorial peripheral neurotoxicity in breast cancer patients receiving weekly paclitaxel

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Background: Sensorial peripheral neuropathy (SPN) is a common adverse event occurred patients (pts) treated with microtubule targeting agent, including paclitaxel (P). P neurotoxicity is determined by microtubule structure destruction, resulting in an assoplasmic transport system alteration with subsequent cellular death. Three-four grade (G) SPN incidence in weekly P ranges approximately from 9-24% in metastatic breast cancer pts to 4-8% in adjuvant setting. Furthermore, SPN recovery can be long and not completely solved. To date, there is no a standard of care for chemotherapy induced SPN. Recently, an oral liquid (R)-α-Lipoic acid (ALA) formulation proved efficacy in SPN, diabetic polyneuropathy and radiculopathy opposing oxygen free radicals damage on peripheral nerve fibers.

Material (patients) and methods: Based on clinical data observed in diabetic polyneuropathy, we conducted a pilot study to evaluate the effect of an innovative oral liquid ALA formulation (300 mg vial once a day) on SPN, occurred in breast cancer pts treated with adjuvant/neoadjuvant weekly P. ALA was administered until clinical evidence of SPN deterioration or complete resolution. SPN was evaluated according to NCI CTcriteria, version 4.0.

Results: From December 2014 to March 2015, we collected data from 20 breast cancer women (median age 58 years, range 35-74) treated with adjuvant (16 patients) or neoadjuvant (4 patients) epirubicin combined to cyclophosphamide followed by weekly P (80 mg/mq for 12 weeks). All pts had a negative medical history for neuropathy and/or diabetes. During P treatment, 12 (60%) pts developed a G1 SPN, 6 (30%) a G2 PN and 2 (10%) a G3 SPN, respectively. SPN median time onset from the beginning of P was 35 days (range 14-84). Pts started to intake ALA at SPN onset. G1/2/3 PN improved in 5 (42%)/3 (50%)/1 (50%), respectively, stabilized in 5 (42%)/ 2 (33%)/1 (50%) respectively and worsened in 2 (16%)/1 (17%)/0 pts respectively. Overall, 16 (80%) of 20 treated women had a SPN relied. Median time to response was 21 days (range 7-84). Seventeen (85%) pts completed P chemotherapy; 1 needed a P dose reduction and 2 stopped P (at IX and X cycle, respectively), due to SPN worsening. ALA treatment was well tolerated, excepting 2 pts who experienced heartburn, resolved after ALA withdrawal.

Conclusions: Although preliminary, ALA appears to have a role in reducing SPN induced by weekly P. Further studies are needed to prospectively evaluate these promising findings.

A67 Nab-paclitaxel plus bevacizumab in heavily pretreated HER2-negative metastatic breast cancer

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Background: Many agents have been used for the treatment of metastatic breast cancer (MBC) patients, including antitubulin drugs and antimetabolites, but none demonstrated a clear superiority. Furthermore, although some combinations of cytotoxic agents provide a small progression free survival (PFS) advantage, none showed an overall survival (OS) advantage, and toxicity is generally greater than for single agents. Therefore, at present, there is no standard for this treatment setting. New treatments that could delay disease progression without systemic toxicity would represent a significant advancement. In this regard, Nab-paclitaxel showed improved PFS and tolerability compared with standard cremophor-solubilized paclitaxel; based on this, we examined the efficacy and safety of combining weekly nab-paclitaxel and bevacizumab in patients with heavily treated MBC. The combination of bevacizumab with a taxane significantly improved progression-free survival (PFS) compared with taxane monotherapy in the first-line treatment of human epidermal growth factor receptor 2 (HER2)-negative MBC in a number of randomized, Phase III studies.

Patients and methods: In this study, patients with HER2 negative MBC received Nab-paclitaxel 125 mg/m(2) intravenously on days 1, 8, 15, and bevacizumab (10 mg/

kg) intravenously on days 1 and 15 of a 28-day cycle. The primary end point was to assess the safety of this combination. Secondary end points included PFS and overall response rate (ORR).

Results: From September 2014 to March 2015, 20 patients were enrolled in this trial. Median age was 53.0 (range, 30-76) years and all patients had received previous therapy. Median PFS was 9.2 months (95% confidence interval [CI], 7.8-25.1 months) and ORR was 85% (95% CI, 69%-95%) for the combination. The regimen was well tolerated with the most common grade 3/4 adverse events being neutropenia (75%) and thrombocytopenia (25%), and other serious events including 1 grade 3 and 1 grade 4 thrombotic event and 1 febrile neutropenia.

Conclusion: The combination of nab-paclitaxel and bevacizumab for with HER2 negative MBC proved to be efficient and safe. Nab-paclitaxel can safely be offered to many women with MBC, with reasonable expectations of clinical benefit and without concern of significant toxicity. Nab-paclitaxel may be particularly beneficial for patients with aggressive disease, including those with mTNBC.

A68 Docetaxel and Ifosfamide as salvage treatment in relapsed breast cancer

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Background: The current standard regimen for advanced breast cancer is anthracyclines and taxanes. Metastatic breast cancer (MBC) progressing after first and second line chemotherapy has poor prognosis. A wide variety of chemotherapeutic agents, as single agent and as combination chemotherapy, have been efficacious in relapsed MBC. To evaluate the efficacy and toxicity of combination of Docetaxel and Ifosfamide in heavily pretreated metastatic breast cancer (MBC). Docetaxel is one of the most active drug in MBC, that improved response rate, overall survival and quality of life in patients with progressive MBC. Ifosfamide is a broadly active antitumor agent.

Material and methods: Sixteen evaluable patients (pts) with histological proven relapsed breast cancer, bidimensional measurable disease, PS < 2 and adequate haematological, hepatic and renal function received docetaxel 60 mg/m^2 day 1 and Ifosfamide 1500 mg/m^2 day 1,2,3 with mesna rescue, every 3 weeks until disease progression or appearance of non- tolerable toxicity.

Results: Baseline data, activity data and toxicity ar available in sixteen pts. Patients with median age 52 years (range 34-63) were treated for a median of three cycles (range 1-8 cycles). Ten pts had lung metastases, seven lymph nodes, five liver, seven bone and ten other metastases.The hematologic toxicity was moderate. Nine pts experienced grade 3 neutropenia without fever. Anemia grade 3 occurred in five pts, Additional non-hematological toxicities experienced include asthenia (all pts) and alopecia. Out of 16 evaluable pts for resonse, we obtained 6 partial responses, 5 stable disease and 5 disease progression.Patient in response had evident clinical benefit.

Conclusion: Combined chemotherapy with Docetaxel and Ifosfamide has demonstrated clinical activity with clinical benefit and moderate toxicity for pts with preatreated metastatic breast cancer.

A69 Inflammatory breast cancer management: a single centre experience

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Introduction: Inflammatory breast cancer is a particular aggressive form of invasive breast cancer, more frequent in younger and associated to higher incidence of locoregional relapseand poor prognosis. Chemotherapy plays a fundamental role, because most of inflammatory breast cancer is not resectable at diagnosis. The standard approach is the neoadjuvant chemotherapy with the aim to permit surgery, following by local radiotherapy and adjuvant chemotherapy/hormonotherapy. We have analyzed a small cohort of 8 patients affected by inflammatory breast cancer, undergoing neoadjuvant chemotherapy with weekly carboplatin and paclitaxel and in case of inadeguate response, with anthracycline based chemotherapy.

Patients: Our patients, median age 52 (range 45-74), were treated from 2000 to 2014 in our Department, both with locally advanced and with metastatic disease. A core needle biopsy confirmed a Luminal B phenotype for 4 patients, HER2 like for 2 patients and Basal like for 2 patients. 4 patients were in premenopausal, while 4 in postmenopausal status. All patients underwent neoadjuvant chemotherapy with weekly Carbolatin and Paclitaxel (Carboplatin AUC 2 and Paclitaxel 80 mg/mq d 1,8,15 q28), with the addiction of Trastuzumab (4 mg/Kg following by 2 mg/Kg weekly) for 12 cycles, and those patients whose response did not permit surgery, underwent chemotherapy with Epirubicin 90 mg/mq and Cyclophosphamide 600 mg/mq q14 for 4 cycles. The clinical response was evaluated according to RECIST criteria. Relapse-free survival (RFS) and Disease free survival (DFS) were the primary end point.

Results: 4 patients (2 HER2 like, 1 basal like, 1 luminal B) achieved pCR (pathologic complete response) and 4 (3 luminal B and 1 basal like) achieved pPR (pathological partial response) after 12 courses of weekly Carboplatin and Paclitaxel; the only 4 patients achieving pPR have undergone both taxanes and anthracycline. All patients received breast conservative surgery and radiotherapy. Only 1 basal like patient had a local relapse, treated with mastectomy (RFS was 2 years). 3 Luminal B became metastatic patients (2 with bone metastasis and 1 with liver metastasis), such as 1 basal like patient (1 liver metastasis, successfully treated with chemoablation). DFS was 38 months.

Conclusions: Inflammatory breast cancer has a very aggressive nature; with taxane-based chemotherapy a long lasting response can be achieved in these patients, especially in basal like women.

A70 Factors affecting recurrence risk in her2 positive dcis

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Background: The aim of this study is to evaluate the prognostic role of human epidermal growth factor receptor 2 (HER2) overexpression in patients affected by ductal carcinoma in situ (DCIS).

Patients and methods: We evaluated 48 cases of DCIS, divided in two groups according to HER2 amplification status. Nuclear grade and "Retrograde-Lobular-Cancerization" were determined within primary DCIS and Ki67, ER, PR and HER2 expression was established using immunohistochemistry (IHC). The histopathological variables in HER2-positive and in HER2-negative patients were compared to determine the recurrence risk. We also considered the median age at the time of surgery according to HER2 status.

Results: There were 11 recurrences (23%), 6 DCIS (55%) and 5 invasive cancer (45%). In a 8 years long median follow-up, we hypothesized high risk of recurrence in HER2-positive DCIS. Patients with HER2-positive DCIS were younger than HER2-negative ones ($P = 0.002$). HER2-positive DCIS was also related to histopathological predictors of recurrence such as high nuclear grade ($P < 0.001$), high Ki67 expression ($P = 0.003$), low ER and PgR levels ($P < 0.001$) and the presence of "Retrograde Lobular Cancerization" ($P < 0.049$). We also considered other variables of recurrence risk and we found that HER2-positive DCIS were larger in size than HER2-negative ones, without statistical significance ($P = 0.48$). Our data showed no benefit from radiotherapy ($P = 0.56$) or hormone therapy ($P = 0.77$) in patients with HER2-positive DCIS. We analyzed the presence of comedonecrosis ($P = 0.097$) and calcifications ($P = 0.416$) which were related to poor prognosis, regardless of HER2 status.

Conclusions: Our trial confirms that HER2 amplification in primary DCIS is identified more frequently in younger patients and it is related to histopathological predictors of overall relapse as high nuclear grade, high Ki67 expression, low ER and PgR levels and the presence of "Retrograde-Lobular-Cancerization". In HER2-positive DCIS other variables of recurrence risk are compared to HER2-negative lesions, without statistical significance. These results are probably related to the evidence that some variables of recurrence risk are independent from HER2 status. Our results show that HER2 testing might suggest clinicians the optimal treatment of patients affected by DCIS.

A71 Abraxane monotherapy in patients with advanced breast cancer: evaluation of efficacy and tolerability in our clinical practice

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Introduction: Abraxane is an anticancer agent approved for the treatment of metastatic breast cancer. Abraxane is a colloidal suspension of paclitaxel and human serum albumin that can be administered without premedication, it is able to improve overall response rate and time to progression in patients with progressive metastatic breast cancer. This study reports efficacy and safety in patients treated with abraxane in our center.

Materials and methods: We analized retrospectively 31 patients treated with abraxane from January 2012 to February 2015 Abraxane 260 mg/m2 was administered every three weeks. The main characteristics of patients were as follow: median age 58,12 years (range:36-77), performance status 0-2 (ECOG), estrogen positive disease 83,8% and progesterone positive 71%. Seven patients were HER 2 positive. Three/thirty-one patients had only bony metastases, 8/31 patients had only visceral metastases, 20 women had visceral and bony disease. Nine/thirty-one patients received treatment by 3 line, 16/31 patients were on 4-5 line, 6/31 patients received treatment over 5 line. Median number of cycles received was 2,16 (range 1-12)

Results: Patients receiving abraxane had a median overall survival of 10,22 months and a progression free survival of 4,45 months. A partial response was seen in 19,3% of cases and a stable disease in 38,7% of cases. ORR was 58 %. Fatigue was the most commonly reported toxicity, being reported in approximately 77,42% of patients. Other adverse events included: febrile neutropenia 41,93%, neurosensory toxicity 19,35%, anemia 9,68%, vomiting 3,23%.

Conclusions: We conclude that our experience on real life confirm the tolerability and the efficacy of abraxane in women with metastatic breast cancer.

A72 Efficacy and tolerability of Everolimus-Exemestane combination therapy in metastatic breast cancer patients: experience in Real Life

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Background: PI3K/Akt/mTOR pathway aberration is reported in breast cancer (BC) with PIK3CA activating mutations detected in about 25% of BCs. Based on the results of BOLERO-2 study, the mTOR inhibitor everolimus has been approved, in combination with exemestane, for post-menopausal patients (pts) with hormone-receptor positive/HER2-negative metastatic BC progressed on prior nonsteroidal aromatase inhibitor.

Methods: Twenty-two unselected metastatic BC pts were treated in clinical practice. Pts received exemestane 25 mg/die plus everolimus 10 mg/die; two subsequent reduction dose levels to 5 mg/die and 5 mg every other day were allowed in case of limiting toxicity: G4 haematological; G3 non-haematological; any toxicity resulting in >28 days delay. Response assessment was performed by RECIST criteria; progression-free survival (PFS) was calculated by Kaplan-Meier method. Mutational analysis of PIK3CA on primary and metastatic specimen is ongoing.

Results: Median age was 61 years (range 52-81). Eleven pts (50%) had visceral disease, 11 (50%) non-visceral, 5 (23%) bone-only. Eighteen pts (82%) were treated from I to IV lines of therapy, 4 (18%) in > V lines, 3 pts(14%) received I line therapy. Features of primary tumors: ER + /PR + , 77%; ER + /PR-, 18%; features of metastasis (16 pts, 73%): ER + /PR + , 44%; ER + /PR-, 50%; ER + /PR unknown, 6%. The most common grade 3/4 adverse events were stomatitis (9%), hyperglycemia (9%, in diabetic pts), anemia (4.5%), thrombocytopenia (4.5%), fatigue (4.5%), diarrhea (4.5%). Everolimus dose reduction to 5 mg/die was required by 6 pts (27%), 2 of which needed further reduction to 5 mg every other day due to G2 interstitial pneumonitis. Median administered cycles per patient were 11 (range 2-23). Among 20 ptsevaluable for activity at the time of data cut-off: clinical complete response (cCR), 1 (5%); partial response (PR), 9 (45%); stable disease (SD), 7 (35%); progressive disease, 1 (5%); clinical response rate (cCR + PR), 50%; clinical benefit rate (cCR + PR + SD) 85%; for 2 pts(10%) response evaluation was not assessed due to compliance issue. Median PFS was 18 months overall (range 3 + -24 + ; CI ±2,83), 18 months for the visceral subgroup, 19 months for the non-visceral subgroup, not reached for the bone-only subgroup.

Conclusion: In our experience in clinical practice, the combination of everolimus and exemestane confirms activity and efficacy and maintains a good tolerability, if supported by an adequate and proactive management of adverse events.

A73 Eribulin in metastatic breast cancer: our experience

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Introduction: Metastatic breast cancer represents an incurable disease but novel agents are able to prolong survival in some cases.

Materials and methods: Between January 2012 and February 2015, 31 patients with MBC were observed. All patients had a diffuse disease (bony and visceral metastases), a median age of 55 years (range 40-76) and a performance status (PS) 0-2 (ECOG). All patients received eribulin over first line (15 patients by 3 line, 16 patients over 3 line), with a dose of 1,23 mg/mq i.v. day 1-8 every 21 days. Median number of cycles was 3,45 (range 1-10). Twenty-six/thirty-one patients had estrogen positive disease, 20/31 patients had progesterone positive disease. 9 patients had HER2 positive status. Twenty-five/thirty-one patients had bony metastases, 14/31 patients had liver metastases, 14/31 patients had lung metastases, 6/31 patients had brain metastases, only one patient had skin lesions. The other lines in patients HR positive and HER 2 positive included one or more hormonal therapies and Her-2 blocked treatments, respectively.

Results: At a median follow-up of 12 months, results included: median overall survival of 7,44 months; progression free survival of 2,67 months; partial response in 4 patients; stable disease in 4 patients; progression disease in 23 patients. Overall survival was better in patients only with bony metastases. The main observed all grade toxicities were: leukopenia 58%, febrile neutropenia 48,3%, fatigue 70,9%, anemia 48,3%, algie 41,9%, peripheral neuropathy 9,6%, asma 32,2%, headache 35,4%, stipsis 22,5%, nausea 38,7%, mucositis 48,3%.

Conclusions: Our experience on real life confirmed that treatment with eribulin is safe in patients with progressive metastatic breast cancer, with results on efficacy consistent with the previous phase III studies.

A74 Aromatase inhibitor exemestane in elderly over 85 year's breast cancer treatment, personal clinical experience

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Background: This clinical experience confirmed the significant endocrine dependence of the breast cancer in the elderly patients. The up-front exemestane treatment did shown a significant activity in the elderly patients with an acceptable toxicity profile.

Patients and methods: Elderly women over 85, with known and unknown ER and PgR status breast carcinoma were treated as palliative care with exemestane. Responses were assessed every 12 weeks by clinical and laboratory follow-up. It was scheduled a switch of exemestane at disease progression.

Results: Between February 2012 and April 2015, a total of 9 women over 85 year's, with advanced, never treated breast cancer, started exemestane palliative treatment. The treatment of the patients is still going on, getting a good patients outcome. Significant clinical responses: disease stabilization and prolonged stable disease were observed. Moreover, it has been observed a significant blood level cancer marker Ca 15-3 decrease ($P < 0.05$). No severe toxicities were encountered.

Conclusions: These data confirm a hight exemestane efficacy in the elderly women subsetting, over 85 year's, with known and unknown ER and PgR status breast carcinoma, an alternative, which avoids exposure to Tamoxifene.

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A75 Acupuncture for the treatment of arthralgia related to adjuvant aromatase inhibitor therapy in postmenopausal breast cancer patients

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Purpose: Aromatase inhibitors (AIs) are the standard of care for adjuvant treatment of postmenopausal, hormone sensitive breast cancer. However, up to half of women on AIs therapy experience arthralgia which may lead to early discontinuation of this effective therapy or to reduction of quality of life. The management of arthralgia is not yet defined in clinical practice. We conduced a pilot study to evaluate the safety and efficacy of acupuncture for AIs-symptoms management.

Patients and methods: Postmenopausal patients (pts) with early breast cancer experiencing arthralgia attributable to AIs were enrolled to receive Yamamoto New Scalp Acupuncture (YNSA) twice weekly for 3 weeks and once for the next three weeks. We evaluated changes in Brief Pain Inventory-Short Form (BPI-SF), Health Assessment Questionnaire Disability Index (HAQ), Pain Visual Analog Scale (VAS) stiffness, Functional Assessment of Cancer Therapy-General (FACT-G) quality of life measure and after 3 and 6 weeks of acupuncture compared to baseline. We also evaluated the possible reduction in the use of anti-inflammatory medication the end of the treatment.

Results: We enrolled 27 pts (26 evaluable). The median age was 61 (range 50-78) and the median time since menopause were 10,3. At the beginning of the treatment, 20 pts reported taking nonsteroidal anti-inflammatory drugs for pain relief. From baseline to the end of treatment, patients reported improvement in the mean BPI-SF worst pain score (7,26 to 3,85, p = 0,0001), pain severity (5,77 to 2,88, p = 0,0001), pain-related functional interference (4,82 to 2,82, p = 0,0001), in the mean HAQ score (0,95 to 0,62, p = 0,002), in the mean VAS score stiffness (71,52 to 30,59 p = 0,0001) and in the mean FACT-G physical (19,56 to 23,19, p = 0,03) and emotional well-being score (16,29 to 19, p = 0,031). Twenty pts (77%) reported the use of nonsteroidal anti-inflammatory drugs for pain relief at baseline. At the end of treatment only 11 of them (42%)

continued to use pain relief.The acupuncture intervention was well-tolerated and no adverse events were reported.

Conclusions: All pts had a significant improvement in AIs related join pain and stiffness. Our study suggests that acupuncture may be an effective intervention in treating AIs-related arthralgia and may play an important role in reducing discomfort from this common side effect. We will conduct a larger study with an adequate follow-up to confirm these results and to determine the duration of the benefit.

A76 Homeopathy in the treatment of menopausal symptoms in patients with early breast cancer

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Background: Menopausal symptoms are a frequent problem for breast cancer survivors, resulting from several treatment options that can induce an estrogen deprivation state. Since hormone replacement therapy in these patients is not recommended and the efficacy of non-hormonal therapies is still unclear, the aim of this study was to evaluate the efficacy of a homeopathic treatment to relieve menopausal symptoms in patients with a history of non metastatic breast cancer.

Study design: The study was carried out between 2005 and 2011 in a single centre and was conducted in two steps: a phase II pilot study, where ten patients received a homeopathic treatment for three months (phase A) followed by a phase III randomised study, where 35 patients received either homeopathic treatment or placebo for six months (phase B). Women with a history of breast cancer, without metastatic disease, suffering from menopausal symptoms were included in the study. A 5-point numerical scale was used to evaluate the severity of the menopausal symptoms. The sum of the scores (total score) at baseline and after 3 months (phase A) or 6 months (phase B) were compared.

Results: In the pilot study (phase A) we observed a mean reduction in the total score of 2.27 (SD + /-0.59) and a statistically significant reduction of the severity of hot flashes ($p = 0.01$), vaginal dryness ($p = 0.027$) and headache ($p = 0.015$). In the placebo controlled study (phase B) we observed a statistically significant difference in favour of the homeopathic treatment for night sweats ($p = 0.0097$), gastric symptoms ($p = 0.039$) and for the total score ($p = 0.018$).

Conclusions: According to the results, this homeopathic treatment showed a significant effect on some menopausal symptoms compared with placebo and can be considered as a safe and valid option for the treatment of menopausal symptoms in breast cancer survivors.

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Session B. Melanoma and skin cancer

B01* Negative influence of Melanocortin-1 receptor (MC1R) polymorphisms on clinical outcomes of metastatic melanoma (MM) patients (pts) harboring BRAF mutation and treated with BRAF inhibitors (BRAFi)

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Background: In the pigmentation of hair and skin a key role is played by MC1R gene whose inherited variations encoding for a non-functional receptor are linked with melanoma risk. MC1R also mediates cell signals regulating DNA repair, survival and migration of melanoma. MC1R status does not seem to affect melanoma histology while its association with BRAF V600 mutation and pts survival are still debated. Our aim was to evaluate the effect of MC1R variants on outcomes of BRAF V600 pts treated with BRAFi considering that no data are available.

Patients and methods: Fifty-three pts treated with BRAFi (vemurafenib 46, dabrafenib 7) were studied. We divided pts in 2 groups according to MC1R status (wild type, 21 pts *vs* minor/major functional variants, 32 pts). BRAF and MC1R status was evaluated by sequencing methods on tumor tissue and peripheral blood samples, respectively. Baseline characteristics of pts and disease (age, sex, M stage, number and site of metastases, site of progression), overall survival (OS), overall response rate (ORR) and progression free survival (PFS) under BRAFi were compared between the 2 groups. MAPK pathway activation was also studied by measuring p/ERK and p/p38 levels in 2 representative BRAF V600 mutated melanoma cell lines (MBA72, Hmel-1) with different MC1R status (wt and presence of variants) in order to reproduce *in vitro* the features of the two pts groups.

Results: Baseline evaluation revealed a significant association between the presence of bone metastases and MC1R polymorphisms (p 0.0172). Moreover, the presence of MC1R variants was significantly associated with a worst outcomes under BRAFi in term of both ORR and median PFS (respectively 59% *vs* 95% [p 0.018 Ods Ratio 9.980] and 5 months *vs* 8 months [p 0.017Hazard Ratio 2.107] in MC1R variant *vs* wt). No significant difference was found in OS probably owing the influence of prior or subsequent treatments on this outcome. Data *in vitro* demonstrated high levels of p-Erk1/2 in both cell lines but significant higher levels in activation of p38 MAPK was found in MC1R variants**.**

Conclusions: These data demonstrated for the first time that MC1R variants have detrimental effects on clinical outcomes of pts treated with BRAFi by increasing the state of the hyperactivation of MAPK pathway. These evidences could shed further light on BRAFi resistance and suggest new therapeutic targets for MM.

B02* There is a difference of vitamin D receptor gene (VDR) single-nucleotide polymorphisms (SNPs) frequencies between malignant melanoma patients and healthy volunteers and by sex?

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Background: Malignant melanoma is notoriously heterogeneous neoplasm with deep difference in clinical and morphologic features and molecular profiling. Female melanoma patients generally exhibit longer survival than male patients. To improve our understanding of the melanoma molecular biology, we evaluated the role of gender on outcome. Then we compared the genomic DNA of a subgroup melanoma patients with that of healthy volunteers to analyze the role of *VDR* SNPs on the risk to develop malignant melanoma shared by sex.

Patients and methods: Firstly we included 1,023 patients treated between 1987 and 2014. Disease free survival (DFS) and overall survival (OS) were estimated with the Kaplan-Meier method. A Cox regression model was used for univariate and multivariate analyses. In a second step the genomic DNA of 190 subgroup subjects was extracted from blood samples. We selected *VDR* SNPs rs2228570A > G (FokI), rs1544410C > T (Bsm1) and rs731236A > G (TaqI). SNPs were determined by Real-Time PCR using TaqMan assays.

Results: Male/female (M/F) ratio was: 47.6%/52.4%. According to stage of disease at initial diagnosis, we showed a significant difference in DFS and in OS in favour of females in stage I (median DFS (mDFS) and median OS (mOS) not reached $p = 0.001$ and $p = 0.01$ respectively) and in stage II (mDFS= M/F: 4/12 months, $p = 0.02$; mOS= M/F: 7/16 months, $p = 0.009$). Furthermore women had a significant improvement in 12-year DFS and 12-year OS adjusted for Breslow thickness, ulceration, "absent" and "non brisk" tumor-infiltrating lymphocytes. Then the second phase of the study counted 190 subjects: 139 healthy volunteers (M/F= 61/78) and 51 melanoma patients (M/F= 30/21). We observed a major frequency of *VDR* rs2228570A in male patients and in female healthy volunteers and then *VDR* rs2228570G showed a higher expression in male healthy volunteers than in female patients. We noticed no differences between males and females in the frequency of the other SNPs examined.

Conclusions: Our results showed that women present a better outcome if compared with men after adjusting for those variables that can reduce mortality risk in female melanoma patients. Furthermore males and females probably possessed a different *VDR* polymorphisms frequency that could become the object of further investigations. Then we are collecting blood samples from metastatic patients to evaluate differences of frequency of SNPs shared by sex. These results will be available at the forthcoming AIOM congress.

B03 Sequential combination of low dose chemo-modulating Temozolomide and Fotemustine in metastatic melanoma: clinical and molecular evaluation

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Introduction: The role of chemotherapy in the management of metastatic melanoma (MM) is still controversial due to the availability of targeted and immuno-based therapies. However, the majority of patients relapsed after few months and then other therapeutic options are needed. Temozolomide (TMZ), an oral alkylating agent, and the nitrosurea fotemustine (FM) are two active chemotherapeutic agents in MM. At the biological level, TMZ activity is due to its ability to form alkyl adducts with DNA, which are repaired by MGMT. Base Excision Repair (BER) has an important role in repairing chemically damaged bases (deamination, oxydation or alkylation). For this reason, BER has having an emerging role in enhancing the cytotoxicity of DNA damaging agents. The present study aimed: 1. to evaluate the efficacy and safety of sequential full doses FM preceded by low doses of chemo-modulating TMZ; 2. to analyze molecular parameters involved in the response as MGMT methylation status and expression of some BER pathway genes (APE1, XRCC1, PARP1).

Materials and methods: Sixty nine patients were enrolled. We used oral TMZ 100 mg/m2 on days 1 and 2; FM iv 100 mg/m2 on day 2, 4 hours after TMZ. The regimen was repeated every 3 weeks up to of 9 cycles. The analysis of MGMT methylation status and BER gene expression was performed in a subset of 14 patients.

Results: The overall response rate was 30.3% including 3 complete and 18 partial responses. A stable disease was further obtained in 20.2%. The toxicity profile was acceptable and easy manageable. Moreover, we reported a median PFS of 6 months and a median OS of 10 months. No correlation between MGMT methylation status and clinical response was found; while, interestingly, mean expression levels of the BER genes showed an association with PFS. In particular, we found that the mean expression level of APE1, XRCC1 and PARP1 genes was higher in patients who did not respond to therapy. Furthermore, patients with downregulation of the 3 genes showed a longer median PFS.

Conclusion: A sequential combination of low dose TMZ and full dose FM demonstrated a high activity with an acceptable and manageable toxicity. Thus, this

schedule could represent a good alternative for patients not eligible for novel therapies or who failed previous therapies. Moreover, preliminary results on BER pathway components suggest their role in melanoma treatment, both as predictive biomarkers and as molecular targets in order to enhance current therapeutic settings.

B04 Primary cutaneous melanoma in elderly patients: analyses and considerations from a retrospective observational study

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Background: Cutaneous melanoma is an immunogenic cancer and the interaction of the aging immune system with melanoma could have an important effect on the biologic behaviour of this disease. Compared with younger patients (pts), primary cutaneous melanoma observed in elderly pts tend to be thicker, more often ulcerated and usually exhibit an increased mitotic activity. Tumor infiltrating lymphocytes (TILs) is a potential marker of effective host immunological response to the tumor. The aim of the study is to evaluate pathological features, including TILs, and lymph node status of primary cutaneous melanoma in elderly pts.

Patients and methods: The study analyzed 96 consecutive cases of early melanoma occurred in pts aged 65 years or older at the time of diagnosis. The series included cases observed between Jan 2010 and Mar 2014 at the Department of Oncology of Udine. We tested the association of TILs and other pathological data with disease-free survival (DFS).

Results: Among 96 elderly pts, 39 (41%) were female and 57 (59%) were male pts. The median age was 74 years (65-89 years). Concerning pathological characteristics of primary cutaneous melanoma, median thickness was 2 mm, the ulceration was present in 39 (42%) melanomas and number of mitosis was lower than 1 in 16 (17%). TILs grade, classified as Brisk, No Brisk, TILs Absent were found in 12 (13%), 47 (49%) and 37 (38%) cases, respectively. Overall, 79 pts (82%) underwent lymphatic mapping and sentinel lymph node (SLN) biopsy; among them, 63 pts (80%) presented negative SLN. TILs grade was not associated to SLN status. Only 6 pts underwent a lymph node dissection for clinical evidence of regional lymph node involvement at diagnosis. With a median follow-up of 36 months, 26 pts (27%) developed recurrence. No visceral recurrence (skin and nodes) occurred in 19 pts (20%), whereas 7 patients (8%) had visceral recurrence. DFS was not associated to TILs grade. However, primary melanomas with no TILs were associated with a trend of worse DFS, the median DFS was 50.8 months versus not reached (p = 0.089).

Conclusions: TILs grade was not associated with other pathological features and lymph nodes status in elderly pts with early melanoma. A considerable number of elderly pts underwent SLN biopsy, an important staging step for clinical decision making process. DFS seems not to be associated with TILs grade, although pts with a diagnosis of early melanoma with absence of TILS tended to present worse DFS.

B05 Lenalidomide exerts cytostatic activity on melanoma cells by negative regulation of their cell cycle

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Background: Recurrence free survival in patients with metastatic melanoma (MM) is recently improved by targeted and immunotherapy regimens although the prognosis remains poor and requires further therapeutic efforts. Lenalidomide (Len) is an immunomodulant drug (IMiD) showing anti-inflammatory and anti-tumor properties in hematologic disorders as well as safety and tolerability in phase 2/3 clinical trials in MM. In addition it exerts anti-angiogenic effect once combined to sorafenib in the human ocular melanoma xenograft model. While it has been demonstrated that Len activates CD28 checkpoint expressed by T cells that drives the NF-kB activation downstream p21 cell cycle regulator and increases the T cell cytotoxicity by overcoming the inhibitory effect of CTLA4. Therefore, this research is aimed to investigate the potential role of Len in melanoma.

Materials and methods: Three melanoma cell lines (A375, SKMEL28, WN266) were cultured for 24 hours in serum free medium to synchronize the cell cycle phases and then in complete medium supplemented with Len at different concentrations from 0.01 to 100 μM. A standard curve of cytotoxicity was completed to measure the IC^{50} whereas both viability and proliferation of melanoma cells was evaluated by MTT assay. The effect of Len on the cycle phases was investigated by measuring the DNA content by flow-cytometry after cell staining with propidium iodide (PI). Finally, real-time PCR explored the gene expression levels of *p21*.

Results: Melanoma cells showed a 3-fold decrease of their proliferation extent by Len at 10 μM (640 ± 30 OD vs 1.915 ± 15 OD, p<0.05). However, the majority of cells were viable (>91%) although frozen at the G0-G1 phase of the cell-cycle (64 ± 10%) with respect to untreated cells (38 ± 4.6%). Percentage number of apoptotic cells was apparently similar (Len-treated: 0.7 ± 0.02 vs untreated: 1.7 ± 0.04%) as well as those undergoing to the S and G2-M phases (Len-treated: 35 ± 3 vs untreated: 60 ± 2%). Len-treated melanoma cells resulted up-regulated in *p21* RNA content.

Conclusions: In agreement with the antiproliferative activity on multiple myeloma cells, Len exerts cytostatic effect in melanoma cell lines through *p21* up-regulation and potential CDK4/6 modulation. This provides the rationale for planning further pre-clinical investigations with IMiDs in combination with CDK4/6 inhibitors in MM.

B06 Isolated limb infusion chemotherapy with or without hemofiltration for recurrent limb melanoma

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Aim: To better define the efficacy and the safety of intra-arterial infusion performed with or without hemofiltration for recurrent limb melanoma.

Methods: Patients with the following characteristics were included in the study: recurrent limb melanoma not indicated for surgical resection, measurable disease in the extremity, >18 years, performances status (ECOG) was 0-1 and life expectancy of at least 6 months. Twenty nine consecutive patients were enrolled in the study. Patients underwent fluoroscopic placement of angiographic arterial and venous catheters to infuse the drug in the artery (isolated limb infusion, ILI), and to stop the out flow (venous). Melphalan was rapidly infused into the isolated limb via the arterial catheter after the inflation of venous balloon catheter. Then the circulation of the limb was completely blocked with a pneumatic cuff at the root of the limb. Haemofiltration (HF) was available only in the main center, and was performed with an extracorporeal perfusion system, in order to reduce high systemic toxic peaks of drug.

Results: Thirty seven ILI were done in 29 cases (31 ILI-HF and 6 ILI) between 2001 and 2014 at Ancona and Pesaro Hospitals, Italy. Clinical outcomes were monitored 30 days aftertreatment. Eleven patients (38%) received infusion of melphalan alone, 7 (24%) melphalan associated to mitomicin C and 7 (24%) melphalan associated to cisplatin, the remaining 4 were treated with cisplatin, melphalan and epirubicin or cisplatin and mitomicin C.The overall response rate was 66%, in particular, 3 patients (10%) were complete responders and 16 (56%) were partial responders; whereas 7 patients (24%) had stable disease, and 3 (10%) showed progressive disease. Limb toxicity was assessed adopting Wieberdink scale, with evidence of 90% of low grade (I and II) toxicity.

Conclusion: ILI-HF and ILI are effective and safe treatments for recurrent non-resectable limb melanoma. They presentevidence of favorable clinical benefit and is effective in delaying progression.

B07 Effect of nivolumab (NIVO) on quality of life (QoL) in patients (pts) with treatment-naïve advanced melanoma (MEL): results of a phase III study (CheckMate 066)

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Background: While treatments exist that extend survival in advanced MEL, the quality of that survival is not often evaluated. There is a need for treatments that demonstrate increased survival while preserving long-term QoL. In a phase III, randomized,

double-blind study, NIVO (a PD-1 immune checkpoint inhibitor; 3 mg/kg every 2 weeks [wks; Q2W]) improved overall survival compared with dacarbazine (DTIC; 1,000 mg/m2 Q3W) in treatment-naïve pts with advanced MEL.

Methods: In this study, QoL measured by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and the EuroQol-five dimension questionnaire (EQ-5D) was evaluated at baseline (BL) and at treatment cycles Q6W. Mean changes and non-parametric comparisons are reported. Further analyses are planned to examine longitudinal QoL and the relationship between clinical and pt outcomes.

Results: A total of 418 pts were randomized to NIVO (n = 210) or DTIC (n = 208). Adjusted completion rates at BL for EQ-5D utilities were 69.5% with NIVO and 64.9% with DTIC, and those for EORTC QLQ-C30 were 70.0% with NIVO and 64.9% with DTIC. While rates remained similar throughout the study, analysis of QoL involving DTIC was not feasible after wk 13 due to a high attrition rate in the DTIC arm ($n \leq 41$). Mean BL QoL scores were similar for NIVO versus DTIC (EQ-5D utilities: 0.778 vs 0.711; EQ-5D visual analog scale [VAS] scores: 70.9 vs 69.1; EORTC Global Health: 68.9 vs 66.2). No QoL change was noted for DTIC prior to study dropout. For NIVO, improvements from BL were noted in EQ-5D utilities from wk 7 (0.027; n = 132; P = 0.011) through wk 49 (0.045; n = 38; P = 0.034), and in EQ-5D VAS scores at wks 25, 31, 37, 49 and 61 ($P \leq 0.03$). EORTC subscale scores did not change over time.

Conclusions: These results demonstrate that NIVO does not impair QoL and may enhance it compared with BL, while also conferring survival benefits, in treatment-naïve pts with advanced MEL. Dropout rates in DTIC after wk 13 limited QoL data interpretation for this treatment group.

B08 CheckMate 067: a phase III randomized double-blind study of nivolumab (NIVO) monotherapy or NIVO combined with ipilimumab (IPI) versus IPI monotherapy in previously untreated patients (pts) with advanced melanoma (MEL)

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Background: Results from a phase I study in MEL pts suggested complementary clinical activity between NIVO (a programmed death-1 [PD-1] immune checkpoint inhibitor) and IPI (a cytotoxic T lymphocyte antigen-4 [CTLA-4] checkpoint inhibitor), and was used to determine the combination dosing for phase III trials. Combination treatment resulted in a higher frequency of pts with tumor volume reduction and unprecedented rates of 1-yr survival (94%) compared with data from other NIVO (73%) or IPI (47%) trials in a similar population. The combination resulted in a safety profile with similar types of adverse events (AEs) as IPI alone, albeit a greater frequency in some cases. This phase III double-blind study evaluates the contribution of monotherapy components to the combination activity and safety, in order to best characterize this regimen in pts with either BRAF wild-type or V600 mutation-positive advanced MEL.

Methods: The co-primary endpoints are PFS and OS in the NIVO + IPI combination group or NIVO alone compared with IPI. Secondary objectives include objective response rate (ORR) and PD ligand-1 (PD-L1) expression correlated with efficacy outcomes. Treatment-naïve pts (N = 945) with metastatic or unresectable MEL were randomized 1:1:1 to receive NIVO 3 mg/kg every 2 weeks (Q2W) + IPI placebo (PBO) Q3W, or NIVO 1 mg/kg Q2W combined with IPI 3 mg/kg Q3W for 4 doses followed by NIVO 3 mg/kg Q2W, or IPI 3 mg/kg Q3W + NIVO PBO Q2W for a total of 4 doses followed by NIVO PBO Q2W until progression or unacceptable toxicity. Pts were stratified by PD-L1 status, BRAF status and M Stage. Tumor assessments first occurred at 12 weeks after randomization, Q6W for 49 weeks and Q12W thereafter. The co-primary endpoint of PFS will be reported with a median follow-up greater than 12 months based on a planned data analysis in early March 2015. Additional endpoints will include ORR, duration of response, tumor burden reduction and PD-L1 correlation with efficacy across prospectively defined pt subgroups. Safety will be reported in all treated pts and will include the incidence and resolution of select AEs.

B09 Efficacy and safety of single agent pan-HER inhibitor Dacomitinib in the treatment of unresectable or metastatic skin squamous cell cancer – Trial in progress

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Background: Squamous cell cancers (SCCs) of the skin are showing an increased incidence in recent years. Prognosis is generally favorable, except for a small percentage recurrent cases not amenable of surgery or radiation, or in case of distant metastasis. Chemotherapy is till now the elective treatment for the recurrent and or metastatic disease. However, clinical response is limited, underlining the medical need for new therapies.

Methods: This is an Investigator Initiated phase II, multicenter study with Dacomitinib, a pan-HER inhibitor, in unresectable or metastatic skin SCC. Forty-three patients with histological diagnosis of skin SCC not amenable to surgical treatment with curative purposes or with clinical contraindication to surgery can be enrolled in the study over two years. Patients should not have previously treated with tyrosine kinase inhibitors or monoclonal antibodies anti-EGFR. Enrolled patients will assume Dacomitinib 30mg/day for the first 2 weeks. If the highest skin toxicity will be lower than grade 2 according to CTCAE v4.0, patients will start Dacomitinib at 45mg/day. Tumor evaluation will be performed every two cycles according to RECIST 1.1. Patients will continue to assume study drug until disease progression, toxicity or any medical condition that will suggest to stop treatment. Tumoral tissue samples will be also collected for those patients who will consent, in order to conduct translational projects aiming at detecting molecular targets able to predict response to treatment and improve treatment strategies. Response rate, disease control, progression free survival and overall survival will evaluated as well as the percentage of patients initially not considered for surgery due to difficulty to obtain a curative treatment that undergo surgery after Dacomitinib.

Results: The trial started in November 2014 and it has already enrolled 10 patients as of April 2015.

Conclusions: Primary hypothesis is that Dacomitinib is more effective than standard chemotherapy treatments. tudy drug will be considered worth for further evaluations if response rate (RR) is at least 45%, with an increase of 17% respect to previous study with cetuximab in the same disease setting, which showed 28% RR.

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Session C. Sarcoma

C01* Randomized phase III trial of regorafenib in patients (pts) with metastatic and/or unresectable gastrointestinal stromal tumor (GIST) progressing despite prior treatment with at least imatinib (IM) and sunitinib (SU): GRID trial

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Background: Oral multikinase inhibitor regorafenib (REG) demonstrated substantial activity in a phase II trial in pts with GIST after failure of both IM and SU (*J Clin Oncol.* 2011; 29:606s; abstr 10007). This phase III, randomized, double-blind, placebo-controlled trial evaluated the efficacy and safety of REG for this unmet clinical need.

Methods: Eligible pts had metastatic and/or unresectable GIST, objective failure of both prior IM and SU (progressive disease [PD] on, or intolerance to, IM and PD on SU), ≥1 measurable lesion, ECOG performance status 0 or 1. Pts were randomized 2:1 to receive best supportive care plus either REG 160 mg po once daily (3 wks on/1 wk off) or placebo (PL). The primary endpoint was progression-free survival (PFS) (modified RECIST 1.1, independent central review). Secondary endpoints included overall survival (OS), disease control rate (DCR, defined as rate of partial response [PR] plus stable disease [SD] lasting for ≥12 wks), response rate and duration, safety and correlative genotype analyses. At time of PD, pts were eligible for unblinding and crossover to open-label REG.

Results: Between Jan and Aug of 2011, 234 pts were screened; 199 were randomized (REG: 133, PL: 66). Pts were stratified at randomization according to number of prior systemic therapies and geographical region. Baseline characteristics were balanced between the two arms. The primary endpoint was met: median PFS was 4.8 months for REG vs. 0.9 months for PL. Hazard ratio for PFS was 0.27 (95% CI, 0.18-0.39), $p < 0.0001$. PFS rates at 3 and 6 months were 60% and 38% for REG vs. 11% and 0% for PL. DCR was 53% (REG) vs. 9% (PL). The HR for OS was 0.77 ($p = 0.20$) with 85% PL pts having crossed over to REG. The most common > grade 3 treatment-emergent AEs in the REG arm during double-blind study were hypertension (28%), hand-foot skin reaction (21%), and diarrhea (8%).

Conclusions: This randomized trial demonstrated that REG significantly improved PFS and DCR in pts with advanced GIST after failure of at least prior IM and SU. REG was well tolerated, with AEs as expected for this class and manageable with dose.

C02 High-grade bone sarcomas with synchronous metastases in patients older than 40. Results of the European Bone over 40: Sarcoma Study (EURO.B.O.S.S.)

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Background: European Bone over 40 Sarcoma Study (EURO.B.O.S.S.) is an European prospective intergroup collaboration for the study of patients older than 40 years with high-grade (HG) bone sarcomas. The results obtained in patients with metastatic disease at diagnosis are here presented.

Methods: Patients with HG Osteosarcoma (OS), HG sarcoma (HGS), Leyomiosarcoma (L), Dedifferentiated chondrosarcoma (DCh), were included into the study. An intensive chemotherapy protocol with cisplatinum, doxorubicin, ifosfamide ± methotrexate combined to surgery was offered to the patients.

Results: Amongst 422 evaluable patients who entered EURO.B.O.S.S., 122 (29%) had metastases at diagnosis, 51 female and 71 male, median age 53 years (41-65). The Lung was the most common site of metastases (86% of patients), skeletal involvement was reported in 26%, 15% had other sites of metastases. The incidence of synchronous metastases differed according to histology (DCh 40%, OS 30%, HGS (22%, L 5%, $p = 0.02$), site (spine 57%, pelvis 41%, humerus 35%, femur 27%, other 23%, maxillofacial 11%, $p< 0.02$), LDH (high 41%, normal 21%, $p = 0.001$) serum alkaline phosphatase (SAP) (high 41%, normal 23%, $p = 0.005$). One toxic death was recorded, 20% of patients had febrile neutropenia, renal toxicity grade 1 to 3 was observed in 26% of patients, neurotoxicity grade 1- to 3 in 16%. Overall survival at 3 and 5 years was 36% (95%CI 24%-47%) and 26% (95%CI 13%-38%), respectively. 5-y OS was 46% (95%CI 21%-72%) in case of surgical complete remission (SCR) and 8% (95%CI 0-21) in patients without SCR ($p = 0.001$). Survival did not correlate with gender, histology and SAP, but it was influenced by metastatic pattern [5-y OS: Lung only 30% (95%CI 14%-45%), bone only 29% (95%CI 0-63%), multiple sites 14% (95%CI 0-30%)], site of primary (5-y OS: spine 0, pelvis 8% (95%CI 0-23%), humerus 0, femur 47% (95%CI 24-69%), other 33% (95%CI 0-87%), maxillofacial 67% (95%CI 13-100%), and LDH (5-y OS: High 0, normal 41% (24%-58%).

Conclusions: Site of primary, histology, SAP and LDH levels correlate with the incidence of metastases at diagnosis Primary tumor site, metastatic pattern and LDH levels are significant prognostic factors. About 25% of patients older than40 with metastatic bone sarcomas can be long term survivors thanks to an aggressive strategy of treatment. Any attempt must be done to achieve surgical complete remission.

C03 Into the Wild of long non-coding RNAs in Gastrointestinal Stromal Tumors (GISTs) to explore new prognostic/predictive biomarkers

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Background: Long Non-coding RNAs (lncRNA) are emerging as essential regulators of genetic and epigenetic networks, and their deregulation may underlie complex diseases, such as carcinogenesis. Several studies have described lncRNAs alterations in patients with solid tumors. In particular, in Gastrointestinal Stromal Tumors (GIST), upregulation of HOTAIR has been associated with aggressiveness, metastasis, and poor patients' survival. In order to gain more detailed insight on the molecular role of lncRNAs in GIST, we analyzed *in vivo* the expression levels of lncRNAs H19 and MALAT1 in surgically resected patients.

Material and methods: The expression of the lnc-RNAs H19 and MALAT1 was evaluated in primary tumor tissue from 20 GIST patients undergoing surgical

resection, and paired normal mucosa samples, using quantitative real-time reverse transcriptase qRT-PCR. The result was considered reliable if the tumor tissue harboured at least 70% of cancer cells.

Results: H19 was evaluable in 20 patients, MALAT 1 in 8 patients. H19 was overexpressed in 66% (12/20) cancer tissue from GIST patients, and the difference of expression between the two groups (tumor tissue vs normal tissue) was found to be statistically significant (P= 0.0496). MALAT1 was overexpressed also in 100% (8/8) cancer tissue from GIST patients.

Conclusions: H19 and MALAT1 appear frequently upregulated in GIST patients. Further analyses are needed to confirm these data, and evaluate the potential role of such lncRNAs, as prognostic/predictive biomarkers.

C04 The DOG1 scoring system in GIST: a novel factor for measurement of the recurrence risk

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Background: DOG1 is a membrane protein expressed with high sensitivity and specificity by GIST. This protein controls the proliferation of malignant cells through downstream signals triggering both RAS/RAF/MEK/ERK and insulin-like growth factor pathways. However, its role has been limited to the diagnosis of CD117$^-$ GIST and never correlated with other risk factors. Here we explored the potential prognostic role of DOG1 based on its variable expression intensity to be correlated with other risk factors of recurrence.

Material and methods: We collected demographic, histological, immunohistochemical (IHC) features and mutational status of 59 patients with GIST. The expression of DOG1 was investigated by IHC and scored according to the Allred scoring system, based on staining intensity (scale: 0-3) and percentage of positive tumor cells (scale: 0-5), the sum of which provided the final score classified as negative (score 0), weak (score 1-3), moderate (score 4-6) or strong (score 7-8). Recurrence-free survival was calculated by Kaplan-Meier curve.

Results: DOG1 was positive in 39 (group A; 66%) and negative in 20 (group B; 34%) CD117$^+$ patients with cytoplasmic and/or membranaceous localization that resulted strong in 24 (A-1), moderate in 12 (A-2) and weak in 3 (A-3). DOG1 expression was not correlated with gender, age, primary site, histology and mitoses. By contrast, the mean tumor size from group A was higher (10.1 ± 5.8 cm) in comparison to B (4.7 ± 1.9 cm; $p < 0.001$) as well as the lower frequency of the wild-type (WT) (14.3% vs. 50%; $p = 0.009$). The cumulative RFS curve revealed that A had a worsened but not significant 2-year RFS rate (84.5%) compared to B (95%). Subgrouping patients from A in relation to Allred score, A-1 experienced the worse RFS (80.3%) compared to A-2 and A-3 as well as those of group B (93.5%). To further investigate the potential relationship of tumor size and mutational status with the grade of DOG1 expression, A-1 patients were divided by tumor size greater or lower than 5 cm. The 2year RFS rate was 66.2% and 100%, respectively ($p = 0.01$). Moreover, the 14 patients of group A-1, showing a tumor size >5 cm and any mutation, have a 2-year RFS rate of 57.7% with respect to WT (100%; $p = 0.16$).

Conclusions: DOG1 is a promising tool for diagnosis of CD117$^-$ GIST. Its variable expression, however, identifies patients with poor prognosis and thus, its measurement by Allred scoring system may integrate the current risk stratification systems for resected GIST.

C05 MicroRNA profiling in KIT and SDH mutated Gastrointestinal stromal tumor (GIST)

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Background: Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract. The molecular mechanism of GIST formation is among the best characterized of all human tumors. Activating mutations of the c-Kit-kinase (KIT), a member of the receptor tyrosine kinase III family, are present in 80% of GISTs. Gain-of-function mutations of platelet-derived growth factor receptor A (PDGFRA), a member of the same kinase family, are present in 35% of GISTs that lack KIT mutations. In a small subset of patients, the desease does not harbor any mutations on these receptors and is defined as wild type (WT). The gene expression profiling and SNP analysis are strongly different between WT and mutated cases. Up to now, really few data are available on microRNA in GIST. We studied the microRNA profiles in GIST correlated with kinase genotype. Material and methods: We analyzed the miRNA profile of 13 GIST tumor samples, of which nine carry either KIT or PDGFRA mutation, and 4 samples are from patients with a WT disease. Total RNA was labeled, hybridized to Agilent microRNA microarrays; differential microRNA were selected by a two-fold change cutoff and Benjamini and Hochberg-corrected unpaired t test results and discussion.

Results: The microRNA profile is different in WT and mutated GIST samples, with 56 microRNA differentially expressed at the 0.05 cutoff p-value. Mutated GIST show enrichment in microRNA targeting tumor suppressor genes, as TP53 and PTEN, but also tyrosine kinase receptors, in particular IGF1R. Indeed WT GISTs show a marked overexpression of IGF1R, not supported by gene amplification, that could be explained by the downregulation of specific microRNA, targeting these genes. Validation with single miRNa assays and the identification of the specific target are ongoing.

Conclusions: Mutated GIST have a different microRNA profile compared with WT patients. This difference needs to be more investigated in order to understand the biological role on the pathogenesis, clinical behavior and treatment responsiveness.

C06 PET-FDG as a predictor of efficacy of Sunitinib in patients with metastatic GIST, progressing after treatment of Imatinib 400 mg/day

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Background: Imatinib 400 mg/day is currently the standard treatment of I line in patients with metastatic GIST. In case of progression, administration of Imatinib high dose (800 mg/day) showed a short time to progression (TTP) and is not currently available a comparison study between Imatinib 800 and Sunitinib in this setting. Our aim is to analyze the validity of PET-FDG as a possible predictor of response to treatment with Sunitinib vs high-dose Imatinib in patients progressing at the standard dose of Imatinib.

Material and methods: 49 patients with metastatic GIST (21 women/28 men) were evaluated. All patients received a treatment of I line with Imatinib 400 mg/day, Imatinib 800 mg/day in II line and Sunitinib 37.5 mg/day in III line. We studied the correlation between the response to treatment in terms of TTP and the uptake or less of baseline FDG PET examination, at the diagnosis of metastatic disease. The patients were divided into two groups: Group1 = PET-FDG positive; Group 2 = PET-FDG negative.

Results: Our data show that in all three lines of treatment, the better clinical outcome in terms of TTP was observed in patients of Group 1 than patients of Group 2, that is, when there is an uptake on PET baseline than patients PET negative. This advantage (TTP higher) seems greater for patients who are treated with Sunitinib in III line compared to those treated with Imatinib 800 in II line. Analyzing the data by subgroups, that advantage of Sunitinib is observed mainly in patients with metastases peritoneal localization rather than liver. This is probably due to the greater propensity to angiogenesis of peritoneal metastases would suffer greater antiangiogenic effect of Sunitinib.

Conclusions: With data obtained would be possible to anticipate the treatment with Sunitinib in II line in patients with metastatic GIST PET positive with peritoneal metastases.

Table: C06

	TTP (months) Group 1 (PET-FDG positive)	TTP (months) Group 2 (PET-FDG negative)
Imatinib 400 mg/day I line	42,2	32,1
Imatinib 800 mg/day II line	7	8
Sunitinib 37.5 mg/day III line	11	5

C07 Soft tissue sarcoma after haematological malignancies in childhood/adolescence: a hospital series

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Background: Soft tissue sarcomas are rare neoplasms with a poor prognosis. The etiopathogenic role of previous radiation therapy (RT) is well established, whereas the role of previous chemotherapy (CT) is still unclear. We analyzed the outcome of patients with secondary soft tissue sarcoma treated in our Institution.

Patients and methods: We retrospectively collected histopathological type and treatment of both hematologic malignancies and secondary sarcomas for patients who developed a secondary soft tissue sarcoma after previous haematologic neoplasms from 2011 to 2014. Tumor response was evaluated according to RECIST criteria. Median overall survival (mOS) was defined as the interval between the diagnosis of sarcoma to death or last follow-up visit.

Results: We collected data from 5 patients with soft tissue sarcomas, 4/5 of tumors arised in the previous radiation fields. Regarding the type of haematologic neoplasm 3 cases were of Hodgkin disease, 1 case of Lymphoblastic Acute Leukemia T and 1 case of anaplastic non-Hodgkin lymphoma, developed at a median age of 18 years (range 3-19) and treated with CT and RT. Histopathological examination revealed 2 cases of high-grade leiomyosarcoma, 1 of abdominal clear-cell sarcoma, 1 high-grade undifferentiated sarcoma and 1 abdominal low grade fibromixoid sarcoma. Median interval between haematologic malignancies and the development of sarcoma was of 29 years (range 13-32). All patients had metastatic disease at diagnosis and received a median of two lines of CT (range 1-4), comprising different drugs, such as anthracyclines, ifosfamide, gemcitabine, taxanes, dacarbazine, trabectedine and pazopanib. mOS was 7 months (range 3-18). No response to CT was observed, except for a ten-months disease stabilization with high dose ifosfamide in one patient with leiomyosarcoma.

Conclusions: Sarcomas arising after haematologic malignancies are rare but have a very poor prognosis and response to chemotherapy. Radical surgery remains the only curative treatment, but most cases have a metastatic onset. Even if the predisposing role of previous RT is established, only a small percentage of patients treated with RT will develop a secondary sarcoma. In the future the possible role of mutations, in genes such as p53, should be investigated as a possible risk factor in this setting. A better identification of high risk patients may be useful for an early diagnosis and treatment of secondary sarcoma, aiming at improving survival.

C08 Pleuro-pulmonary synovial sarcoma: clinico-pathologic and molecular characteristics from a multi-institutional series of 48 cases

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Introduction: Synovial sarcoma (Sy-S) is a high grade malignant soft tissue tumor that commonly occurs in young adult extremities. Primary Sy-S of the thoracic region is rare, but pleura and lung represent the most common visceral sites. Sy-S may pose diagnostic difficulties at imaging, histology and immunohistochemical study, but the finding of the specific chromosomal translocation t(X;18) (p11.2;q11.2) is highly specific in challenging cases. Surgery (Su) with margin-free margins is the only curative therapy; chemotherapy (CT) and radiotherapy (RT) had little therapeutic effect; the prognosis is generally dismal. We collected a series of primary pleuro-pulmonary synovial sarcoma (PPSS) in order to detail on the main clinico-pathologic, molecular and prognostic features.

Materials and methods: 48 patients (pts) of primary PPSS were identified (routine practice/consultation files, 8 centers). Data on symptoms, imaging, histologic, immunohistochemistry and therapeutical features were collected. Molecular data of EGFR (exons 18-21),c-KIT (exons 9,11,13,17), BRAF (exon 15) and PDGFRsgene mutations by direct sequencing analysis were performed.

Results: N 48 pts were included: 29 male and 19 female, mean age at diagnosis 54 years (range, 16-86); 11 pts were smokers (23%); none had significant exposure to asbestos fibers. Chest pain was the most common symptom (67%). Left thoracic side was involved in 29 pts (60%), 16 pts showed multifocality (33%). At imaging, 33 (69%) appeared as lung tumors, 7 (14.5%) as mesothelioma. Diagnosis of Sy-S was performed in 33 cases (69%), 7 were recognized as sarcomas not otherwise specified, 3 as sarcomatoid mesotheliomas, 2 each of sarcomatoid carcinoma and malignant solitary fibrous tumor and 1 fibrosarcoma. 38 pts (79%) showed a monophasic histology. Half of pts received Su alone, 13 pts CT alone (27%), 8 Su + CT (17%), 2 pts CRT (4%) and 1 RT alone (2%). 31 pts recurred, 33 died of disease; median follow up was 21 months (range, 1-110). Molecular evidence of t(X;18) involving SYT-SSX fusion gene was performed in all pts (44 by FISH and 4 by RT-PCR). No mutations were detected in EGFR, BRAF, c-KIT and PDGFR-alpha and –beta genes. As expected, pts receiving Su and monophasic type had a significantly better survival ($p < 0.001$).

Conclusion: PPSS may mimic conventional tumors arising in this site. The prognosis is dismal and no targeted therapy is so far available. Surgical treatment and monophasic type are related to a better prognosis.

C09 Treatment of pulmonary artery sarcoma (PAS): a single center experience

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Background: Pulmonary artery sarcoma (PAS) is a rare tumor arising from the intimal or subintimal layer of the pulmonary artery wall. In most cases PAS presents with pulmonary hypertension (PI), mimicing a thromoboembolic disease. The therapeutic approach is mainly based on surgery, either pneumonectomy or pulmonary endarterectomy (PEA), whose feasibility depends on the extension of the disease and the patient's clinical condition. The prognosis reported in published series is very poor, with survival of 1.5 months without surgical resection and approximately 1 year in case of surgery.

Patients and methods: From October 2010 to April 2015, 10 pts referred to our hospital for symptoms of acute or chronic pulmonary thromboembolic disease, and radiological findings of PAS were considered eligible for PEA. Seven pts had PI, two with severe hemodynamic instability requiring emergency surgical treatment. Median age was 64.5 years (range 32-84); 6 pts were female. Most patients had a long history of symptoms due to pulmonary hypertension, having a median time from onset of symptoms and surgery, of 7.5 months (range 2-33). In 8 pts the disease was bilateral, and 3 had also lung metastases. In most cases (8 patients) the disease involved the main pulmonary artery.

Results: All pts underwent PEA, none having life-threatening complications from surgery. Pathology showed 5 high grade sarcoma. Following PEA and a short course of cardiopulmonary rehabilitation, 7 pts were able to received conventional chemotherapy (CT) with doxorubicin and ifosfamide, starting a median of 42 days (range 22-69) from surgery. Two pts also received radiotherapy after completion of the CT program. Four pts have died for disease progression at 6, 6, 8, and 26 months from surgery while 6 are still alive, three being disease free at 12, 19, and 41 months; three patients are still ongoing post-surgery treatment.

Conclusions: In pts with PAS a multimodal approach including PEA, CT and radiotherapy is feasible but it should be evaluated individually, according to the tumor extension and the patient's clinical condition. Other than improving quality of life mainly by reducing or delaying symptoms due to PI, it appears to considerably improve prognosis.

C10 Study of mutational status of Sicilian GISTs patients

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Background: Gastrointestinal Stromal Tumors (GISTs) are the most frequent mesenchymal tumors of the GI tract. The discovery of kinase mutations has changed the natural course of GISTs and the response to tyrosine kinase inhibitors is indeed determined by the type of mutation.

Table 1 : C10

Exon	Number and Mutation type
11	39 deletion 19 substitution 9 insertion 2 complex mutation
9	9 duplication 1 substitution 1 deletion
12	2 substitution 2 deletion
18	4 substitution 2 insertion

Table 2 : C10

	Our Study	Literature data
KIT (tot)	**69.5%**	**75%**
-Exon 11	58.5%	65%
-Exon 9	10%	8%
-Exon 13	1%	1%
PDGFRA (tot)	**8.5%**	**10%**
-Exon 12	3.5%	2%
-Exon 18	5%	8%
WT	22%	15%

Approximately 75% of all GISTs have c-KIT activating mutations, most frequently exon 11 (75%) and exon 9 (7-10%);10% have PDGFRA mutations (exon 12-14-18) and 15% do not have a detectable mutation in KIT or PDGFRA (wild-type). The aim of the study is to assess the mutational characteristics of a Sicilian GIST patient series and to compare it with literature data.

Material and methods: 152 patients, were followed from June 2008 to date in UOC of Oncology at the University Hospital of Palermo. Study population evaluable is composed by 118 patients. DNA from paraffin-embedded tumor tissue is obtained through the QIAmp DNA FFPE Tissue kit. Mutational analysis is obtained by Genetic Analyzer ABI 3130xl and data analysis are performed through Sequencing Analysis software v3.2.

Results: Of the 118 patients evaluated (39% women; 61% man), 82 patients have c-KIT mutations (69.5%), 10 patients have PDGFRa mutations (8.5%) and 26 patients are wild-type (22%). Among the series of c-KIT mutated patients we have identified 4 cases of LOH (Loss of Heterozigosity). The type of mutation found is shown in Table 1. The mutation frequency in different exons and the comparison with the data of the literature is specified in Table 2.

Conclusions: Our data show a frequency of KIT mutations lower than that reported in the literature (69.5% vs 75%); in particular it is less frequent mutation of exon 11 and appears slightly more frequently mutation of exon 9. Mutation rate in PDGFRa reflects data reported in literature. In our series the number of WT is higher and we are currently evaluating the presence of other alterations (e.g. BRAF, KRAS). The relative mutation type of PDGFRA and KIT genes is in line with other studies, with prevalence of deletions in KIT exon 11, and duplication in KIT exon 9.

C11 Diagnostic and therapeutic pathways in Head & Neck sarcomas (H&NS): an effective example of good clinical practice in Piedmontese Oncologic Network

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Background: H&N S commonly present as a painless submucosal or subcutaneous mass of undefined origin. H&NS represent <5% of Soft Tissue Sarcomas and 0,05% of total tumors in Italian population. Those tumors display a great variance in hystology, clinical presentation and prognosis. The anatomical position, the surgical approach, the importance of radiotherapy and rehabilitation strictly request a multidisciplinary approach. The Piedmontese Oncological Network since 2001 has created multidisciplinary groups to face in the most modern approach the problems in H&N S.

Patients and methods: Since 2002 we have organized multidisciplinary visits for patients with H&N S. Radiologists, Otolaryngologists, Pathologists, Radiotherapists, Oncologists and Nurses are the principal component of the group. Nutrition and Rehabilitation specialists are as the same component of the group but only in the last 8 years. In our series from 2002 to 2015 22 cases of H&NS were treated: 4 laringeal (3 pleomorphic, 1 rhabdomio), 4 maxilla and sinuses sarcomas (Undifferentiated), 3 Rhinopharingeal (2 undifferentiated 1 Fibros), 2 S. of the cheek (1 Leiomyo, 1 synovial), 1 hypopharingeal (Leiomyo), 3 Ewing S, 3 oral S (1Leiomyo, 1 undifferentiated, 1 epitheloid). All Patients were treated following a common DTAP including: anamnesis, clinical and physical exam, ORL exam, biopsy. After histology definition a multidisciplinary approach was done with two different approaches: immediate surgery followed by Radiotherapy ± chemotherapy (7 cases) or neoadjuvant therapy (CT ±RT) followed by surgery (11 cases). Four cases received exclusive RT + CT since no surgical approach was possible (2 Ewing, 1 Hypopharingeal, 1 Maxillary).

Results: 3 over 4 laryngeal S are alive and free from disease (at 4, 6, 10 years). 1 died from disease. 2 cheek S are alive and free from disease, only 1/4 of maxillary S is alive, none of hypopharingeal, 1/3 Ewing sarcoma is alive, 1 rhinopharynx is alive. Oral sarcomas had a good prognosis (3/3 alive but 1 with disease and currently in therapy). 50% survival with a median of 78 months is the result.

Conclusions: The multidisciplinary approach is fundamental in diagnosis and treatment of STS of H&N. Prognosis is determined by: anatomical position, grading and histology, radical intervention with free margins, expertise of the Otolaryngologist. Exclusive Radio- chemotherapeutic approach is not resolutive and all patients treated without surgical resection had a dismal prognosis.

C12 Safety and efficacy of gemcitabine plus prednisone for previously treated metastatic kaposi sarcoma: a monoistitutional experience

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Background: To evaluate outcomes in the use of single-agent Gemcitabine plus prednisone for the treatment of progressive Kaposi Sarcoma (KS). KS is an indolent pigmented mucocutaneous malignancy with several variant presentations and clinical courses. A wide variety of systemic chemotherapeutic agents have been efficacious in KS, both as single agents and as combination chemotherapy, including vincristine, bleomycin, anthracyclines, paclitaxel, etoposide and interferon. In metastatic setting liposome-encapsulated doxorubicin is the standard chemotherapy, with response rate up to 60-80% and durable remission of disease lasting for years are common. However a gold standard for therapy remains unclear. Progressive disease remains a challenge for the oncologist, but results are poor. Gemcitanine is an S-phase nucleoside anti-metabolite that has demonstrated activity in a variety of solid tumors, including sarcomas. The most common dose e schedule of this agent is 1.000 mg/m^2, given on day 1,8,15 of a 21 day cicle. The toxicity profile of gemcitabine is acceptable, with a dose-limiting toxicity of thrombocytopenia.

Material and methods: We collected and analysed data from four patients (pts) with KS who had previously failed first-line chemotherapy with liposome-encapsulated doxorubicin. The pts have been treated until disease progression or appearance of non -tolerable toxicity with Gemcitabine 1.000 mg/m^2, given on day 1,8,15 of a 28 day cicle and prednisone 25 mg orally twice daily starting on day 1 to reduce the related symptoms of disease and toxicity of chemotherapy.

Results: Baseline data, activity and toxicity are available in four patients. Patients with median age 75 years (range 71-87) were treated for a median of ten cycles (range 5-12) . All pts had skin metastases only. Out of four pts with measurable disease, 2 had complete response, 2 partial response, with clinical benefit (improvement in performance status, pain, pruritus). All pts are on treatment. The haematological toxicity was moderate with anemia G 2 in two pts. Additional non-haematological toxicities experienced include mild asthenia.

Conclusion: This work show that gemcitabime plus prednisone has promising activity and is safe in previously treated metastatic Kaposi Sarcoma, with both objective responses and clinical benefit observed in this care setting. This combination merits further investigation for pre-treated KS.

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Session D. Gynecologic cancer

D01* MITO (Multicentre Italian Trials in Ovarian cancer) - CERV 2 trial: a randomized phase II study of carboplatin and paclitaxel +/- cetuximab, in advanced and/or recurrent cervical cancer

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Background: Carboplatin (C) plus paclitaxel (P) is among standard options for treatment of advanced or recurrent cervical cancer (ARCC) patients (pts). Cervical cancer cells often express Epidermal Growth Factor receptor (EGFR). Cetuximab (CET), an anti-EGFR monoclonal antibody, can be safely combined with CP. MITO-CERV 2 is a comparative randomized phase 2 study, testing the addition of CET to CP.

Methods: ARCC pts, <2 previous chemotherapy, ECOG PS = 1, were randomized to CP (C AUC5 + P 175 mg/m^2, d1q21) for 6 cycles +/- CET (400 mg/m^2 one week before starting CP, then 250 mg/m^2 weekly) until disease progression or unacceptable toxicity. Primary endpoint was event-free survival (EFS), i.e. time from randomization to progression, death, definitive discontinuation of the whole treatment or loss to follow-up, whichever occurred first. With a 4.5 mos expected median EFS and a 6.4 mos auspicated EFS (HR 0.70), 0.20 one-tailed a and 80% power, 89 events were required for the final intent-to-treat analysis.

Results: 108 pts were randomly assigned to CP (n = 53) or to CP-CET (n = 55). Median age was 50, 69% were PS0, 76% had recurrent disease, 91% had distant metastasis and 57% had received previous chemotherapy. A median number of 6 CP cycles was given in both arms. After a median follow-up of 23 mos (95% CI:20-26), 102 pts had an event, 97 progressed and 61 died. Median EFS was 4.7 and 6.0 mos (one-tail p = 0.43), median PFS was 5.2 and 7.6 mos (one-tail p = 0.20) and median OS was 17.7 and 17 mos (one-tail p = 0.27), with CP and CP-CET, respectively. One patient died for a stroke during standard treatment. There was no difference in the occurrence of severe side-effects, except grade 3-4 skin toxicity reported only with CP-CET (8 cases, 6 with acneiform rash, p = 0.004). Out of 86 patients eligible for RECIST, objective response rate was 43% and 38% with CP and CP-CET respectively (p = 0.63).

Conclusion: The addition of CET to CP is not worthy of further investigation in unselected ARCC pts. Efforts are ongoing to retrospectively collect tumor samples for an exploratory biomarker analysis. ClinicalTrials.gov NCT00997009. Partially supported by Merck Serono.

D02 Feasibility and outcome of interval debulking surgery (IDS) after carboplatin-paclitaxel-bevacizumab (CPB): results from a subgroup of patient from the MITO-16A-MANGO OV2A phase 4 trial

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Background: Few data are available on the outcome of surgery after a bevacizumab-containing regimen. The MITO 16A- MANGO OV2A phase 4 trial evaluates the outcomes of first-line CPB in a clinical-practice-like setting. Here we present the results of the subgroup of patients undergoing IDS after neoadjuvant treatment or suboptimal primary surgery.

Methods: 400 patients aged ≥ 18 with untreated AOC, ECOG PS 0-2 were eligible to receive C (AUC 5 d1, q21) plus P (175mg/m^2 d1, q21) and B (15 mg/kg d1 q21) for 6 cycles followed by B maintenance until cycle 22nd within the MITO 16 trial.

Results: With data available at Dec 31, 2014, 79/400 patients (20%) underwent IDS; bevacizumab was omitted before IDS in 5 patients. In the remaining 74 patients, median age was 61.2, 72% had FIGO IIIC disease, 23% FIGO IV and 5% FIGO IIIB. 60 patients (82.3%) had a suboptimal (>1cm) primary surgery, while in 14 cases a neoadjuvant therapy was given after a biopsy with no attempt of resection. The median number of cycles before IDS was 3 (Interquartile range, IQR: 3-4) and 3 (IQR: 2-3) for chemotherapy and bevacizumab respectively, with a median interval between the last bevacizumab and the IDS of 38 days (IQR: 34-47). The median duration of the IDS was 3.5 hours (IQR: 2.8-5) and discharge of the patients was after a median of 7.5 days (IQR: 6-10). The outcome of IDS is unknown for 3 patients; 10 patients (12.7%) were suboptimally debulked, while the residual disease was absent or ≤1 cm in 61 patients (82.4%). After IDS there was no major adverse events. Fever complicated 4% of the interventions and 4% of the patients required blood transfusion after surgery. Surgical wound infection and/or dehiscence, pelvic abscess, intestinal sub-occlusion and fistula were experienced by one patient each.

Conclusions: In the MITO16A-MANGO OV2A phase 4 trial, combined chemotherapy and bevacizumab did not prevent IDS and the rate of perioperative complications was similar to what expected without bevacizumab. These data support the hypothesis that the opportunity to add bevacizumab to chemotherapy in first line treatment of ovarian cancer might not be denied to patients for whom IDS is planned.

D03 Role of targeted therapy in ovarian cancer treatment: a systematic review and meta-analysis of randomized trials

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Introduction: Ovarian cancer is the leading cause of death among gynaecological tumors. By results of several clinical trials, new gold-standard for the first line treatment is represented by the combination of carboplatin, paclitaxel and bevacizumab. In the era of personalized medicine, there is still uncertain on the impact of several targeted agents evaluated in the management of this disease. To clarify the weight of this class of agents in common clinical practice a meta-analysis was preformed.

Patients and methods: Clinical trials were selected by searching "Pubmed" database and abstracts from major cancer meetings within 2004-2014 time frame. Primary end point was overall survival (OS), secondary end-points were progression free survival (PFS) and response rate (RR). Hazard ratios (HRs) of OS and PFS, with confidence intervals, odds-ratios (ORs) of RR, and risk ratios of grade 3-4 toxicity rates, as presented in retrieved studies, were extracted and used for current analysis. Meta-analysis was carried out by the fixed effect and random effect.

Results: 36 randomized trials for a total of 13.395 patients were selected and included in the final analysis. In the targeted therapy arm a benefit in terms of OS (pooled HR: 0.91; 95%CI: 0.83-0.98; p = 0,016), particularly in second line of treatment (pooled HR: 0.88; 95%CI: 0.79-0.98) and in anti-angiogenetic agents (pooled HR: 0.86; 95%CI: 0.76-0.98), respectively, was observed. As far as platinum status setting, a significant advantage for targeted therapy in platinum-resistant subgroup (pooled HR: 0.86; 95% CI: 0.75-0.97) was also found. These data were confirmed in term of PFS and RR. Among toxicities, no difference was reported in the evaluated arms.

Conclusions: Targeted therapy improves survival in ovarian cancer patients. In particular we underlined the role of this important strategy in the platinum-resistant setting that represents the *pain in the neck* in ovarian cancer management.

D04 Evaluation of clinical and pathological features in patients with Lynch Syndrome-related Endometrial Cancer: a single centre experience

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Background: Endometrial carcinoma (EC) is a common gynaecological malignancy in Lynch syndrome (also known as Hereditary Non Polyposis Colorectal Cancer, HNPCC). HNPCC is caused by germline mutations in any of the MisMatch Repair (MMR) genes, even if mutations in MLH1, MSH2 and MSH6 account for almost 90% of identified defects. EC represents the second most common cancer type among HNPCC patients, following colorectal cancer, with an occurrence rate up to 60%. In contrast to colorectal cancer, data regarding clinical and pathologic characteristics of EC in HNPCC patients have not been studied in detail. The aim of our study was to evaluate clinical and pathologic features of EC in HNPCC patients.

Patients and methods: From 2003 to 2014, 31 EC patients were selected on the basis of Amsterdam or Revised Bethesda criteria to undergo genetic testing: direct sequencing of DNA and MLPA were used to examine the entire MLH1, MSH2 and MSH6 coding sequence. Enrolled patients were classified as mutation-positive or mutation-negative according to the genetic testing result. Patients who carried a Variants of Uncertain Significance (VUS) were excluded from the analysis, due to the uncertain role of this class of mutations.

Results: Among the 31 tested patients, in 13 patients a deleterious MMR mutation was found (8 MSH2, 2 MLH1 and 3 MSH6 mutations), while in 15 patients genetic testing resulted negative. Three patients harboring a VUS were excluded from the analysis. In patients with HNPCC-related EC, a trend toward a higher stage at diagnosis (International Federation of Gynecology and Obstetrics stage II and above), when compared with mutation negative EC patients, was observed (p = 0.07). No differences in terms of histological subtypes or tumour grading were observed between mutation-positive and mutation-negative patients. Median overall survival (OS) did not differ between the two groups of patients.

Conclusions: Our analysis failed to show a statistically significant difference in terms of histopathological and clinical features between MMR-gene mutation-positive and mutation-negative EC patients. This may be partly due to the small sample size. However, given the significant differences between the biology of MMR-deficient and -proficient tumors, further multicentric studies enrolling a larger number of patients could be useful to extend our insights on the matter.

D05 Intraperitoneal chemotherapy in pretreated ovarian cancer patients: a retrospective case-control study

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Background: The treatment of ovarian cancer by intraperitoneal (IP) chemotherapy has been studied for a long time. Numerous studies have been performed to investigate this route of administration but there is a lack of studies analysing the IP therapy in patients pretreated.

Objective: The aim of this retrospective study was the evaluation of overall survival and hazard ratio for IP chemotherapy in patients with recurrent or refractory epithelial ovarian cancer who have received multiple prior chemotherapy regimens. We also wanted to evaluate the feasibility of the administration of IP chemotherapy by direct puncture of the abdomen under ultrasound guidance.

Materials and methods: We analysed the treatment of 99 patients. Thirty-three patients with ascitis or peritoneal carcinomatosis were identified and treated with IP Platinum or Platinum-Taxol administered by direct puncture of the abdomen. We performed a case-control retrospective study: every patient treated with IP therapy was matched with two patients treated with intravenous (EV) chemotherapy who presented the same following characteristics: age (divided into <50, 50–70, >70), platinum sensitivity or resistance, histology and grade, year of first diagnosis.

Results: Age group (62 IP vs 65 EV p = 0,203), platinum-sensitivity (75,8% IP vs 75,8% EV) -resistance (24,2% IP vs 24,2% EV), histologic grade (G2 6,1% IP vs 9,1% EV; G3 90,9% IP vs 87,9% EV; G4 3% IP vs 3% EV), year of first diagnosis well balanced by two treatment arms. We also recorded a lower local toxicity and infections with IP chemotherapy unlike other studies that used permanent devices. When analyzed for hazard ratio, only the number of previous treatments and the IP vs EV therapy resulted significant (HR = 1.55 for EV and HR = 1.58 for each incremental number of previous treatments lines, multivariate analysis gave a p < 0,001). When analysing the patients with less than 3 previous treatments, IP chemotherapy had a survival advantage of 3 months (IP = 10.02 vs 7.77, p= 0.011). The survival advantage in heavily pretreated patients (with 3 or more previous treatments) resulted not significant.

Conclusions: Our results confirm the feasibility and efficacy of IP chemotherapy in not selected patients, validating the recent reports of randomized trials: IP treatment is feasible, and not-permanent catheter seems advantageous. Moreover, IP treatment seems to confer an advantage of survival, particularly in not heavily pretreated patients.

D06 Concurrent chemoradiotherapy (cCTRT) with weekly cisplatin (wCDDP) in locally advanced cervical cancer (LACC) patients (pts): a monoinstitutional experience

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Background: Patients affected by LACC (stage Ib2-IV) could be equally treated with neoadjuvant CT followed by surgery or with radical cCTRT. The standard CT is based on wCDDP given concurrently to RT. The present report is aimed to describe the toxicities and the clinical outcomes of pts treated with wCDDP plus RT for LACC.

Patients and methods: From May 2001 to November 2014, we treated a consecutive series of 87 patients. The treatment consisted of whole pelvic external RT (plus RT boost in patients with parametrial invasion) and brachytherapy (B) in selected cases, with good clinical response to external RT. CDDP was given weekly at the dose of 40 mg/sqm, starting on day 1 of RT. Acute and late toxicities were evaluated according to NCIC and LENT-SOMA criteria respectively.

Results: Major pts characteristics were: median age 55 yrs (range 30-79); median PS 0 (range 0-2); FIGO stage: Ib2 in 7 pts, IIa in 7, IIb in 28, IIIa in 3, IIIb in 26, IVa in 8, IVb (without visceral metastasis) in 8. Histology: squamous in 77 pts, adenocarcinoma in 8, mixed (squamous and adenocarcinoma) in 1, and undifferentiated in 1. Pts treated with external RT alone (39 pts) received a median total dose of 63 Gy (range 43.-67), which was 74.4 Gy (range 50-85) in pts receiving also B (48 pts). The treatment was completed in 71% of the pts. The median number of delivered CT courses was 5 (range 1-8): one patient received only 1 course of wCDDP due to gastrointestinal toxicity. Out of the 372 administered courses of wCDDP, 3 were at reduced dose due to patient compliance, 9 due to haematological toxicities, 10 due to non-hematological toxicities, 11 due to age; admistration of therapy was delayed due to haematological and non-haematological toxicities in 10 and 4 courses, respectively. Grade 3-4 toxicities consisted of anemia (1 pt), neutropenia (4 pts), nausea (2 pts), diarrhoea (2 pts), constipation (1 pt), fatigue (1 pt). No grade late toxicity 3-4 was observed. The response was evaluable in 78 pts with a rate was 88.4% (54 CR and 15 PR). After a

median follow-up of 34 mos, the 2-year OS and DFS were 79.9% and 69.2% respectively, with median OS and DFS not reached.

Conclusions: Our experience confirms the good activity and tolerability of this combined CT-RT treatment in LACC, according to the literature data.

D07 The impact of fasting glucose on clinical-pathological features in epithelial ovarian cancer: results from a historic cohort

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Background: Over the last fifty years, the efforts of the scientific community devoted to the comprehension and treatment of ovarian cancer have remained poorly remunerative, with the case-fatality ratio of this disease remaining disappointedly high. Limited knowledge of the basic principles regulating ovarian carcinogenesis and factors impacting the course of disease may significantly impair our ability to intervene in early stages and lessen our expectations in terms of treatment outcomes. In the present study, we sought to assess whether metabolic factors, i.e., pre-treatment fasting glucose, are associated with renown cancer related prognostic factors such as tumour stage and grade at diagnosis.

Materials and methods: Study participants were 147 women diagnosed with epithelial ovarian cancer and treated with platinum based regimens and/or surgery at the Regina Elena National Cancer Institute of Rome, Italy. Glucose levels were assessed at the institutional laboratories in venous blood collected in overnight fasting conditions and prior to any therapeutic procedure. Stage was coded according to the FIGO staging system based on the results of the diagnostic workup, while tumour grade was locally assessed by an expert pathologist. Participants' characteristics were descriptively analyzed for the overall study population and in a subgroup of 70 patients for whom data on BMI were available. FIGO stage and grade were compared by categories of pre-treatment fasting glucose defined upon the median value, i.e., 89 mg/dl. The association of interest was tested in regression models including BMI.

Results: For the overall study population, patients in the lowest category of fasting glucose were significantly more likely to exhibit a FIGO stage III-IV at diagnosis compared with their counterpart in the highest glucose category (81.3 vs 66.7%, p: 0.021). Subgroup analysis in 70 patients with BMI data confirmed this association (81.5 vs 55.8, p: 0.049), which remained significant when tested in regression models including BMI (HR: 0.28 95% CI 0.086-0.89, p: 0.031). No relevant evidence emerged when testing the association between fasting glucose and tumour grade.

Conclusions: In patients diagnosed with epithelial ovarian cancer, glucose levels appear to be inversely associated with FIGO stage. Further studies are warranted to eventually confirm and correctly interpret the implications of this novel finding.

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Session E. Gastrointestinal (colorectal) cancer

E01* PIK3CA mutation, aspirin use after diagnosis and survival of colorectal cancer. A systematic review and meta-analysis of epidemiological studies

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Background: Regular aspirin (ASA) use has been associated with inhibition of the whole spectrum of colorectal carcinogenesis, including prevention of metastases and reduced total mortality in colorectal cancer (CRC). Preclinical data have demonstrated that ASA down-regulates PI3K signaling activity through COX2 inhibition leading to the hypothesis that the effect of ASA might be different according to *PIK3CA* mutational status, but epidemiological studies have led to conflicting results.

Purpose: To perform a systematic review and meta-analysis of the modifying effect of *PIK3CA* status on the efficacy of post-diagnosis aspirin use in colorectal cancer.

Methods: We searched up to January 31, 2014 to identify studies that compared post-diagnosis aspirin efficacy in colorectal cancer patients identified by *PIK3CA* status. Log hazard ratios (HRs) for overall survival (OS) were meta-analyzed according to *PIK3CA* status by inverse variance weighting. A pooled test for treatment by *PIK3CA* status interaction was performed by weighted linear meta-regression. All statistical tests were two sided.

Results: Five studies consisting of 3 cohort studies, 1 clinical trial and 1 nested cohort within a randomized controlled trial were eligible for this meta-analysis accounting for a total of 4589 patients. The mean prevalence of *PIK3CA* mutation was 14.5%. Overall effect of aspirin was not significant (SRE, summary risk estimate, = 0.82; 95%CI, 0.63-1.08, p = 0.16; heterogeneity I^2 = 57%). In *PIK3CA* mutant disease (n = 588), aspirin use reduced total mortality by 29% (SRE = 0.71; 95%CI, 0.51-0.99, p = 0.04; I^2 = 0%), whereas in *PIK3CA* wild-type disease (n = 4001), aspirin use did not reduce overall mortality (SRE = 0.93; 95%CI, 0.61-1.40; P = 0.7; I^2 = 80%) (p-interaction = 0.39). There was a beneficial trend for aspirin on cancer specific survival in PI3KCA mutated subjects (SRE = 0.37, 95%CI, 0.11-1.32, p = 0.1), albeit with high heterogeneity (Q chi-squared = 3.41, p = 0.07, I^2 = 70.7%).

Conclusion: These findings suggest that the benefit of post-diagnosis aspirin treatment on overall mortality in colorectal cancer may be more marked in *PIK3CA* mutated tumors, although the low number of studies prevents definitive conclusions. Adjuvant trials addressing this issue are warranted.

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E02* Anti-EGFR or Bevacizumab in first line treatment of RAS wild type metastatic colorectal neoplasm (RwtMCRC): meta-analysis of randomized clincal trials

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Background: It is well known that anti-EGFR molecules (cetuximab or panitumumab) for patients with wild-type all-ras status or bevacizumab have radically changed the outcome of patients with metastatic colorectal cancer and data from an head-to-head comparison are surely relevant for planning the correct approach against all-ras wild type metastatic colorectal cancer. Moreover, the definitive results from the FIRE-3 trial arrived in a period when also two other experiences (the PEAK and the CALGB trials) contributed with their results to clarify the dilemma of the first line approach against all-ras wild type metastatic colorectal cancer.

Patients and methods: A systematic review of MEDLINE, EMBASE and Cochrane Systematic reviews databases from January 1966 to May 2015 was performed independently by two Authors. All randomized phase III trials comparing first line Bevacizumab versus Cetuximab or Panitunumab in RwtMCRC were considered eligible and included into the analysis. A subgroup analysis of Cetuximab versus Bevacizumab was also performed. The pooled analyses were performed using a random effect model, and assuming an alpha error of 5% as index of statistical significance. Heterogeneity between the trials was assessed using the I2 test; I2 values > 50% were deemed to suggest large among-trial heterogeneity, values of 25%-50% were deemed to show moderate heterogeneity and values < 25% were deemed to represent low heterogeneity.

Results: We analyzed the outcomes of 1096 all-RAS wild type patients treated with bevacizumab or anti-EGFR agents. Despite a large to moderate heterogeneity among the trials, a significant improvement of the Hazard Ratio in term of Overall Survival in favor of cetuximab/panitumumab was observed considering all-RAS wild type patients [Hazard Ratio 0.763 (Confidence Interval 95%: 0.61-0.955, p = 0.018]. Moreover, a trend in favor of cetuximab versus Bevacizumab could be at least hypothesized [Hazard Ratio of 0.794 (Confidence Interval 95%: 0.633-0.977, p = 0.047) for all-RAS wilt type patients].

Conclusions: These results are just preliminary, but they seem to suggest a superiority of anti-EGFR in the first line treatment of RAS wild type metastatic colorectal cancer. The combination of chemotherapy with cetuximab or panitumumab should be preferred as first line approach in RAS wild type metastatic colorectal cancer.

E03* Efficacy of Mitomycin C plus a Fluoropyrimidine in pre-treated patients with metastatic colo-rectal cancer eligible to Regorafenib. Results of a retrospective study

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Background: Advanced colorectal cancer patients that progressed after two or more lines of therapy represent a challenge for oncologists; until two years ago there was no treatment with proven efficacy and the association of Mytomicin C (MMC) and a Fluoropyrimidines (FPDs) had become de facto a standard option in this setting. The CORRECT study, published in 2013, demonstrated the efficacy of Regorafenib to improve both progression-free and overall survival when compared to placebo; in fact, benefit were reached in terms of median survival time (6.4 months) and median progression-free survival (1.9 months). All the subjects enrolled into CORRECT displayed PS 0-1 according to the ECOG scale and had previously failed all standard therapies which must have included FPDs, Oxaliplatin, Irinotecan, Bevacizumab, and Cetuximab or Panitumumab (for K-RAS WT pts).

Methods: In the aim to investigate the impact of MMC plus FPDs on outcome parameters in a real life setting and in a population of patients superimposable to those enrolled into CORRECT study, we retrospectively evaluated the clinical records of mCRC pts treated at our institutions.

Results: Records from 87 pts were collected in two Sicilian centers with 61 pts fulfilling the inclusion criteria for this analysis. Pts characteristics were: Male/Female: 38/23; median age: 69.3 (range 37-80); ECOG PS0/1: 45/16; primary site of disease: colon/rectum/colon and rectum 41/19/1; K-RAS status: WT/mutated/unknown 37/22/2; number of previous systemic anticancer therapies: 1-2/3/ $\geq$ 4 32/20/9; previous anti-VEGF treatment: Bevacizumab/Aflibercept and Bevacizumab 42/5; previous Cetuximab or Panitumumab or both 34/1/2. Median OS was 9.3 month (95% C.I. 9.0 to 15.4); median PFS was 3.3 month (95% CI 2.9-3.8). Partial remission, stable disease and disease control were achieved in 5%, 24.5% and 29.5% of pts respectively. No significant differences in OS and PFS were found between K-RAS WT and K-RAS mutant individuals. Likewise, PS and the primary site of disease were not associated with response differences.

Conclusions: These results may suggest the need for a prospective study assessing RGR cost-effectiveness compared to MMC + FPDs in mCRC pts progressed after two or more lines of therapies.

E04 Regorafenib for previously treated metastatic colorectal cancer (mCRC): results from 683 Italian patients treated in the open-label phase IIIB CONSIGN study

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Background: Regorafenib an oral multikinase inhibitor significantly improves survival vs placebo (P) in patients (pts) with mCRC previously treated with standard therapy. The registration CORRECT study reported improved overall survival (OS) and progression-free survival (PFS) of Regorafenib vs. P (median OS 6.4 vs 5.0 months(mos), HR = 0.77; median PFS 1.9 vs 1.7 mos, HR = 0.49). CONSIGN (NCT01538680) was a large (N = 2872), open-label, phase IIIB study performed in 25 countries to provide continued access to Regorafenib for pts with mCRC who failed standard therapy and to characterize the safety of Regorafenib in a large number of pts. In the overall cohort, adverse events (AE) and PFS were consistent with the CORRECT study data. We present the results of the Italian cohort in CONSIGN, the largest subgroup of pts in a single country.

Methods: Pts with mCRC, ECOG PS 0—1, received Regorafenib 160 mg o.d. (3 weeks of each 4-week cycle). Treatment continued until disease progression, death or unacceptable toxicity; treatment beyond progression was allowed at investigator's discretion. The primary endpoint was safety. PFS based on investigator assessment was the only efficacy variable assessed.

Results: In Italy 686 pts were enrolled from Apr 2012 to Mar 2013. The cut-off date for this analysis is Jan 2, 2015. The safety analysis set includes 683 treated pts. Median age was 62 years, 76% ECOG PS 0 and 24% ECOG PS 1. KRAS mutation was present in 48% of pts; 96% pts had ≥2 prior lines of treatment for metastatic disease. Median treatment duration was 2.6 mos (range: 0-30). Estimated median PFS was 2.9 mos (3.1 mos KRAS wild type; 2.8 mos KRAS mut). NCI-CTCAE v4.0 grade ≥3 AEs occurred in 74% of pts (Table). Grade ≥3 hepatobiliary disorders occurred in 2% of pts. Grade ≥3 lab abnormalities in bilirubin (13%), ALT (6%), and AST (5%) were reported.

Conclusions: Pts in the Italian cohort of CONSIGN appeared similar to those in the overall cohort, except that a higher proportion of pts in the Italian cohort had a baseline ECOG PS of 0 (76% vs 47% in the overall cohort). The safety profile in the Italian cohort was similar to that in the overall cohort, and median PFS in the Italian cohort (2.9 mos) was similar to that in the overall cohort (2.7 mos).

Table: E04

AEs, %	Italian cohort N= 683	All patients N= 2864
Grade ≥3	74	80
Drug-related	55	57
Fatigue	16	18
Hypertension	14	17
HFSR	10	14
Diarrhea	5	6
Hypophosphatemia	10	7
Serious	23	44
Drug-related	4	9
Leading to discontinuation	19	25
Drug-related	6	9

E05 Review of RAISE, a Randomized, Double-Blind, Multicenter Phase III Study of Irinotecan, Folinic Acid, and 5-Fluorouracil (FOLFIRI) Plus Ramucirumab (RAM) or Placebo (PBO) in Patients (pts) With Metastatic Colorectal Carcinoma (mCRC) Progressive During or Following First-Line Combination Therapy With Bevacizumab (bev), Oxaliplatin (ox), and a Fluoropyrimidine (fp): Primary Results and Subgroup Analysis by KRAS Status

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Background: Angiogenesis is an important therapeutic target in CRC; VEGF plays a key role in angiogenesis. RAM is a human IgG1 monoclonal antibody that targets the extracellular domain of VEGFR-2. The RAISE study evaluated the efficacy and safety of adding RAM to standard second-line treatment FOLFIRI. A KRAS preplanned analysis was performed to evaluate the outcomes of RAM + FOLFIRI by KRAS subgroup.

Methods: Eligible pts with mCRC who progressed on or after first-line therapy with bev, ox, and fp were randomized 1:1 to receive RAM (8mg/kg) + FOLFIRI or PBO + FOLFIRI every 2 weeks. The primary endpoint was overall survival (OS). Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), and safety. ForKRAS subgroups, OS and PFS were evaluated by unstratified Kaplan-Meier analysis, log-rank tests and Cox proportional hazards model to estimate the HR (ITT population = stratified analyses).

Results: 1072 pts were randomized (RAM 536; PBO 536). Baseline pt characteristics were similar between treatment arms. OS HR was 0.84 (95%CI:0.73,0.98;p = 0.022). Median OS was 13.3 months (m) for RAM vs 11.7m for PBO. PFS HR was 0.79 (95% CI:0.70,0.90;p = 0.0005). Median PFS with RAM was 5.7m and 4.5m for PBO. ORR was 13.4% RAM; 12.5% PBO (p = 0.63). Subgroup results were consistent with the OS and PFS results. Grade ≥3 adverse events (AEs) occurring in >5% pts in RAM + FOLFIRI were: neutropenia, hypertension, diarrhea, and fatigue. OS and PFS benefits were observed for pts receiving RAM + FOLFIRI in both KRAS subgroups, compared with pts on PBO + FOLFIRI, as noted by HRs and medians (Table); KRAS status was not predictive of RAM efficacy (interaction p ≥ 0.50).RAM + FOLFIRI was well tolerated in KRAS wild-type and mutant subgroups.

Conclusions: RAISE met its primary endpoint, demonstrating a statistically significant improvement in OS for RAM plus FOLFIRI vs PBO plus FOLFIRI in second-line mCRC pts and no unexpected AEs were identified. Efficacy and safety results were similar for both mutant and wild-type tumor KRAS status.

E06 Circulating microRNAs in metastatic colorectal cancer (mCRC) patients (pts) treated with regorafenib

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Background: Regorafenib is indicated for the treatment of mCRC patients who have failed all other therapies. Nevertheless a substantial percentage of patients experiences rapid disease progression (PD) and serious adverse events may occur. For these reasons, clinical and/or molecular markers able to improve the cost/benefit ratio are urgently needed. Circulating microRNAs (c-miRNAs) have been recognized as possible prognostic and diagnostic markers in mCRC. The aim of this study was to describe the early changes in plasma levels of 10 selected c-miRNAs during the treatment with regorafenib and to investigate their correlation with clinical outcome.

Patients and methods: Plasma samples of patients treated with regorafenib at our Institution were collected at baseline (D1) and after 15 days of treatment (D15). Plasma levels of c-miR-17, c-miR-21, c-miR-29, c-miR-34, c-miR-92, c-miR-126, c-miR-141, c-miR-221, c-miR-601, c-miR-760 were analysed by means of real-time PCR. Paired levels at D1 and D15 were compared by means of Wilcoxon test for each c-miRNA. C-miRNAs showing significant changes were further analysed in order to identify possible correlations with outcome.

Results: Thirty-four patients were included in the present study. Main characteristics were the following: M/F = 50%/50%; median age = 65 (range 48-78 years); ECOG-PS 0/1-2 = 71%/29%; time from diagnosis of metastases </ = 18 months 15%/85%. Median PFS and OS were 2.4 and 6.5 months, respectively. One (3%) patient achieved a response and 16 (47%) had disease stabilization (disease control rate: 50%). As compared to D1, the following c-miRNAs increased at D15: c-miR-601 (p = 0.01), c-miR-141 (p = 0.04) and c-miR-21 (p = 0.06). Despite a median increase in the overall population, 12 (35%) out of 34 patients showed reduced level of c-miR-21 at D15. Nine out of 12 (75%) patients with reduced levels of c-miR-21 achieved disease control, as compared to 8 out of 23 (35%) patients with increased levels (Fisher 's Exact Test, p = 0.035). Median PFS of patients with increased and decreased level of levels of c-miR-21 were 2.1 and 3.9 months, respectively (HR = 1.89 95%CI 0.92-4.14 p = 0.08). Data on OS are not yet mature. Early modifications of c-miR-21 levels showed a sensitivity of 82% in predicting benefit from regorafenib.

Conclusions: The early modulation of c-miR-21 levels may predict benefit from regorafenib in terms of disease control. These results need validation in independent series.

E07 DPYD c.1905 + 1G > A and c.2846A > T and UGT1A1*28 allelic variants as predictors of toxicity: Pharmacogenetic translational analysis from the phase III TRIBE study in metastatic colorectal cancer

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Background: Adverse drug reactions (ADRs) caused by fluoropyrimidines depend, at least in part, from DPD deficiency resulting from the loss-of-function mutations c.1905 + 1G > A and c.2846A > T. Moreover, irinotecan ADRs appear frequently in patients bearing the *UGT1A1**28 variant, associated with reduced UGT1A1 expression. In this study, we analyse the association between *DPYD* and *UGT* variants with ADRs by 5-fluorouracil and irinotecan in subjects enrolled within the phase III TRIBE study, whose final results have been recently reported.

Methods: Out of 508 randomized patients, blood samples for pharmacogenetic analyses were available for 440 patients. DNA was extracted from 200 µl of blood and analyses of *DPYD* c.1905 + 1G > A, c.2846T > C and *UGT1A1**28 was performed by a Pyrosequencing platform (Qiagen, USA). The study was approved by the local Ethics Committee.

Results: Each of the *DPYD* c.1905 + 1GA and c.2846AT genotypes were found in 5 out of 440 subjects, with a combined frequency of 2.2%. c.1905 + 1GA and c.2846AT had the same impact on ADRs and, taken together, patients bearing these variants (N = 10) had an increased risk of G3/4 neutropenia (OR: 4.14, p = 0.043) and stomatitis (OR: 10.36, p = 0.003) as compared to wild-type patients. Five out of 10 DPYD mutant patients experienced a G4 ADR after the first cycle of therapy. *UGT1A1**28/*28 was found in 39/436 patients (8.9%); these patients had an increased risk of G3/4 neutropenia as compared to both *1/*1 (OR: 3.81, p < 0.001) and *1/*28 (OR: 2.28, p = 0.022) genotypes. Patients bearing *DPYD* c.1905 + 1GA, c.2846AT and *UGT1A1**28/*28 (N = 49) had an increased risk of G3/4 neutropenia (OR: 2.98, p < 0.001), febrile neutropenia (OR: 2.78, p = 0.023) and G3/4 stomatitis (OR: 6.83, p < 0.001). No significant correlation with G3/4 diarrhea was found.

Conclusions: *DPYD* c.1905 + 1GA, c.2846AT and *UGT1A1**28/*28 are associated with a higher risk of G3/4 ADRs also in the TRIBE trial, underscoring the predictive role of *DPYD* and *UGT1A1* variants across various fluoropyrimidine and irinotecan-containing schedules, and therefore their potential usefulness in treatment tailoring.

E08 Prognostic significance of KRAS mutation rate in metastatic colorectal cancer patients

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Background: Activating mutations of K-Ras gene have a well-established role as predictors of resistance to anti-EGFR monoclonal antibodies in metastatic colorectal cancer (mCRC) patients. Their prognostic value is controversial, and no data regarding the prognostic value of mutation rate, defined as the percentage of mutated alleles/tumor sample, are available. We aimed to evaluate the prognostic value of K-Ras mutation rate in a homogenous cohort of mCRC patients receiving first-line doublet plus bevacizumab.

Patients and methods: This retrospective study enrolled 397 K-Ras mutant mCRC patients from 6 Italian centers, and 263 patients were fully evaluable for our analysis. K-Ras mutation rate was assessed by means of pyrosequencing analysis. Patients with less than 60% of cancer cells in tumor tissue were excluded. No patients received anti-EGFR containing anticancer therapy, at any time. Median mutation rate was 40% and was adopted as cut-off value. The primary endpoint was PFS, OS was a secondary endpoint.

Results: At univariate analysis, a K-Ras mutation rate higher than 40% was significantly associated with lower PFS (7.3 vs 9.1 months; P < 0.0001) and OS (21 vs 31 months; P = 0.004). A multivariate model adjusted for age at diagnosis, site of origin of tumor tissue (primary cancer *vs* metastases), referral center, number of metastatic sites, and first-line chemotherapy backbone, showed that K-Ras mutation rate remained a significant predictor of PFS and OS in the whole population.

Conclusions: Our data demonstrate an association between K-Ras mutation rate and prognosis in patients treated with bevacizumab-containing first-line therapy for mCRC. These data deserve to be verified in an independent validation set.

E09 Prognostic role of serum concentrations of high-sensitivity C-reactive protein in patients with metastatic colon rectal cancer: Results from the ITACa trial

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Background: Serum levels of interleukine-6 and C-reactive protein are significatively higher in patients with neoplastic conditions. Therefore, the determination of high-sensitivity C-reactive protein (hs-PCR) has been widely used as a surrogate marker for chronic elevation of circulating cytokines. Increased hs-CRP concentrations have been reported in many conditions, in particular in patients with cardiovascular diseases, obesity, diabetes, autoimmunity, inflammatory bowel diseases and cancer risk. Some authors, on the basis of these findings, have encouraged further studies to clarify the etiologic and prognostic role of the aforementioned test. Our study has been conducted in patients enrolled in the phase III prospective multicentric randomized "Italian Trial in Advanced Colorectal Cancer (ITACa)," in order to assess hs-CRP levels at diagnosis and their significance with respect to overall survival (OS) and progresion free survival.

Methods: Peripheral blood samples from 133 consecutive patients were collected into EDTA tubes. The collection was obtained before the beginning of first line chemotherapy. The supernatant was immediately transfer into a cryovial and stored at –80°C. Samples were thawed and hs-CRP has been measured with Cobas c501 analyzer.

Results: Levels of hs-CRP >13.1 mg/L were associated with a worse median PFS, 8.9 months (95% CI 6.8-9.6) vs. 12.1 months (95% CI 9.3-14.9) in patients with levels <13.1 mg/L (p < ;0.0001). Similarly, levels >13.1 mg/L were associated with worse median OS, 14.4 (95% CI 11.5-17.1) vs. 28.8 (95% CI 24.3-36.6) in patients with a

concentration <13.1 mg/L (p < 0.0001). In multivariate analysis, hs-PCR adjusted for baseline factors including age (<70, ≥70 years), gender, ECOG perfomance status (0,1-2), tumor localization (rectum, colon), stage at diagnosis (I-III, IV), CT regimen (Folfiri, Folfox), KRAS status (wild type, mutant), site of metastases (liver, other metastases), was found to be independently associated with PFS and OS.

Conclusions: Our study demonstrates the prognostic value of hs-CRP in patients with metastatic carcinoma of the colon and rectum.

E10 ERCC1 as biomarker of response to oxaliplatin in colorectal cancer: To induce or not induce ... this is the problem. preliminary data from liquid biopsy

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Background: Basing on preliminary observations of OPUS and PRIME studies, our group retrospectively suggested that KRAS mutational status could affect response to oxaliplatin. We further confirmed this evidence in vitro demonstrating that KRAS mutated cell lines were more sensitive to oxaliplatin due to their inability to induce ERCC1 after drug exposure. Using CTCs as a surrogate, dynamic tissue, in this study we sought to confirm in vivo the relationship between KRAS mutational status, ERCC1 inducibility and clinical outcome in oxaliplatin-treated colorectal cancer patients.

Methods: We collected blood samples from colorectal cancer patients treated with oxaliplatin-based regimen at 0 and 48 hours during the first cycle of chemotherapy. The presence of CTC was detected by AdnaGene system followed by multiplex RT-PCR including ERCC1 transcript. In CTC-positive ERCC1-positive patients, ERCC1 mRNA expression was measured using a quantitative real time RT-PCR method, before and after drug exposure. We evaluated the relationship between ERCC1 induction and KRAS mutational status and we tried to correlate this association with clinical outcome.

Results: On a total of 38 patients enrolled, 19 were KRAS wild type and 19 KRAS mutated. CTCs were detected in 12 (31,5 %) patients. ERCC1 was expressed in 8/12 CTCs-positive patients, 5 KRAS wild type and 3 mutated. After Oxaliplatin exposure, among ERCC1-positive patients, only 3 showed a significant induction of ERCC1 expression; interestingly all of them were KRAS wild-type and experimented a rapid progression of disease. The median PFS of patients with ERCC1 induction was shorter than that observed in patients with stable or reduced ERCC1 (2,5 months vs 7,2 months; p 0.002, HR: 0,2). Notably none of the KRAS mutated ERCC1-positive CTCs was able to induce ERCC1 and median PFS was 11,6 months.

Conclusions: Although based on a small sample size, this is the first report proposing the ability to induce ERCC1 as a blood-based biomarker for oxaliplatin resistance in colorectal cancer. Moreover this study could support the relationship between KRAS mutational status, ERCC1 inducibility, and clinical outcome, corroborating our hypothesis that KRAS mutational status could be a surrogate marker of efficacy of oxaliplatin therapy in colorectal cancer. Further studies are warranted to confirm these associations.

E11 Pooled analysis of clinical outcome of patients with chemorefractory metastatic colorectal cancer treated within clinical studies based on individual molecular alterations at Niguarda Cancer Center

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Background: Patients with metastatic colorectal cancer (mCRC) refractory to standard therapies have poor prognosis. Rechallenge with previously used chemotherapeutics is often attempted by clinicians and considered in guidelines, but results are scanty. In this setting a reasonable approach is recruitment in clinical trials, and studies driven by selection according to individual tumor molecular characteristics are expected to provide added value.

Patients and methods: We retrospectively analyzed data of patients with mCRC resistant to standard therapies treated at Niguarda Cancer Center (NCC) with chemotherapy or targeted agents in Phase I/II clinical studies based on the presence of a specific molecular profile as *per* inclusion criteria. Objective tumor response and progression-free survival were evaluated.

Results: From June 2011 and March 2015, 1544 patients with mCRC underwent molecular screening for potentially actionable targets in phase I/II trials at NCC. 75 patients (4.9%) were enrolled in *ad hoc* studies; median age was 60 years (range 36-86), median number of previous treatment lines 4 (range 1-7). Molecular characteristics exploited were MGMT promoter hypermethylation (52%), Her2 amplification (24%), $BRAF^{V600E}$ mutation (12%), gene fusions involving ALK or TRKA (2%). Among the whole cohort, any KRAS (exon 2) mutation was present in 44% of patients. According to RECIST criteria, 11 patients (15%) had PR and 27 (36%) SD, accounting for a 51% disease control rate (DCR: PR + SD); DCR was more frequent in patients with KRAS wild type tumor (73 vs 39%, p = 0.01). Median progression-free survival was 2.8 months (range 2.47–3.93), and 25% of patients displayed a PFS > 5 months; among the 66 patients with known KRAS status, those with KRAS wild type tumors had longer PFS than mutated (3.8 [95% CI 3.03–7.83] vs 2.1 months [95% CI 1.83–2.87], respectively) (p < 0.001).

Conclusions: Our single-institution case series indicates that, in a heavily pretreated mCRC population, about 5% of tumors display a potential actionable molecular context suitable for phase I/II trials with matched therapeutics. Response rate and progression-free survival in our cohort were similar to earlier settings. The presence of a *KRAS* mutation exerts an overall negative impact, also because it was among exclusion criteria in some studies. Application of molecular selection in mCRC is challenging and improves clinical outcome even in later lines of treatment.

E12 Molecular profile of brain metastases from colorectal cancer and concordance with matched primary tumors

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Background: Although brain metastases (BM) from colorectal cancer (CRC) are relatively uncommon, their incidence is growing. The mutational profile of BM has not been extensively investigated yet and few data are available on the prognostic role of the molecular biology of BM.

Patients and methods: By merging two independent Hospital datasets including 730 patients (pts) with BM and 2,500 pts with CRC, 56 consecutive pts who underwent neurosurgical resection of BM were found. Formalin-fixed, paraffin-embedded samples were reviewed and tested by pyrosequencing for KRAS, NRAS, BRAF and PIK3CA. All wild-type samples were then analyzed on a MALDI-TOF Mass spectrometry platform. When available, the molecular profile of the BM was compared with that of corresponding primary tumour. Survival curves were estimated using the Kaplan Maier method and compared by log-rank analysis. Concordance between mutational status of the BM and corresponding primary tumour was calculated as the ratio of concordant cases to total cases.

Results: In our population, 62.5% of pts were males and 37.5% were females. Median age at the time of neurosurgery was 65.8 years. Most pts (41, 73.2%) had only one BM and the most frequent location was supratentorial (62.5%). KRAS mutations were detected in 36 pts (64.3%): among KRAS mutant pts the most frequent mutations were located in codon 12 (42.9%), codon 13 (14.3%), codon 117 (3.6%) and codon 146 (3.6%). Exon 15 BRAF mutations were found in 6 cases (10.7%, 5 with V600E and 1 with D594G mutation) and PIK3CA mutations in 9 (16.1%) BM specimens. No NRAS mutations were detected. In 41 matched cases, the molecular profile concordance rate was 95.1%, with only 2 discordant cases (1 case with primary tumour KRAS mutant and all wild-type BM, 1 case with all wild-type primary tumour and KRAS mutant BM). Median brain PFS (defined as the time interval from the date of stage IV to neurosurgery) was 9 months (95%CI 1.8-16.2), median survival after neurosurgery was 5.5 months (95%CI 4.7-6.3); median overall survival was 24.0 months (95%CI 15.6-32.4). Patients with brain PFS longer than the median had a significantly better survival (p = 0.002).

Conclusions: We report a high frequency of KRAS mutations in patients resected for BM from CRC with a very high concordance rate between the molecular profile of BM and its matched primary tumour. The mutational status of BM did not seem to correlate with the outcome.

E13 Subgroup analysis of patients with metastatic colorectal cancer (mCRC) treated with regorafenib (REG) in the CORRECT trial who had progression-free survival (PFS) longer than 4 months

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Background: In the CORRECT phase III trial (NCT01103323), the multikinase inhibitor REG significantly improved overall survival (OS) and PFS *vs* placebo in patients with mCRC who had disease progression after other standard therapies (HR for OS: 0.77; 1-sided p = 0.0052; Grothey 2013). A post-hoc exploratory subgroup analysis was conducted to evaluate patients in the REG treatment group who had a PFS longer than 4 months (long-PFS) defined as patients who progressed, died, or discontinued treatment for other reasons after 4 months.

Methods: Of the505 patients randomized to REG in CORRECT, 98 (19.4%) were classified as having a long-PFS benefit. Baseline characteristics, safety, and dosing parameters were analyzed descriptively.

Results: The long-PFS subpopulation was representative of the overall study population (Table). Long-PFS patients received a median of 6 cycles of REG (1-12), 92% received ≥5 cycles, and 20% had > 8 cycles. Overall 34% of patients had dose reductions and 87% had dose interruptions. The actual mean daily dose was 139 mg and the mean percent of the planned dose was 81%. Adverse events (AE) of any grade were experienced by all long-PFS patients, and the most common grade ≥3 AEs were hand-foot skin reaction (20%), hypertension (17%), diarrhea (17%), and fatigue (16%).

Conclusions: A subset of 98 (19.4%) patients treated with REG in the CORRECT study had a PFS > 4 months, confirming the clinical benefit and tolerability of REG as a treatment option for patients with mCRC. Prospective validation of these findings in conjunction with biomarker analysis from real-life clinical experience is needed.

Clinical trial information: NCT01103323

Table: E13

Baseline characteristics of all REG-treated patients and the long-PFS subgroup in CORRECT.

		All patients (n=505)	Long-PFS (n=98)
Median age, yrs (range)		61 (22–82)	61 (34–82)
ECOG PS, %	0	52	63
	1	48	37
Primary tumor, %	Colon	64	52
	Rectum	30	37
Tumor sites, %	1	19	30
	2	36	38
	3	27	16
***KRAS* status, %**	Mutant	54	47
	Wild-type	41	44

E14 Retrospective evaluation of ADCC activity and cetuximab response in KRAS wild-type metastatic colorectal cancer patients (mCRC)

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Introduction: Cetuximab is a IgG1 monoclonal antibody against epidermal growth factor receptor (EGFR) used in mCRC and in Head and Neck Cancer treatment. The proposed working mechanism of cetuximab is thought to include antibody-dependent cell-mediated cytotoxicity (ADCC). Cetuximab has been restricted to mCRC patients (pts) with wild-type RAS. Whether ADCC is associated with EGFR expression and/or mutational status of RAS and BRAF in mCRC remains unclear.

Methods: We retrospectively identified, from March 2008 to September 2014, 41 mCRC pts who received chemotherapy with cetuximab (9 received cetuximab in first, 26 insecond and 6 inthird line). Peripheral blood samples were collected at start of therapy and during treatment.ADCC was evaluated over time of ex vivoNK-dependent activity measuring LDH release by a non radioactive cytotoxicity assay. Genotyping of FcgRII, FcgRIII and rs61764370 SNPs was done on DNA extracted from total peripheral blood using the appropriate "allelic discrimination assay". RAS(codon 12-13-59-61-146) and BRAF(V600E) genotypes were determined by pyrosequencing in patients' tumoral Formalin Fixed Paraffin Embedded (FFPE) tissues archived at diagnosis.

Results: Median ADCC activity at treatment start for all 41 mCRC pts was 68.5% (range 10-99%). Correlation with OS and PFS was evaluated only in the sub-group of 26 ptstreated with cetuximab in second line. All pts resulted KRASwt. For this latter group, median follow-up was 13 months (range 3-37) for OS and 5.5 months (range 2-37) for PFS. Pts performing ADCC activity above the median value showed an improved OS compared to pts with ADCC activity below this value (median 21 vs12 months; p = 0.045; Long-rank Mantel-Cox Test). Correlation in terms of OS and PFS with FcgR and rs61764370 genotypes resulted significant for FcgRII in PFS where allele frequencies were 52% for A and 48% for G. Pts carrying alleles with A presented a longer PFS in comparison with GG genotype (median 8 vs3 months; p = 0.04; Long-rank Mantel-Cox Test). This effect resulted even amplified when PFS was evaluated in FcgRII favourable alleles stratified for FcgRIII. Pts presented with both FcgRII AA/AG and FcgRIII TT performed better than all the other subgroups (median 11 vs 5 months; p= 0.03;Long-rank Mantel-Cox Test).

Conclusion: These results indicate a link between ADCC activity, FcgR genotypes and efficacy of cetuximab in KRAS wild-type mCRC pts. Our results should be confirmed by further large prospective studies.

E15 Effectiveness of Cetuximab (Cet) and Bevacizumab (Bev) for metastatic colorectal cancer (mCRC) according to primary tumor location (PTL): findings from a 'real-world' retrospective analysis

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Background: According to recent findings from large randomized trials, PTL is suggested to have a role as both prognostic and predictive factor for mCRC. In this regard, the purpose of such analysis was to verify the clinical outcomes and the relationships between upfront treatment with Cet or Bev and PTL in consecutive KRAS-wild-type (wt) mCRC patients (pts) in the context of a '*real-world*' setting.

Material and methods: A retrospective database including pts with pathologically confirmed wt mCRC undergone upfront Cet or Bev-based chemotherapy from January 2009 to December 2014 at two Oncology Units of Verona was developed. With regard to PTL, left-sided tumors were defined as tumors originating from the splenic flexure to the rectum. Kaplan-Meier analysis and Cox univariate and multivariate model were performed. Log-rank test was adopted to compare survival curves.

Results: Data from 141 consecutive wt mCRC pts were gathered; median OS and PFS were 31.1 months (CI 95% 19.6–49.4) and 11.8 (CI 95% 9.1-17.9), respectively. Pts' characteristics: median age 63 (range 36-80); PTL left/right: 101/40 (71.6%/28.4%); liver only metastases: 50 (35.5%); single-site: 80 (56.7%); PS-ECOG (0-1/ ≥ 2): 132/9 (93.6%/6.4%); Cet/Bev: 64/81 (45.4%/54.6%); surgery for metastases: 61 (43.3%). Resection of metastases and PTL resulted to be both independent predictors of OS and PFS. With regard to PTL, median OS was 29.7 versus 20.4 months for left-sided versus right-sided mCRC, respectively ($p = 0.013$). For patients receiving Cet, median OS was 39.7 months for left-sided tumors and 20.1 months for right-sided ($p = 0.022$); median OS did not differ according to PTL in pts receiving Bev (25.6 versus 20.4 months, respectively, $p = 0.08$).

Conclusions: Despite the biases in the retrospective nature of this analysis, these data support the hypothesis that a differential effect of Cet or Bev as upfront treatment for wt mCRC pts in a '*real-world*' scenario according to PTL might exist. A validation in a larger cohort is mandatory.

E16 Risk of thromboembolic events (TEE) in metastatic colorectal cancer (mCRC) patients with single nucleotide polymorphisms (SNPs) in Factor V Leiden (FVL), Prothrombin, Plasminogen Activator Inhibitor-1 (PAI-1) and Methylenetetrahydrofolate Reductase (MTHFR)

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Background: Several risk factors for TTE are present in mCRC, as central catheter, chemotherapy and antiangiogenics. SNPs related to hereditary thrombophilia are known, but their contribution to TEE risk in mCRC was never explored. In this study, we aimed at assessing the effect of FVL G1691A, prothrombin G20210A, PAI-1 4G, or MTHFR C677T and A1298C on TEE risk.

Methods: We included 179 mCRC patients from 2 Italian centers, with no previous history of TEE, not taking anticoagulants, treated with first-line chemotherapy and bevacizumab. DNA was extracted from peripheral blood; genotypes were determined by Real-Time PCR, using LightSNiP (TIB MOLBIOL) on LightCycler 480 (Roche). The percentage of patients with TEE was calculated from diagnosis of mCRC to death or last follow up. Clinical risk factors included age and obesity (BMI $\geq$ 30).

Results: All SNPs were in Hardy-Weinberg equilibrium (chi-squared test $p > 0.20$). FVL and prothrombin G20210A were present only in heterozygosis in4 (2.2%) and 7 (3.9%) pts, respectively. MTHFR C677T in heterozygosis in 95 (53.1%) and in homozygosis in 29 (16.2%) pts, respectively. MTHFR A1298C in heterozygosis in 82 (45.8%) and in homozygosis in 13 (7.3%), respectively. PAI-1 4G/4G in 41 (23%), 4G/5G in 98 (54.7%) and 5G/5G in 40 (22.3%). TEE occurred in 52 (29%) pts. Obesity and age were not associated with TEE ($p = 0.324$and $p = 0.488$, respectively). TEE occurred in all 4 patients with A allele at FVL G1691A. TEE prevalence was higher in prothrombin G20210A carriers vs. non-carriers (71.4% vs. 27.3%; OR = 6.65; 95%CI, 1.24-35.45; $p = 0.027$), as well as in MTHFR C677T homozygous TT vs. CC (55.2% vs. 23.6%; OR = 3.98; 95%CI, 1.52-10.39; $p = 0.005$). MTHFR A1298C SNP was not associated with TEE risk ($p = 0.445$), while a trend was observed for presence of PAI-1 4G allele ($p = 0.061$). Recessive model for MTHFR C677T and dominant model for PAI-1 4G allele were statistically significant (OR = 3.9; 95%CI, 1.71-8.87; $p = 0.001$ and OR = 2.8; 95%CI, 1.10-7.15; $p = 0.031$, respectively). In multivariate model including age, obesity, MTHFR C677T and PAI-1 4G allele, both SNPs were significantly associated with risk of TEE ($p = 0.026$ and $p = 0.028$, respectively).

Conclusions: Given the low prevalence of SNPs usually associated with higher risk (FVL G1691A and prothrombin G20210A) and the preliminary association of frequent SNPs (MTHFR C677T and PAI-1 4G), studies on larger datasets are needed. A prospective study on TEE prophylaxis in carriers of risk SNPs is warranted.

E17 Cavitation of lung metastases induced by regorafenib is associated with radiological response in metastatic colorectal cancer: data from the phase III correct study

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Background: We previously described radiological changes in metastatic lesions induced byregorafenib (REGO), including cavitation of lung metastases (mets), as an imaging marker potentially associated with clinical outcome (Ricotta et al., Lancet 2013).

Methods: This is a retrospective evaluation of baseline and week-8 (w8) contrast-enhanced computed tomography in pts with lung mets randomized to REGO or placebo (PL) in high recruiting centers that participated in the phase III CORRECT study. The occurrence of cavitation was evaluated in lung mets $\geq$ 10 mm at w8 and compared to baseline. Cavitation was defined as the onset of an air-filled cavity of $\geq$ 10%, or increase of a pre-existent cavitation, in at least one lung lesion. Assessment was carried out by an independent radiologist blinded to treatment assignment. Results were matched with RECIST responseand tumor shrinkage of any degree (shrinkage) from the CORRECT study.

Results: 108 pts were evaluated (75 REGO and 33 PL). Partial response (PR), stable disease (SD) and progressive disease (PD) at w8 were 0 (0%), 41 (38.7%) and 65 (61.3%), respectively. Two pts were not evaluable for response because only a subset of lesions was measured at w8. Cavitation in lung mets was present at baseline in 18 (16.7%) pts (15 REGO and 3 PL). At w8, cavitation was observed in 29/75 (38.7%) pts treated with REGO vs 0/33 (0%) pts treated with PL (Fisher's exact test 2-tailed, $p < 0.01$). Of the 29 REGO treated pts 21 displayed de novo cavitation and 8 ptshad an increase of a pre-existent cavitation at baseline. In the73 REGO treated pts evaluable for response, PD at w8 was observed in 8/27 (29.6%) pts vs 28/46 (60.9%) pts with or without onset/increase of cavitation, respectively (Fisher's exact test 2-tailed, $p = 0.015$). Tumor shrinkage was observed in 12/27 (44.4%) pts vs10/46 (21.7%) pts with or without onset/increase of cavitation, respectively [Fisher's exact test 2-tailed, $p = 0.064$; Odds Ratio = 2.84 (95% CI0.91-9.18)]; median shrinkage was 1.3% (IQR = -6.2 to 9.7) vs 9% (IQR = 0 to 21.6) for pts with or without onset/increase of cavitation, respectively [Wilcoxon rank sum test 2-tailed, $p = 0.005$].

Conclusion: Cavitation of lung mets is observed during treatment with REGO in mCRC pts. This radiological change is associated with tumor shrinkage and absence of progression at w8, making it an imaging marker to be prospectively validatedfor early prediction of progression-free survival in this setting.

E18 A post-reaction regimen for CRC patients manifesting hypersensitivity to oxaliplatin : an effective alternative not to rule out an important option of treatment

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Background: Oxaliplatin based regimens are highly effective treatments for colorectal cancer (CRC) in both metastatic and adjuvant settings. Hypersensitivity reactions (HSRs) to Oxaliplatin are reported in about 12% of patients (pts), although life-threatening HSRs occur in only 1% of pts. Clinical manifestations include anaphylactic-like reactions : rush, urticaria, erythema, pruritus and rarely bronchospasm and hypotension.Different desensitization protocols involve serial diluitions of the total oxaliplatin dose or prolonged administration of oxaliplatin after premedication with steroids and antihistaminics.

Patients and methods: We retrospectively evaluated hypersensitivity reactions in CRC pts treated with Oxaliplatin regimens at our Unit from Jan 2012 to Dec 2014. We adopted a post reaction regimen containing prolonged steroid premedication and slower oxaliplatin infusion as follows:
Post- reaction Regimen (p-rR)

Table: E18

drug	dose	duration	time
prednisone	50 mg		days -2,-1
dexamethasone	20 mg i.v.		45 min before oxaliplatin
chlorphenamine	10 mg		30 min before oxaliplatin
ranitidine	50 mg i.v.		30 min before oxaliplatin
Oxaliplatin	85 mg/mq -q14 ore 135 mg/mq -q21	360 min	0

Results: Thirteen of 241 (5.4%) CRC pts treated with Oxaliplatin showed symptoms of HSRs and 8 of them had history of allergy. The HSRs occurred after a median course number of 2 (range 1–10). Three of 13 pts showed mild HSRs including a case of dry cough and 2 cases of itchy throat. 9/13 experienced severe HSRs according to CTAE v 2.0, including 8 cases of broncho-laringospasm (2 cases with dysphonia) and a case of diffuse skin rash. Each patient subsequently received oxaliplatin p-rR cycles and completed the treatment both in adjuvant and metastatic setting without further reactions. Median p-rR course number was 5.5 (2-8). A pt presented anaphylactic shock and definitively discontinued Oxaliplatin.

Conclusion: We conclude that a post-reaction regimen including extended premedication and prolonged infusion of oxaliplatin might be safely adopted in the majority of patients after a severe HRSs.

E19 Chemotherapy rechallenge after regorafenib treatment in metastatic colorectal cancer. Still hope after the last hope?

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Introduction: The introduction of biological agents is changing the natural history of metastatic (CRC). Nowadays the mechanisms of resistance to biological agents is an emerging problem; the disease progression is caused by the development of resistant clones. According to some authors, these clones can be resensitized to traditional and previously utilized chemotherapy agents. The results of CORRECT study demonstrated the efficacy of regorafenib monotherapy both in KRAS wild type and mutant pretreated patients (pts). Recently, two reports showed the possibility to reintroduce chemotherapy even after regorafenib.

Methods: We performed a retrospective review of clinical data of pts treated with regorafenib at our institution, from March 2012 to March 2013. We analyzed pts characteristics, KRAS/NRAS status, responses to treatments (evaluated by RECIST v1.1 criteria) and survival.

Results: Regorafenib was given to 128 pts, 11 (8,6%) of them received post regorafenib therapy (to our knowledge). Median age was 56 years (range 42-59), male/female ratio 6/5, median PS (ECOG) 1 (range 0-2). 7 (63,6%) pts were KRAS/NRAS wild type. Post regorafenib therapy represented for all the pts at least the fourth line: all the pts received both oxaliplatin and irinotecan based chemotherapy, all of them were treated with bevacizumab and 7 pts received also cetuximab. Regorafenib represents the 3rd line of therapy for 4 pts, the 4th line for 5 pts, the 5th line for 1 patient (pt) and the 6th line for 1 pt. 8 pts (72,7%) were treated with standard chemotherapy after regorafenib (irinotecan monotherapy, capecitabine plus oxaliplatin or irinotecan, dacarbazine, raltitrexed) while 3 (27.3%) received experimental therapy (clinical trial). 9 pts out of 11 (81,8%) had PD and 2 (18.2%) had SD. Median PFS was 1.6+ months (range 0.5-3.5), median OS post regorafenib was 2.1+ months (range 0.5-10.2) and 6-months OS was 27,3%+.

Conclusion: Our retrospective analysis shows that after regorafenib, re-introducing chemotherapy is possible. Unfortunately we reported a high percentage of progression beyond regorafenib; this is probably due to the high percentage of heavily pretreated pts (some received four or five lines therapy before regorafenib). We think that regorafenib could represent a chemotherapy resensitizing agent but further studies are need in less pretreated patients.

E20 Adjuvant hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with colorectal cancer at high risk for the development of peritoneal metastases. A matched case-control study

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Background: Prognosis of colorectal cancer (CRC) peritoneal metastases (PM) is maximally improved when cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) are performed in early-stage patients. Despite the strong rationale, adjuvant HIPEC remains controversial. This matched case-control study assessed adjuvant HIPEC in CRC patients at high risk for metachronous PM.

Methods: From 2006 to 2013, twenty CRC patients with no systemic metastases were prospectively selected to undergo curative surgery, adjuvant HIPEC, and systemic chemotherapy (oxaliplatin/irinotecan-containing ±biologics), based onprimary tumor-associated criteria: resected synchronous ovarian (n = 2), or minimal peritoneal (n = 5) metastases, primary directly invading other organs (n = 4), or penetrating visceral peritoneum (n = 9). Forty matched (1:2) patients undergoing standard treatments and no HIPEC during the same period in our center were retrospectively included in control group. Cumulative PM incidence was calculated in a competing-risks framework.

Results: Groups were comparable for all characteristics. Median follow-up was 41.2 months (95% confidence interval (CI) = 29.4-52.9). Five-year cumulative PM incidence was 5.0% in HIPEC group, and 42.5% in control group (P = 0.004). Five-year overall and progression-free survival were significantly higher in HIPEC group, than in control group: 81.3% vs. 60.1% (P = 0.04), and 70.0% vs. 8.3% (P = 0.01). Severe morbidity occurred in 4/20 and 11/40 patients (P = 0.75), respectively. No operative death occurred.At multivariate analysis, HIPEC independently correlated to lower PM cumulative incidence (hazard ratio [HR] = 0.04; 95%CI = 0.01-0.31), higher overall survival (HR = 0.28; 95% CI = 0.08-1.03),and higher progression-free survival (HR = 0.31; 95%CI = 0.11-0.85).

Conclusion: Adjuvant HIPEC may benefit CRC patients at high risk for PM development. These results warrant confirmation in a phase-III trial.

E21 Histological subtype analysis of colon cancer: a population-based study. Is mucinous carcinoma a different disease? What clinical dilemma

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Background: Several retrospective studies suggested unfavourable outcome of mucinous tumours (MAC). However, if mucinous histology is a predictive and prognostic factor in colon cancer is uncertain.

Material and methods: We systematically collected data about incidence, survival, clinical features of the colon adenocarcinomas in the incident colon cancer population of Parma Province Cancer Registry between 2004 and 2009. Genetic alterations were studied in mucinous carcinomas. Mucinous adenocarcinoma was defined if > 50% of the lesion was composed of extracellular mucin. Histopathological slides of mucinous carcinomas were re-assessed for the final analysis.

Results: 1619 patients with a diagnosis of stage I to IV colon cancer were analyzed for study purposes: 165 mucinous (10%) and 1454 (90%) non-mucinous tumours (NMAC). A higher proportion of mucinous carcinomas compared with non-mucinous tumours were diagnosed at advanced stage (stage III 34% and stage I 11% vs 26% and 23%, respectively; p = 0.00), showed a higher percentage of poorly differentiated tumours (71% vs 30%; p = 0.000) and high microsatellite instability (44% vs 15%; p = 0.051). The peritoneum was the most common metastatic site in MAC (53%; p = 0.000) and the liver in NMAC (68%; p = 0.000). Multiple sites of metastases were more frequent in mucinous than non-mucinous tumours (52% vs 35%; p = 0.010). Radical surgery of metastasis was feasible in 24% of NMAC and 13% of MAC (p = 0.049). Tumours in the right colon reported a lower incidence of NMAC compared to MAC (32% vs 67%; p = 0.000), which more frequently showed advanced stage of disease regardless of the side (left colon stage I 10%, III 38%, IV 25%; p = 0.01 and right colon stage I 12%, III 32%, IV 22%; p = 0.043). There was different survival between right and left NMAC (left 63% vs right 53% at 60-month follow up; p = 0.000). If disease progression occurred, MACs were dramatically worse than other histology (7% vs 25% at 3-year follow up; p = 0.04). Both groups received chemotherapy for advanced disease in the same percentage (54%).

Conclusions: MACs are more often not suitable to loco-regional therapy and, if relapse occurs, they show less responsiveness to systemic therapy. Right colon carcinomas show worse outcome.

E22 HLA-G 3'UTR +2960 14-bp INDEL (Ins/Del) polymorphism is associated to improved DFS of stage II-III CRC patients

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Background: An important hallmark of Colorectal Cancer (CRC) is the evasion of immune surveillance. Human leukocyte antigen-G (HLA-G) HLA-G is a negative regulator of host immune response involved in tumor escape mechanisms. A reduced Overall Survival (OS) has been independently associated to HLA-G protein overexpression in primary CRC lesions.The 3'UTR +2960 14-bp INDEL (Ins/Del) SNP influence the protein magnitude by modulating HLA-G mRNA stability. The presence of the 14-bp Insertion has been associated to lower HLA-G protein levels. HLA-G3'UTR 14-bp SNP has never been explored in CRC outcome. The purpose of

this study was to investigate if HLA-G 3'UTR +2960 14-bp Ins/Del polymorphism have an impact on survival of non-metastatic CRC patients.

Patients and methods: A total of stage II-III 253 CRC patients was included from a prospective non-selected patient collection from Experimental and Clinical Pharmacology Unit of CRO-Aviano based on two previous published studies. Overall patients after diagnosis received adjuvant chemotherapy (ADJ-CT) based on fluoropyrimidine (FL) after primary surgery. The 3'UTR of the HLA-Ggene was amplified from genomic DNA by PCR and direct genotyping was performed. Our primary endpoints, Disease Free Survival (DFS) and OS, were analyzed by using Kaplan-Meier and multivariate Cox-regression models for survival analysis.

Results: Median age was 62.5 years (range 24-82) at onset. Median follow-up time was 56.3 months (range 1.2-186.3) for DFS and 62.8 months (range 4.6-186.3) for OS. In multivariate analysis after adjustments with clinical variables, we estimated an association with improved DFS in Ins/Del heterozygous (HR 0.59, 95% 0.36-0.96, p = 0.035) and in Insallele (Ins/Del +Ins/Ins, dominant model) carriers (HR 0.60, 95% 0.38-0.93, p = 0.023). Del/Del genotype was associated to a reduced 5-years DFS % (54%) compared to both Ins/Del (70%) and Ins/Ins genotypes (70%).Insallele was associated to improved OS even if not significantly.

Conclusions: This work for the first time estimates associations between HLA-G3'UTR +2960 14-bp Ins/Del and the prognosis of stage II-III CRC patients treated with FL-based ADJ-CT. Our study shows a prognostic and independent potential in multivariate analysis with a protective role for Insallele (lower HLA-G producer) in DFS. HLA-G3'UTR 14-bp Ins/Del polymorphism has emerged as novel prognostic biomarker in determining survival outcome of CRC. A validation in independent CRC cohorts is required.

E23 DEBIRI and cetuximab (DEBIRITUX) as a secondline treatment for unresectable colorectal liver metastases (UCLM): results of a phase II trial exploring a new sequence

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Aim: To investigate efficacy and safety of second-line treatment with Irinotecan-loaded Drug-eluting Beads (DEBIRI) and cetuximab of unresectable colorectal liver metastases.

Methods: Patients with the following characteristics were included in the study: unresectable hepatic metastases from colorectal carcinoma (CRC), progression after first line chemotherapy (any type of chemotherapeutic drug and combination was allowed), second line treatment (mandatory), which included for each patient (unregarding the K-Ras status) two cycles of DEBIRI (using 100-300 µm beads loaded with Irinotecan at a total dose 200 mg) followed by 12 cycles of cetuximab that was administered weekly at a first dose of 400 mg/m^2 and then 250 mg/m2; good performace status (0-2) and liver functionality (ALT and gamma-GT not exceeding three times the upper limit of normal, total bilirubin not exceeding 2.5 mg/ml). Data were collected retrospectively and included: tumor response (evaluated monthly for 6 months then every 3 months), KRas status, type and intensity of adverse events, overall survival and progression free survival.

Results: 40 patients with liver metastases from CRC were enrolled. The median duration of DEBIRITUX was 4.4 months (range, 4.0-6.5). All patients received the planned 2 cycles of DEBIRI and a median of 10 (range 8-12) cycles of cetuximab. The overall response rate was 50% with 4 complete responses (10%) and 16 (40%) partial responses. The most frequent grade 2 adverse events were: post-embolization syndrome (30%), diarrhea (25%), skin rushes (38%) and asthenia (35%). The retrospective evaluation of KRas status (24 wild type, 16 mutated) showed a significant higher response rate in the group of patients with wild type KRas. After a median follow-up of 29 months (range 8- 48 months), the median progression-free survival (PFS) and overall survival (OS) were 9.8 months and 20.4 months, respectively.Future randomized studies are needed in this setting to establish a role for locoregional treatment plus targeted agents compared with systemic chemotherapy.

Conclusion: The DEBIRITUX regimen appears to be effective and feasible in second line treatment of unresectable liver metastases from CRC.

E24 Clinical characteristics of a series of patients with prolonged clinical benefit after anti-EGFR treatment in metastatic colorectal cancer

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Background: The occurrence of clinical benefit (CB), defined as sustained stable diasese (SD) or partial or complete response (PR or CR), from anti-EGFR therapy in metastatic colorectal cancer (mCRC) is expected in nearly 50-60% of patients, especially when cetuximab or panitumumab are administered together with chemotherapy (CT) [Cunningham NEJM 2004; Douillard, JCO 2010; Heinemann Lancet Oncol 2014]. However prolonged CB over 12 months is not the standard and the occurrence of secondary resistance is expected in the majority of patients within 6-12 months from the beginning of treatment. Case series about prolonged CB in mCRC in a real practice setting are lacking.

Methods: We retrospectively reviewed our clinical chart records to identify patients that received an anti-EGFR treatment for mCRC starting from 2006. Patients were included if they experienced a CB, SD or better, lasting more than 12 months after receiving continuous anti-EGFR treatment in association or not with chemotherapy.

Results: 17 out of 215 (7,9%) patients experienced a CB of more than 12 months, with a median of 19 months of CB. The mean age was 62 ± 8 years, 64% of patients were male and 84% had liver metastases. Mean overall survival from the diagnosis of mCRC was 5 ± 2.2 years. In 88,2% of cases the anti-EGFR was cetuximab, in all cases administered with CT, while in 2 cases panitumumab monotherapy was administered. In 57,8% of cases the anti-EGFR was administered as a third line treatment or beyond. Other main prognostic/predictive characteristics of this population are described in the following table.

Table: E24

Prognostic/predictive factors	Description
Right-Left Colon - Rectum	35,3% - 52,9% - 11,8%
Stage IV at diagnosis	70,5%
KRAS wild-type - mutated	94,1% - 5,9%
1 only metastatic site or disease < 2 cm in every site	41,1%
Best Response at imaging : RC - RP - SD	11,8% - 35,3% - 52,9%
Local liver therapy during EGFR administration: None - Radical Surgery – Liver RFA	47,1% - 29,4% - 23,5%
Baseline CEA: < 100–100/1000 - > 1000 ng/ml	82,3% - 5,9% - 11,8%

Conclusions: prolonged responses to anti-EGFR treatment in mCRC, mainly in association with chemotherapy, are rare but not exceptional, even beyond the second line of treatment. Stage IV at diagnosis, a high disease burden or a not-response (i.e. SD) at the imaging evaluation don't exclude a prolonged CB over 12 months. As expected, a prolonged response to treatment is associated with a survival beyond 3 years from the diagnosis of metastatic disease.

E25 Fluoropyrimidine-related toxicity in gastrointestinal cancer patients. Assessment of risk factors

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Background: Fluoropyrimidines (FPs) (5-fluorouracil and capecitabine) represent the backbone of many chemotherapy (CHT) regimens for the treatment (TX) of gastrointestinal (GI) cancers. However, a narrow therapeutic index characterizes these drugs. Major side effects are frequently observed, sometimes leading to patient (pt)

death. Moreover, toxicity (tox) often implies TX discontinuation or delayed drug administration.A potential relationship between clinical and/or genetic (Gt) characteristics and the development of side effects during FP administration has been shown.The aim of our study was the identification of clinical, pathological and pharmacoGt factors related to the development of FP-related tox in a retrospective cohort.

Patients and methods: 157 pts affected by GI neoplasms (colorectal and gastric cancers) treated with FP-based CHT (single agents or combinations mainly with platins) were included. FP-related tox was evaluated by NCI-CTCAE 4.03. Dihydropyrimidine dehydrogenase (*DYPD*) variants were analyzed by Sanger sequencing and TaqMan allelic discrimination assay. Statistical correlations were established by χ^2 or Kruskall Wallis. All tests were performed by SPSS V.21 software. $P < 0.05$ was considered statistically significant.

Results: The study of correlations between clinical, pathological factors and tox evidenced a relationship between development of tox (especially that occurring during the first three cycles) and gender (greater in females vs males), CHT regimen (greater in polyCHT vs monoCHT), and disease stage (greater in IV vs II-III stage). 83 pts (a cohort with baseline characteristics similar to the entire population) were genotyped for *DYPD* polymorphisms, including 3 nonfunctional *DYPD* variants related to FP tox (c.1905 + 1G > A, c.2846A > T and c.1679T > G) and the putative deleterious variant hapB3. A statistically significant association was observed between GI tox and *DYPD* c.1905 + 1G > A and c.2846A T polymorphisms. In particular, these polymorphisms were associated with grade ≥2 tox ($p = 0.004$ and $p = 0.005$, respectively). *DYPD* c.1905 + 1G> A was also correlated with asthenia ($p = 0.001$).

Conclusions: Our results confirm the role of clinical and pathological factors (e.g. gender, CHT regimen, disease stage) in predicting the risk of tox. These factors in addition to the Gt analysis of *DYPD* variants (e.g. c.1905 + 1G > A, c.2846A > T and c.1679T > G), could help in the development of a predictive algorithm of tox in pts with GI cancer treated with FP-based CHT.

E26 Changing incidence and clinical implications of bone metastases in colorectal cancer: a pooled analysis

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Background: Bone metastases (BM) in colorectal cancer (CRC) are uncommon, usually present late in the natural history of metastatic disease, and are associated with liver or lung metastases. Affected patients had limited survival. Higher survival rates in CRC and multiple systemic treatments have led to a change in the temporal pattern of metastatic spread and consequent clinical implications.

Methods: Articles retrieved by MEDLINE search (English language, 1970-2015). We analyzed data from nine studies involving 13134 patients with CRC, in order to evaluate BM incidence and patient outcomes.

Results: Our analysis documented an incidence of BM of approximately 9.2% (range 4.5-23.7%.) The median time from CRC diagnosis to BM detection was 21.6 months (range 11-33.8). Median overall survival after BM diagnosis was 10.3 months (range 7-15.9). No clear data are available on tumor histology and tumor site.

Conclusions: These results show a notable variability in the several studies of BM rates and prognosis, probably related to the different therapeutic approach, changing in the last 40 years. However, survival after bone metastases remain poor. Therefore, the early detection is imperative to significantly improve prognosis and prevent skeletal events. Further insights into tumor histology, RAS status correlations and OPG/RANK/RANKL expression analysis are warranted for better understanding the molecular biology of BM in CRC.

E27 Obesity and colorectal cancer: adiponectin and tumor necrosis factor alfa a representative link between inflammation and cancer

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Background: Adiponectin (APN) is a protein synthesized and secreted by adipocytes into the peripheral blood with pleiotropic functions in lipid/glucose metabolism, and beneficial roles in cardiovascular functions and inflammation. However, circulating APN level is inversely related with body weight. In obesity, decreased APN serum levels correlate with tumor development and progression and are inversely associated with markers of inflammation. In particular APN was shown to reduce TNF-a induced effects on cell proliferation and migration. Study aim's was to explore the correlation of serum APN and TNF-a with CRC risk in relation to obesity.

Materials and method: We conducted a case-control study comprising 52 CRC patients 26 women and 26 men, median age 70.5 years (33-86) and 30 healthy subjects, median age 56 years (26-75). Blood samples were obtained from all subjects at the time of diagnosis. The enzyme-linked immunosorbent assay was used to measure APN and TNF-a serum levels. Using the height and weight value of all participants, body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

Results: Serum APN in CRC patients were significantly lower than the controls (98.7 ± 55.6 *vs* 6641 ± 3263 ng/ml), while serum TNF-a were higher than control (168 ± 93 *vs* 0.5-5.5 pg/ml), $p < 0.0001$. A significant inverse correlation between the two markers was found, $p = 0.006$. Calculated BMI (kg/m2) values were <25 (normal weight, n = 23 pts), ≥25 (overweight, n = 17 pts) and ≥29 (obese, n = 12 pts). A inverse correlation was observed between serum APN and BMI, APN levels decreased in relation to BMI increases; while serum TNF-a increases with increasing BMI. Also a negative correlation was present between tumor stage and APN ($p < 0.001$).

Conclusions: APN concentrations are strongly determined by obesity status and its expression is decreased by TNF-a. In our series the negative correlation between tumor stage and circulating APN, suggests that APN may have an important protective role in carcinogenesis induced by inflammation influencing cancer biology regulating cell proliferation and inducing apoptosis. In obesity alteration of APN and TNF-a signaling could be an active local player determining the peritumoral milieu that promotes tumor rise and progression. Our study support that the links between obesity and inflammation and between chronic inflammation and cancer suggest that inflammation might be important in the obesity-cancer link.

Table: E26

Study	N° Pts with CRC and BM	N° Pts with CC and BM	N° Pts with RC and BM	N° Pts with CC and exclusive BM	N° Pts with RC and exclusive BM	TH: Non-mucinous	TH: Mucinous	TH: Others	Median time from PT diagnosis to BM diagnosis (months)	OS after BM diagnosis (months)	OS from CRC diagnosis (months)
Besbeas S, *1977*	53/765 (6.9%)	21/53	32/53	14/53		NI			33.8	13.2	44.7
Bonnheim DC, *1986*	66	47/66		19/66		NI			21	7	–
Jimi S, *2013*	32/627 (5.1%)	NI		5/32		30/32		2/ 32	17.6	9.3	NI
Kanthan R, *1999*	355/5352 (6.6%)	295/355		60/355		NI			NI		
Katoh M, *1995*	28/118 (23.7%)	16/28	12/28	0/28		26/28	2/28	0/28	NI		
Portales F, *2015*	110/2434 (4.5%)	69/ 110	41/110	15/110	11/110	NI			25.1	9.4	NI
Roth ES, *2009*	14/252 (5.5%)	NI		0		NI			21.2	15.9	42.4
Santini D, *2012*	264/2500 (10.6%)	163/264	98/264	NI		174/264	56/264	34/264	11	7	NI
Sundermeyer ML, *2005*	106/1020 (10.4%)	66/106	40/106	NI		NI			NI		21

Abbreviations: Pts, patients; CRC, colorectal cancer; CC, colon cancer; RC, rectal cancer; BM, bone metastases; TH, tumor histology; PT, primary tumor; OS, overall survival; NI, Not Indicated.

E28 Circannual variation of efficacy outcomes in patients with newly diagnosed metastatic colorectal cancer and treated with first-line chemotherapy

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Seasonal variation of initial diagnosis of localized colorectal cancer (stage I-III) has been reported in literature as an independent variable that influences overall survival. On the contrary, no data about such a rhythm in advanced stage patients are actually availabile. In this study we collected data about 1610 newly diagnosed advanced colorectal cancer patients treated at four independent centers; responses to first line chemotherapy were available for 1495 patients. A strong circadian rythm in response rate was evident (MESOR 37.7%, double amplitude 11.1%, acrophase in January; $p < 0.001$). At the time of data cutoff, 1322 patients progressed, with a median progression free survival of 11 months. A circannual rhythmicity of the proportion of patients progressing at 6 months was demonstrated, with MESOR 79%, double amplitude 5.2%, and acrophase in February ($p < 0.001$). Survival rate at one year showed a synchronized rhythm with MESOR 80.0%, a double amplitude of 4.2% and acrophase in January ($p = 0.05$). Several interpretation about the genesis of this cyclic variation could be claimed: the rhythm in sunlight exposure and consequently of vitamin D serum levels and folate degradation, the variability in toxic effect intensity of chemotherapy, and the rhythm in the biological behavior of tumor cells. Further investigation on our observation both in preclinical and clinical settings are needed, in order to better clarify the underlying mechanisms.

E29 Disease progression and overall survival in sardinian patients with colorectal cancer according to the kras mutational status

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Background: Mutation in *KRAS* gene has been extensively demonstrated to act as a predictor of response to EGFR-targeted agents in patients with colorectal cancer. Less is known about the significance of *KRAS* mutation as a prognostic factor of disease progression and survival, independently of anti-EGFR therapy. The aim of the present study is to evaluate the prognostic role of the KRAS mutational status in a cohort of Sardinian patients with colorectal cancer.

Materials and methods: Five hundred and fifty-one consecutive Sardinian patients with histologically proven diagnosis of invasive colorectal carcinoma were included into the study, regardless of age at diagnosis and disease characteristics. Clinical and pathological disease features were confirmed by medical records, pathology reports, and cancer registry data. For mutational analysis, paraffin embedded tissue samples with at least 70% neoplastic cells were processed; genomic DNA was isolated from tissue sections and DNA quality assessed for each specimen. The coding sequences and splice junctions of exons 2, 3, and 4 in *KRAS* gene were screened for mutations by direct automated sequencing.

Results: *KRAS* mutations were detected in 183/551 (33%) patients; three of them presented the coexistence of two *KRAS* mutations in the same primary tumor tissue. Among the 186 *KRAS* mutations identified, two thirds (125; 67%) were located in codon 12, about one fifth (36; 19.4%) in codon 13, and about one tenth (18; 9.7%) in codon 61. The remaining mutations (7; 3.8%) were detected in uncommonly-affected codons of the *KRAS* gene. No significant correlations between *KRAS* mutations and sex, age at diagnosis, anatomical location, and disease stage at the time of diagnosis were found. No prognostic values of *KRAS* mutations were found for either the time to progression as metastatic disease or the overall survival. When patients were stratified by both *KRAS* mutational status and sex, a significantly better metastasis-free survival was observed for *KRAS*-mutated male cases. Considering the gene positions of the identified *KRAS* mutations, no correlation with both the time to progression as metastatic disease and overall survival was observed.

Conclusions: Our data suggest that *KRAS* mutations are correlated to a slower progression of the disease in males with colorectal cancer from Sardinia, irrespectively of the diagnosis age and the mutation position. Such findings were not confirmed considering the overall survival in both sexes.

E30 KRAS status and risk of venous thromboembolic events in patients with metastatic colorectal cancer: a case-control study

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Background: Cancer patients are at increased risk of venous thrombotic events (VTE). Tissue factor (TF) is the primary initiator of blood coagulation and preclinical data suggest that its expression is also controlled by KRAS. Higher levels of TF seem to be associated with mutations of KRAS; the latter therefore might be a plausible link to hypercoagulability and increased VTE risk for metastatic colorectal cancer (mCRC) patients (pts).

Patients and methods: A retrospective case-control study was conducted. Cases had VTE (deep vein thrombosis (DVT), pulmonary embolism (PE), and/or migratory superficial thrombophlebitis) occurring after diagnosis of metastatic disease. Controls were pts with mCRC without VTE, matched for age, sex, year of diagnosis of metastatic disease, and presence of a central venous access device. Cases and controls were identified from the electronic health records of the Department of Oncology, Udine, and of the Department of Oncology, Pisa. Formalin-fixed, paraffin-embedded samples were reviewed and tested by pyrosequencing for KRAS status (codons 12, 13, 61 and 146). Estimating that about 40% of mCRC harbor a KRAS mutation and with a cases/controls ratio of 1:2, the sample size needed to determine a significant odds ratio (OR) of 2.5 was approximately 77 cases and 154 controls, with $\alpha = 0.05$ and a power of 80%.

Results: Between January 2008 and December 2014 a total of 68 cases with VTE and 177 controls without VTE were included. Thirty-four of the cases had DVT, 34 had PE. Of note, 6 patients had both thrombotic events. When VTE occurred, 37% of pts were receiving a bevacizumab-containing regimen. Among the controls, 38% received bevacizumab. Fifty-three (78%) of the cases and 137 (77%) of the controls had a central venous access device. The OR for thrombosis in KRAS mutated (codon 12, 13, 61 and 146) mCRC pts was 1.34 (95%CI 0.77-2.36, $p = 0.303$).

Conclusions: Despite the trend towards an increased risk of VTE for pts with KRAS-mutant mCRC, our results were not statistically significant and did not confirm the findings of a similar retrospective study conducted in pts with mCRC [Ades S, et al. J Thromb Haemost 2015]. Whether tumor genetic profile may contribute to the thrombotic risk assessment of CRC cancer pts remains uncertain.

E31 A phase II study employing Hepatic Intrarterial Irinotecan Drug-Eluiting Beads (DEBIRI) as salvatage therapy in liver metastatic colorectal cancer patients: the first South Italy experience

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Background: Liver metastases (LM) from colorectal cancer (CRC) represent a predominant cause of death. Transarterial chemoembolization (TACE) has been investigated in patients (pts) with LM and available data suggest that TACE can achieve disease stabilization or improvement in heavily pretreated patients.

Methods: Twenty-five pts with LMCRC, who failed second- and/or third-line systemic chemotherapy, received TACE with drug-eluting beads preloaded with 100 mg or 200 mg of irinotecan (DEBIRI). A total number of 44 DEBIRI treatments were performed. Primary endpoint was response rate (RR) assessed using modified Response Evaluation

Criteria in Solid Tumor (mRECIST version 1.1). Secondary endpoints were overall survival (OS) and toxicity, analyzed using the Kaplan-Meier method and Common Terminology Criteria for Adverse Events version 3.0, respectively.

Results: RR (complete + partial response) was 35%. Complete and partial response were observed in 22% and 13% of pts, respectively. Stable and progressive disease were observed in 52% and 13% of pts, respectively. Median OS was 37 months (95%CI: 13.881 to 60.119). Toxicity was reversible following treatment, including mainly grade 1 or 2 adverse events such as hypertransaminasemia (46%), pain (20%) and fever (16%).

Conclusions: The favorable tumor response and good safety profile make DEBIRI a potential therapy in pretreated LMCRC pts. Notwithstanding further larger phase III studies are needed to confirm these data, we can state that DEBIRI is an emerging attractive treatment in these pts.

E32 Tumor-associated macrophages correlate with microvascular density and endothelial area in locally advanced colorectal cancer patients undergone to surgery

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Background: Tumor-associated macrophages (TAMs) represent pivotal components of tumor microenvironment promoting angiogenesis, tumor progression and invasion. In colorectal cancer (CRC) there are no conclusive data about the role of TAMs in angiogenesis-mediated tumor progression. In this study we aimed to evaluate a correlation between TAMs, TAMs immunostained area (TAMIA), microvascular density (MVD) and endothelial area (EA) in primary tumor tissue of locally advanced colorectal cancer (CRC) patients undergone to radical surgery.

Material and methods: A series of 76 patients with CRC were selected and evaluated by immunohistochemistry and image analysis. An anti-CD68 antibody was employed to assess TAMs and TAMIA expression and anti CD34 antibody was utilized to detect MVD and EA expression; then tumor sections were evaluated by image analysis methods.

Results: The mean ± s.d. of TAMs and MVD was 65,58 ± 21,14 and 28,53 ± 7,75 and the mean ± s.d. of TAMIA and EA was 438,37 ± 124,14 μ^2 and 186,73 ± 67,22 μ^2, respectively. A significant correlation was found between: TAMs, TAMIA, MVD and EA each other (r ranging from 0,69 to 0,84; p ranging from 0.000 to 0.004).

Conclusions: The high level of expression of TAMs and TAMIA in tumor tissue and the significant correlation with both MVD and EA illustrate that TAMs could represent a marker that plays an important role in promoting angiogenesis-mediated CRC. In this context novel agents killing TAMs (e.g. trabectedin, peptide M2, PLX3397) might be evaluated in clinical trials as a new anti-angiogenic approach.

E33 Thymidylate-synthase poly-epitope peptide vaccination in pretreated metastatic cancer patients; a multi-arm phase Ib trial

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Thymidylate-synthase (TS) poly-epitope (27-mer) peptide (TSPP) is a vaccine containing the amino-acidic sequences of three CTL epitopes with HLA-A2.1-binding motifs of TS, an enzyme over-expressed in cancer cells, which plays a crucial role for DNA repair and replication and inhibited by 5'-fluorouracil. Preclinical characterization granted the rationale to design a dose-finding multi-arm phase Ib trial (TSPP/VAC1) to test in metastatic cancer patients TSPP vaccination alone (arm A) or in combination with the IG1 immunomodulation regimen[1] (with GM-CSF scIL2) (arm B) or in combination with the GOLFIG poly-chemoimmunotherapy[2] (arm C). This trial was designed to test the safety and immunobiological activity of TSPP vaccination in different therapeutic conditions. Forty-nine pretreated metastatic cancer patients, with a good performance status (ECOG < 2) were enrolled in the study between April 2011 and July 2013 (12 in arm A, 9 in arm B, 29 in arm C). All patients received every 2/3 weeks sc. injections of TSPP/montanide (1:1 emulsion) at escalating dosage [9, 100 µg (DL-1); 9, 200 µg (DL-2) and 31, 300 µg (DL-3)]. Dosage and schedules of IG1 and GOLFIG regimen have been published in previous reports[1,2]. TSPP resulted safe and its MTD was not achieved. There was no grade 4 toxicity. The most common adverse events were grade 2 dermatological reactions; cough, rhinitis, fever, poly-arthralgia, gastro-enteric symptoms and to a lesser extent, moderate hypertension and hypothyroidism. The majority of adverse events recorded in the arm C were related to GOLFIG regimen and consisted G1-2 haematological (16 cases) and gastro-enteric events (12). TSPP vaccination was associated with rise in auto-antibodies and TS-epitope-specific CTL precursors with substantial differences in the expression of regulatory-T-cells, CTL subsets, and cytokine functional phenotype among the arms. TSPP vaccination showed evidence of antitumor activity with a disease control rate of 66.7% in arm A, 33.3% in arm B, and 79.3% in arm C with a median PFS of 6.4 (95% CI = 3.66-9.2), 3.69 (95%CI = 1.55-5.82), and 4.93 (95%CI = 3,79-6,065) months respectively, and an OS of 10.98 (95% CI = 7.56-14.4), 5.9 (95% CI = 4.11-7.69), and 11.96 (95% CI= 8,92-14.98) months, respectively. Our findings provide the framework to evaluate TSPP anti-tumor activity in further trials.

References [1]P Correale, et al, Eur J Cancer.2001, 37:892-902; [2]P. Correale, et al, J Clin Oncol. 2005, 23:8950-8.

E34 Evaluation of Tumor Response after first line combined therapy (Bevacizumab plus chemotherapy) in unresectable liver metastases from colorectal cancer: predictive value of RECIST 1.1 and CHOI criteria in short-term follow-up

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Background: Since the introduction of antiangiogenic agents, RECIST criteria seemed to be insufficient in assessing response to therapy in colorectal liver metastases (CLM).

Methods: Forty-one pts affected with CLM were retrospectively observed after first line therapy. We performed multidetector computed tomography at baseline and after therapy at ttime 1 (2 months) and at time 2 (5 months). We compared tumor responses according to RECIST 1.1 and Choi criteria and investigated their association with time to progression (TTP).

Results: Median TTP was 281 days (95% CI 175.555-386.445) as assessed with RECIST, 361 days (95% CI 324.131-397.869) as assessed with Choi criteria; median OS was 644 days (95% CI 457.624-708.376). At T1, according to RECIST, no patient had CR, while 14 patients (34.1%) were characterized as having achieved PR. In contrast, stable disease (SD) was the most common tumor response found in 39% (n = 16) of patients, whereas 26.8% (n = 11) of patients were categorized as PD. When Choi criteria were applied, no patient qualified for CR, 90.2% (n = 37) of patients were categorized as PR, 7.3% (n = 3) as SD, and 2.4% (n = 1) as PD. At T2, when RECIST were used for response assessment, 14.6% (n = 6) of patients were characterized as having PR, the vast majority of patients (58.8%, n = 24) were classified as SD, while 26.8% (n = 11) were rated as PD. According to Choi criteria, 56.1% (n = 23) of patients were categorized as PR, 24.4% (n = 10) as SD, and 19.5% (n = 8, beforehand categorized as PR) as PD. An overview of median TTP according to response categorization with RECIST and Choi criteria at T1 and T2 is given in Table 1.

Table: E34

Response catergory	T1					T2				
	RECIST		Choi		p (log-rank test)	RECIST		Choi		p (log-rank test)
	N	TTP (days)	N	TTP (days)		N	TTP (days)	N	TTP (days)	
PR	14	380	37	281	0.335	6	281	23	355	0.767
SD	16	355	3	333	0.495	24	380	10	333	0.905
PD	11	99	1	79	0.121	11	172	8	150	1

Based on different TTP data, we categorized pts as Responders (PR + SD) and Non Responders (PD) and we compared mTTP among these subgroups of pts pointing out shorter mTTP for NR vs. R (T1 99 vs. 375 days, p < 0.0001; T2 172 vs. 357 days p < 0.0001) according to RECIST, meanwhile significant shorter mTTP for NR vs. R (172 vs. 357 days p < 0.0001) only at T2 according to Choi criteria.

Conclusions: The best predictive marker of therapeutic benefit in this setting of cancer treatment seems to be the absence of progression, no matter which response evaluation criteria were applied both at T2. Perhaps, at T1 Choi criteria might overestimate response rate.

E35 Chemotherapy delivery in patients with hereditary angioedema

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Background: Hereditary angioedema (HAE) is an autosomal dominant hereditary disorder (mutations in the C1-INH gene on chromosome 11) characterized by episodic swelling of many body regions (especially throat and abdomen), potentially triggered by medications. No data are available for cancer patients approaching standard chemotherapy. The aim of our study was to identify circulating mediators potentially predictive of acute HAE attacks during chemotherapy.

Patients and methods: 16 repeated blood testing (approximately every week) for C3, C4, CH50, C1 INH, FUNCT C1 INH, C1Q, d-dimer and for routine hematochemistry were performed in a 42-year-old male affected by HAE type 2, during standard adjuvant oxaliplatin/fluorouracil-based chemotherapy administered for a Stage III radically resected rectal cancer. Premedication with Berinert inhibitor C1 1000 U was administered every week during the whole treatment. Mann-Whitney U test was used to determine statistical differences between the first 30 days of therapy and beyond day 30 of therapy.

Results: Pre-chemotherapy values of tested variables (day 0) were: C3 101 mg/dl; C4 5.71 mg/dl; CH50 74%; C1 INH 43.4 mg/dl; FUNCT C1 INH 18%; C1Q 150 mg/dl and D dimer 113 µg/ml. The mean values of each circulating biomarker were calculated for the first 30 days of treatment (8 tests) and for the following treatment period (beyond day 30, other 8 tests): C3 114,5 vs 127,5 mg/dl; C4 2,4750 vs 3,165 mg/dl; CH50 9,5 vs 9,5%; C1 INH 28.75 mg/dl vs 33.8 mg/dl; C1 INH FUNCT 3,5 vs 38%; C1Q 123,95 vs 134 mg/dl; d dimer 571 vs 2940,5 µg/ml. According to Mann-Whitney U test, a significant change in circulating values was observed for C3 (p 0.009), d-dimer (p 0.0008) and FUNCT_C1_INH (p 0.01). Three HAE attacks were observed, they started since the forth cycle of treatment and were all manageable. Changes in C3, d-dimer and FUNCT C1 INH preceded the attacks.

Conclusions: The stress induced by chemotherapy such as standard oxaliplatin/fluorouracil increases the risk of attacks in patients with HAE,. However, circulating biomarkers such as D DIMER, C3 and FUNCT C1 INH may serve as early predictors of acute HAE crisis.

E36 Resection of lung metastases from colorectal cancer: analysis of outcome and prognostic factors

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Background: Surgical removal of liver metastases can provide a chance of cure for selected patients (pts) with metastatic colorectal cancer (CRC). Less data are currently available on CRC lung metastases resection. The aim of our study was to analyse the effectiveness of CRC lung or lung and hepatic metastases resection.

Material and methods: We retrospectively analysed outcome and clinicopathologic features of 79 pts who underwent only lung or both liver and lung resection for metastatic CRC from 2000 to 2014 at our institution.

Results: Among pts, 45 were men and 34 women. Mean age was 62.6 years. All pts underwent resection of primary tumour and 81% received an adjuvant chemotherapy treatment. Pts with unilateral metastases were 90% and 64.6% had a single metastasis. Most of pts (64.6%) had small lung nodules with larger diameter less than 2 cm. Most of them (70.9%) received also a peri-operative chemotherapy treatment. Fifthy-two pts (65.8%) had lung and liver resection, 42 pts (80.8%) liver first, 9 (17.3%) lung first and 1 a simultaneous resection of liver and lung. At a median follow-up of 35.1 months, 77.1% are alive and 64.1 are disease-free. Median survival was 26.3 months (87.3% at 1 year, 34.7% at 3 years and 23.6% at 5 years). Pts with unilateral disease had a significantly higher survival (87 vs 31 months; p = 0.02; confidence interval 0.04-0.8). Survival from lung resection for pts who underwent both liver and lung resection was 29.2 months. Prognostic factors for this subset of pts were the presence of solitary or multiple lung metastases (87 vs. 31 months, respectively, p = 0.03; confidence interval 0,11-0,91) and unilateral vs bilateral disease (87 vs 23 months; p = < 0,0001; confidence interval 0,11-0,91). A trend of benefit on survival was observed in pts with K-RAS wild-type tumours and disease-free interval = 36 months.

Conclusion: Our data suggest that the resection of lung metastases for patients with CRC is feasible and could have an impact on overall survival, also for those who underwent hepatic resection. More data on clinical and biological prognostic factors from larger and prospective studies are necessary for a better selection of patients who could benefit from a repeated surgical approach in the continuum of care.

E37 Pattern of metastasis and outcome in patients with colorectal cancer

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Background: Although the mechanisms of cancer spread are not fully understood, recent data suggest there may be differences in metastatic pattern (MP) according to clinico-pathological characteristics of colorectal cancer (CRC) patients (pts). Aim of this study is to analyze the specific pattern of metastatic dissemination during the course of the disease according to different features.

Patients: We analyzed a retrospective series of 528 metastatic CRC pts diagnosed at University Hospital of Udine from 1998 to 2015. Clinico-pathological factors were evaluated to test their association with site-specific MP spread both at the time of diagnosis (DT) and at any time (AT). Unconditional logistic regression was performed with uni- and multivariate models.

Results: Median follow-up was 64.2 months (95%CI 56.0-74.8), median OS was 23.8 months (95%CI 22.0-26.4). After metastasectomy, 54 pts had no evidence of disease at the last follow-up. Multivariate analysis results are showed in table 1. Surgery on primary tumor and RAS wild-type (wt) molecular profile were associated with metastases located at a single anatomic site at AT. BRAF wt CRC developed more frequently liver metastases. Lung involvement was less frequent in RAS wt both at DT and at AT, and after primary resection at DT; conversely, it was more frequent at AT in male pts. MP at DT was also related to the primary tumor location, with a high rate of lung metastases in left colon and rectal primary sites, whereas tumors of right colon more often had peritoneal localization. Non-mucinous histotype was associated with lower rate of peritoneal localization.

Conclusions: Specific clinico-pathological features such as sex, resection and location of the primary tumor, and molecular biology may help defining the MP in CRC pts. If confirmed by larger studies, our findings could result into more tailored treatments, influencing multidisciplinary approach and surveillance protocols.

Table: E37 Characteristics influencing site-specific MP at DT and AT

	Site	DT		AT	
		Odds Ratio	95% CI	Odds Ratio	95% CI
Male	***Multiple***	–	–	1.61	1.02–2.54
	Lung	–	–	1.73	1.11–2.69
Resected primary	***multiple***	0.18	0.11–0.29	0.46	0.25–0.83
	Liver	0.55	0.32–0.92	–	–
	Lung	0.59	0.36–0.97	–	–
Rectal	**Lung**	5.25	2.91–9.50	3.34	1.77–6.31
	Peritoneum	0.21	0.09–0.50	0.31	0.16–0.62
Left-side	**Lung**	1.71	1.00–2.91	–	–
	Peritoneum	0.56	0.32–0.96	0.56	0.34–0.90
Non-mucinous	**Peritoneum**	–	–	0.54	0.31–0.96
BRAF wt	***Multiple***	0.30	0.14–0.60	–	–
	Liver	2.54	1.27–5.10	2.49	1.22–5.08
RAS wt	***Multiple***	–	–	0.57	0.36–0.90
	Lung	0.36	0.23–0.56	0.43	0.27–0.68

E38 Predictive value of bevacizumab –related hypertension and proteinuria in patients with mCRC in the real practice

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Background: The anti-VEGF monoclonal antibody Bevacizumab has shown to prolong both PFS and OS in patients with metastatic colorectal cancer (mCRC) in association with chemotherapy in many randomized trials. Although Bevacizumab – containing first or second therapies are largely administrated, not all pts benefit from it

and there are no biomarkers available for the prediction of its efficacy. Several studies demonstrated a connection between hypertension, proteinuria (common side effects of bevacizumab) and improvement of disease outcome in pts with mCRC.

Patients and methods: In this study we retrospectively assessed whether treatment-related hypertension and proteinuria are associated with outcome in consecutive mCRC pts treated with bevacizumab at the Oncology Unit of Ferrara before March 2014. Clinical, radiological and laboratory data were available on electronic medical records of our Hospital. We performed an univariate analysis of survival in order to compare TTP and OS between pts developing hypertension or proteinuria and those who have not presented these side effects.

Results: We collected data from 61 pts, median age 61 (range 40-75). The site of primitive tumor was colon in 67% and rectum in 33% of pts. KRAS exon 2 (codons 12/13) analysis was performed in 50 pts (37.7% mutated, 43% wild type). The majority of them (77%) received Bevacizumab – containing therapy as first line of treatment while 23% as second line. Eight pts (13%) developed grade 2-4 hypertension during the treatment with bevacizumab after a median period of 8 weeks (range 4–17). All pts received antihypertensive drugs with good control of the adverse event The median TTP was 9 months (95% CI 5.7–12.2) in pts developing hypertension vs 6 months (95% CI 5.1–6.9) in pts without hypertension, p= 0.03 . No association between G2-G4 hypertension and OS was found. A total of 20 pts (33%) had proteinuria during bevacizumab treatment; this was moderate to severe in 6 pts (9%). Proteinuria occurs after a median period of 14 weeks (range 11–25) and was not significantly correlated to TTP and OS in our analysis.

Conclusion: Treatment of mCRC with bevacizumab was shown to be well tolerated and easily manageable. Our analysis of the data confirms that the development of hypertension could be a predictive factor for response.

E39 Everolimus in locally advanced rectal cancer (E-LARC study, Ib): biomarkers evaluation

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Background: mTOR and p-ERK pathway are constitutively activated in colon-rectal cancer, but few data are published in literature on the role of mTOR inhibitors in this setting. We recently presented at ESMO Congress in Madrid (2014) the clinical results of a phase Ib trial of Everolimus (Eve) in association with 5-fluorouracil (5FU) and radiotherapy (RT) in locally advanced rectal cancer (LARC). Aim of the present report is to describe evaluation of biological parameters of inhibition of target (tissue expression of phospho-mTOR and phospho-p70S6K) before (T0), after 2 weeks of treatment (T1) (before concomitant treatment) and on surgical specimen (T2) of pts enrolled in this trial (secondary objective).

Material and methods: Between March 2011 and December 2013, 13 patients (pts) with histologically confirmed diagnosis of LARC (T3-T4; N0-1; within 15 cm from anal rhyma) were enrolled at Modena University Hospital. Pts have been sequentially assigned to one of the following 4 cohorts and have been administered with the following dose levels: Eve 2,5 mg; 5 mg; 7,5 mg; 10 mg daily per os starting from 14 days before 5FU and RT and for all the duration of the concomitant treatment. mTOR and p-S6 determinations were performed on paraffin-embedded tumor tissue specimens (timing defined above).

Results: All pts were evaluable for biological parameters evaluation: 13 pts on T0, 12 pts on T1 (1 pt refused second biopsy) and 10 pts on T2 (3 pts experienced complete pathological response, pCR, with no residual tumor cells). The expression mTOR and p-S6 was tested by immunohistochemistry and defined as follows: 1+ weak, focus expression; 2+ intense widespread expression. mTOR expression was as follows: T0, 2+ in 7 pts (53,8%), 1+ in 6 pts (46,2%); T1, 2+ in 8 pts (66,6%), 1+ in 4 pts (33,4%); T2, 2 + 4 pts (40%), 1+ 6 pts (60%). p-S6 expression was as follows: T0, 2+ in 7 pts (53,8%), 1 + 6 pts (46,2%); T1, 2+ in 7 pts (58,3%), 1+ in 5 pts (41,7); T2, 2+ in 4 pts (40%), 1+ in 6 pts (60%). No concordance was found within the pt for mTOR and p-S6 expression. Pts who experienced pCR had different biomarkers assessment: pt N5 had 2+ expression of both mTOR and p-S6 on T0 and T1, pt N 12 had 1+ expression of both on T0 (refused second biopsy), pt N13 had 1+ of both parameters on T0, 1+ mTOR and 2+ p-S6 on T2.

Conclusions: Relationship between biological parameters of inhibition of target and Eve treatment in rectal cancer remains still unclear and needs further studies.

E40 Clinical Outcome of Patients With Stage IV Colorectal Cancer Receiving Combination Chemotherapy Without Surgery As Initial Treatment

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Background: At the time of diagnosis, 25% of patients (pts) with colorectal cancer (CRC) present synchronous unresectable metastases. The best therapeutic option for this pts is not yet defined: primary tumor resection (PTR) followed by chemotherapy or upfront chemotherapy without PTR?

Methods: We conducted a prospective observation trial. Main study's objective was to describe the incidence of primary tumor–related complications in pts with stage IV CRC who received up-front oxaliplatin- or irinotecan-based combination chemotherapy with or without target therapies. Secondary objectives were: overall response rate (ORR- according to RECIST criteria), toxicity (CTCAE v4), progression free survival (PFS) and clinical benefit (defined as: increase in body weight and appetite, improvement of existing symptoms such as pain, bleeding, anorexia, asthenia).

Results: From July 2013 to January 2015, 38 pts with median age of 65.8 years (range 44-83), were enrolled. Primary tumors were: right colon (cecum, ascending or transverse colon) in 26.3% of pts, left colon (descending or sigmoid) in 52.6% and rectum in 21.1%. The most common sites of metastasis were: liver (65.8%), retroperitoneal nodes (48.1%), lung (52.7%), peritoneum (21.1%), bone (21.1%) and brain (13.2%). Metastases involved one site or organ in 52.6% of pts, two sites in 26.3%, three sites in 13.2% and four sites in 7.9%. Of 38 pts, 97,4% never required surgical palliation of their primary tumor. One patients (2,6%) required medical therapy for primary tumor subobstruction. No bleeding or intestinal perforation were observed in the site of primary tumor. After 6 months, 94.7% of pts was evaluable for response: ORR was 25%, no complete response (CR), was observed, disease control rate (CR + partial response + stable disease) was 75% and progression was 25%; median PFS was 9.3 months (range 3-15). Grade 3/4 toxicities were as follows: neutropenia 19.2%; diarrhea 11.3%; nausea-vomiting 1.6%. Pain improved in 80% of pts, constipation in 60% of pts with less need for medical treatment (laxatives and enemas toileting), appetite improved in 64.8% of pts and an increase in body weight was observed in 48.3% of pts.

Conclusions: These data showed that upfront chemotherapy, without routine prophylactic resection, could be an appropriate therapeutic option for pts with neither obstructed nor hemorrhaging primary colorectal tumors in the setting of metastatic disease.

E41 Treatment of patients with metastatic colorectal cancer over 75 years: Rimini's monoinstitutional experience

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Background: The approach to the elderly patient with colorectal cancer stage IV remains a much debated chapter in oncology. The ability to have parameters predictive of toxicity remains a major challenge to deliver care safely in this population. Aim of our study was to prospectively observe a group of patients followed at our facility to assess if there were clinical predictors of toxicity or efficacy.

Materials and methods: Data from patients over 75 years, evaluated from January 2012 to December 2014, were included into the analysis. Patients' characteristics and main results are described in table 1. We assessed Time to Progression and overall survival using the nonparametric method of Kaplan Meyer.

Table: E41

Number of patients	69
Median age	79
Median Charlson index adjusted for age	5
> 4 concomitant drugs	18 (26%)
Dose intensity	70,5%
Median cycles of chemotherapy	4
Partial response and stable disease	29 (46%)
Patients treated with at least two chemotherapeutic drugs	23 (33%)

Results: 69 patients were included into the analysis. Median TTP was 6 months and median OS was 12 months. No difference in terms of response rate was observed in the subgroup of patients with more than 4 concomitants drugs compared to group with less than 4 concomitants drugs (respectively 44% and 41% of disease control). With a median dose intensity of 70,5% we observed respectively 18% of patients with any hematological toxicity, 76% with any non-hematological toxicity, 10% of patients with grade 3-4 hematological toxicity and 14% of patients with grade 3-4 non-hematological toxicity. 29% of patients were subjected to second line therapy. 6% of the patients died due to toxicity from therapy.

Conclusions: Our data seem to highlight that elderly patient, although representing a very fragile setting, may still benefit from chemotherapy. If, on one side, our prudent approach in a selected population could have reduced the potential benefit deriving from chemotherapy, on the other side extreme caution is recommended since factors predictive of toxicity in this population have not yet been ascertained. In this regard we are currently correlating the toxicity data with co-morbidity indexes to evaluate whether there are predictors of toxicity.

E42 Role of different toxicity profile on outcome for colorectal cancer patients receiving Regorafenib monotherapy

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Background: Regorafenib is a valid option for colorectal cancer patients who progressed under treatment with all active chemotherapy agents, in spite of high incidence of potentially harmful toxic side effects. Management of toxicities is usually complex and may require adjustments of drug dosage. Our analysis focuses on toxicities occurring in the first 6 weeks of Regorafenib and their relationship with survival.

Methods: Patients treated in our institution with Regorafenib monotherapy per drug label were eligible for analysis. We assessed the impact of toxicities on progression free survival (PFS) and overall survival (OS). Toxicites were graded by using NCI CTCAE version 4.0. Stratifying factors were RAS status, age, sex, patients' performance status, Regorafenib dose reductions or delays during treatment. Survival measures were calculated by Kaplan-Meier method and their association with categorical variables was assessed by log-rank test. Cox-regression model was used for multivariate analysis.

Results: 61 patients were eligible and received Regorafenib monotherapy at the dosage of 160 mg/die for 3/4 weeks. Median PFS was 2.6 months and median OS was 5.3 months. 28/61 (46%) patients experienced G2 or higher toxicity. Arterial hypertension (12/61, 20%), skin rash (15/61, 25%), hand-foot syndrome (15/60, 25%) and diarrhoea (5/61, 8%) were the most common. Skin rash showed a statistically significant relationship with PFS (HR:0.51, 95%CI: 0.31-0.87, p = 0.001) and OS (HR:0.42, 95% CI:0.25-0.71, p = 0.002). Hypertension was not associated with PFS (HR: 0.54, 95%CI: 0.31-0.95, p = 0.0514), albeit it was associated with OS (HR: 0.50, 95%CI: 0.29-0.87, p = 0.03). Hand-foot syndrome was not associated with PFS (HR: 0.65, 95%CI: 0.38-1.11, p = 0.13), neither with OS (HR: 0.75, 95%CI: 0.43-1.31, p = 0.34).Diarrhoea was not associated with PFS (HR: 0.66, 95%CI: 0.30-1.44, p = 0.36), neither with OS (HR: 0.49, 95%CI: 0.24-0.98, p = 0.11). Out of all toxicities observed only skin rash maintained its independent role as predictor of different PFS (p = 0.01) and OS (0.004) at the multivariate analysis.

Conclusions: Our analysis suggests that treatment-related toxicities, particularly skin rash, may be considered as potential predictors of treatment outcome. Strategies revolving around optimal management of side effects linked to Regorafenib treatment, rather than dose delays-reductions, should be encouraged.

E43 Co-Morbidity index evaluation as decision tool for chemotherapy in clinical practice in elderly and old elderly patients with early (ECRC) and metastatic colorectal cancer (MCRC)

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Background: The co-morbidity index, evaluated with Cumulative Illness Rating Scale (CIRS) represents a clinical tool in order to evaluate elderly and old-elderly patients (pts) in oncology clinical practice. CIRS gives an estimate of illness burden, even if risk factors seem to be different in old pts, while prognosis can be worse compared young patients. Moreover toxicity risk cannot be certainly predicted by CIRS.

Methods: From January 2006 until December 2014, pts with colon-rectal cancer older than 75 years were admitted to our Unit. CIRS was performed in all patients. Therapeutic choices (surgery, chemotherapy, surgery of metastases and Best Supportive Care BSC) were done by PS-ECOG and CIRS.

Results: 118 (116 men, 63 women) pts with ECRC and 61 pts with MCRC were examinated. 116 (75%) were elderly and 63 (35%) old-elderly with median age 80,6 (± 4,97 S. D.). ECOG-PS in 61 MCRC pts (43 men, 18 women) was: 0 (10%), 1 (23%), 2 (58%) and 3 (9%). According to CIRS was observed: 13 pts (21%) stable stage, 33 pts (54%) intermediate stage, 15 pts (25%) secondary stage and 0 terminal stage. Among MCRC 34 pts (56%) had synchronous metastases and 46 pts (75%) underwent surgery of primary tumor. CIRS stable and intermediate stage underwent a standard treatment (biology + doublet), secondary stage were treated with standard treatment (doublet) at reduced dose. ECOG-PS 3 was excluted from treatment. According to CIRS and ECOG-PS only 37 pts (61%) received first line chemotherapy. 16 pts (43%) underwent target therapy + doublet, 15 pts (40%) doublet, 5 pts (14%) monochemotherapy and 1 (3%) thermoablation. The remaining 15 pts (24%) were not able to receive an active treatment, but only BSC; 9 (15%) refused any chemotherapy. Efficacy and tolerability were the same as observed in the literature.

Conclusions: Our data seem to confirm that CIRS-stage represents a useful tool for the choice of treatment among elderly and old-elderly patients in clinical practice. ECOG PS mantains its clinical value.

E44 Cisplatin plus capecitabine (CisCape) and concurrent pelvic radiotheapy for the neoadjuvant treatment of rectal cancer (RC)

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Background: Pathological complete response (pCR) after neoadjuvant therapy of RC is recognized as a powerful favourable prognostic factor. We evaluated the potential for increasing pCR rate by adding a widely used radiosensitizer, cisplatin, to standard capecitabine-based chemoradiotherapy (CRT).

Methods: 51 patients (pts) (male:female, 35:16, median age 63 years, range 41-77), clinically staged with endoscopic ultrasound and chest/abdomen/pelvis CT scan as Stage II (18 pts) or III (33 pts) with histologically confirmed moderately (43 pts) or poorly (8 pts) differentiated RC (median distance from the anal verge 5 cm, range 2-13) were treated with standard pelvic radiotherapy (45 Gy/25 fractions) and concurrent capecitabine (825 mg/m2 twice daily days 1 through 14 and 22 through 35) plus cisplatin (40 mg/m2 once every three weeks). Surgery was planned at 8-10 weeks after the end of CRT. 8 cycles of standard adjuvant FOLFOX4 was offered to all patients independently of pathological stage.

Results: Radical abdominoperineal and anterior resection was performed in 36 and 12 pts, respectively, median time elapsed from CRT commencement to surgery was 108 days, 3 pts underwent palliative surgery. pCR (regression AJCC grade 0) was documented in 7 pts (14%), nearly complete response (AJCC grade 1) in 10 pts (20%). In the whole cohort, median disease-free (DFS) was not yet reached after a median follow-up of 30 months; however, there was a strong association between DFS and AJCC grade, with no relapse observed for AJCC grade 0-1 and a 4-year DFS rate of 78% and 22% for AJCC grade 2 and 3, respectively, HR 3.47 (95% CI 0.64-18.9), p 0.03. Among common clinical e biochemical variables, baseline hemoglobin (Hb) was significantly associated with pCR according to logistic regression analysis, with a 43% increased chance of pCR for 1-unit increase in Hb (OR = 0.57, p 0.049). A high frequency of Grade 3-4 toxicities, mainly diarrhoea, was observed (35% of pts). Adjuvant FOLFOX4 was completed in 52% of pts.

Conclusions: Despite a good tumor AJCC regression rate, the high occurrence of grade 3-4 toxicities with CisCape CRT makes this regimen not suitable for larger phase III trials in all RC patients. However, baseline Hb may be a possible patient selection criteria for this intensive treatment strategy.

E45 Use of The Mini Nutritional Assessment to determine the Prevalence of Malnutrition And Cachexia In Patients Undergoing Surgery For Colorectal Carcinoma

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Background: The cancer disease is the clinical condition most often associated with the concept of protein-calorie malnutrition that affects 8% to 84% of cancer patients and can worsen until determining cachexia also called "Wasting Disease".

Cancer-Related Anorexia-Cachexia Syndrome (CACS), is a complex metabolic syndrome characterized by a negative protein balance and energy caused both by a reduced caloric intake from both metabolic abnormalities associated with loss of muscle mass with or without loss of mass fat and considerable weight loss; it is estimated that about 20% of all cancer deaths occur for malnutrition. It is necessary to complement clinical examination of the patient also with review the nutritional status in order to evaluate the therapeutic process in these patients.

Objective: The aim of this study was to assess the prevalence of malnutrition or the risk of malnutrition in patients undergoing to surgery for colorectal carcinoma.

Methods: A total of 53 patients, 26 male and 27 female media age: 70,5 (42-86 yrs) undergoing to surgery for colorectal carcinoma in our Institute between November 2014 and April 2015, were evaluated to determine individual nutritional status, using the Mini Nutritional Assessment (MNA®) that includes 18 items grouped in four rubrics: anthropometric assessment, general assessment and lifestyle, short dietary assessment and subjective perception of health and nutrition.

Results: The overall mean score for the MNA, was 26.2 ± 13.2 (range 6.0-27.0);15/53 patients (24.5%) presented a normal nutritional status (mean 24.8; range 24.0 to 27.5), 25/53 (47%) reported a risk of malnutrition while 13/53 (24.5%) reported a severe malnutrition that was found to be more common in men than in women. Besides, all malnourished patients had in the previous six months from the date of diagnosis, a significant weight loss (> 10 kg), muscle mass loss and severe reduction in the intake of food due loss of appetite and altered taste perception. Instead, patients at risk for malnutrition reported a weight loss of 3 to 5 kg and a moderate reduction in food intake.

Conclusions: More than 50% of patients had moderate or severe malnutrition and the majority of them needed nutritional intervention before and during chemotherapy. Our preliminary data show the importance of nutritional assessment in cancer patients in order to set the appropriate treatment plan, improve its quality of life and increase overall survival in cancer patient.

E46 Phase III study of regorafenib versus placebo as maintenance therapy in RAS wild type metastatic colorectal cancer (RAVELLO trial)

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Background: Treatment of metastatic colorectal cancer (mCRC) has improved due to the introduction of more active chemotherapies (CT) and novel targeted agents that have significantly increased response rate (RR), progression free survival (PFS) and overall survival (OS). Recently, CORRECT and CONCUR trials have demonstrated both activity and efficacy of regorafenib, a small multi-kinase inhibitor, as monotherapy in pretreated mCRC. The wide range of action of regorafenib makes it an ideal candidate for monotherapy in earlier disease treatment lines in which different pathways could be involved in the acquisition of resistance. To improve long term efficacy of first line therapy several therapeutic approaches of maintenance treatment have been explored in mCRC

Material and methods: RAVELLO is an academic randomized, double-blind, placebo-controlled, multi-center, phase III study designed to evaluate efficacy and safety of regorafenib as maintenance treatment after first line therapy. Eligible patients: pathologically confirmed mCRC RAS wild type (KRAS and NRAS genes) treated with a first line fluoropyrimidine-based CT in combination with an anti-EGFR (epidermal growth factor receptor) monoclonal antibody for a minimum of 4 to a maximum of 8 months, with a stratification by response to the first line treatment (complete response/partial response or stable disease). 480 patients will be enrolled and randomly assigned in a 1:1 ratio to receive 160 mg regorafenib or placebo per os, every day for 3 weeks of every 4 weeks cycle, until disease progression or unacceptable toxicity. Primary endpoint is PFS. With a two-tailed alpha error of 0.05, the study will have 90% power to detect a 3-month prolongation of median PFS from randomization (corresponding to a hazard ratio of progression of 0.67 with 6-month median PFS expected in the control arm). Secondary endopoint are OS, safety, and biomarker correlative studies. Fifteen Italian centers and twenthyone European centers have been involved in the trial.The First patient was enrolled on September 2014 at the Second University of Naples. Currently, 4 patients has been enrolled and are on treatment.

E47 Multidisciplinary approach in patients with stage IV colorectal cancer with liver metastasis (LCRC): A multidisciplinary group experience from Rimini "Infermi" city Hospital

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Background: In recent years, the strategy for treatment of LCRC has changed switching from a medical approach to an integrated medical and surgical approach. In our multidisciplinary Team, we evaluate patients with LCRC every three months in order to assess indications and limitations of different treatment options.

Materials and methods: Data from patients with LCRC evaluated by our Team from January 2012 to December 2014 were analyzed. Patients' characteristics and main results are described in table 1.We divided the patients into three groups: patients undergoing surgery in the first instance and then chemotherapy, patients undergoing chemotherapy only and never became suitable for surgery or radiofrequency ablation, patients undergoing chemotherapy in the first instance and subsequently had surgery or radiofrequency ablation.We assessed outcomes using the nonparametric method of Kaplan Meyer.

Results: We evaluated 78 patients with a median follow-up of 22 months.The median TTP was 11.5 months in the group receiving chemotherapy alone, 25.5 months in the group receiving chemotherapy and subsequent liver surgery or radiofrequency ablation, 38 months in the group that underwent liver surgery and subsequent chemotherapy. We observed a statistically significant difference in the three arms ($p < 0.001$). There are not yet sufficient data on OS in two of the three arms.

Conclusions: Our experience seems to confirm how the multidisciplinary approach, allowing you to make use of treatments such as surgery or other locoregional therapies, is able to improve the outcomes of patients with LCRC. Future research will have to be designed to standardize patient selection for surgery or other locoregional therapies in patients with LCRC.

Table: E47

	N° patients	Median age	Resectable at time of diagnosis	DFS at 2 years
CT	27	63	2/27	4/13 (PFS)
CT– > CH	34	59	13/34	8/22
CH– > CT	19	63	19/19	6/11

E48 A monocentric retrospective data from 2005-2008 in colon-rectal cancer: an analysis in clinical practice experience

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Aim: we know today as the new biologicals therapies increase the overall survivall (OS) and the progressione free survival (PFS) compared with only conventional chemotherapy,but in the past years and in our experience the use of biological drugs has given results not so exeptional and comforting.

Methods: From 2005 to 2008 122 patients with diagnosis of colorectal cancer documented histologically by surgery or biopsy of metastases came to our day hospital. 66 man and 56 women (median age 57 years) of which 33 patients metastatic at diagnosis or stage D Dukes and 89 with high risk of relapse (Dukes stage B2 high risk or stage C); of the 89 high risk patients in 16 developed metastasis in the following years. While 73 patients remained NED.

Results: Currently at a median follow up of 7–10 years of 33 metastatic at diagnosis or stage D Dukes 3 are alive (9%); only 1 of 16 patients after relapsed is alive (6.25%) and 11 (15,06%) of the 73 patients high risk who performed chemotherapy adjuvant. The group of patients with metastases at diagnosis (stage D Dukes) has performed more lines of chemotherapy or biological drugs compared to the high-risk group that has relapsed later average three versus two linees of chemotherapy or biological agents.

Conclusions: we know that in Dukes's stage D the 5-year survival is about 5%; our data have a slightly better trend in survival: 6% to 7–10 years in the subgroup of patients relapsing later and 9% in the subgroup of patients metastatic at diagnosis. From our data, stratified by age, comorbidity, surgery and cancer protocol, we see also how there is a small difference in survival(+2,75%) in those who were already metastatic at diagnosis and who then became metastatic later; but, in particular, there are no differences between those who underwent chemotherapy alone or those who have used drugs molecular biological(antiEGFR or antiVEGF). Finally 1 of 16 patients who have following relapsed is alive and had undergone chemotherapy + antiEGFR; of 3 patients metastatic d'embleè (stage D Dukes) 2runs chemotherapy alone and 1chemotherapy + antiVEGF. In conclusion, watching these small retrospective data,in our setting of patients we can say that in terms of overall survival at 7–10 years, chemotherapy alone gave the same results of chemotherapy combined with biologic agents; maybe it's due to uncorrect molecular characterization of those years (2005-2008) or not yet know so well the effectiveness of biologics in clinical practice.

E49 Glucose metabolism enzymes gene expression analysis and selective metabolic advantage in the clinical progression of colorectal cancer (CRC)

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Background: Invasive cancer cells mostly produce lactate even in the presence of sufficient levels of oxygen (aerobic glycolysis). This metabolic shift promote a survival advantage in proliferating cells, since it make them insensitive to transient or permanent hypoxia, it contributes to the production of nucleosides/aminoacids, and it constitutes a rapid way to produce energy. The analysis of altered expression of effectors causing redirection of glucose metabolism would improve our knowledge on a possible mechanism for chemoresistance, and secondary resistance to anti-angiogenic compounds. Also, it may optimize the current development of drugs targeting cancer metabolism. This background prompted us to analyze mRNA expression of key-enzymes involved in glycolysis in normal mucosa (NM), primary tumor (PT) and liver metastasis (LM) of CRC patients (pts) who underwent surgery (primary tumor resection and liver metastasectomy) and systemic therapy for advanced disease.

Materials and methods: Tissues of 50 chemotherapy-naive, non-diabetic CRC pts were retrospectively studied by RT-qPCR for mRNA expression of the following genes: hexokinase-1 (HK1) and 2 (HK2), embryonic pyruvate kinase (PKM2), lactate dehydrogenase-A (LDH-A), glucose transporter-1 (GLUT-1), voltage-dependent anion-selective channel protein-1 (VDAC1). The RT-qPCR DCt values (Cttarget–Ctreference) were used for calculating the expression level of each target gene with B2M and GUS adopted as reference genes. The primary end-point was to verify whether differences were detectable between tissues. T-test (Tt) and Wilcoxon test (Wt) were used for comparing DCt values between tissues (PT versus NM, LM versus NM, PT versus LM).

Results: In 49 assessable pts, essays repeated with B2M and GUS showed higher PT mRNA expression elevsl than NM for HK1 (Tt $p = 0.0001$; Wt $p = 0.0004$); LDH-A (Tt $p < 0.0001$, Wt $p < 0.0001$); PKM2 (Tt $p < 0.0001$, Wt $p < 0.0001$); GLUT-1 (Tt $p < 0.0001$, Wt $p < 0.0001$); VDAC1 (Tt $p = 0.0002$, Wt $p = 0.0004$). The same significant associations were found when comparing LM versus NM tissues. There was a borderline or not-significant trend for higher mRNA expression of these genes in LM versus PT tissues.

Conclusions.: The results indicate enhanced glucose uptake (GLUT-1), up-regulated aerobic glycolysis (HK, LDH, PKM2) and altered mithocondrial trafficking (VDAC1) in CRC. Additional analyses for association with RAS mutations status, progression-free survival after first-line chemotherapy plus bevacizumab and overall survival are ongoing.

E50 Safety and toxicity in elderly patients in treatment for metastatic colon cancer

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Background: Despite the prevalence of metastatic colorectal cancer in the over 65 years population, such patients elderly and frail are often under-represented in clinical trials. As a result, additional data about appropriate treatment options for elderly patients are needed.We aimed to assess the safety and toxicity of two drugs chemotherapy schedules compared with three-drug regimens in elderly patients treated in our department.

Patients and methods: We have retrospective analyzed 79 patients with metastatic colorectal cancer,previously untreated for advanced disease assigned to receive a first line chemotherapy with two or three drugs in order to evaluate the tolerability of treatment in patients older than 65 years with adequate bone marrow,renal and hepatic function and Performance Status (ECOG PS) 0-2.Toxicity was assessed using the NCI CTCAE v. 3.0 Patients characteristics were as follow: 45 males(57%) and 35 females (43%); 54 (68,35%),23 (29,11%),2 (2,54%) patients had an ECOG PS of 0,1, and 2 respectively.

Results: We found that 40.5% of patients were treated with FOLFOX-Bevacizumab, 17,72% with FOLFIRI-Bevacizumab,8,9% with FOLFIRI- Cetuximab,1,3% with FOLFOX-Panitumumab15,2% with FOLFOXIRI-Bevacizumab,5,06% with FOLFOX, 6,33% with FOLFIRI and 5,06% with IRINOX.Gastrointestinal toxicities were observed in 83,5% of cases (70 % in two drugs chemotherapy regimens and 30% three-drug regimens),in particular diarrhea occurred in 51patients (64,56% tot) and was grade 3 in 6(7,6%),(63% in two drugs regimens and 37% three-drugs),nausea appeared in 41 patients(51,9%) and was grade 3 in 3 (3,8%).Forty-eight percent developed hematological toxicity; neutropenia grade 3 or 4, occurred in 9 and 6 patients respectively (19% grade 3-4);anemia was examined in 24.4% of cases and was grade 3 in 2,5%.Only one patient showed a grade 4 thrombocytopenia(1,3%).During therapy, the dose was reduced in 16(20.25%) and suspended in 10(12,7%) patients.

Conclusion: Our study suggest that 2 or 3 drug regimens are well tolerated In the over 65 years old patients affected by metastatic colorectal cancer at the first line of therapy, infact we have found a very small percentage of major toxicity in all patients treated. Even if we have found a major percentage of adverse effects in the FOLFOX-Bevacizumab regimen, the most represented in this analysis, our sample is limited and does not permit definitive conclusion about the safety and toxicity of a regimen respect to the others.

E51 A mono institutional retrospective analysis on the safety and efficacy of first-line Folfiri or Folfox (CT) plus bevacizumab (B) in young and elderly patients with metastatic colorectal cancer (MCC)

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Background: Chemotherapy with Folfiri or Folfox + bevacizumab is considered a standard treatment in MCC, but their use is often limited by toxicity in elderly patients. The aim of this study was to evaluate, retrospectively, toxicity and efficacy in "young" ($\leq$ 65 years) and "elderly" patients (> 65 years) with metastatic colorectal cancer.

Methods: The clinical data of 63 patients with unresectable MCC treated with Folfiri or Folfox plus bevacizumab (5 mg/kg on day 1) every 2 weeks as first-line therapy were reviewed. At least 6 cycles of treatment were required for being evaluable.

Results: The main pt characteristics' were: M/F 37/26; median age 64 yrs (range 27–77 years); ECOG PS = 0-1 in all pts; $\leq$ 65/ > 65 years: 32/31; primary colon/rectal cancer: 43/20, primary tumor resected: 50/13; metastases at diagnosis: 36 (57.1%), liver metastases alone: 25 pts, liver plus extrahepatic metastases: 23 pts, extrahepatic metastases alone: 15 pts. Outside the liver the most frequent sites of metastases were lungs, abdominal lymph nodes and peritoneum. Forty-one pts (65.1%) completed the entire treatment (12 cycles) and 22 pts (34.9%) did not. The most frequent Gr 3-4 toxicities observed in the entire group were: hypertension 16%, neutropenia 14%, diarrhea 13%. No toxic deaths were observed. Considering the two cohorts of pts neutropenia Gr 3-4 was higher in the youngest group (19 % vs 10 %) while diarrhea Gr 3-4 was more frequent in the oldest group (16% vs 9.0 %), no difference was observed for hypertension. The overall response rate (ORR) evaluated at the end of chemotherapy was 46% (CR 10%, PR 36%). A stable disease was observed in 29% of pts, and 25% had progressive disease (PDR). Considering pts $\leq$ 65 years versus pts > 65 years both the CRR and the PDR rate were higher in the youngest group 12% vs 6%

and 37% vs 13% respectively. No difference in PFS was observed (11 months, 95% CI 8-14 in pts ≤ 65 years and 12 months, 95% CI 10-13 in pts > 65 years). Furthermore, in a small number (16 pts) of very elderly pts (≥ 70 years) the Gr 3-4 toxicities were 37.5% with a disease control rate of 81 % vs 72% at the end of chemotherapy.

Conclusions: In our analysis the combined therapy with Folfiri or Folfox plus bevacizumab used in the first-line metastatic setting was effective and well tolerated across all ages groups. The sample will be enlarged in order to perform an analysis of the outcome of the very elderly patients.

E52 Safety and efficacy of modified schedula of anti-EGFR monoclonal antibodies plus chemotherapy as first line treatment in metastatic colorectal cancer patients

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Background: Overexpression of the epidermal growth factor receptor (EGFR) is associated with cancer development and progression. EGFR inhibitors, cetuximab and panitumumab, are targeted agents for treating cancer patients and are often used as first line through third line treatment, alone or in combination with chemotherapy in wilde-type colorectal cancer with significant improvement of overall response rate (ORR) and progression free survival (PFS). Commonly experienced dermatologic side effects include acneiform rash, hair changes, pruritus, mucositis, xerosis, paronychia. Clinical presentation incidence, impact on quality of life and cost. When severe, dermatologic toxicities may to lead to dose modification or discontinuation of treatment.

Patients and methods: We have studied ten eligible patients (pts) with wilde-type metastatic colorectal cancer, bidimensional measurable disease, PS< 2 and adeguate haematological, hepatic, renal functional, treated with EGFR inhibitors and chemotherapy, six with cetuximab and FOLFOX 4, and four with panitumumab and FOLFOX 4, until disease progression or appearance of non tolerable toxicity. Patients with median age of 60 years (range 46–74) were treated for a median of twelve cycles (range 6-18 cycles). The original schedule provide for the concomitant use of monoclonal antibody with Oxaliplatin in the 1° day, with oxaliplatin infusion 60 minutes after the end of monoclonal antibody infusion.

Results: In our cohorte, during the first weeks to months of EGFRI therapy all pts experienced severe acneiform rash, with papules and pustules develop in skin of scalp, face, upper chest and back with pruritus. Oral complication commonly reported was mucositis with xerosis and fissures. The late toxicity evaluation showed : taste impairment, and conjuntivitis. The most frequent non dermatologic toxicities were: asthenia in all pts, anaemia G2 (20%). The schedule was therefore modified with monoclonal antibody infusion 24 hour before oxaliplatin infusion. With this schedule the dermatologic toxicities resolved in all pts, with no appearance in the subsequent cycles. The efficacy is comparable with the results of literature.

Conclusion: Although the limited numbers of pts hampers the analysis, these results may suggest that the modified schedule can provide clinical benefits to pts with metastatic colorectal cancer. A prospective evaluation is required to either confirm or discard these preliminary results.

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Session F. Genitourinary cancer

F01* New prognostic factors for second-line targeted therapy (TT) in metastatic renal cell carcinoma (mRCC)

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Background: The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model has been validated for patients with mRCC in the 2nd line TT setting. This model does not consider time from first to second line therapy, tumor shrinkage during first line and tumor burden before second-line. We sought to investigate these factors in addition to IMDC ones.

Methods: Data from patients (pts) treated with TT between January 2005-December 2013 in prospective clinical trials for mRCC were collected from the Gustave Roussy database. All pts who received 2nd-line TT and had available information from 1st line were nalyzed. Data collected included known IMDC prognostic factors (anemia, hypercalcemia, thrombocytosis, neutrophilia, Karnofsky performance status <80, time from diagnosis to treatment <1year) as well as tumor burden (TB), tumor shrinkage (TS), time from first to second line, occurrence of new metastatic sites, number of metastatic sites at second line and histology. Variables with a significant association with overall survival from the start of second line (OS) were estimated by proportional hazard regression and a backward stepwise multivariable analysis identified the independent prognostic factors.

Results: From the initial cohort of 316 pts, 222 pts met inclusion criteria and were included in the final analysis. 2nd line treatment was everolimus (27%), sunitinib (24%), sorafenib (22%), axitinib (8%) and other (19%). The median follow-up was 49.4 [range: 2.3 to 97.1] months (mos) and the median OS was 16.8 [95%CI = 12.6, 21.7] mos (79.3% of deaths). By IMDC criteria, mOS was 21•3 mos (95% CI 7.5–49.5) in the good risk group (n = 22), 21•7 mos (15.1–24.9) in the intermediate risk group (n = 142), and 9•3 mos (5.2–12.4) in the poor risk group (n = 58). In univariate analysis, all adverse prognostic factors previously identified by IMDC, except hypercalcemia, TB greater than 9•5 cm, TS greater than 30% and occurrence of new metastatic site were associated with shorter survival. In multivariable analysis, only TS greater than 30% was an independent prognostic factor (p: 0.0004), among new potential prognostic factors.

Conclusion: TS during 1st line is an independent prognostic factor for outcome of mRCC in second line. A new prognostic model considering components of the IMDC model with the addition of TS will be presented during the meeting.

F02* Multidisciplinary management of prostate cancer patients: the PerSTEP data

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Besides promoting the cultural and organizational change to multidisciplinarity, PerSTEP supported by the Italian Society for Urologic Oncology (SIUrO) and the Board of Medical Oncology Directors (CIPOMO) wanted to make a picture of the multidisciplinary activities performed by the 23 participating centers and start a discussion on the efficacy of the interdisciplinary collaboration in the management of prostate cancer (PC) patients.
The centers were invited to collect the data of 3 months' activity. Nineteen joined the call and gathered information on:

- patients with genito-urinary cancers managed with a multidisciplinary approach
- patients to whom the Multidisciplinary Team changed the stage
- patients to whom the Multidisciplinary Team changed the therapeutic and observational options
- patients who had received partial or incorrect information in previous consultations
- patients who required psychological support

The patients with genito-urinary cancers managed with a multidisciplinary approach were 1420. PC patients were 920. Fourteen centers reported the multidisciplinary evaluation to be effective in better definning the stage (80 cases, 8.7%). Fifteen centers reported that the multidisciplinary approach led to changing the therapeutic and observational options that patients had received before (153 cases, 12.5%). Sixteen centers reported that patients had received partial or incorrect information in previous consultations (197 cases, 21.4%). Ten centers reported that patients asked for psychological support (86 cases, 0.9%).
Despite the limitations of this data collection, PerSTEP centers wanted to see if the interaction of urologists, radiation oncologists and medical oncologists, supported by other specialists such as pathologists, psychologists and imaging specialists, could prove effective in the management of PC patients and confirm the theoretical assumption of the advantages of multidisciplinary working. Further data on the way the centers work are needed to make a more detailed picture and to support these preliminary interesting results. Further effort will be necessary to promote the cultural and organizational change towards a multidisciplinary management of PC patients and overcome the barriers towards multiprofessional team working effective for health professionals and patients.
A special thank to SANOFI for supporting the communication plan of PerSTEP

F03* Effectiveness and possible molecular factors predictive of clinical outcomes in patients with transitional cell carcinoma of the urothelial tract (TCCU) treated with VInfluninE: a multicenter retrospective study (MOVIE) of the Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC)

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Background: In Italy more than 700 patients have received VFL after platinum-based regimens for metastatic bladder cancer and no data on the Italian population currently exists enabling us to assess the potential impact of this therapy and the determinants for its therapeutic success or failure.

Material and methods: This is a retrospective, observational, multicenter trial. Centers where selected if, according to the Italian Regulatory Agency Registry (AIFA), at least 4 pts have been treated with VFL from February 2011 to June 2014. Eligible pts have histological diagnosis of metastatic TCCU, progressive disease after a platinum-based chemotherapy and were treated with VFL according to clinical practice. Primary objective is to test whether efficacy in terms of overall survival (OS) obtained in the registration study are confirmed in the clinical practice. Secondary objectives are to evaluate toxicity, progression-free survival (PFS) and disease control rate (DCR) and to explore the relation between potential histological and bio-molecular factors with clinical outcome. According to statistical evaluation, a sample size of 197 pts has to be enrolled.

Results: At the present time 121 pts have been included. Preliminary analysis has been performed on the first 92 patients registered of whom 84 are evaluable for response. Median age was 72 yrs old (IQR 62-74), ECOG PS was 0/1/2 in 38/55/7% respectively, 84% were males; 66% pts received VFL as 2nd line and 34% in 3rd. The mean number of VFL cycles was 4.13 (DS 3,08). 28% of pts received the standard dose of 320 mg/m2, 35% were treated with 280 mg/m2and 37% with a lower dose. We observed 2% CR, 6% PR, 26% SD and 65% PD with ORR 8% (IC95% 2%-14%) and DCR 35% (IC95% 24%-45%). Hematological toxicities G 3-4 were: neutropenia (10%), leucopenia (3%), anemia and thrombocytopenia < 2%; non- hematological toxicities G 3-4 were: asthenia/fatigue (7%), constipation (3%).

Conclusions: In this preliminary analysis for pts in real life, the ORR seems to be similar to pivot trial of VFL and tolerability is better. The registration of about 200 cases will be completed by August 2015 and the final analysis will be presented at the meeting.

Table: F03*

BASELINE CHARACTERISTICS	Elv.Pts (N.84)	CR (%)	PR (%)	SD (%)	PD (%)	DCR (%)
2L	55	4	5	29	62	38
3L	29	0	7	21	72	28
PS 0	32	3	6	25	66	34
1	46	2	4	28	65	35
2	6	0	17	17	67	34
Hb < 10g/dl	7	0	0	0	100	0
Hb > = 10g/dl	77	3	6	29	62	38
Liver Meta Yes	17	0	6	18	76	24
No	67	3	6	28	63	37

F04 Conventional-dose (CDCT) versus high-dose chemotherapy (HDCT) in the salvage management of relapsed pure seminoma: results from an international database

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Background: The optimal management of relapsed seminoma is still unknown. We retrospectively analyzed the outcomes of CDCT versus HDCT in the salvage treatment strategy of patients (pts) failing ≥1 CT regimens.

Patients and methods: Eligibility included adult male pts with pure seminomatous histology, and treatment with salvage CT. Pts with elevated alfa-fetoprotein were excluded. Consecutive pts who received CDCT were identified in the database of Fondazione INT Milano, while the transplantation registry of EBMT (from 13 European Centers) was used to retrieve all cases of salvage HDCT. Multivariable Cox analyses (MVA) evaluated the association of prespecified factors (type of CT, line of CT, prior radiotherapy [RT], and chemosensitivity according to standard definition), with progression-free (PFS) and overall survival (OS). Interaction models between treatment and singly taken covariates were also undertaken.

Results: From 05/1990 to 12/2012, 73 cases were identified, 27 received CDCT and 46 HDCT. Median age was 37 years (IQR: 34-44), 5 pts has a retroperitoneal primary and 11 had an intermediate prognosis. HDCT was given in second line (n = 14) and third line or beyond (n = 20, 12 had missing information). 25 had received paraortic ± iliac RT, 13 were cisplatin refractory/absolutely refractory. Median follow up was 42 months (IQR: 13-71). 5-y OS was 36.2% (95%CI, 21.5-60.9) and 61.2% (95%CI, 44.6-83.9) for CDCT and HDCT, respectively. On MVA for PFS, refractory disease (HR: 2.49, 95%CI: 1.14-5.46) and HDCT (HR: 0.19, 95%CI: 0.06-0.67, p = 0.009) were significant predictors. For OS, prior RT (HR: 2.13, 95%CI: 1.00-4.52, p = 0.048) and refractoriness (HR: 3.48, 95%CI: 1.41-8.62, p = 0.007) were significantly prognostic, while HDCT trended to significance (HR: 0.29, 95%CI: 0.07-1.25, p = 0.098), as it was confirmed in the subgroup analysis for second line only (HR: 0.18, 95%CI: 0.02-1.38. p = 0.099).

Conclusions: Despite the limited numbers, our retrospective analysis suggests that HDCT may represent the first therapeutic option in pts with a pure seminoma after failure of one or multiple lines of CT. Our observation requires validation through a prospective study.

F05 Relationship and predictive role of the dual expression of FGFR and IL8 in metastatic renal cell carcinoma (mRCC)

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Background: The expression of interleukin-8 (IL8) has been related with worse prognosis and primary resistance to targeted agents in mRCC. Despite these data, no agents are specifically available for these patients. GOLD trial (Lancet Oncol 2014), reported such as dovitinib, a tyrosine kinas inhibitors (TKI) targeting the fibroblast growth factor receptor (FGFR), is effective as well as sorafenib in third-line treatment of mRCC. We aim to investigate the relationship between IL8 and FGFR in mRCC.

Material and methods: Patients affected by mRCC and treated with targeted agents in two University centers in Italy were reviewed for availability of histological samples of primary tumor. Clinical information were collected from patient's files. The expression of IL8, FGFR1 and FGFR2 was evaluated by immunohistochemistry (IHC). Only cased with IHC expression >5% were considered positive. Spearman's and Chi's square tests were used to define the correlation and the difference in expression of tumor markers, respectively. The Kaplan-Meier was used to estimate median survivals. Study was approved by IRB.

Results: A total of 36 patients have been analyzed. 94% received nephrectomy, 92% had clear cell histology, 42% were metastatic at diagnosis, 89% received TKI and the other had bevacizumab or temsirolimus. The FGFR1, FGFR2 and IL8 were found expressed in 8.3%, 30.6% and 36.1% of cases, respectively; all cases positive for FGFR1 were also positive for FGFR2. Significant correlations was found between FGFR1/2 and IL8 (rs = 0.51; p = 0.002). FGFR1/2 was found expressed in 72.7% and 27.3% of cases with or without expression of IL8 (p = 0.002). When patients with dual expression of FGFR and IL8 were compared to others, a significant difference was found in terms of PFS (5.1 vs. 12.0 months; p = 0.04), and a clinically but not statistically significant difference was found in terms of OS (14.2 vs. 41.2 months), probably due to the low number of cases.

Conclusions: This analysis first investigated and found a relationship between the expression of the IL8 and FGFR in patients affected by RCC and treated with targeted agents for the metastatic disease. Further studies are awaited to assess the role of FGFR inhibitors in mRCC patients who express the IL8.

F06 Outcome of patients with pancreatic metastases from renal cell carcinoma: when the site matters

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Background: Pancreatic metastases from renal cell carcinoma (PmRCC) are uncommon and their prognostic value in the era of targeted terapies (TTs) is not well defined. We evaluated the outcome of a cohort of PmRCC patients (pts) who were treated with either surgery and TTs

Patients and methods: PmRCC pts treated between 1993 and 2014 were identified from the databases of 11 European centers. Clinical records were retrospectively reviewed and pts characteristics including demographics and clinical outcome were analyzed. Kaplan-Meier methods and log-rank test were used to evaluate progression-free survival (PFS) and overall survival (OS). Cox's proportional hazard models were used to analyse covariates associated to OS

Results: A total of 276 pts were evaluated. Median age was 62 years (range 26-82), sex ratio male/female was 179/97 and PmRCC were synchronous to the primary in 80 pts (29%). Pts treated with pancreatic surgery (including radiosurgery) were 77 (28%) while patients receiving systemic treatment were 256(93%). Pts with only PmRCC were 42 (15%) whereas in the other 234 cases: lung (47%), lymphnodes (28%) and liver (23%) were the most common metastatic sites. The majority of pts (95%) received nephrectomy (Nx). Median time from Nx to PmRCC occurrence was 91 months (IQR 54-142). First-line TTs included: sunitinib (44%), sorafenib (12%), pazopanib (9%), interferon + bevacizumab (6%) and temsirolimus (1%), 37% of pts received cytokines and 53% of pts received subsequent lines of TTs. Best response to first-line treatment were complete response (5%) partial response (40%) and stable disease (39%) with a disease control rate (DCR) of 84% and a median PFS of 12 months (IQR 10-14). Median OS (calculated from the time of PmRCC occurrence to death) was 73 months (IQR 61-86) with a 5-yr OS of 58%. Median OS for pts treated with local treatment to the pancreas was 106 months (IQR 78-204) with a 5-yr OS of 75%. At univariate analysis Motzer/Heng prognostic score ($p = .0004$), Nx ($p = .0002$) and local treatment ($p = < .0001$) were significantly associated with OS. At multivariate analysis these variables confirmed their prognostic role.

Conclusions: PmRCC are associated with long-term survival, usually occur many years after Nx and lead to a less aggressive disease. Surgery should be considered in oligometastatic disease as it can be associated with prolonged survival. TTs are active in these pts and achieve high DCR.

F07 3-year safety follow-up of radium-223 dichloride (Ra-223) in patients (Pts) with castration resistant prostate cancer (CRPC) and symptomatic bone metastases (Mets) from ALSYMPCA

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Background: In ALSYMPCA, the first-in-class α-emitter Ra-223 had a highly favorable safety profile and was well tolerated. Safety monitoring of Ra-223 is essential for a complete safety profile.

Table: F07

Pts with tx-emergent AEs of interest, n (%)*	Ra-223 n = 600 All grades	Ra-223 n = 600 Grades 3/4	Pbo n = 301 All grades	Pbo n = 301 Grades 3/4
Heme				
Anemia	187 (31)	79 (13)	93 (31)	39 (13)
Neutropenia	30 (5)	13 (2)	3 (1)	2 (1)
Thrombocytopenia	69 (12)	39 (7)	17 (6)	6 (2)
Nonheme				
Bone pain	310 (52)	132 (22)	192 (64)	79 (26)
Diarrhea	154 (26)	8 (1)	45 (15)	6 (2)
Nausea	215 (36)	10 (2)	102 (34)	6 (2)
Vomiting	116 (19)	10 (2)	41 (14)	7 (2)
Constipation	109 (18)	7 (1)	64 (21)	4 (1)
Fatigue	160 (27)	27 (5)	79 (26)	18 (6)

*AEs that started on or after first inj up to 12 wks after last inj.

Here are final safety data including long-term follow-up safety 3 years after last pt's first injection (inj).

Methods: Pts received 6 inj and entered designated follow-up from 4 wks after their last inj to 3 years after first inj. Pts were to be evaluated during tx period and 9 follow-up visits. All adverse events (AEs) were collected until 12 wks after last inj; thereafter, only AEs deemed tx-related were collected. Additional long-term safety data were assessed by specific diseases including acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), aplastic anemia, and new primary cancer in bone or other organs.

Results: Safety population (pts receiving ≥ 1 inj) included 901 pts (Ra -223, n = 600; placebo [pbo], n = 301); 572 pts (Ra-223, n = 405; pbo, n = 167) entered follow-up. 60 pts (Ra-223, n = 49; pbo, n = 11) completed all follow-up visits. Overall, 564 (94%) Ra-223 and 292 (97%) pbo pts had ≥ 1 tx-emergent AE (Table). During long-term follow-up, there were no reports of AML, MDS, or new primary bone cancer. New primary cancers in other organs were reported: 2 Ra-223 (1 bladder, 1 lymph node mets), 3 pbo (2 skin, 1 adenocarcinoma rectum and sigmoideum), and 2 pbo cross-over pts (1 skin, 1 meningioma). Aplastic anemia was reported in 1 Ra-223 pt.

Conclusions: Ra-223 remained safe and well tolerated 3 years after the last pt's first inj. No major safety issues were identified during the ALSYMPCA 3-year long-term follow-up.

Clinical trial information: NCT00699751

F08 Single agent versus doublet chemotherapy as second-line therapy of metastatic urothelial carcinoma (UC): a meta-analysis

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Background: The efficacy and safety of adding a second chemotherapeutic agent to single agent chemotherapy (CT), i.e. taxanes or vinflunine, in the second-line setting of UC is unclear. We compared the efficacy and safety of these two strategies through a trial level meta-analysis.

Patients and methods: PubMed, EMBASE, and ASCO abstracts were searched for trials including single agent or doublet CT in the second-line setting of UC following platinum-based CT. Random-effects models were used to pool trial level data according to treatment arm, including median PFS and OS, objective reponse-rate (ORR), and G3-4 toxicities. Multivariable analyses (MVA) were performed to compare single agent vs doublet CT, overall and by subgroups, adjusting for percentage of patients (pts) with ECOG performance status = 2 and visceral metastases. Model weights were estimators inverse variances for ORR and toxicities; the logarithm of the trial sample sizes were used for OS and PFS.

Results: 47 arms of phase II and III trials including 1964 pts were selected: 22 with single agent [n = 1202], including 3 (n = 486) vinflunine and 6 paclitaxel/docetaxel (n = 232). Of the 25 arms with doublets (n = 762), 6 were with cis- or carboplatin (n = 423), 21 (n = 656) with a taxane.The pooled ORR with single agents was 0.14 (95% CI: 0.11-0.18) vs 0.32 (95%CI: 0.28-0.37) with doublets. Pooled median PFS was 3.02 months (mo) and 5.03 mo, respectively. Pooled median OS was 7.5 mo and 9.33 mo. Multivariably, ORR odds ratio of doublet vs single agent was 2.95 (95%CI: 2.11-4.12, $p < 0.001$), pooled median difference was 2.21 mo (95%CI: 0.99, 3.43, $p < 0.001$) for PFS, and 1.92 mo (95%CI: 0.44-3.39, $p = 0.011$) for OS. There were no significant differences in G3-4 anemia ($p = 0.392$), neutropenia ($p = 0.487$), and thrombocytopenia ($p = 0.822$) in MVA. No differences were found between vinflunine and taxanes, and between different doublets for any outcome.

Conclusions: In this meta-analysis, doublet CT regimens improved ORR and extended PFS and OS compared to single agents in pts receiving second-line CT for UC. The prospective evaluation of potent combinations of second-line CT may be rational in order to improve outcomes and serve as the foundation to combine with biologic agents.

F09 Gemcitabine and Platinum (GC) chemotherapy alone or with a Taxane (GC-T) as first-line therapy for urothelial cancer (UC): a meta-analysis

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Background: The impact of adding T to GC as first-line therapy for metastatic UC needs to be clarified. We aimed to address this question through a meta-analysis of efficacy and safety results.

Patients and methods: PubMed, EMBASE, and ASCO abstracts were searched for studies including GC +/- T in the first-line setting. We pooled trial level data including the median, proportions and confidence intervals on PFS, OS, and adverse effects. Descriptive statistics were used to summarize information across trials, and grouped by whether they contained T (docetaxel or paclitaxel) and by platinum (CBDCA or CDDP). Uni- and multivariable regression models evaluated the prognostic role of T or platinum type, after adjusting for each other, performance status (PS), and visceral disease. Data were weighted by the logarithm of the trial sample size.

Results: 31 arms of trials including 2057 patients were selected (7 with T [n = 617], 15 with CBDCA [n = 623] and 16 CDDP [n = 1434]). Median OS was univariably significantly ($p = 0.029$) different between trials with T and those without T. Across trials, the median 'median OS' amongst trials containing T was 15.5 months (mo), compared with 12.5 mo in trials which did not. The % of pts with neuropathy ($p = 0.025$) and with neutropenic fever ($p = 0.033$) were also statistically significantly higher in T arms. Median of median OS was also statistically significantly superior ($p = 0.041$) in trials with CDDP compared to CBDCA (13.9 vs. 10.3 mo). Additionally,

the rate of G3 pulmonary side effects was significantly higher in the CBDCA group (p = 0.039) while GCSF use was more frequent with CDDP (p = 0.042). Multivariably, visceral disease and PS were significantly associated with OS, while the addition of T trended to significantly better OS (p = 0.092), and platinum type was not statistically significant. The CBDCA group had a significantly higher rate of febrile neutropenia than the CDDP group (p = 0.035).

Conclusions: In this meta-analysis, adding T to GC significantly extended OS on univariable analysis and trended towards improved OS on multivariable analysis. The evaluation of a more potent and tolerable tubulin inhibitor in combination with GC in a well-powered trial may be considered.

F10 Clinical outcome of circulating tumor cells in metastatic castration-resistant prostate cancer patients treated with docetaxel: long-term prospective single-centre study

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Background: To evaluate the long-term effects of circulating tumor cells (CTCs) in patients with metastatic castration-resistant prostate cancer (mCRPC) treated with docetaxel-based chemotherapy.

Patients and methods: From January 2006 to April 2010, blood samples were prospectively collected from 58 patients with progressive mCRPC at baseline (before initiating therapy), after 1st and 2nd cycle of chemotherapy, at the 1st instrumental re-evaluation and at the time of disease progression. CTCs were enumerated using the CellSearch System setting a cut-off of > 5 CTCs per 7.5 mL of whole blood. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method. The log-rank test was used to evaluate differences among patients according to CTC count distribution.

Results: Forty-seven (81%) patients had detectable CTCs with a median of 12 cells (range 0-1959). Baseline CTC number was correlated with PSA (p = 0.05), alkaline phosphatase (p < 0.01), bone metastases (p = 0.01) and number of previous chemotherapy lines (p = 0.03). At univariate survival analysis, baseline CTC number > 5, PSA > 100 ng/ml, alkaline phosphatase > upper normal level and the presence of bone metastases were associated with poor OS (p < 0.001, p = 0.022, p = 0.001 and p = 0.018, respectively). Three groups of patients were considered for survival and tumor response: group 1 with < 5 CTCs at both baseline and first cycle, group 2 with decreased CTCs from > 5 to < 5, and group 3 with rising or persistent number of CTCs > 5. CTCs trend (from baseline to 1st and 2nd cycle of chemotherapy and to 1st re-evaluation) of the three groups was significantly associated with OS (p < 0.001): the best survival for group 1, intermediate for group 2 and the worst for group 3. CTCs changes from baseline to 1st cycle of chemotherapy were significantly associated with disease control, 28 out of 29 patients (96%) of group 1 and 2 versus 17 out of 25 patients (68%) of group 3 had partial response/stable disease (p = 0.03) according to RECIST criteria.

Conclusions: At a median follow-up of 5 years, our data confirm the prognostic role of CTCs at baseline and during docetaxel chemotherapy and hypothesize a predictive role potentially serving as an early metric to help redirect and optimize therapy in mCRPC patients.

F11 Incidence and prognostic role of cumulative toxicity by tyrosine kinase inhibitors (TKI) in metastatic renal cell carcinoma (mRCC)

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Background: TKI related toxicities have been reported to be predictive and/or prognostic factors in patients affected by mRCC. We investigate the incidence and the prognostic role of cumulative toxicity in mRCC patients treated with sunitinib (SU) or pazopanib (PA).

Material and methods: mRCC patients treated at the European Institute of Oncology in Milan were reviewed for incidence of adverse events (AEs) such as hypertension, hand-foot syndrome and hypothyroidism during treatment. Cumulative toxicity was defined as more than one selected AE of any grade. Prognostic class was evaluated by IMDC (Heng) prognostic factors. The median PFS and OS were estimated by Kaplan-Meier method, correlation of prognostic factors with survival was evaluated by Cox analysis.

Results: 72 consecutive mRCC patients were evaluated. 87.5% of whom had partial or radical nephrectomy, 75% had clear cell RCC, and 62.5% were metastatic at diagnosis. Prognosis by IMDC was good in 57% of patients, intermediate in 40% and poor in 3%. ECOG performance status was 0 in 65%, 1 in 32% and 2 in 3% of patients. First-line treatment was sunitinib in 85% and pazopanib in 15% of patients. Any grade and high grade toxicity was present in 57% and 1.3% of patients for hypertension, in 43% and 0% for hypothyroidism and in 43% and 1.4% for hand-foot syndrome. Patients without selected AE were 23.6%, while 30.6%, 26.4, and 19.4% had one, two or all selected toxicity, respectively. The median follow-up was 30.6 months and the median PFS and OS was 12.4 and 61.2 months, respectively. Significant differences in PFS were found in patients experienced hypertension (p = 0.011) and hand-foot-syndrome (p = 0.010) but not in patients experienced hypothyroidism (p = 0.12). In patients who experienced none, one or two toxicities in terms of hypertension and hand-foot syndrome, the median PFSs were 6.9, 15.3 and 29.0 months (p = 0.001), and the median OSs were 23.5, 35.1 and 81.1 months (p = 0.019), respectively. Cumulative toxicity was confirmed as prognostic factor for PFS (p = 0.001) and OS (p = 0.012) when compared to IMDC prognostic factors.

Conclusions: In the present study we report that the presence of cumulative toxicity (mainly hypertension and hand-foot syndrome), related to the use of SU and PA as first-line treatment in mRCC may select patients with a better PFS and OS.

F12 C-Met : a possible predictive role for response to treatment in metastatic renal cel carcinoma

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Metastatic renal cell carcinoma (mRCC) is a fatal urological cancer with a 5-year survival rate of more or less 10%. During the last decade, seven different molecules have been approved for the treatment of mRCC
With the advent of targeted therapies, the recognition of predictive response factors that identify the patient population that could really benefit from a treatment rather than another, is critical.
No predictive biological factors have been identified to date.Despite improvements in terms of progression-free survival (PFS) and overall survival (OS), acquired resistance to targeted therapies during treatment is common. Among possible mechanisms of resistance, an important role seems to be given by c-Met.
We evaluated c-Met as predictor of response analyzing the association between c-Met immunohistochemical expression on mRCC paraffin tissue and response to first-line treatment with targeted therapies.Secondary end points included: correlation between c-Met state and histology, OS and TTP.

Methods: We retrospectively analyzed the data from 40 patients from our center with mRCC, treated in first-line consecutively with targeted therapies. Patients with mRCC different histologies and measurable disease were included.The first-line treatment choice was decided according to risk category by Motzer. Standard dose reductions were applied in case of toxicity. The expression of c-Met was assessed by the use of two antibodies, by Invitrogen and Ventana, as well as Roche, on paraffin tissue. C-met state was analyzed in patients treated in first-line with tirosin kinase or mTOR inhibitors and was correlated with treatment response. In every patient, immunostaining intensity was rated considering: 0 as negative,1+ as weak, 2+ as moderate and 3+ as strong. Data were collected regarding disease, the treatment performed, toxicity, response to treatment, disease progression and survival.

Results: No correlation between c-Met expression and response to treatment was found regardless the different metabolic pathway inhibition.Similarly, no association between c-Met expression and histology subtype was observed. Finally, in the OS and TTP analysis, c -Met expression seemed to be of prognostic value. In fact, when c-Met expression was positive, the OS and TTP curves were significantly lower suggesting a worse prognosis for this population. An exception was observed for TTP with Invitrogen's antibody for which confidence interval included the unit hazard ratio (HR).

F13 Era 223-A Phase 3 Trial of Radium-223 Dichloride (Ra-223) in Combination with Abiraterone Acetate (Aa) and prednisone in the treatment of asymptomatic or mildly symptomatic chemotherapynaïve patients with bone-predominant metastatic Castration Resistant Prostate Cancer (Crpc)

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Background: Ra-223, a first-in-class alpha-radiopharmaceutical targeting bone metastases (mets), reduced risk of death by 30% and delayed time to first symptomatic skeletal event (SSE) versus placebo (15.6 vs 9.8 mo; HR = 0.66) in the phase 3 ALSYMPCA trial (Parker et al. NEJM 2013). Ra-223 has favorable safety, and the lack of significant toxicity supports combining Ra-223 with other agents. AA improved radiologic progression-free survival (rPFS) and overall survival (OS) (Ryan et al. NEJM 2012), and its safety profile indicates no overlapping toxicity with Ra-223. This study investigates the efficacy and safety of Ra-223 plus AA versus AA alone in chemotherapy-naïve patients (pts) with bone-metastatic CRPC.

Trial design: This phase 3, double-blind, placebo-controlled, multinational trial (ERA 223, NCT02043678) will randomize approximately 800 pts with asymptomatic or mildly symptomatic, chemotherapy-naïve, bone-predominant metastatic CRPC 1:1 to receive Ra-223 (50 kBq/kg IV) every 4 weeks for 6 cycles or matching placebo plus AA (oral 1000 mg daily) and prednisone (oral 5 mg twice daily), followed by AA plus prednisone thereafter until an SSE or death occurs. Randomization is stratified by geographic region, concurrent use of denosumab or bisphosphonates, and total alkaline phosphatase. The primary end point is SSE-free survival. Secondary end points include OS, time to opiate use for cancer pain, time to pain progression, time to cytotoxic chemotherapy, rPFS, and acute and long-term safety. All pts are assessed at each treatment visit for efficacy, safety, and health-related quality of life, and every 3 months for progression and long-term safety. Pts who complete all study treatment and do not have an SSE enter an active follow-up period. Long-term follow-up begins after pts experience an SSE and ends 7 years after the last dose of Ra-223 or at death, loss to follow-up, or withdrawal. This trial is currently recruiting pts.

F14 Complete remission (CR) during treatment for metastatic renal cell carcinoma (mRCC) with tyrosine kinase inhibitors (TKIs)

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Background: Data about complete remission in patient with metastatic mRCC in TKIs era are extremely limited. We performed a multicenter, retrospective analysis of patients who obtained CR during treatment with TKIs, either alone or with local treatment.

Material and methods: 63 patients who achieve complete clinical remissions (absence of clinically or radiologically identifiable signs of the disease) after at least one line treatment with targeted therapies, obtained with or without adjuvant loco-regional treatment of the metastases, were retrospectively collected in 13 Italian centers. Overall and disease-free survival (OS and DFS respectively) of the whole population and by subgroups were investigated by means of Kaplan-Meier method; univariate comparison between groups was performed with the Mantel-Haenszel log-rank test.

Results: We included patients with good (40 pts) or intermediate (23 pts) prognosis, according to Motzer modified criteria. Metastatic sites before tki: lung (43%) and lymph-nodes (30%), bone (14%), the contralateral kidney (16%), adrenal gland (14%), liver (13%), pancreas (11%) and brain (13%). CR obtained with tki alone: 23(37%); with tki plus locoregional therapy: 40 (63%). Tki achieving CR: sunitinib 51(81%); pazopanib 9 (15%); others 3 (4%). Second line therapy in patients recurring after CR: same tki 15 (56%); switch to different tki (7 (26%); m-TOR inhibitor 5 (19%). Median OS from first line was 52 months (95% CI 42 -71). Median DFS from RC was 52 months (34-71). DFS was not significant different if CR was obtained with or without local therapy [34 months (18.2-NA) vs 53 month (47-NA) p = 0.141].No differences according to type of tki (p = 0.656), neither according to who stopped or not tki at the moment of CR [47 months (49–71) vs 53 months (42 - NA) p = 0.113]. Median time to recurrence from CR was significantly lower for peritoneal [17 (15-NA) vs 52 (42-NA), p = 0.039] and cerebral metastases [16 (15-NA) vs 53 (47-74), p < 0.001]. No differences in DFS were found according to the number of sites at presentation and to Motzer risk group (p = 0.150).

Conclusions: The prognostic value of CR depends from the site where was obtained. Cessation of tki can be an option in selected CR patients.

F15 Inflammatory status and lymphocyte of infiltration of primary tumor predict survival of prostate cancer patients undergone prostate radical radiotherapy

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Immune-surveillance system can modify tumor development and patients' outcome; in more recent times it has been shown that radiotherapy may affect lymphocyte mediated anticancer immune-response and enhance the therapeutic effects of immunomodulating agents such as ipimilumab (anti-CTLA-4) and nivolumab (anti PD1) in cancer patients. We have designed a retrospective study aimed to investigate whether tumor immunological microenvironment may affect the time to relapse and survival of locally advanced prostate cancer patients undergone to radical radiotherapy. Twenty-four patients with locally advanced prostate carcinoma (stage T2/T4), with average age of 67 (+/- 3,93) year at the diagnosis, a baseline PSA value of 2,60 (+/- 2,62) ng/dl, were enrolled in the study between june 1981 and january 2006. All of them underwent biochemical and/or clinical recurrence and (All of them) received adjuvant or salvage radical radiotherapy with 69,66 (+/- 3,178) Gy in 8 weeks with a median follow up of 123 (+/- 55,82) months. We therefore, carried out an immune-histochemical analysis on the histological samples of primary tumors taken at the diagnosis and at the first relapse after RT. We examined the expression of tumor infiltrating CD4 + , CD8 + , CCR7+ and FoxP3+ T cells and myeloid cells (LCA+) in term of score value and then, correlated these scores with either time to relapse and survival of these patients by performing a Spearman test. Results- Our analysis revealed that LCA and CD8+ tumor infiltration score, respectively showed an inverse (P= 0.06) and a direct correlation with patients' survival (P = 0.01). In this context, LCA.T.relapse and CD8.I.relapse tumor infiltration score shoved an inverse correlation between them (p = 0.015). The tumor infiltration score of CD4 + , central memory T cells (CCR7+) and regulatory (FoxP3+) T cells failed to show any significant correlation with either relapse and survival; On the contrary, there was a direct correlation between $CCR7^{+}$. T.relapse and $CD8^{+}$ T cells (p= 0.040). Both T cell subsets showed an inverse correlation with tumor extension (TNM) at diagnosis and grading. None of these parameters showed a clear correlation with RT dosage and baseline PSA. These data confirm the critical role of tumor inflammatory and immunological microenvironment in conditioning either tumor development and survival and offer the rationale to design new immunotherapeutic strategies for prostate cancer patients.

F16 Towards the multidisciplinary management of prostate cancer patients: the PerSTEP Project experience

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The multidisciplinary management is acknowledged as the best approach to cancer patients. The multiprofessional interaction enables to offer prostate cancer (PC) patients objective information, reduce the number of consultations and favour individualized proposals. PerSTEP is an educational project which promotes the cultural and organizational change to multidisciplinarity supported by the Italian Society for Urologic Oncology (SIUrO) and the Board of Medical Oncology Directors (CIPOMO).
PerSTEP Activities:

1. collection of information on 23 participating centers
2. meetings of the centers
3. communication (newsletters, press releases).

The information enabled to have a picture of the working models. Some centers were organized according to formalized multidisciplinary models, others enjoyed good collaboration among specialists, others worked in monodisciplinary setting and requested specialistic consultations occasionally. Some centers organized multidisciplinarily improved their organizational models and centers working in a monodisciplinary setting started the reorganizational process.
The centers shared information, discussed experiences in the literature and identified minimal requirements favouring the organizational change:

1. support from Admins and Directors of the specialties
2. creation of a multidisciplinary team and identification of a leader
3. adoption of evidence-based guidelines and paths of care
4. decision on multidisciplinary activities (i.e. clinics, case discussions)
5. activation of regular case discussions

The meetings were the occasion to discuss on problems:

1. resistance towards working multidisciplinarily
2. not univocal interpretation of guidelines
3. no formalized collaboration to overcome the unavailability of a specialty
4. unavailability of contractual time to attend multidisciplinary activities

The communication plan favoured sensibilization actions on the importance of the multidisciplinary approach.
Last updated March 2015, PerSTEP produced marvelous results such as:

1. good interaction among centers
2. formalization and update of 6 PC Units
3. constitution of 7 new multidisciplinary teams
4. activation of 10 tumor boards

Further effort is needed to support the change towards the multidisciplinary management of PC patients.
Thanks to SANOFI for supporting the communication plan

F17 Prognostic role of PD-L1 expression in renal cell carcinoma. A systematic review and meta-analysis

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Background: Therapies targeting the programmed death-1 (PD1) and its ligand (PD-L1) have reported to improve patient's outcome in several clinical trials and tumor response has been related to PD-L1 expression. Herein we investigate the prognostic role of the PD-L1 expression in patients affected by renal cell carcinoma (RCC).

Material and methods: MEDLINE/PubMed, Cochrane Library and ASCO University were searched for studies investigating the prognostic role of PD-L1 expression in renal cell carcinoma published until March 25, 2015. The entry terms for the search were "PD-L1", "B7-H1" and "renal cancer". Data extraction was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The analysis was conducted in overall cohort and in patients with clear cell histology or with advanced stage at diagnosis.

Results: Six studies and 1323 cases were included in the final analysis. PD-L1 was expressed 24.2% of clear cell compared to 10.9% of non clear cell tumors (p = 0.002). In the overall population a higher level of PD-L1 expression increased the risk of death by 81% (random effect, HR; 1.81, 95%CI 1.31–2.49; p < 0.001), significant heterogeneity was found (Chi2 = 12.2, p = 0.03; I2 = 59%).When the analysis was restricted to cases with clear cell histology, the higher PD-L1 expression increased the risk of death by 53% (HR; 1.53, 95%CI 1.27–1.84; p < 0.001); no significant heterogeneity was found (Chi2 = 5.61, p = 0.23; I2 = 29%). In patients with advanced stage at diagnosis the higher PD-L1 expression increased the risk of death by 45% (HR; 1.45, 95%CI 1.08–1.93; p = 0.01), no significant heterogeneity was found (Chi2 = 0.03, p = 0.86; I2 = 0%).

Conclusions: We reported such as patients whose tumors expressed the PD-L1 have worse prognosis compared to patients who did not. Moreover, the expression of PD-L1 seems to be higher in patients with clear cell histology. Its validation as independent prognostic factor compared to other clinical parameters traditionally used in localized or advanced disease is awaited.

F18 Incidence and relative-risk (RR) of cardiovascular toxicity in patients treated with new hormonal agents for metastatic castration-resistant prostate cancer (mCRPC)

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Background: Several studies have suggested an increased risk of cardiovascular events and mortality in patients treated with androgen deprivation therapy. New hormonal agents (NHA), enzalutamide and abiraterone, are considered standard of care in mCRPC and are characterized by a favourable toxicity profile compared to chemotherapy. Herein, we aim to evaluate the incidence and the relative risk (RR) of cardiovascular events in mCRPC patients treated with NHA.

Methods: Prospective randomized controlled phase III studies were identified by searching the MEDLINE/PubMed, Cochrane Library, and ASCO meeting abstracts until January 2015. The MeSH terms used for the search were "abiraterone" or "enzalutamide" or "orteronel or TAK700". For evaluation of cardiovascular toxicity were considered both the cardiac events and the arterial hypertension. Combined relative risks (RRs) and 95% confidence intervals (CIs) were calculated using fixed or random effects methods.

Results: Five studies and 6,735 patients were available for the analysis of cardiac toxicity. In patients treated with NHA compared to a placebo the incidence of any grade cardiac events was 10.4% and 8.4%, respectively and the RR was 1.22 (95%CI, 1.05–1.42; p = 0.009). The incidence of high grade cardiac events was 3.0% and 2.0%, respectively and the RR was 1.36 (RR = 1.36, 95%CI, 0.84–2.19; p = 0.21).Six studies and 7,830 patients were used to evaluate hypertension. In patients treated with NHA compared to placebo the incidence of any grade hypertension was 10.4% and 5.5%, respectively and the RR was 1.87 (95%CI, 1.34–2.61; p < 0.001). The incidence of high grade hypertension was 3.0% and 1.6%, respectively and the RR was 2.04 (95%CI, 1.48–2.80; p < 0.001).

Conclusions: This analysis showed as NHA significant increase the risk of all grade cardiac events and both all and high grades hypertension compared to placebo. Even if the absolute incidence of cardiovascular toxicity is about 10%, patients should be monitored during treatment with NHA.

F19 Correlation between plasmatic levels of vitamin D and testicular cancer

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Background: Testicular Germ cell Tumor (TGT) is the most common cancer in young male. Multidisciplinary integrated therapeutic strategies have been showed to be very efficent with excellent cure rate and a long life expectancy. Unfortunately treatment-related long-term sequelas can affect the quality and the length of life of these patients. Vitamin D deficiency was already described after orchiectomy but its severity and correlation with clinical features in TGT patients remains unknown.

Material and methods: ELISA assay was used to evaluate the plasmatic levels of 25-OH vitamin D. A total of 78 patients affected by TGT, between 18 and 43 years old, 3 - 96 months after the orchiectomy, were enrolled. Patients were divided in two groups according to histological characteristics: Seminomas (S), presenting pure seminomas, and Non-Seminomas (NS), presenting mixed (seminomas and non-seminomas) or pure non-seminomas. T-and $\chi 2$ tests were used to compare serum levels of 25-OH vitamin D, calcium, FSH, LH, testosterone, progesterone and 17-β-estradiol in the two groups. Linear regression test was used to correlate serum 25-OH vitamin D to clinical stage, histology and treatment received. The results were normalized for the age of patients and light exposure at the moment of blood withdrawal (low season and high season). P< 0.05 was considered statistical significant.

Results: 83% of analyzed patients presented unsufficient (< 30ng/ml) 25-OH vitamin D levels and 43% of them showed deficient (< 20 ng/ml) 25-OH vitamin D levels . The deficiency was not influenced by time from diagnosis, treatment received and ligh exposure at the time of blood withdrawal. Among patients with NS the deficiency of vitamin D positively correlated with aggressive embrional carcinoma (EC) histologic subtype (O.R. 13.2000 (2.9571 - 58.9223, p 0.0007) and advanced stage of disease (stage III-IV vs I-II: O.R. 4.8810 (1.3663 - 17.4371), p 0.0147) . In patients with EC vitamin D levels also correlated with high (> 15 ng/ml) a-FPT levels (O.R. 22.0000 (1.8568 - 260.6595), p 0.0143).

Conclusions: Our study showed high prevalence of 25-OH vitamin D deficency in patients affected by TGT. Moreover in TGT patients vitamin D deficiency correlated with EC histology and advanced clinical stage.

F20 Targeted therapies in Collecting Duct Carcinoma: something new from next generation sequencing?

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Background: Collecting duct carcinoma (CDC) of Bellini is a rare, aggressive form of primary renal tumor occurring in less than 1% of all renal cell carcinoma (RCC). More than two third of patients with CDC exhibit locoregional or systemic symptoms on presentation but currently no equivocal indication exists for surgical and medical treatment of metastatic disease.Medical therapeutic approach is actually based on chemotherapy regimens; we previously published data on promising activity of target agents in this orphan disease highlighting that modern therapy may improve outcomes.

Material and methods: Sixteen patients with advanced CDC, referring to our Center, were treated from December 2004 up today. All patients were relapsed after nephrectomy, median age was 58 years and they were treated with targeted therapies until progressive disease or unacceptable toxicity.In this subset of patients Ion Torrent ® next generation sequencing technology ("Hot-spot Cancer Panel") was used to obtain molecular data.The aim of the study is to evaluate the activity of targeted therapies in metastatic CDC and to collect molecular data in order to identify predictive biomarker for the development of evidence-based treatment strategies.

Results: Nine patients (57%) were treated with sunitinib in first line, two (12%) with temsirolimus, three (19%) with sorafenib, 2 (12%) with pazopanib. Eight patients (50%) were treated with 2 or more therapeutic lines. Four patients, two treated with sunitinib, two with soarfenib and one with temsirolimus obtained a satisfying response (disease control lasting 4-33 months). Median overall survival was 5 months and safety data were consistent with the literature.Next generation sequencing was successfully performed in two samples until today, other results are not available currently.Rare gene mutations were found: FBXW7 in one case, JAK 3and KRAS in the other case.FBXW7 encodes for a member of the F-box protein family which function in phosphorylation-dependent ubiquitination while JAK3 encodes for an intracellular tyrosine kinase involved in cytokine signaling related to T cell development and proliferation.

Conclusion: CDC has a poor prognosis compared to non-CDC renal cell carcinoma; new targeted agents may represent an alternative therapeutic strategy . The identification of predictive biomarkers is a priority for a better knowledge of the disease natural history and for the development of specific treatment for this pathology.

F21 When the time matters: Metastatic Castration Resistant Prostate Cancer (mCRPC) patients long responders to Abiraterone acetate (AA) in post-docetaxel setting

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Background: The COU-AA 301 trial showed that AA improved survival for men with mCRPC progressing to docetaxel. No predictive factors are available to identify patients (pts) that may better respond to AA. In this trial the median duration of drug exposure was 7.4 months (range 0.2-25.6). Our aim was to describe clinical features of pts long responding to AA defined as those receiving AA in clinical practice for more than 12 months without evidence of disease progression.

Patients and methods: A total of 143 mCRPC pts treated with AA for more than 12 months at 16 Italian centers from Oct 2011 to Jul 2014 were identified. Clinical records were retrospectively collected and analyzed. Descriptive statistics (median and range for continuous variables and absolute and percentage frequencies for categorical variables) were used to describe clinical features; the Cox regression model was used to detect and estimate statistical association between clinical features and duration of drug exposure; HR was reported for each unit x 100.

Results: Median duration of treatment was 19.8 months (range 12-49) and 24% of patients still receive treatment. Median age was 73 years (range 47-87). Median PSA value at initial drug exposure was 38 ng/ml (range: 5-3850), Median Gleason score value was 8. Synchronous metastases to the primary were present in 33% of pts. Pts pretreated with chemotherapy were 88% and bone was the most frequent site of metastases (91%) with a remarkable 12% of pts had visceral disease (including lung, nonregional lymph nodes and liver). Pts receiving AA due to only PSA progression were 33%, while 54% of cases showed either PSA and radiological progression. PSA response ≥50% was observed in 80% of pts and those with measurable disease achieved a disease control rate of 88%. Risk of disease progression was stats associated with the following biomarkers values at baseline (before start AA): PSA (HR 1.10, p 0.008), alkaline fosfatase (HR 1.07,p 0.074) and LDH (HR 1.22, p 0.027).Regarding Gleason score surprising but in part according to what reported in clinical trials, higher Gleason was stats associated with less risk of disease progression (HR 0.82, p 0.012).Treatment was safe with 40% reporting only G1-G2 adverse events.

Conclusions: Clinical features may help to better identify the "best responder patient". A better understanding of the biological phenotype of mCRPC would lead to discover candidate predictive biomarkers of response.

F22 Survival analysis of patients with metastatic renal cell carcinoma treated with sunitinib: a single centre, real-word experience.

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Background: Sunitinib is a multi-target tyrosine-kinase inhibitor (TKI) largely used for the treatment of metastatic renal cell carcinoma (mRCC) in first or subsequent lines of therapy.

Material (Patients) and methods: We retrospectively reviewed clinical data of patients with mRCC treated with sunitinib with standard schedule (4 wks on and 2wks off) at our Institution from January 2007 to December 2014.

Results: We evaluated 114 patients, median age 62 years (range 26-90), 71% males, almost all had undergone prior nephrectomy (96.4%), with a prevalence of clear cell histology (90.3%). Sunitinib was used as first line TKI upfront (84.3%) or after cytokines or chemotherapy (15.8%). The median number of cycles received was 8 (1- 55). Grade 3 or 4 toxicities were found in 44% of the patients but only 3.4% discontinued treatment because of unacceptable toxicities. Out of 110 evaluable patients, 5 complete responses and 37 partial remissions according to RECIST were reported; stabilization of disease has been observed in 42 patients while progressive disease in 26 (primary refractory, 22.8%). Median PFS and OS were 14.3 and 28.4 months, respectively. The prognostic relevance of Heng score was maintained either for PFS and OS. Patients who received at least 4 cycles at standard dose (50 mg) had a significantly better OS compared to patients who did not (50.4 vs 19.5 months p = 0.02). A neutrophils to lymphocytes ratio (NLR) ≥ 3 has been found to be statistically associated with both OS (8.4 vs 50.4 months, p < 0.00001) and PFS (3.3 vs 20.0 months, p = 0.00004).

Conclusions: Sunitinib demonstrated to be active and well tolerated in a large population of real-world mRCC patients, achieving a median PFS and OS results apparently superior compared to pivotal trials. These results can be explained by patient selection, better management of drug toxicities, less strict criteria for radiological progression, and availability of further sequential treatments. Patients receiving at least four cycles at full dose achieved statistically significant better outcomes in this study, although the correlation between TKI dose and outcome remains elusive in mRCC. A NLR > = 3 reflects the imbalance between inflammation and immune-competence and represents a new and robust prognostic factor for survival.

F23 Abiraterone acetate in metastatic castration-resistant prostate cancer after chemotherapy. A retrospective analysis of progression-free (PFS) and overall survival (OS) in the "Real Life"

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Background: Abiraterone acetate (AA) is a potent, selective androgen (CYP17) biosynthesis inhibitor, which showed to improve overall survival (HR = 0.646) in

mCRPC patients progressing after docetaxel. In this retrospective analysis we assessed the PFS and OS safety in patients affected with mCRPC progressing after chemotherapy, treated in the normal clinical practice, in several Italian Oncologic Units.

Material and methods: We retrospectively reviewed the clinical data of patients affected with mCRCP progressive after chemotherapy who received AA (1000 mg/d) plus prednisone (5 mg/twice daily). Pts were considered eligible if they had received docetaxel as prior chemotherapy. A total of 189 patients were included in the analysis. Main patient characteristics were: median age: 70 years (range 44-89), Gleason score >7: 84%; median PSA at AA start: 35 (range 0.36–2100); duration of prior hormonal therapy <12 vs ≥ 12 months: 38 vs 62%; no. of metastatic sites: 1 vs ≥ 2: 73 vs 27%; bone only 48%, presence of visceral disease 51%; symptomatic vs non-symptomatic: 53 vs 47%; median number of prior docetaxel courses: 6 (range 1-20); second-line cabazitaxel: 14%. Forty-four percent of patients received bisphosphonates during AA treatment.

Results: At a median follow-up of 8.5 months (range 1-51) the median progression-free survival (PFS) and the median overall survival (OS) were 10 months (95% CI: 7-13) and 26 months (95% CI: 17-35) respectively. No differences in PFS and OS were found based on the response to docetaxel. Patients who received hormonal treatment for ≥ 12 months had a statistically significant longer PFS (13 vs 7 months, p = 0.009) and OS (28 vs 17 months, p = 0.03 months). The median decrease in the PSA level > 50% was observed in 36% of patients. Patients with only bone metastasis had a PFS of 13 (95% CI: 7.18) and OS 28 months (95% CI:16-40). Twelve patients (6%) presented a scheletal-related event (SRE). AA was well tolerated and no relevant toxicity were observed.

Conclusions: The PFS and the OS achieved in this analysis although retrospective, confirms the activity and safety of AA in these subset of patients.

F24 Efficacy and safety of axitinib as third line therapy in metastatic renal cell carcinoma (mRCC): retrospective analysis

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Background: Axitinib is approved after tyrosine kinase inhibitors (TKI) failure in mRCC, and is often used in second line. Few data are available when axitinib is used in third line. The goal of the study is to report our experience with axitinib in the 3rd line setting.

Methods: Data from mRCC patients (pts) treated at Gustave Roussy with axitinib as third line therapy have been analyzed. Prognostic factors from International Metastatic Renal Cell Carcinoma Database Consortium (IMDC), patient characteristics, safety and outcome were collected.

Results: 29 pts have been treated from November 2012 to February 2015. The median age was 55 years (38-73). All pts had clear cell histology. IMDC was assessed in 28 pts (77%): 5 (17%) were in the good risk group, 16 (55%) in the intermediate risk group and 7 (24%) in the poor risk group. The number of metastatic sites involved was: 1 in 2 pts (7%), 2 in 8 pts (26%), 3 in 7 pts (24%) and >3 in 12 pts (41%). As first line therapy 24 pts (83%) received TKI (sunitinb 69%), 2 (7%) bevacizumab + interferon, 1 (3%) temsirolimus and 2 (7%) clinical trial. The second line therapy was: everolimus in 17 pts (59%), nivolumab in 6 (21%), anti VEGF therapy in 6 (21%). At the time of the analysis, 11 pts (38%) are on therapy. Median PFS is 8.1 months (95% CI 5,7–10,6). 7 pts (24%) reached partial response and 19 pts (66%) achieved a stable disease, as best RECIST response. In 20 pts (69%), axitinib dose titration was feasible. At dose of 5 mg/bid 9 pts (31%) and 11 pts (38%) reported grade 1 and grade 2 adverse events (AEs) respectively, 6 (21%) pts reported grade 3 AEs. The most common grade 3 AEs reported was hypertension. At escalated dose of 7 mg/bid 14 pts (48%) and 6 pts (21%) reported grade 1 AEs, 5 (17%) grade 2 (diarrhea, fatigue, dysphonia, HFS) and 1 (3%) grade 3 (fatigue). 5 pts (17%) received the highest dose of 10 mg/bid, 2 presented grade 2 AEs (fatigue, hypertension) and 2 pts grade 3 (fatigue, HFS). One grade 4 AE was observed. 6 pts (21%) requiring dose reduction and 3 (10%) discontinued treatment because of toxicities. Among the 16 pts that discontinued treatment, 8 pts received a subsequent line of therapy. Median overall survival is not yet reached.

Conclusion: This study confirms safety and efficacy of axitinib, even when given in the third line setting. Response rate as well as PFS suggest that efficacy is not reduced when axitinib is given in this patient population. Further prospective data are warranted.

F25 Multigene profiling in incidentally- and clinically detected prostate cancer

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Background: Many prostate cancers never become clinically evident even in the absence of treatment. Randomized trials have confirmed an early survival advantage for surgery in higher-risk disease. Novel biomarkers can improve prediction and decision making about treatment. One promising tool is the expression of genes related to cell cycle progression (CCP). Analysis of their expression yields a CCP score that is an independent factor in radical prostatectomy (RP) and in transurethral resection of the prostate (TURP) [1]. Information on the expression of such genes in clinically insignificant prostate cancer, present in approximately 40% of men, has never been assessed. We aimed to validate the performance of the CCP score in a small cohort of incidental prostate cancer in comparison with clinically-detected prostate cancer.

Methods: We collected specimen of 7 radical prostatectomy, 3 incidentally and 4 clinically detected prostate cancers. Gene profiling analysis was conducted at the Myriad Genetics Laboratory, Salt Lake City, Utah, USA. Samples were taken from the dominant tumor focus. RNA was extracted using miRNeasy (Qiagen, Valencia, CA), and expression levels were determined using TaqMan low-density arrays (Applied Biosystems, Foster City, CA) for a set of 46 predetermined genes (31 CCP and 15 housekeeper genes). All genes were centered by their average expression in a set of commercial prostate tumor samples.

Results: Among all 46 studied genes, BIRC5 and FOXM1 showed statistically significant differences in expression according to clinical presentation (p = 0,0286). BIRC5, also known as survivin, is a key player in mitosis. FOXM1 expression in prostate epithelial cells is critical for prostate carcinogenesis.

Conclusions: The current study, even though based on a small number of cases shows that there are subtle differences in terms of gene expression between incidental and clinically detected prostate cancers. This investigation may represent a clinical tool to categorize patients with different prognosis.

References: 1) Cooperberg MR, Simko JP, Cowan JE, et al. Validation of a Cell-Cycle Progression Gene Panel to Improve Risk Stratification in a Contemporary Prostatectomy Cohort. J Clin Oncol 2013, 31.

F26 Prognostic and predictive role of 18F-choline (c) positron emission tomography (PET) in patients (pts) with metastatic castration resistant prostate cancer (mCRPC) treated with enzalutamide (ENZ) after docetaxel (DOC) failure

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Background: The low rate of measurable lesions in pts with mCRPC usually limits the applicability of RECIST criteria in this population. This led to a growing interest in cPET use to assess the response to the treatments but its potential prognostic value, too. We prospectively investigated the prognostic and predictive role of cPET in pts with mCRPC treated with ENZ after DOC failure.

Patients and methods: Between November 2012 and March 2013, all pts treated with ENZ 160 mg once a day under a Named Patient Program (NPP) were monitored by cPET. cPET scans were performed before starting ENZ (PET0), after the first three mos of treatment (PET1), and thereafter every four mos (PET2, PET3). The maximum standardized uptake value (SUVmax) of five target lesions and its changes over the time were assessed. Clinical response and PSA levels were monthly evaluated. Cox proportional hazards regression model was used to assess the association between metabolic parameters and biochemical response (bR), progression-free survival (PFS), biochemical progression-free survival (bPFS), radiological progression-free survival (rPFS) and overall survival (OS).

Results: We assessed a consecutive series of 30 pts with a median age of 76.9 yrs (range 59.2-86.7). PET0 data was available for all pts, PET1 and PET2 for 28 pts and 19 pts, respectively. Median duration of ENZ treatment was 10.2 mos, 23 pts experienced a PSA response >50%, median bPFS was 6.3 mos, median rPFS was 9.3 mos and OS was

17 mos. After a median follow-up of 16.5 mos, ENZ therapy was still ongoing in 5 pts while it was discontinued in 25 pts due to progression disease. A reduction of SUVmax >25% was observed in 11 pts (39%), 14 pts (50%) experienced a stable disease and 3 pts (10.7%) developed a disease progression. At univariate analysis, no significant correlation was observed between PSA response and cPET response. At multivariate analysis, only baseline SUVmax showed a significant correlation with bPFS (HR 1.22; 95%CI 1.09-1.37; p < 0.0001), rPFS (HR 1.13; 95% CI 1.02-1.24; p = 0.014), PFS (HR 1.12; 95%CI 1.03-1.22; p = 0.08) and OS (HR 1.21; 95%CI 1.01-1.44; p = 0.03).

Conclusions: Our study showed that cPET may have a role in defining prognosis of mCRPC pts receiving ENZ; in particular, baseline SUVmax is an independent prognostic factor for bPFS, rPFS and OS. However, its role in predicting response remains under evaluation and need to be further investigated in larger prospective clinical trials.

F27 LDH as prognostic factor for survival in castration-resistant prostate cancer (CRPC): a systematic review and pooled analysis of the literature

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Background: Several prognostic factors as performance status, alkaline phosphatase, visceral metastases, hemoglobin, PSA, and time from diagnosis were all previously validated in patients with CRPC treated with docetaxel. Lactate dehydrogenase (LDH) catalyzes the reduction of pyruvate to form lactate, and serum level is often raised in aggressive cancer. This parameter has not yet fully validated systematically for it's association with survival. We have assessed the independent prognostic value of LDH in CRPC.

Material and methods: A systematic search of Pubmed up 12th April 2015 was performed. Studies in English language that reported the correlation of LDH with overall survival (OS) in CRPC as multivariate analysis, in at least 10 patients, were extracted. Overall survival was the primary outcome. Only data from studies reporting a hazard ratio (HR) and 95% confidence interval (CI) were pooled in a meta-analysis. Pooled HRs were computed and weighted using generic inverse-variance and random-effect modeling.

Results: A total of 12 studies reporting outcome of 4132 patients was included in the final analysis. All patients were castration-resistant and metastatic, and were pretreated (n = 2 studies) or not with docetaxel (n = 10 studies). Overall, higher LDH levels were associated with a HR for OS of 2.04 (95% CI = 1.63 to 2.55; P < 0.00001) according to random effect model. Result was near identical in CRPC patients not previously exposed to docetaxel (HR = 1.99, 95%CI 1.57-2.52; P < 0.00001) according to random effect model.

Conclusion: LDH is a poor prognostic factor in other genitourinary malignancies as renal cell carcinoma and testicular cancer. Here we present correlation of LDH with OS in CRPC treated with systemic therapy in mainly pre-docetaxel setting. We can confirm that high LDH levels are associated with a 2-fold increased risk of death. LDH has recently been added in a prognostic model for OS in CRPC for selection of patients according to their prognosis. With the availability of new anti-androgen therapies in pre-docetaxel setting, LDH add further prognostic value and can be useful to recognize patients which need aggressive treatment (chemotherapy?) after castration failure.

F28 Safety and clinical outcomes of abiraterone acetate (aa) after docetaxel (doc) in octogenarians with metastatic castration-resistant prostate cancer (mcrpc)

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Background: AA demonstrated to significantly prolong survival of mCRPC patients (pts) after first line DOC. Although its favorable toxicity profile, the administration of AA in very old patients, who usually show reduced physiological reserves and multiple comorbidities, could raise raises questions about its safety due to the risk of metabolic and cardiovascular side effects in very old pts. We assessed the tolerability of AA in a cohort of mCRPC octogenarians enrolled in the Italian AA NPP, and evaluated their clinical outcomes.

Patients and methods: We retrospectively reviewed the clinical records of all pts treated with AA for mCRPC by NPP in our Institutions. All pts have been previously treated with a DOC-based first line chemotherapy and received the standard AA dose of 1,000 mg po daily plus prednisone 10 mg po daily. For each pt we recorded the pre and post-AA clinical history, the AA treatment details toxicities and clinical outcomes and separately assessed the pts aged = 80 years.

Results: Among the overall population of 265 pts, we found 47 octogenarians: the median age was 82 yrs (range 80-91). The median exposure to AA was 8 mos with major toxicity consisting of grade 3-4 anemia, nausea, diarrhea, fatigue, bone pain, constipation, and edema, each observed in one pt respectively. In these very old men the PSA response rate was 48.9%, and the median progression-free and overall survival were respectively 8 and 18 months. In comparison with younger patients, there were no significant differences in both toxicities and clinical outcomes.

Conclusions: Our data suggests that AA is active and safe also in octogenarians and leads to outcomes that are similar to those observed in younger patients, thus confirming that AA is a manageable therapeutic option in this patient population.

F29 Association between levels of hormones implied in steroid biosynthesis pathway and activity of abiraterone acetate (AA) in patients (pts) with metastatic castration- resistant prostate cancer (mCRPC): an exploratory analysis

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Background: AA is an inhibitor of CYP450 that impairs androgen-signaling by depleting adrenal and intratumoral androgens. It is approved for treatment of patients with mCRPC. Aim of this study was to describe changes in hormonal levels determined by AA and explore the association between levels (both baseline and changes) of hormones implied in steroid biosynthesis pathway and drug activity in order to identify a predictive serum biomarker and a mechanism of resistance to AA.

Patients and methods: Patients with mCRPC, after failure docetaxel, were prospectively enrolled in this mono-institutional study at San Luigi Hospital, Orbassano, Turin between June 2010 and December 2010. AA 1000 mg daily + prednisone 5 mg twice daily was administered until disease progression or unacceptable toxicity. Serum levels of progesterone, 17OH-progesterone, cortisol, DHEA sulphate, androstenedione, testosterone, sex hormone binding globulin, aldosterone, plasma renin activity, ACTH and cholesterol were determined at baseline and every 12 wks, until progression. Hormonal levels at baseline vs subsequent samples were compared by Wilcoxon matched-pairs test. Association between hormones and treatment activity (=50% PSA reduction) was tested (1) comparing baseline levels of responders vs non-responders; (2) comparing progression-free survival (PFS) of pts with baseline low vs high values of each hormone; (3) comparing levels after 12 wks of responders vs non-responders, adjusted by baseline levels.

Results: 49 pts were included in the analysis (median age 70, ECOG PS 0/1/2 61%/33%/6%, median baseline PSA 116.95). 82% were metastatic to bone. PSA reduction was obtained in 26 pts (53.1%). Median PFS was 10.2 months. Baseline levels of all hormones were not statistically different between responders and non-responders. For all hormones, difference in PFS of pts with low baseline values vs pts with high baseline values was not statistically significant. Several hormones showed significant and sustained changes vs baseline, but all significant changes were similar between responders and non-responders.

Conclusions: Although limited by low statistical power, our exploratory analysis does not suggest a significant association between baseline levels of hormones implied in steroid biosynthesis, or changes induced by AA, and treatment activity.

F30 New agents (nas) in metastatic castration-resistant prostate cancer (mcrpc): is there a sequence better than the others?

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Background: The availability of NAs (abiraterone, cabazitaxel and enzalutamide) for the treatment of mCRPC patients who progress after docetaxel and the possibility of using them sequentially has significantly improved clinical outcomes in advanced disease. However, the lack of head to head clinical trials as well as recent evidences of a possible cross-resistance among NAs have opened a debate about the best treatment

sequence when these drugs are used the one after the other. We performed a systematic review and analysis of the retrospective studies assessing the outcomes of mCRPC patients treated with one third-line NA after having previously received docetaxel and another NA, in order to assess if a sequence strategy was better than the others.

Methods: We analyzed all studies reporting monthly OS rates of mCRPC patients receiving two NAs after docetaxel published or reported until March 2015. The treatments were merged into three groups: one HNA followed by another, one NHA followed by CABA, and CABA followed by one HNA. The cumulative monthly OS rates in each group were determined using a weighted-average approach. To exclude potential selection biases, known prognostic factors (age, performance status, sites of metastases and Gleason score) were also evaluated.

Results: 13 retrospective studies including 1022 patients who received one specific third-line NA after another NA administered as second-line: 1) 481 patients (HNA?HNA); 2) 312 patients (HNA?CABA); 3) 229 patients (CABA?HNA), were analyzed. No statistically significant differences in terms of baseline known prognostic factors have been observed. The 12-months OS rates were 28.5%, 61.3% and 76.4%, respectively.

Conclusions: With all limits of retrospective nature, limited cohort size and potential selection biases of included studies, the present report did not demonstrate a clear superiority of a single drug over the others in the third-line setting of mCRPC. A possible OS advantage seems to be observed in the treatment sequences with CABA. However, prospective larger studies are required to validate these results, hoping head to head comparison trials. Our analysis confirms a potential cumulative survival benefit of sequential use of NAs in mCRPC.

F31 External beam radiation therapy (EBRT) use and safety with radium-223 dichloride (Ra-223) in patients (pts) with castration-resistant prostate cancer (CRPC) and symptomatic bone metastases (mets) from the ALSYMPCA trial

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Background: In ALSYMPCA, Ra-223, a first-in-class α-emitter, improved overall survival and delayed time to first symptomatic skeletal event vs placebo (pbo). This post hoc analysis evaluated safety and efficacy of Ra-223 plus EBRT.

Methods: Pts had symptomatic (recent EBRT for bone pain or any regular analgesic use) CRPC with ≥ 2 bone and no visceral mets; best standard of care; and prior docetaxel (pD) or were unfit for or declined docetaxel (no pD). Pts were stratified by pD use (yes/no), baseline total alkaline phosphatase level (tALP; < 220 U/L or ≥ 220 U/L), and current bisphosphonate (bp) use (yes/no) and randomized 2:1 to 6 Ra-223 injections (50 kBq/kg IV q 4 wk) or pbo. EBRT for bone pain was permitted within 12 weeks prior to randomization and during study.Baseline pain by prior EBRT, time to first on-study EBRT use for bone pain, and adverse events (AEs) by concomitant EBRT (cEBRT) were analyzed.

Results: Pts with no prior EBRT had less pain at baseline; a WHO pain score ≤ 1 (no opioid use) was present in 46% (355/724) of pts with no prior EBRT vs 36% (53/147) of pts with prior EBRT. Ra-223 vs pbo significantly reduced EBRT use in the overall population (HR = 0.67, $P = 0.001$) and in pts with ≤ 20 bone mets (HR = 0.49, $P < 0.001$), current bp use (HR = 0.47, $P = 0.004$), tALP < 220 U/L (HR = 0.66, $P = 0.008$), and no pD (HR = 0.65, $P = 0.038$). At 6 months, the percentage of Ra-223 pts requiring EBRT was similar for prior and no prior EBRT subgroups (24% vs 20%), increasing at 12 months (38% vs 29%). cEBRT did not affect Ra-223 safety, and myelosuppression was low (Table).

Conclusions: cEBRT did not adversely affect Ra-223 hematologic safety. Ra-223 significantly reduced risk of EBRT use. In Ra-223 pts, prior EBRT did not appear to affect later EBRT use.

Clinical trial information: NCT00699751

Table: F31

Patients with AEs, n (%)	cEBRT Ra-223 n = 227	cEBRT Pbo n = 140	No cEBRT Ra-223 n = 373	No cEBRT Pbo n = 161
Hematologic				
Anemia	77 (34)	51 (36)	110 (30)	41 (26)
Neutropenia	14 (6)	1 (1)	16 (4)	2 (1)
Thrombocytopenia	27 (12)	8 (6)	42 (11)	9 (6)
Nonhematologic				
Diarrhea	71 (31)	26 (19)	80 (21)	19 (12)
Nausea	98 (43)	61 (44)	115 (31)	43 (27)
Vomiting	56 (25)	26 (19)	55 (15)	15 (9)
Constipation	54 (24)	35 (25)	54 (15)	29 (18)

F32 Feasibility and efficacy of 223Ra-dichloride (223Ra) to treat bone metastases in patients (pts) with castration resistant prostate cancer (mCRPC)

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Aim: To share the Tuscany single-centre experience about the employing of the novel therapeutic radiopharmaceutical 223Ra in the treatment planning of mCRPC pts.

Methods: Thirteen pts were treated from August 2013 to date. Five pts have been enrolled in the Bayer EAP and 8 have been treated as routine application. Pts (age 67 ± 8.4 yrs, median PSA 149.5 ng/mL, excluding one case of neuroendocrine differentiation) received 223Ra 50 kBq/kg i.v. on day 1 every 28 days for a maximum of 6 cycles. Pre-treatment evaluations were made using bone scan, and WB-CT in order to exclude visceral metastases. Pts have been evaluated at every cycle with complete blood chemistry (including serum ALP, PSA and LDH), pain VAS score, quality of life questionnaire (FACT-p), and analgesic consumption. The last group of pts started the cure in March 2015.

Results: At the current time-point 13 patients received 72 cycles of 223Ra. No issues in vial manipulation, dose preparation and administration occurred. A multidisciplinary team has followed pts during both screening and treatment period. Only 3 cycles have been delayed (2 due to blood toxicity, 1 due to drug's manufacturing hitches) and 3 pts discontinued the treatment (2 because of non reversible blood toxicity and anorexia, and 1 because of hepatic disease progression). Regarding valuable clinical data, bone marrow toxicity resulted in G3 anemia in 2 pts, G2 neutropenia in 2 pts, and G1 thrombocytopenia in 1 patient. Anorexia G3 occurred in 3 pts, while no case of diarrhoea was observed. Biomarkers response showed median ALP decline of -50% and median LDH decline of -5%. We observed mean PSA decline of -15%. One patient who presented with superscan at baseline received 223Ra 5 cycles before hepatic progression, showing ALP levels decline of -89%, LDH -44% and PSA -48%. According to VAS score and FACT-p, most of pts had bone pain relief and reduced pain drugs intake.

Conclusion: Single-centre experience shows the feasibility and efficacy of therapy with 223Ra in mCRPC pts. Multidisciplinary careful evaluation of bone marrow toxicity and gastrointestinal adverse events must be carried out to optimize individual compliance. Palliative effect allows decreasing pain drugs consume. The mild toxicity could permit the use of 223Ra in combination with other treatments.

F33 A path for diagnosis, therapy, follow up and research of kidney cancer: a continuous quality improvement

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Background: PDTA is a path of diagnosis, therapy, follow up and research of patients with renal cell carcinoma (RCC), based on a multidisciplinary approach in order to have the highest quality of patient care. Our aim is to improve and make more easily accessible path to the person facing the disease.

Material and methods: The patient who comes to Cardarelli Hospital with suspect or certain RCC is evaluated in a specific path. Protocols of diagnosis, staging, surgical or medical treatment and follow-up are defined.Indicators of process and result have been identified and will be periodically verified in order to evaluate the implementation of the path and the improvement of patient care.The main indicators are summarized below:

- median time between access to the hospital and starting medical treatment or surgery
- hospitalization rate in emergency for suspected RCC
- ratio between n. of pts who have suspended or interrupted drug therapy autonomously and n. of pts treated
- IP1: time between the date of the radiological findings of localized renal mass and surgery
- IP2-IP3: time between the date of the radiological findings of metastatic disease and cytoreductive surgery or medical treatment
- IR1-2: time to recurrence after radical or conservative surgery
- IR3: % OS
- IR4-IR5: % G3 or G4 toxicity (sec CTCAE)
- IR6-IR7 = Time to disease progression during 1° or 2° line treatment
- IR8: % of OS after starting of medical treatment
- IA1 =% adherence to guidelines
- IA2 =% pts evaluated by the multidisciplinary team

The degree of satisfaction of the patient is evaluated through a questionnaire and results will allow us to improve the path.

Results: From 01.11.2014 to 31.04.2015, 58 pts were included in the path.The main results are:

- Median time between access to the hospital and starting medical treatment or surgery: 20 days and 10 days, respectively
- % of hospitalization in emergency for suspected RCC: 47%
- ratio between n. of pts who have suspended or interrupted drug therapy autonomously and n. of pts treated: 0/18 It is still too early to collect data on recurrence and survival.

Conclusions: Our experience of creation of PDTA with the detection of indicators of process and result to monitor the path and a periodic activity of clinical audit may become an important tool to ensure quality care. In December 2014, we have received the certification of excellence IS0 9001-2008 for diagnosis, treatment and research of RCC through a multidisciplinary approach.

F34 Circulating tumor cells status in metastatic renal cell carcinoma (mRCC) after metastasectomy (RESORT trial)

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Background: Complete responses with targeted therapies (TTs) for mRCC are rarely achieved. Retrospective findings seem to indicate that metastasectomy (Mtx) may improve survival in selected patients (pts). The RESORT study was designed to evaluate whether Mtx followed by Sorafenib (SO) may provide an additional clinical benefit in terms of disease-free survival (DFS) when compared with observation. Circulating tumor cells (CTCs) fluctuations may reflect and possibly anticipate treatment outcome or cancer relapse. We would aim to assess the role of CTCs as prognostic and pharmacodynamic biomarkers and to explore the association between baseline CTCs count and DFS.

Material and methods: The RESORT trial is a multicentre, open label, randomized phase II study that will be randomize 132 mRCC pts to receive sorafenib or best supportive care (BSC) for one year after radical metastasectomy. At the time of this analysis 31 pts were enrolled. Blood samples were collected from consenting pts in both study arms at baseline, at 3 months after randomization, after one year and at disease progression (whenever it occurs). Blood samples were processed with the AdnaTest ProstateCancerSelect kit for CTC-enrichment. CTCs were identified based on expression levels of EpCAM, MUC1 and ERBB2 using RT-multiplexPCR (BreastCancerDetect AdnaTest kit) using on purpose defined cut-offs. Patients were evaluable for CTCs count if at least one blood sample was available after randomization.

Results: Out of the 22 cases enrolled at our coordinating center, 16 pts were evaluable for CTCs count. According to the count levels of CTCs at baseline and after at least 3 months from randomization we could classify patients in 4 subgroups: CTCs-negative group (6 pts), CTCs-positive turning into CTCs-negative group (6 pts), CTCs-negative turning into CTCs-positive (3 pts) and CTCs-positive group (1 pt). Interestingly, all pts of the baseline CTCs-positive turning into CTCs-negative group showed disease relapse. Four of this 6 pts were in the SO arm while 2 pts in the BSC arm. In the other subgroups there was heterogeneity in terms of either disease relapse rate and arm of treatment.

Conclusions: It may be hypothesized that the lack of predictive value of CTCs may depends on the use of SO that may down-regulate epitelial markers (e.g. EpCam) preventing from capturing CTCs.Further accrual may possibly help to explain this preliminary findings and better address the role of CTCs in this setting.

F35 Weekly paclitaxel (wptx) as second-line chemotherapy in elderly patients (pts) with advanced urothelial cancer: data from a single-centre experience

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Background: Older pts are generally under represented in clinical trials: few data exist about the role of second-line chemotherapy in elderly pts with advanced urothelial cancer. In this study we retrospectively evaluated safety and efficacy of weekly administration of paclitaxel (wPTX) in elderly pts (> 70yrs) with metastatic urothelial cancer who progressed after first-line chemotherapy.

Patients and methods: We retrospectively reviewed the medical records of 21 elderly pts with metastatic urothelial carcinoma. Main characteristics of pts were as follows: M: F= 15:6, median ECOG PS 1 (1-2), median age 72 yrs (range: 70-82 yrs), median number of metastatic sites 2 (range: 1-4). All pts were previously treated for advanced disease with platinum-based first-line chemotherapy. Primary sites were: bladder in 16 pts (77%), ureter in 3 pts (14%), renal pelvis in 2 pts (9%). Pts were treated with PTX 90 mg/m^2 i.v. administered on days 1, 8 and 15 every 28 days until appearance of unacceptable toxicity or progressive disease.

Results: No CRs were observed. Six pts (29%) had PR, seven pts (33%) obtained SD with a disease control rate of 62%. Eight pts (38%) progressed. The median time to progression was 4.3 months (range: 2.8-5.4) with a median overall survival of 6.1months (range: 4.1-9.2). Treatment was well tolerated: no G4 haematological and non-haematological toxicities were observed. Three pts (14%) developed G3 neutropenia and four pts (19%) G3 anemia. Asthenia, anorexia and peripheral neuropathy occurred in 2 (9%), 2 (9%) and 3 (14%) pts, respectively. No treatment-related deaths were registered.

Conclusions: Although this is a retrospective experience and despite the small number of patients evaluated, due to its moderate efficacy with a favourable profile of toxicity, wPTX could represent an interesting therapeutic option as second-line chemotherapy in elderly pts with advanced urothelial cancer.

F36 Long-term survival in patients with metastatic castration resistant prostate cancer (mCRPC) treated with enzalutamide in a named patient programs (NPP)

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Background: The majority of patients (pts) with metastatic prostate cancer (mPC) becomes resistant to established androgen deprivation therapies (ADT). Men who develop mCRPC have a poor prognosis. Enzalutamide (ENZ) is one of the most exciting new hormonal agents which demonstrated a survival gain in pts with CRPC.

Methods: We retrospectively evaluated a consecutive series of pts with mCRPC who have received ENZ, before his approval in Italy, in a NPP conducted in our hospital. We defined two cohorts of pts depending on overall survival (OS) defined as time of date starting ENZ to date of death/last follow up. Group 1 (G1) included pts with OS ^{3} 14 months and group 2 (G2) included pts with OS < 14 months. Baseline pts characteristics, treatment details and outcomes data were compared in the two groups with the aim to evaluate potential factors outcome-related.

Results: From June 2010 to April 2013 18 pts were treated with ENZ in a NPP in our institution. All the pts received docetaxel (TXT) as first line therapy. Median OS for ENZ was 14 months (95% CI 6-22). Each group counts 9 pts. Median age at diagnosis of PC was 65 years (yrs) for G1 and 64 yrs for G2. In both groups 7/9 pts (78%) have Gleason score ^{3} 7. Prostatectomy was performed in 4 pts (44%) of G1 and in 1 pt (11%) of G2 (p = 0.29). Metastatic disease at diagnosis was present in 4 pts (44%) of G1 and in 6 pts (67%) of G2. Metastatic free interval (MFI) was 10 yrs for G1 and 7 yrs for G2 (p = 0.79). As first metastatic site (FMS) nodal involvement is more frequent in the G1 (68%), while bone disease was FMS in the 77% of the pts of G2 (p > 0.05). The median

duration of ADT was 5.4 yrs for G1 and 1.7 yrs for G2 (p = 0.51). ENZ was second line therapy in all pts of G1 and in only 4 pts in (p = 0.02). Median prostate-specific antigen (PSA) level before starting ENZ was 45 ng/ml for G1 and 97 ng/ml for G2 (p = 0.66); median PSA nadir level during ENZ was 0.43 ng/ml in G1 and 47 ng/ml in G2 (p = 0,39). PSA response rate ^{3}50% was detected in 6 pts (67%) of G1 and in 3 pts (33%) of G2 (p = 0.31).

Conclusion: Our preliminary results, even if based on a limited number of pts, suggest that mCRPC pts with radical prostatectomy, nodal involvement as first metastatic site, androgen-deprivation long response, ENZ treatment after TXT (II-line) and ENZ-PSA response rate ^{3}50% have a good prognosis with a survival time of more than 14 months. These data should be confirmed in a larger patient population.

F37 De novo renal cell neoplasia after kidney transplantation, according to the International Society of Urological Pathology (ISUP 2013) Vancouver Classification

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Bakground: Renal cell carcinoma (RCCs) may arise after kidney transplant (KTx). The recent International Consensus in Vancouver (ISUP Vancouver Classification - 2013) introduced 5 new subtypes of RCCs. It is not yet established how this new classification impacts on overall survival, if there is a correlation between RCC histological subtypes and KTx, and how the KTx may affect the RCC behavior and the survival of renal transplant patients.

Methods: We reviewed several cases of de novo RCCs after KTx through a period of 30 years. According to the recent ISUP Vancouver Classification we performed an immunophenotypical analysis including CD13, CD10, CK7, AMACR, CAIX, GATA-3, S100A1 and parvalbumin. phmTOR and ph70S6K were also assessed.

Results: Five clear cell, five papillary, one sarcomatoid NAS, and two unclassificable RCCs were identified. Two new neoplastic entities were recognized sec. ISUP, a tubulocystic and a clear cell-papillary RCC respectively (2/13). Among variants, one papillary RCC showed clear cell changes and one oncocytic changes (2/13). Regarding tumor stage, nine cases were pT1, three pT3, and one pT3 with sarcomatoid features. With respect to tumor clinical behavior, one patient affected by a G4 clear cell RCC died due to lung metastases after 1 year, and two patients affected by a G3 clear cell RCC with sarcomatoid features developed recurrences after two and 5 years, respectively; the remaining cases are still alive without tumor recurrence. All tumors revealed intense and diffuse positivity for both ph mTOR and ph 70S6K molecules. One clear cell and the low grade clear cell-papillary RCCs showed a weaker staining for mTOR.

Conclusion: We report two new nosological histotypes (15%) and two variant subtypes of de novo neoplasia (15%) after KTx. Both the new hystotypes and the new variant subtypes do not show aggressive behaviour. A thorough understanding of histological subtypes, molecular characteristics, and clinical behaviour of de novo RCC after KTx, is strongly advocated to better manage affected patient during follow-up and to guide the development of future targeted therapeutic strategies so as to improve the prognosis of these unlucky patients.

F38 Autophagy and transplantation: organ injury and cancerogenesis by molecular expression of LC3B

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Bakground: LC3B is the only reliable marker of autophagosomes. In particular the levels of LC3-II correlate with autophagosome formation, being associated with the autophagosome membrane. The autophagy process represents a key catabolic mechanism essential to maintain cellular homeostasis, having a major role during regeneration of injured tissues or ensuring tumor cells survival in adverse conditions. The mTOR complex is known as an inhibitor of the autophagic process and it is described constitutively active in the renal angiomyolipoma tumor model. Recent studies suggested that TORC2 signaling pathway regulates autophagy separately from TORC1, in order to obtain a response correlated to the cellular metabolic state. De novo tumors may arise from transplanted organs and may need to be treated with mTOR inhibitors and other targeted drugs. The autophagy processes occurring in transplanted organ can be exploited to detect new generation treatments. We sought to identify the presence of LC3B, indicator of autophagy processes and its regulatory mechanisms in neoplastic model such as renal angiomyolipoma, archetypal of an mTOR-related tumor.

Materials and methods: Fourteen renal angiomyolipoma (2/14 de novo tumors after transplantation) underwent to immunohistochemical, immunofluorescence and Western blot analysis, for detecting proteins that occur in autophagy and lysosomal activities. Electron microscopy study was also performed on tumor cells in 5 cases.

Results: We observed the presence of LC3B using the all three tissue-based techniques in 13/14 cases and the functional activation of TORC1, through presence of ph-S6K protein, in 12/14. In 4 out of 5 cases, the electron microscopy study showed several cytoplasmic double membrane organelles, indicating autophagosomes.

Conclusions: We observed a high expression of LC3B in an mTOR-related neoplastic model, as the renal angiomyolipoma is. The constitutive activation of TORC1 and the presence of autophagy, determined by the LC3B tissue-based indicator, play an important role for the development of targeted therapy when these neoplastic lesions are de novo observed in organ transplants. Molecules targeting the autophagic process (i.e. chloroquin) and TORC1 inhibitors may be combined when balancing anti-neoplastic activity while preserving organ transplants functionality.

F39 Radium-223 alpha emitter agent in safety study in mCRPC popUlation for long-teRm evaluation (REASSURE)

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Background: The skeletal system is the most common site of metastases (mets) in advanced prostate cancer, impacting on survival and quality of life in more than 90% of patients (pts) with castration-resistant prostate cancer (CRPC). Radium-223, a first-in-class alpha-pharmaceutical targeting bone mets, reduced the risk of death by 30% versus placebo in CRPC pts with symptomatic bone mets in the phase 3 ALSYMPCA trial and reduced the median time to first symptomatic skeletal related event by 34% (Parker et al. NEJM 2013). Radium-223 is approved for the treatment of pts with CRPC, with symptomatic bone mets and no known visceral disease. The international prospective observational single arm cohort REASSURE study is aimed to assess the safety and tolerability of radium-223 and the risk of developing second primary malignances over time among CRPC pts treated in the routine clinical practice.

Methods/design: The treatment decision for radium-223 needs to be made independent from and before patient enrollment in the study. Pts aged ≥18 years with CRPC and bone mets not previously or currently treated with radium-223 or planned for the systemic concomitant use of other radiopharmaceuticals for prostate cancer or other cancers are eligible. Inclusion and exclusion criteria should follow the locally approved radium-223 product information. REASSURE primary objectives are to assess the effects of radium-223 over time, including the incidence of second primary malignancies (myelodysplastic syndrome/acute myeloid leukemia and osteosarcoma). Patients will be followed up until death, withdrawal of consent, lost at follow-up or until the end of the study, whichever occurs earlier. Overall survival and pain-related data will be collected. The study will be conducted in routine clinical practice settings. The design is to include approximately 1,334 pts from approximately 20 countries worldwide. Accrual is already open in some countries.Final analysis will be performed when the last enrolled pt has been followed for a maximum of 7 years after last administration of radium-223 according to local clinical practice. (ClinicalTrials.gov identifier: NCT02141438).

F40 Prostate cancer unit : a single institution two years experience

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Background: Prostate cancer is the most frequent malignant tumour in men, and the third highest cause of death from cancer. The widely recognised benefits of a multidisciplinary approach to treating cancer may be particularly important in prostate cancer, where there are so many treatment options to choose from. It offers patients the best chance of receiving high-quality medical procedures administered by a team of specialists in prostate disease, which is able to tailor treatment and observational strategies to their needs, and ensure access to specialist counselling, supportive care and rehabilitation.

Material and methods: In april 2013 we began our activity as a Prostate Cancer Unit (PCU). The Unit is organised into a multidisciplinary team which devises and monitors treatment plans specific to each clinical situation. This team of specialists, which includes medical oncologists, urologists, radiotherapists, radiologists, pathologists, nuclear medicine specialists, nurses, psycho-oncologists, data managers, palliative care specialist and physical therapists, addresses the disease at each stage in order to offer personalized diagnosis, treatment, advice and rehabilitation. The PCU

meets every other week in Carpi at the Medical Oncology Unit and through videoconference with the Modena Hospital Policlinico.

Results: In these two years of activity, we discuss 384 cases of prostate cancer. The discussion have changed the initial proposal in 21 % of cases and have facilitate access to care. We maintened records of the patients who were discussed and from January 2014 we have ECM certification.

Conclusions: The establishment of Prostate Cancer Units could provide financial savings and avoid multiple consultations,inappropriate treatments and secondary therapies. Prostate Cancer Units can deliver high-quality care to patients with prostate disease and provide for a multiprofessional management of the disease, due to the continuous interchange among different specialists and care. Our team of specialists is committed to offering the best advice to patients with prostate cancer diagnosis and looking for the most appropriate solutions in each case.

F41 Hypophosphatemia in Prostate Cancer Patients Treated with Abiraterone

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Background: Abiraterone strongly inhibits androgen synthesis but may lead to an increase in mineralocorticoid hormones that may impair its long term tolerability in patients with prostate cancer. At present, the best conceivable treatment for managing the abiraterone-induced mineralocorticoid excess consists of the administration of glucocorticoid replacement at the lowest effective dose and salt deprivation. The drug dose should be modulated by monitoring blood pressure, fluid retention and potassium levels during therapy.

Materials and methods: We evaluated prospectively phosphorus, calcium and potassium serum levels in 28 metastatic prostate cancer patients receveing abiraterone in pre and postchemotherapy setting. 10 out of 28 receveid zoledronic acid and calcium supplement as concomitant medication. Biochemical assessment was performed before receveing the first dose of abiraterone and every first day of every cycle.

Results: All patients had potassium serum level within normal limits. Hypocalcemia G1 was present in 10% of patients not receveing zoledronic acid . 25% of patients (7/28) showed phosphate serum-low level G3 . In these patients we decided to administer a daily supplement of oral phosphorus with the resolution of the adverse event within 28 days in 6 out of 7 patients.

Conclusions: To our knowledge there are no data reporting hypophosphatemia on abiraterone therapy. Patients with metastatic prostate cancer often showed anorexia, fatigue, confusion, anxiety, musculoskeletal pain, tremors. These symptoms could be related to malignancy or advanced age, owing to a combination of several factors. Severe hypophosphatemia cause the same symptomatology. Mild phosphate serum-low level does not require any treatment. However it is important that we identify the presence of moderate or severe hypophosphatemia because a rapid supplementation can result in a better tolerance of abiraterone and a better outcome of these patients.

F42 Multiple access and hospitalization predictors in patients with Urological Cancer: a retrospective analysis

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Background: The increasing incidence of urological cancers as well as the many treatment options available nowadays have both led to frequent multiple and unplanned consultations of urological cancer patients. As such, we aim to define main causes and features of this phenomenon, identifying the major risk factors predicting repeated accesses and hospitalization.

Materials and methods: Records from 616 consecutive unplanned consultations were analyzed from October 2006 to December 2014. Collected data included baseline demographic, clinical variables, reasons for presentation, laboratory results and outcome of the visit. Cross-tables, $\chi 2$ test, and logistic regression have been utilized for the analysis. We studied the association between potential predictive factors and two established events: multiple presentations and hospitalization.

Results: Median age was 70.5 (range 23-88). Kidney cancer (36.4%), prostate cancer (34.7%) and bladder cancer (19.8%) were the most common tumor types. The main reasons for unplanned consultations were: pain (31.2%), hematological toxicities (20.8%) and fatigue (20.3%). The median number of causes of presentation was 1.0 (range 1.0 -7.0). In univariate analysis, the most important predictive factors for hospitalization were multiple reasons for consultation ($p < 0.001$), dyspnea ($p < 0.001$), fatigue ($p < 0.001$), pain ($p = 0.002$), urinary tract disorders ($p = 0.007$), nausea/vomiting ($p = 0.021$), and thromboembolic events ($p = 0.034$). On multivariate analysis, only multiple reasons for visit ($p = 0.008$, IC 95% 1.28-5.13, OR 2.56) and dyspnea ($p = 0.029$, IC 95%1.09-4.47, OR 2.20) were significant. When assessing the potential risk factors for multiple accesses, univariate analysis showed a significant correlation with hematological toxicities ($p < 0.001$), chemotherapy administered within the last 90 days ($p < 0.001$) and pleural effusion/ascites ($p = 0.031$). On multivariate analysis, chemotherapy within 90 days ($p < 0.001$, IC 95% 1.59-4.31, OR 2.62), hematological disorders ($p = 0.002$, IC 95% 1.63-8.37, OR 3.70) and pleural effusion/ascites ($p = 0.029$, IC 95% 1.21-32.44, OR 6.26) were associated with multiple presentations.

Conclusion: In patients with urological cancers the phenomenon of unplanned visits and hospitalization for side effects of anticancer therapy is not negligible. In the present analysis, chemotherapy within 90, hematological toxicities and pleural effusions were linked with an increased risk of repeated unscheduled visits.

F43 20 years single center experience with testicular cancer

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Background: Testicular cancer, either seminoma (S) or non seminoma (non-S) have an exceptional survival that reach near 100% for stage I disease. Even in more advanced stages adjuvant chemotherapy is curative in almost all cases. Adjuvant therapy has changed in particular for stage I S, and chemotherapy (CT) with single agent carboplatin has now replaced radiotherapy (RT). We have revised the experience of Treviglio Hospital in the management of S and non-S in the last 20 years.

Table: F43

Histology	Stages	Adjuvant therapy	Relapses (N°)	Median OS (months)
Seminoma **(n = 24)**	I (N = 21)	N = 3 CT (Carboplatin) N = 12 RT N = 4 follow up N = 1 RPLND N = 1 NA	1	114
	II-III (N = 3)	N = 2 CT (PEB) N = 1 follow up	1	85
Nonseminoma or mixed (n = 30)	I (N = 16)	N = 6 CT (PEB) N = 2 surgery N = 8 follow up	1	108
	II-III (N = 12)	N = 6 CT (PEB)	0	131
	Unknown (N = 2)	N = 7 RPLND + CT (PEB) N = 1 NA		

Material and methods: The database of patients which accessed to Oncology Unit of Treviglio Hospital with a diagnosis of testicular cancer (up to March 2015) was analysed for demographic, hystopathology, postoperative treatment and outcome. Data were analysed separately for histology (S vs non-S/mixed histologies) and stages (I vs II-IV). Median overall survival (OS) was reported in months for patients with data available.

Results: A total of 54 patients with diagnosis of testicular cancer from 1989 to 2014 accessed to our Day Hospital (n = 24 with S and n = 30 with non-S or mixed histologies). Median age was 32 (range 19-52). In 2 patients stage was not available. Only 3 patients relapsed, conversely n = 46 are actually free of disease (for n = 5 patients data was not available). Relapse-free survival is 94% for all stages. For all patients, at last follow up (April 2015) the OS is 100% (median 9 years). Not late toxicities were recorded these patients.

Conclusions: In our experience with testicular cancer OS was excellent, with no cancer-related death. Two patients with stage I disease relapsed (1 S and 1 non-S respectively). Only 19% and 50% respectively of stage I S and non-S underwent surveillance only. Accordingly to literature data, adjuvant carboplatin was introduced as adjuvant therapy of stage I S after 2008, conversely RT was offered mainly in patients diagnosed before 2008. Stage I cancers have near similar median OS.

F44 Testicular cancer: clinical features in a retrospective survey analysis of a single institution of Sardinia

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Background: Primary testicular cancer (TC) is the most common solid malignant tumor in men between the ages of 20 and 35 years in Italy. The unusual age distribution shows one peak in incidence in young adults (aged 20-39) and a second peak in over 60. The italian annual incidence is about 11% in men younger than 50 years. The incidence of TC increased during the last century. The five year survival rate is about 95%. Even in cases of advanced disease, cht offers a cure rate of at least 80%.

Patients and methods: We retrospectively queried all pts diagnosed with TC in our institution from1998 to 2014. Clinical features and outcome parameters were the primary endpoints. 64 patients with TC were identified. Median age was 33 years (IQR 19-71), 37 seminomas, 19 embryonal carcinoma, 3 teratomas,1 teratocarcinoma,1 Leydig cell tumor,1 mixed form carcinoma; in 38 pts the primary tumor was localized in the right testicle, in 23 pts in the left, 1 the primary tumor was mediastinical and 1 was retroperitoneal. By the AJCC tumor stage classification: 40 pts presented stage I disease, 10 pts stage II,10 pts stage III, 4 pts stage IV. 18 pts had metastatic sites, 9 addominal limphonodes, 1 upper diaphragmatic lymphonode, 5 lungs and 1 liver; 5 pts with stage I disease received 3 cycles of adjuvant PEB (Cisplatin-Etoposide-Bleomycin), 2 pts with seminoma received 1 single dose of carboplatin AUC 7, 35 pts received first line chemotherapy: 32 pts were treated with PEB for 3-4 cycles, 1 with PVB (Cisplatin-Vinblastine-Bleomycin), 2 with carboplatin AUC 7.

Results: The overall response rate (RR) was 91.3%. CC remission was achieved in 24pts, PR in 8 (22,8%) pts, 1pt died due to toxicity related to the treatment (neutropenic sepsis), and 1 pt showed PD under treatment; 6 pts received second line chemotherapy, 3 ICE (ifosfamide, carboplatin, etoposide), 2 TIP (paclitaxel, ifosfamide, cisplatinum), 1 PEI (cisplatin, etoposide, ifosfamide). After a median follow up of 63 month (IQR 12-204), 93,7% were alive and disease free, 4,6% died due to disease progression. All the patients with stage I and II disease didn't not relapse. The patients who died were 2 on stage III and 2 on stage IV.

Conclusions: Testicular cancer is increasing in incidence in many countries; however, mortality rates remain low and most men are cured. Our study confirm the excellent prognosis among all tumor stages with an extremely low rate of disease progressions and deaths which are limited to advanced stages.

F45 Prostate cancer unit initiative in europe: a consensus on standards of care

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Comprehensive multidisciplinary management of prostate cancer (PC) optimizes patients' access to care, rehabilitation and counseling delivered by a team of qualified experts. This is in line with the need for a paradigm shift from a disease-focused to a patient-centered approach underlined also by the European Partnership for Action Against Cancer.
The concept of specialised interdisciplinary and multiprofessional PC care to be formalized in Prostate Cancer Units (PCU) was developed by the Prostate Cancer Programme of the European School of Oncology. The first step was the publication in 2011 of the collaborative article "The Requirements of a Specialist Prostate Cancer Unit: A Discussion Paper From the European School of Oncology". It was followed by the launch of the PCU Initiative in Europein 2012 in which internationally recognized opinion leaders, among whom representatives of scientific societies, and patient advocates were invited to set standards for quality comprehensive care in PCUs.

F46 New biomarkers of sunitinib efficacy in metastatic renal cell carcinoma

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Background: Hypertension, hypothyroidism, thrombocytopenia and neutropenia are frequent side effects of sunitinib. Preliminary studies suggested that drug- related toxicity may correlate with a better prognosis.

Material and methods: We retrospectively analyzed clinical records of patients (pts) affected by metastatic renal cell carcinoma (mRCC) treated with sunitinib as first-line therapy. We evaluated the following toxicities: hypertension (blood pressure > 140/90 mmHg or blood pressure requiring intensification of a pre-existing anti-hypertensive medication), hypothyroidism (requiring hormone replacement therapy, with or without symptoms), thrombocytopenia (platelet count <100.000) and neutropenia (neutrophils <500). Overall survival (OS) and progression free survival (PFS) were calculated until 24 months of follow up. OS and PFS in patients who developed and who did not develop a drug- related toxicity were compared using T-test and X^2 or Fisher exact test.

Results: Thirty pts (19 males), median age 70.4 years, were evaluated; 20 pts (66%) had pre-existing controlled hypertension and four pts (13,3%) pre-existing hypothyroidism (in therapy). Complete blood count was normal in all the pts before starting the treatment. Twenty-two pts (73,3%) experienced at least one toxicity: 14 pts (46.6%) developed hypothyroidism, 8 pts (26,6%) hypertension that required medical therapy, 13 pts (43%) thrombocytopenia and 2 pts (6.6%) neutropenia. We found that median OS and median PFS of pts who developed hypothyroidism was 21.6 vs 12.8 months (p = 0.04), and 13.7 vs 8 months (p = 0.064), respectively. Median OS and median PFS of pts who developed hypertension was 22.3 vs 14.7 months (p = 0.028), and 16.5 vs 8.8 months (p = 0.023), respectively. No significant difference in OS and PFS was found in pts who developed only thrombocytopenia or neutropenia (probably due to the small number of patients included). Median OS and median PFS were significantly longer in patients who developed at least one toxicity vs patients who did not: 20,5 vs 8 months (p = 0.0001) and 12.7 vs 6,7 months (p = 0.088), respectively.

Conclusions: In patients with mRCC treated with sunitinib, the development of drug-related toxicity, in particular hypertension and hypothiroidism appeared associated with a longer OS and PFS. Other studies are necessary to confirm our preliminary findings.

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Session G. Head and neck cancer

G01* The phase III study INTERCEPTOR in locally advanced head and neck cancer (LA-HNC). Preliminary safety report

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Background: INTERCEPTOR is a randomized multicentre phase III study comparing CRT (Aldestein 2003) vs induction (Vermorken 2007) followed by RT and Cetuximab (bioRT)(Bonner 2006). The study started in October 2009. The maine objective is overal survival, secondary end-points are response rate, progressione free survival, toxicities and role of biomolecular prognostic factors. Hereby we present the preliminary safety report of the study.

Table: G01*

Neutropenia	Grade 0-2	Grade 3-4	P value
ARM A	67	18	0.017
ARM B	78	7	

Methods: Naïve patients with LA-HNC histological proven, adequate bone marrow, renal and hepatic function and age > 18 yr old are eligible. Treatment consisted of : Arm A docetaxel = 75 mg/mq, cisplatin (C) = 75 mg/mq day 1, FU c.i. = 750mg/mq 96h, every 3 weeks for 3 times then cetuximab loading dose 400 mg/mq followed by weekly 250mg/mq with a standard Radiotherapy (RT) program equivalent daily dose 2Gy up to 70 Gy. Arm B C = 100 mg/mq day 1,22,43 concurrent with standard RT as in arm A. Statistic: We hypothesized to treat 278 pts to have a statistical power of 0.80 with a two tail design, α error < 0.05. The study will close on March 2016 and the final analyses will be provided by 2017. Hereby we report the safety analysis of the first 170 pts.

Results: INTERCEPTOR accrued 228 pts at March 31, 2015. The first 170 are considered in the present analysis (85 and 85 on Arm A and B). M/F were 70/15 and 66/19 in Arm A and B respectively. Toxicities are reported as the worst grade observed during the treatment. Haematological toxicities G1 + G2, G3 + G4 in Arm A and B were: leukopenia 23/8 and 33/6 (N.S.); neutropenia: 15/18 and 23/7 (p = 0.017); anaemia: 61/2 and 54/3 (N.S.); thrombocytopenia were 20/0 and 12/1 respectively in arm A and arm B (N.S.). Stomatitis G1/2/3/4 were 9/32/28/4 and 14/26/23/1 (N.S.). Weight loss was classified using CTACAE 3.0. G1/2/3 weight loss was 25/10/2 and 25/12/2 in arm A and in Arm B respectively (N.S.). Radio-dermatitis G1/2/3/4 was 11/34/14/1 and 17/30/3/0 in Arm A and B (N.S.). Dysphagia G1/2/3 was reported in 9/16/11 and 10/10/15 patients at first post treatment clinical evaluation (N.S.). 2 patients (1 in Arm A and 1 in Arm B) developed Renal Failure.

Conclusions: Safety analysis allows study progression. Overall the only significant difference between the two arms was G 3–4 neutropenia. The excess of neutropenia in Arm A is entirely due to the induction phase.

G02 How clinical characteristics of recurrent/metastatic salivary gland malignancies (RMSGM) treated with first line chemotherapy (CT) impact on survival: multivariate analysis of 108 cases

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Background: The role of CT for RMSGM is palliative only. In this abstract we report multivariate analysis of clinical characteristcs impact on survival.

Table: G02 Crude and Adjusted Hazards Ratios for Mortality

Variables	Unadjusted Hazrd Ratio (UHR)	UHR IC 95%	UHR P-value	Adjusted Hazard Ratio (AHR)	AHR IC 95%	UHR P-value
Platinum-based agents						
no	1	-		1	-	
yes	0.96	0.65-1.43	0.84	1.17	0-75-1.84	0.49
Performance Status						
0	1	-		1	-	
1-2	2.54	1.68-3.83	<0.01	2.81	1.78-4.44	<0.01
Histology						
Adenocarcinoma	1	-		1	-	
Adenoid cystic carcinoma	1.30	0.84-2.01	0.24	1.66	0.98-2.8	0.06
Undifferential carcinoma	3.77	1.88-7.58	<0.01	3.23	1.49-6.97	<0.01
Malignat mixed	4.26	1.60-11.38	<0.01	6.99	2.38-20.49	<0.01
Metastasis						
Absent	1	-		1	-	
Present	1.41	0.95-2.10	0.09	0.9	0.52-1.54	0.7

Material and methods: We enrolled 108 patients. Five patients received cisplatin (DDP) 100 mg/sm d1,q 3wks; 8 patients doxorubicin 75 mg/sm d1, q 3wks; 30 patients vinorelbine (VNB) 30 mg/sm d.1,8, q 3wks; 9 patients DDP+ epirubicin 60 mg/sm + 5-FU 600 mg/sm d.1, q 3wks; 42 patients DDP 80 mg/sm d.1 +VNB 25 mg/sm d.1,8, q 3wks and 14 patients carboplatin AUC 5.5. + paclitaxel 175 mg/sm d.1, q 3wks.

Results: Patients characteristics were as follows: 64 males (59%) and 44 females (41%); median age: 57 years (20-74); 42 patients (39%) had ECOG PS 0 (47%) and 66 PS1-2 (61%); histology: adenocarcinoma (AC) 32 (30%), adenoid cystic cacinoma (ACC) 59 (55%), undifferentiated carcinoma (UC) 12 patients (11%) and malignant mixed tumor (MMT) 5 (4%); site of disease: local 41 (38%), mts + local 29 (27%), mts only 38 (35%). Responses: 3 CR, 24 PR, 36 NC and 45 PD; clinical benefit: PolyCT vs Mono CT : 63% vs 51%; DDP based vs NoDDP (64% vs 47%). Median TTP was 3.25 months and OS was 8.33 months.

Conclusions: PS and histology had a profound impact on survival; even if polyCT and DDP-based CT had significant better response rates these results don't impact on survival.

G03 Circulating pretreatment Epstein Barr Virus DNA quantification as a prognostic factor in nasopharyngeal cancer patients in a non endemic area

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Background: The value of plasma Epstein Barr Virus (EBV) DNA viral load in nasopharyngeal cancer (NPC) patients before treatment correlates with tumor stage

and outcome in endemic areas. The aim of our analysis is to explore the role of EBV DNA in the Italian non endemic setting where just one experience has been previously reported (Ferrari D et al, 2012).

Material and methods: The medical records of all the patients with positive EBV encoded RNA (EBER) NPC, treated in our institution from 2006 to 2014 with chemotherapy (CT) concurrent with radiation (RT), were retrospectively evaluated. Information about the known prognostic factors, as established in NPC endemic areas, were collected, as well as pretreatment plasma EBV DNA viral load, detected and quantified by real-time PCR.

Results: A total of 134 patients were evaluated (median age 48 years; M:F ratio 2:1; stage II 13%, III 31%, IV 56%). Neo-adjuvant CT (TPF scheme) was administered to 78% of the patients. Platinum based CT was delivered concurrently with RT. At a median follow up of 41 months, 25 patients (19%) experienced locoregional and/or distant recurrence and 70% of them died. Overall, pretreatment plasma EBV DNA was detected in 97 patients (72%), with median viral load of 544 cp/mL (range 50 - $1.5x10^5$ cp/mL), and showed a significant positive correlation with T stage ($p = 0.02$), N3a stage ($p = 0.045$) and a negative correlation with previous neck surgery ($p= 0.03$). Progression-Free Survival (PFS) was significantly longer in patients with pretreatment negative EBV DNA value than in positive ones (56 vs 26.5 months, $p = 0.014$). A relationship between higher EBV DNA viral load and risk for distant metastasis was marginally noted ($p = 0.06$).

Conclusions: In a non endemic area, pretreatment plasma EBV DNA was detected only in 72% of the EBER positive NPC patients, lower than what reported in endemic areas (87-100%). Patients with negative pretreatment EBV DNA had a significant better prognosis in terms of PFS, while EBV DNA viral load correlated with tumor burden (T and N3a stage). The value of EBV-DNA as reliable prognostic biomarker of PFS in NPC in non-endemic areas needs to be confirmed in larger series.

G04 Role of induction chemotherapy in the multimodal management of locally advanced epithelial sinonasal cancer

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Background: Outcomes of locally advanced epithelial sinonasal cancer remain unsatisfactory, despite the improvement in surgical approaches and advances in radiotherapy techniques. The incorporation of induction chemotherapy (IC) in the multimodal treatment strategy has shown promising results in few studies. Only limited and heterogeneous data exist on prognostic factors, due to the rarity of this disease.

Table: G04

	Number of pts	%
Histology		
Sinonasal undifferentiated carcinoma - SNUC	25	40
Squamous cell carcinoma - SCC	24	38
Pure neuroendocrine cancer - SNEC	8	13
Small cell carcinoma - SmCC	6	9
Any neuroendocrine differentiation		
Yes	18	29
No	45	71
Stage		
III	13	21
IV	50	79
Response to IC		
Complete response	8	13
Partial response	45	71
Stable disease	7	11
Progressive disease	3	5
Treatment strategy after IC		
Surgery +/- radio(chemo)therapy	27	43
Chemoradiation	36	57

Material and methods: We reviewed consecutive patients (pts) with AJCC stage III-IV epithelial non glandular sinonasal cancer, treated at National Cancer Institute of Milan with IC followed by locoregional treatment, since 1996 to 2013. Overall survival (OS) and disease free survival (DFS) were calculated with Kaplan Meier method. The log rank test and Cox multivariate regression analysis were used to build a prognostic model for outcome according to clinical and pathological variables.

Results: We identified 63 pts, whose clinical and treatment characteristics are reported in the table. IC was platinum based, associated with 5FU and lederfolin or 5FU and docetaxel. Cisplatin and etoposide alternating with ifosfamide and doxorubicin was employed for neuroendocrine cancer. Globally, 34 pts experienced a recurrence (28 at locoregional level and 6 at distant sites); 14 pts received salvage surgery (12 on primary tumor and 2 on neck nodes), but only 2 of them remained free of disease (1 salvaged on T and 1 on N level). With a median follow up of 45 months, 5-year OS and DFS was 58% and 40% respectively. Only response to IC retained a prognostic value for OS ($p = 0.0017$), while the presence of any tumoral neuroendocrine differentiation showed a marginally significant worse outcome ($p = 0.077$).

Conclusions: The prognosis of locally advanced epithelial sinonasal cancer remains unsatisfactory. Response to IC was the most important prognostic factor. Two phase II trials are ongoing to investigate the role of IC in these tumors (Clinicaltrials.gov identifier: NCT02099175 and NCT02099188).

G05 Effect of patient's alcohol abuse on caregiver's psychological asset: analysis of 60 couples of Head and Neck cancer patients and their caregivers

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Background: Alcohol abuse affects 30-60% of head and neck cancer patients. It produces important effects on patient's physical and psychological wellbeing and can influence the entire family's functioning. Aim of this study is investigate and define how alcoholism can influence the psychological sphere of caregivers and their relationship with patients affected by Head and Neck cancer.

Material and methods: ixty couples of patients and caregivers were enrolled this observational cross sectional study on the base of the following inclusion criteria: age 18-80 years, Italian native language, stable patient-caregiver relationship established before cancer onset, oropharyngeal or hypopharyngeal SCC, advanced stage disease (stage III-IV of AJCC, 7th edition, 2010), completion of curative treatment and no evidence of disease at the enrollment. Patients and caregivers completed questionnaires that assessed demographic variables, anxiety and depression (STAI Y1-Y2, BDI and MDRS) and quality of life (EORTC-QLQ-C30 and Head and Neck-35 module for patients and CQOLC for caregivers).

Results: The 43% of patients' sample had a history of alcohol abuse. Alcohol abuse was defined according to criteria established by World Health Organization.
Patient-caregiver dyads were divided according to patient alcohol abuse: 34 couple with abuse (43%) and 26 couples without abuse (57%). Caregivers of patients with a history of alcohol abuse have a statistically lower quality of life compared with caregivers of patients with no history of alcohol abuse ($p < 0.0493$). No differences were found in terms of caregivers' anxiety and depression ($p > 0.05$). Moreover patients' quality of life anxiety and depression doesn't change depending on alcohol abuse ($p = 0.9760$).

Conclusions: It's necessary to detect patients with alcohol abuse not only to better target their treatment but to provide a particular attention to their cargiver. Caregiver's wellbeing can influence patient's compliance to treatments.

G06 Site of metastatic disease influences adenoid cystic cancer (ACC) patients' outcome

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Background: Distant metastases are common in ACC patients. Lung, followed by bone and liver, are the most involved sites. Despite its limited activity, systemic chemotherapy is the standard of care and it is reserved to symptomatic and/or rapidly progressive disease. Watchful waiting is a common choice. We hypothesized that different site of metastasis could influence the patients' outcome.

Materials and methods: 132 patients with metastatic ACC treated from 1985 to 2013 were retrospectively reviewed. Regardless of loco-regional failure, patients were classified according to the site of first metastasis: lung, liver, bone and miscellaneous (including multiple sites and soft tissue). Progression - free survival (PFS) and overall survival (OS) were computed as time of survival since the date of assessment of metastatic disease, and were estimated with the Kaplan-Meier method. PFS and OS were evaluated according to the site of distant metastases. Cox proportional hazard regression models were used to evaluate the effect of site of metastases; treatment (any type) for metastatic disease was also used for covariate adjustment in multivariable analysis. Results were considered statistically significant for two-tailed p - value <5%.

Results: 88 patients, 13 patients, 18 patients and 13 patients had lung, liver, bone and miscellaneous disease, respectively. OS and PFS were significantly longer ($p < 0.0001$)

in the lung metastases group than in the remaining groups, liver, bone and miscellaneous: median OS was 72 months (interquartile, IQ, range: 50-122), 32 (IQ range: 9- 90), 20 (IQ range: 11-47) and 31 (IQ range: 10-50), respectively; median PFS was 15 months (IQ range: 8-38), 11 (IQ range: 4-23), 8 (IQ range: 4-20) and 5 (IQ range: 4-10), respectively. At multivariate analyses, OS and PFS were significantly affected by the site of metastases ($p = 0.0002$ and $p < 0.0001$, respectively): Hazard Ratios for liver site vs lung site were 2.98 (CI, 1.42- 6.25) and 2.04 (CI, 1.09-3.81), respectively. Ninety-four out of 132 patients (71%) received a treatment for metastatic disease that did not impact on either OS or PFS.

Conclusions: Lung metastases lead to a significantly better outcome, while liver is associated to a 3-fold (2-fold) higher risk of death (progression) event as compared with lung. Treatment seems not to influence the outcome, although the limited number of patients with liver metastases doesn't allow to draw firm conclusions.

G07 Role of PET/TC in the pre-surgery staging of oral cavity cancers

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Background: Among head and neck cancers oral cavity squamous cell carcinomas (OCSCC) account for about one third of the cases. Traditionally the pre-surgical staging has been based on lymph nodes evaluation by means of Computed Tomography (CT). The superiority of Positron Emission Tomography (PET)/CT in detecting regional nodal involvement has been claimed by some studies recently published. The aim of this study was to evaluate the impact of PET/CT imaging on nodal staging of patients undergoing surgery for OCSCC and to compare PET/CT with CT in this specific setting.

Patients and methods: A retrospective analysis has been conducted on a data-base registry from a single institution. The study population consisted of 50 patients affected by OCSSC who were evaluated with both PET/CT and CT before undergoing surgery on the primary tumor and neck dissection. The study population consisted of 29 males and 21 females, median age was 63 years, the most common involved siites were the retromolar trigonus and the gingival fornyx (34%) and the mobile tongue (28%). After neck dissection (selective or radical, 34% bilateral) the pathologic specimens were thoroughly reviewed by an experienced pathologist. Twenty-nine cases (58%) were classified as T4 and 28 (56%) as N0**.**

Results: Neck dissection resulted in the presence of lymph node metastases in 44% of the patients. PET/CT detected true positive nodes in 20 of 22, and true negative nodes in 21 of 28 specimens while CT detected true positive nodes in 16 of 17 and true negative nodes in 18 of 23 specimens. Sensitivity and specificity of PET/TC were 91% and 75% respectively with an accuracy rate of 82%; sensitivity and specificity of CT were 94% and 78% respectively with an accuracy rate of 85%. Both figures are comparable with previously published data. No significant statistical differences were found between PET/CT and CT ($p = 0.823$).

Conclusions: In our study PET/CT was an effective tool to assess the nodal stage of OCSCC, but did not prove to be more accurate than CT. While its role in detecting unknown primaries and distant metastases is well consolidated, further randomized trials will help in claryfing its real usefulness in loco-regional disease. According to our data some patients could be overstaged, nonetheless the fear of overtreatment with neck dissection is counterbalanced by the effective prophylactic role of the procedure.

G08 Concurrent chemoradiotherapy plus adjuvant chemotherapy versus chemoradiotherapy alone or radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a meta-analysis

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Background: Treatment of locally advanced (stages III-IV) Nasopharyngeal Carcinoma (NPC) has still some controversies. Historically, radiotherapy (RT) was considered the treatment of choice for this inoperable tumors at advanced stages but several studies showed that concurrent chemoradiotherapy (CCRT) led to an improvement in overall survival rates. Anyway, radiotherapy can be considered a valid treatment option avoiding the toxicities of the combined therapy. The benefits of combining CCRT with adjuvant chemotherapy (AC) for treatment of locally advanced NPC have not been established. Aim of this study was to analyze the studies evaluating the different treatment strategies in order to determine the efficacy of CCRT + AC compared to CCRT or RT alone.

Methods: We performed a meta-analysis comparing CCRT + AC *vs* CCRT alone (group 1) and CCRT + AC *vs* RT alone (group 2). In group 1 two studies were included, in group 2 four studies were included. The analysis was based on both randomized clinical trials (RCT) and retrospective studies. The main end-point was Overall Survival (OS). Locoregional (LRF) and distant (DF) failures were also analyzed. Hazard Ratios were used for effect size comparison.

Results: When overall survival was analyzed, *CCRT + AC* showed better outcomes compared with *RT* alone *(HR*: 0.70, 95% *CI* 0.57-0.87 *p-value* <0.005). On the other hand, no statistical significant difference was found regarding the local and distant recurrence of disease (*LRF HR*: 0.57, 95% *CI* 0.39-0.85 *p-value* >0.005, *DF HR*: 0.76, 95% *CI* 0.56-1.01 *p-value* >0.005).When comparing CCRT + AC vs. CCRT alone no significant improvement was found for any of the end-points analyzed (*OS HR = 0.77*, 95% *CI* 0.51-1.18 *p-value* 0.222; *LRF HR*: 0.67, 95% *CI* 0.35-1.28 *p-value* 0.228; *DF HR*: 0.81, 95% *CI* 0.57-1.18 *p-value* 0.262).

Conclusions: CCRT + AC showed better outcomes when compared with RT alone. No difference has been shown when CCRT + AC vs CCRT alone were analyzed. For these reasons, the omission of AC to reduce toxicity can be taken into consideration. On the other hand, it must be pointed out that more studies, in particular well designed RCT, are needed in order to strengthen the results of this meta-analysis. Also, it should be noted that the majority of the studies regarding NPC are conducted on areas in which this cancer is endemic. It can be speculated that some differences in treatment response exist between different populations, so it is auspicable that studies on more heterogeneous populations will be conducted.

G09 Multidisciplinary approach for squamous head and neck cancers: a single report institution

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Background: Head and neck (H&N) cancers are a complex, heterogeneous group of malignancies, which require different treatment strategies and specialist competence. To facilitate timely and appropriate management of H&N cancer patients (pts), our center established a multidisciplinary diagnostic and therapeutic pathway (MDTP) so that accurate tumour staging and treatment plans can be best tailored to each pt. Aim of the present report is to describe the results in terms of pts characteristics and survival of H&N pts discussed and visited in MDTP.

Matherial and methods: At Modena University Hospital between January 2011 and December 2014, N 640 patients with squamous head and neck cancer (oral cavity, oropharynx, larynx/hypopharynx) have been seen in MDTP (new diagnosis and follow-up pts): N 171 oral cavity (26,7%); N 184 oropharynx (28,7%), N 251 larynx (39,2%)/N 34 hypopharynx (5,4%); other histological subtypes or sub-sites such as nasopharynx, salivary glands or nasal cavities are excluded from this analysis. Moreover, we excluded pts with stage IVc at presentation and pts who received previous treatments for their H&N cancer. We recorded data from a web platform in which every pt has a personal form filled with all clinical information (stage of disease, treatment steps, follow-up, quality of life and nutritional issues, i.e.) from pt entrance in MDTP and retrospectively reviewed all data.

Results: N 640 pts have been seen in MDTP: 491 pts were male (76,7%), 149 female (23,3%), median age 64,7 years (range 25-94 years); locally advanced stage (high risk, stage III and IV-excluded T3N0 of glottis) at diagnosis was as follows: oral cavity 102 pts (59,6%), oropharynx 164 pts (89,1%), larynx 128 pts (50,9%), hypopharynx 31 pts (91,1%). After a median follow-up of 25,5 months (range: 1,5-205 months), 490 pts (76,7%) are alive. Survival for sub-sites are as follows: oral cavity 126 pts (73,6%); oropharynx 149 pts (80,9%), larynx 196 pts (78%), hypopharynx 19 (56%). One-hundred and forty-one pts have relapsed (22%); relapses for sub-sites are as follows: larynx 63 pts (25%), oral cavity 46 pts (27%), oropharynx 39 pts (21,1%), hypopharynx 9 pts (26,5%). Median time to relapse, all sub-sites (calculated from the end of treatments till relapse): 20 months (range: 1-117 mo).

Conclusions: survival data are similar to those published in literature, referring to high volume centers. MDTP allows to improve management of pts with squamous head and neck cancer.

G10 Acute Toxicities and their impact on outcome in concomitant chemo-radiotherapy for locally advanced head and neck cancer

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Background: Survival gains were achieved in Head and Neck (H&N) cancer patients (pts) treated with multisciplinary approach, including platinum and Cetuximab-based concurrent chemo radiation, with a substantial increase in toxicity. This cause more unplanned treatment breaks and prolongation of the radiation treatment time that may impact on survival and loco regional control rates. We analyzed retrospectively

schedule modifications due to acute toxicities and their impact on Progression Free Survival (PFS) and Overall Survival (OS).

Patients and methods: From January 2011 to May 2014 we retrospectively analyzed 51 locally advanced H&N pts treated with exclusive concurrent chemo/immuno-radiotherapy. Type of treatment, acute toxicities (RTOG scale), treatment interruptions, PFS, OS were evaluated.

Results: 43 pts underwent Intensity modulated radiation therapy Simultaneous Integrated Boost (IMRT-SIB) and 8 pts sequential IMRT. 41 pts had concomitant chemotherapy (cht) with Cisplatin q21, 2 pts Cisplatin q7 and 8 pts Immunotherapy with Cetuximab. The acute grade 3-4 toxicities observed were: cutaneus (33.5%); oral mucositis (35%); pharyngeal/esophageal (24.5%); leukopenia and neutropenia (18%). We also reported 6% pneumonia and 4% fever with neutropenia (G3). No toxic death was detected. We had 25% of radiation treatment breaks (77%< 1 week; 33%>1 week). 52% of pts received full dose of Cisplatin q21, no patient had full dose of Cisplatin q7 and and only 8% received full dose Cetuximab. All pts who interrupted radiotherapy had no full dose of chemo/immuno treatment. 3 years (ys) global PFS was 56.6% while PSF of pts who had no breaks vs breaks in radiotherapy treatment was respectively 70.7% vs 33.3% (p = 0.0051). 3 ys global OS was 63.2% % while OS of pts who had no breaks vs breaks in radiotherapy treatment was 55.4% vs 66.7% (p = 0.65), while we had no significant difference in OS between the two groups.

Conclusions: Nevertheless the shortness of follow-up and the small number of pts, our findings suggest that treatment breaks due to acute toxicities treatment related have a negative impact on PFS outcome. Toxicity management is important to minimized unplanned treatment breaks in this type of pts where the healing and organ preservation represent goals of care

G11 Outcome of systemic treatments after first line platinum and cetuximab treatment in patients with recurrent/metastatic (RM) head and neck squamous cell cancer (HNSCC): a retrospective analysis

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Background: Second line chemotherapy in RM HNSCC patients (pts) showed dismal results with limited tumor response and a reduced life expectancy. Outside from clinical trials, conducted in selected patient populations, data on efficacy of 2ndline treatment after 1stline anti-EGFR-AB combination therapy are not available. We present the outcome of HNSCC pts after cetuximab and platinum containing pretreatment.

Table: G11 Fist line systemic treatments received

Treatments	n (%)
Carboplatin / Cetuximab	21 (43%)
Cisplatin / Cetuximab	15 (31%)
Cisplatin/ 5-FU / Cetuximab	7 (14%)
Cisplatin / Paclitaxel / Cetuximab	6 (12%)

Material and methods: All the pts treated with cetuximab and platinum therapy from 2009 to 2014 at the National Cancer Institute of Milan for RM HNSCC were retrospectively collected and included for analysis. The PFS and OS curves were estimated with the Kaplan-Meier method and compared using the log-rank test.

Results: We identified 117 pts treated for RM HNSCC with 1stline platinum and cetuximab-based systemic therapy. Sixty-three pts (54%) did not reach 2ndline treatment, 5 were not assessable for response and 49 pts were included for analysis. Primary tumor sites were oropharynx (41%), oral cavity (29%), larynx/hypopharynx (26%) and others (4%). HPV status was available in 22 oropharynx cancer pts with 7 being positive. Fifty-four % were smokers or former smokers and 38 were male (78%). First line treatment combinations are listed in table 1. Regimens used in 2ndline were in the vast majority monotherapies, mostly with methotrexate (55%), or other agents (43%); only one pt received platinum combination chemotherapy. Twenty-two % of the pts were treated within a clinical trial. Response rate (PR, CR) was 8% with 33% showing SD. Median PFS was 81 days (95% CI: 52 to 92) and OS 184 days (95% CI: 115 to 220). No patient or disease characteristic showed to be prognostic in this population. Twenty-seven% of the patients did receive the last chemotherapy administration within 30 days before death.

Conclusion: Within a 5-year single Center experience, only 1 out of 2 pts could receive 2ndline treatment for RM HNSCC. Response rate after pretreatment with an anti-EGFR-AB is however limited, but median overall survival is slightly higher than previously reported in an anti-EGFR-AB naïve pt population (184 days vs 103 days, according to Leon et al, 2005).

G12 Health and economic outcomes of two different follow up strategies in effectively cured advanced head and neck cancer patients–Trial in progress

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Background: Optimal timing and type of examinations for the follow up (FUP) of head and neck squamous cell cancer (HNSCC) survivors have not been established yet. There is a need to find out which is the most cost-effective FUP program in this population. The present trial aims at comparing a more intensive radiologic FUP approach with a less intensive one, also evaluating its economical impact on healthcare system.

Methods: This is an Investigator Initiated randomized, phase II, multicenter trial. Patients with stage III-IV SCC of oral cavity, oropharynx, larynx or hypopharynx having already received radiation therapy as part of curative treatment and in complete remission at six months are randomized in two arms according to different FUP approaches. A non intensive FUP approach foresees only a radiologic evaluation within 6 months since treatment end and subsequently only at signs or symptoms occurrence (according to NCCN guidelines). An intensive FUP approach consists of scheduled radiologic evaluations 2 times/year in the first 2 years and 1 time/year in the third year; PET scans are requested yearly for patients with smoking history. FUP visits consist of physical and fiberoptic endoscopic examinations of head and neck district, laboratory tests, quality of life questionnaires and evaluation of out-of-pocket costs and productivity losses; timing of FUP visits is the same in both arms. An estimated 330 patients are being enrolled; health outcomes and costs will be assessed over the next two years of follow up. The percentage of potentially salvageable recurrences or second primaries, the cause-specific survival and the overall survival of recurring patients will be evaluated in both arms. Incremental cost-effectiveness (cost/life year gained) and cost-utility ratios (cost/QALY) will be calculated referring to WHO thresholds of 1-3 times per capita gross domestic product.

Results: The trial started in September 2014 and as of April 2015 10 Centers have received approval from the Ethical Committee.

Conclusions: According to study results, either a dominant strategy will be found (i.e. one of the arms is more effective and less expensive than the other) or one arm will be more effective but also more expensive. In the latter case, incremental cost/effectiveness and cost/utility ratios will be calculated and compared to thresholds used to judge whether or not an intervention is considered cost/effective or cost/useful.

G13 Phase II study on Lenvatinib in recurrent and/or metastatic adenoid cystic carcinomas (ACC) of the salivary glands of the upper aerodigestive tract

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Background: ACC is rare representing approximately 25% of salivary gland carcinomas. Distant metastases are common and generally characterized by a prolonged and indolent course. Although first-line treatment in this setting of patients is chemotherapy, it has disappointing results and new treatment options are strongly envisaged. Eighty percent of ACCs carries a *MYB-NFIB* translocation that results in the activation of several pathways involved in cell proliferation, apoptosis, differentiation and angiogenesis such as FGFR and VEGFR. Moreover, FGF/IGF/PI3K signaling is altered in 30% of ACC, corroborating the hypothesis that this subset of patients might benefit from inhibitors of this pathway. Lenvatinib is an oral, multiple, tyrosine kinase inhibitor, targeting VEGFR-1-3, FGFR-1-4, RET, c-KIT, and PDGFR. Based on preclinical and clinical data, there is a rational basis to test lenvatinib in patients with relapsed and/or metastatic ACC.

Methods: This is a phase II, monocentric trial, conducted to assess the activity of lenvatinib. We will consider the drug as effective and worth for further evaluation if the response rate will be at least 20%. A 2-stage Simon design will be applied, to test the null hypothesis of RR $\leq$ 5% versus the alternative RR $\geq$ 20%.Type I and type II error rates are set at the 20% and 10% levels. If at least 1/15 response will be observed in the first 15 patients, 11 additional patients will be enrolled up to a final overall sample size of 26 subjects. If at least 3/26 responses will be recorded, the null hypothesis will be rejected in favour of the alternative and the drug considered promising and worthy of further investigation. Lenvatinib will be administered at the daily dose of 24 mg to patients until progression of disease or intolerable toxicity. Tissue paraffin block from primary lesion or metastasis will be collected for translational research (*MYB-NFIB* traslocation analysis).

Conclusions: This is exploratory study to test the activity of lenvatinib in recurrent and/or metastatic ACC. Objective response rate according to RECIST 1.1 is the first aim; overall survival, progression free survival, duration of response, safety and toxicity profile of lenvatinib and quality of life assessment (EORCT QLQ C30 and H&N35; EQ-5D)will be evaluated as secondary end points. This study is currently recruiting participants.

G14 Intensity-modulated radiotherapy and cetuximab for frail patients with loco-regionally advanced head and neck cancer

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Background: The combination of radiotherapy (RT) and concomitant cetuximab demonstrated to be superior to RT alone in loco-regionally advanced squamous cell head and neck cancer (SCHNC). The benefit in terms of response rate, progressions-free survival (PFS) and overall survival (OS) has been obtained without increased toxicity. The objective of this study was to evaluate the clinical impact of such approach in frail patients.

Methods: From january 2010 to december 2014 15 patients affected by stage III-IV SCHNC (oral cavity, oropharynx, and hypopharynx) not candidate to surgery or chemoradiation according to severe comorbidities or age (> 80 years) were treated with a combination of Intensity-Modulated RT (IMRT) and cetuximab with curative intent. Cetuximab was administered starting one week before IMRT at a loading dose of 400 mg/m^2 i.v. followed by 250 mg/m^2 i.v. weekly for a total of 8 infusions.

Results: In this series the male/female ratio was 1.5 and the median age was 79 years. All patients but one completed IMRT along with 8 cycles of concomitant cetuximab whose median dose intensity was 95%. A complete response was achieved in 11 of 15 patients (73.3%). Three patients had residual nodal disease and underwent salvage neck dissection. Seven patients (46.7%) had loco-regional relapse and five of them developed distant metastases. With a median follow up of 58 months, the duration of locoregional control was 21 months (range, 1-59), median PFS was 16 months and median OS 34 months. Four patients (26.7%) were still alive at five years. Grade 3/4 adverse events occurred in 53.3% of cases, mostly oral mucositis and skin rash. With a careful pre-medication consisting of anti-histamine and steroidal drugs no infusional reactions were documented. One toxic death was registered in a 85-year old woman who died during IMRT as a consequence of severe sepsis.

Conclusions: Cetuximab plus definitive IMRT is a feasible and effective treatment for loco-regionally advanced SCHNC. Even in frail patients it can provide good clinical outcomes along with an accettable toxicity profile. This combination allows a chance of cure for a subset of patients not suitable for chemotherapy or major surgery. The results in terms of PFS and OS are clearly inferior if compared to a standard patient population, nonetheless adding cetuximab to IMRT offer some chance of long survivorship to patients in poor clinical conditions, without dramatically altering their quality of life.

G15 Multidisciplinary approach for poor prognosis sinonasal tumors: Phase II studies of chemotherapy, surgery, photon and heavy ion radiotherapy integration for more effective and less toxic treatment–Trials in progress

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Background: Sinonasal tumors are rare diseases comprising several histological subtypes. Surgery followed by radiotherapy (RT) has been the usual approach for loco-regionally advanced disease. In poor-prognosis histological types, 5-year overall survival and disease free survival are less than 40%, with worst scenario for undifferentiated form and unresectable diseases. New therapeutic strategies are needed to obtain more efficient treatment with less morbidity. Some retrospective studies explored the role and feasibility of induction chemotherapy (CT). Histology and molecular pattern can guide the choice of administered CT. Proton/carbon ion beam therapy, compared to conventional photon therapy, provides a more accurate and intense dose to tumor area with less toxic side effects and potentially higher control of disease. Overall, multimodality treatment seems the best approach, although so far prospective data are missing. We started 2 prospective trials (SINTART 1 for operable and 2 for non-operable cancers) with integration of multiple modality of treatment modulated by histology, molecular profile and response to induction CT. Moreover, heavy ion RT combined with photon RT allows the use of latest technology with greater biological effectiveness and reduction of toxicities (Clinicaltrials.gov identifier: NCT02099175 and NCT02099188).

Methods: SINTART 1 and 2 are two open-label, phase II, multicenter clinical trials, designed to assess the efficacy in term of progression-free survival of a multimodality treatment in the management of patients with poor prognosis sinonasal carcinomas (intestinal-type adenocarcinoma, sinonasal undifferentiated cancer, sinonasal neuroendocrine cancer, squamocellular cancer, Hyams grade 3-4 esthesioneuroblastoma) . Safety will also be evaluated, with specific focus on late toxicities. It is planned to recruit 40 patients over two years for SINTART 1 and 25 patients for SINTART 2.

Conclusions: The trials are open to accrual and they will evaluate the effectiveness and safety of a multimodal approach in the treatment of sinonasal cancers.

G16 Phase II study of preoperative TPF chemotherapy in molecularly selected resectable oral cavity cancer–Trial in progress

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Background: For locally advanced oral cavity squamous cell cancer (OCSCC) surgery represents the mainstay of the treatment, followed by radiotherapy or chemoradiotherapy in patients with high risk pathological features. Induction chemotherapy (CT) with cisplatin and fluorouracil (PF) in OCSCC has been studied within a randomized study of 198 operable patients. No survival benefit was obtained in the chemotherapy arm, however a trend toward less mandibulectomies and less postoperative radiotherapy was noted. Induction CT with TPF scheme (taxane plus platinum and FU) showed an increase in radiological response rate and in overall survival over PF scheme in randomized studies. Pathological complete response (pCR) has been associated with the presence of functional p53 protein status, defined as the finding in pre-treatment biopsy of a TP53 wild type gene or a mutation having partial or full transactivation activity. Modifications of the tubulin target by differential expression of β-tubulin isoforms have been proposed by numerous reports as a mechanism of resistance to taxanes and other antimitotic drugs. In this trial (Clinicaltrials.gov: NCT01914900) we investigate the ability of TPF scheme to achieve pCR in selected OCSCC, harboring a functional p53 protein and/or showing low expression of β-tubulin II.

Methods: 67 patients with locally advanced resectable OCSCC will be enrolled over 5 years. Tumor biopsies will be analyzed in order to verify p53 and β-tubulin II status: if p53 is functional and/or low expression of β-tubulin II is present, patient will receive induction TPF, followed by surgery within one month after the last cycle. Adjuvant RT treatment will be delivered according to recognized pathological risk factors.

Conclusions: The main objective of the trial is to assess the rate of pathological complete response after induction CT. Other objectives are the evaluation of the early functional response by diffusion-weighted imaging (DWI) and dynamic contrast-enhanced (DCE) MRI, the assessment of the percentage of patients receiving postoperative radiotherapy and chemotherapy and the evaluation of compliance to the treatment, safety profile and survival.

G17 The impact of nutritional support in head and neck cancer patients treated with chemoradiation therapy

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Background: Head and neck cancer patients are frequently malnourished at the time of diagnosis and prior to the beginning of treatment. In addition, chemo-radiotherapy (CRT) causes or exacerbates symptoms, such as alteration or loss of taste, mucositis, xerostomia, fatigue, nausea and vomiting, with consequent worsening of malnutrition.

Patients and methods: All patients undergoing CRT (60-70 Gy plus concomitant weekly cisplatin at 40 mg/sqm) for head and neck cancer (adjuvant or neoadjuvant setting) underwent to a nutritional evaluation before the beginning of the treatment, in order to pre-plan the best nutritional support for each of them.

Results: 55 patients, mostly affected by oropharyngeal (47.3%), nasopharyngeal (18.2%) and oral (14.5%) cancer, have been evaluated. The cancer stage at time of CRT was: cII 3.6%, cIII 8%, cIVA 43.6%, cIVB 7.3%, pIII 1.8%, pIVA 11%. CRT program has been completed in all patients. 92.8% of them received artificial nutrition during the treatment: 41.8% parenteral nutrition (PN), 29.1% enteral nutrition through PEG (EN), 21.9% oral support (oral supplement containing eicosapentaenoic acid or/and progesterone derivates) only. The choice of artificial nutrition modality (EN vs. PN) was unrelated to disease stage (cIII 28.6% vs. 71.4%, cIVA 50% vs. 50%, cIVB 50% vs. 50%, pIVA 44.4% vs. 55.6% respectively). Effects on nutritional status were evaluated in terms of weight maintenance, body composition and biochemical modifications from baseline. EN seems to guarantee the best results for all variables: weight (-0.45 kg), albumin serum levels (+0.40ng/dl), prealbumin serum levels (+1.28mg/dl), transferrin serum levels (+19.00mg/dl), fat body mass (-1.08kgl), fat free body mass (+0.40kg), total body water (-0.52kg) median variations. Furthermore, a trend toward lower incidence of gr. 3-4 oral mucositis in the EN than in the PN subgroup (50% vs. 66.7% respectively) has been observed, as well as a trend for shorter duration of mucositis (14.68 ± 19.14 days vs. 22.50 ± 21.98 days respectively). 61.5% patients obtained a CR, 12.8% a PR, 10.3% a PD and 2.6% SD, without differences for type of nutrition. A trend toward shorter PFS in pts treated with PN vs. EN (57.3 vs not reached, p = 0.283) has been observed.

Conclusions: Nutritional support with enteral nutrition during CRT for head and neck cancer might guarantee a better outcome in terms of nutritional status, treatment tolerance and PFS.

G18 Breakthrough pain in patients with head and neck cancer: efficacy and safety of buccal fentanyl citrate

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Background: More than 50% of patients with cancer experience pain, which is often of moderate-to-severe intensity. In particular, the highest prevalence of pain is observed in head-neck tumours (70%). In patients with advanced disease, management of pain remains a particular challenge. The breakthrough cancer pain (BTcP) is a transient pain, a temporary exacerbation with variable frequency (1-6 times a day), which occurs in patients with chronic pain normally well controlled by basic analgesic therapy administered at fixed times (therapy around-the-clock).

Material (patients) and methods: from January 2012 to March 2015 we collected data from 50 patients with histological diagnosis of squamous cell carcinoma of the head and neck treated for symptomatic BTcP with fentanyl citrate buccal tablets. Basic pain was treated with oxycodone/naloxone at doses from 10 mg bid to 80 mg bid. The patients were evaluated for BTcP onset and any associated precipitating was considered. Treatment for BTcP with fentanyl citrate buccal tablets has been proposed at a starting dose of 100 micrograms increased up to 800 micrograms and repeatable every 4 hours. During the observation period all patients were assessed weekly by clinical examination and pain was valued through NRS.

Results: basic chronic pain was well controlled with oxycodone/naloxone demonstrated by a reduction in NRS (average score from 7 to 2). Of the 50 patients with carcinoma of the head and neck, 22 patients had BTcP episodes repeated daily related to swallowing and 14 patients had episodes triggered by medication of external lesions; none of these episodes was attributable to the end of basic opioid dose. The maximum number of daily episodes was 5 for the BTcP triggered by swallowing and 3 for the one triggered by medication (average NRS was 8). The average effective dose of fentanyl buccal tablets was 400 micrograms bid and all patients reported disappearance of BTcP episodes. About side effects mainly observed, nausea occurred in 4% of cases and only 2% presented pain and bleeding where the tablet was applied.

Conclusions: over 70% of the patients analyzed in our study suffered of repeated episodes of BTcP reflecting literature data. NRS scale reduction for chronic pain and BTcP episodes disappearance demonstrated efficacy of the therapies. Safety was demonstrated by the minimal side effects so that switching to another formulation of rapid-onset opioids wasn't necessary.

G19 Transarterial (chemo)embolization and radiofrequency ablation for patients with hepatic metastases (mts) of head and neck carcinoma (HNC) resistant to systemic treatment

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Background: Currently, (chemo)embolization isolated or combined with radiofrequency ablation (RFA) is used for unresectable, metastatic or recurrent primary hepatic carcinoma. We retrospectively assessed the safety and long-term survival benefit of this procedure in pts affected by chemoresistant hepatic mts from HNC and treated with (chemo)embolization +/- RFA.

Methods: The following data were retrieved: pts characteristics, tumour histology, number of mts, kind of treatment. We evaluated the safety of the treatment (according to CTCA, version 4.0), tumour response, time to progression (TTP) of treated lesions and overall survival (OS). The efficacy of the procedures were evaluated by dynamic computed tomography or magnetic resonance imaging 2 or 3 months after treatment, according to the RECIST and to CHOI criteria.

Results: Between 2007 and 2015, 20 consecutive pts with liver mts (median age 58 years, range 43 - 75 years) were retrospectively assessed. The primary tumor histotypes were: adenoid cystic carcinoma (11 pts, 55%), undifferentiated carcinoma (4 pts, 20%) and other 5 rare hystotypes. The primary tumor was: salivary glands (60% of cases), thyroid (15%), nasopharynx (15%), paranasal sinus (10%). The pts were divided into 4 groups based on treatment received: transcatheter intrarterial chemotherapy with doxorubicin (TACE) -3 pts-, intrarterial embolization with embozene microspheres (IAE) -3 pts-, RFA -5 pts-, and the combined treatments group (9 pts). The medium follow-up was 430 days (range: 106–1122 days). No complication was observed in 25% of the pts (n = 5); 6 pts (26%) developed one G3 adverse effect (2 cardiovascular accident, 2 abdominal pain and 2 hyponatremia). No G > 3 adverse events were observed. According to RECIST, partial response of the lesions was shown in 9 pts (45%), stable disease in 8 pts (40%) and progression in 3 pts (15%); the CHOI criteria showed a response in 14 pts (70%). No difference in response according to histotypes was observed. Median TTP of treated lesions was 171 days: 186 days for TACE, 150 days for RFA, 220 days for IAE and 111 days for combined procedures. Median OS was 381 days (106–658 days), significantly differing according to treatment group: TACE 747 days, RFA 478 days, IAE 379 days, combined procedures 231 days.

Conclusions: TACE, IAE and RFA alone or combined are feasible and effective modality for treating chemoresistant liver mts from HNC primary. Combined therapy did not show a benefit on TTP or OS.

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Session H. Lung cancer

H01* A multicenter, randomised, phase 3 trial comparing fixed dose versus toxicity-adjusted dose of cisplatin + etoposide in advanced SCLC patients (pts). The STAD-1 trial

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Background: Classic dosing of chemotherapy does not account for pts' variability and some pts could be underdosed. We tested whether toxicity-adjusted dosing of chemotherapy was more active than classic dosing in advanced SCLC pts. (ClinicalTrials.gov NCT00526396).

Methods: Advanced chemonaïve SCLC pts, aged =75, ECOG PS < 2, were randomised to either control (fixed-dose cisplatin/etoposide: C 80mg/m2, d1 + E 100mg/m2,d1-3, q3w) or experimental arm (toxicity-adjusted CE where, in absence of toxicity, dose of both agents were escalated according to the table). Primary endpoint was the objective response rate (ORR) according to RECIST 1.0. 160 pts were required based on 80% power, 2-sided a = 0.05; =80% ORR in the experimental vs =60% ORR in the standard arm.

Results: 161 patients were randomly assigned either to standard (n = 81) or experimental arm (n = 80). Two patients withdrew the consent immediately after the randomisation, one in each arm, and were excluded from the analysis. Median age was 64, most of the patients were males (72%), had PS1 (55%), had not been pre-treated with RT (89%) and did not show brain metastases (75%). A median number of 6 chemotherapy cycles was administered in both the arms. The ORR was 54% and 57% in the control and the experimental arms (p = 0.75). With 44 mos of median follow up, median PFS was 6.0 mos in the control arm and 5.6 mos in the experimental arm (HR = 1.02; 95% CI: 0.73-1.43, p = 0.90), whilst median OS was 9.6 mos and 9.2 mos in the control and experimental arm (HR = 1.01, 95% CI: 0.71-1.42; p = 0.97). Six patients died while on treatment, one in the control arm and 5 in the experimental one. Among grade 3-4 toxicities, neutropenia (p = 0.005) and fatigue (p = 0.04) were significantly more frequent in the experimental arm.

Conclusions: As expected, toxicity-adjusted dosing increases side-effects. However, it does not improve the ORR, nor does prolong PFS or OS in advanced SCLC patients.

Table: H01*

	C (mg/m^2)	E (mg/m^2)
Level –2	stop	stop
Level –1	60 (-25%)	80 (-25%)
Level 0 (starting dose)	**80**	**100**
Level +1	100 (+20%)	120 (+20%)
Level +2	110 (+10%)	120 (-)
Level +3	110 (-)	135 (+12.5%)
Level +4	120 (+9%)	135 (-)
Level +5	120(-)	150 (+11%)

H02* Afatinib vs erlotinib as second-line therapy of patients with advanced SCC of the lung following platinum-based chemotherapy: OS analysis from the global phase III trial LUX-Lung 8 (LL8)

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Background: Treatment options for patients (pts) with advanced squamous cell carcinoma (SCC) of the lung progressing after platinum-based chemotherapy are limited. Overexpression of EGFR, ErbB receptors and the dysregulation of their downstream pathways are implicated in SCC pathobiology. Primary analysis of LL8 (second-line afatinib [A], an irreversible ErbB family blocker vs erlotinib [E], a reversible EGFR tyrosine kinase inhibitor [TKI] and the only TKI approved in this setting, in pts with SCC of the lung) showed significantly better progression-free survival (PFS) with A. Overall survival (OS) and updated PFS for LL8 are reported here.

Material (patients) and methods: Pts with stage IIIB/IV disease were randomised 1:1 to receive A (40 mg/day) or E (150 mg/day) until disease progression. Primary endpoint: PFS; key secondary endpoint: OS. Other endpoints: objective response (ORR), disease control (DCR), patient reported outcomes and safety. 632 events and a sample size of 800 pts were needed to detect a HR of 0.8 with 80% power for OS.

Results: OS was significantly better with A (n = 398) vs E (n = 397), with a 19% reduced risk of death (median 7.9 vs 6.8 mos; HR [95% CI] 0.81 [0.69–0.95]; p = 0.008). Significant differences in OS were seen at 6 (63.6 vs 54.6%; p = 0.010), 12 (36.4 vs 28.2%; p = 0.016) and 18 (22.0 vs 14.4%; p = 0.013) mos. PFS (median 2.6 vs 1.9 mos; HR [95% CI] 0.81 [0.69–0.96]; p = 0.010), ORR (5.5 vs 2.8%; p = 0.055) and DCR (50.5 vs 39.5%; p = 0.002) were all better for A vs E. More pts had improved global health status/quality of life (35.7 vs 28.3%; p = 0.041), cough (43.4 vs 35.2%; p = 0.029) and dyspnea (51.3 vs 44.1%; p = 0.061) with A vs E. Adverse event (AE) profiles were comparable (G = 3 AEs: 57.1 and 57.5% for A vs E) with a higher incidence of drug-related G3/4 diarrhoea (9.9/0.5 vs 2.3/0.3%), G3 stomatitis (4.1 vs 0%) with A and a higher incidence of G3 rash/acne with E (5.9 vs 10.4%). Preliminary data from FoundationOne™ analysis of tumour blocks will be shown.

Conclusion: A significantly improved OS vs E in pts with SCC of the lung in a second-line setting. PFS and DCR were also significantly better. With a manageable AE profile, added QoL benefit, and symptom control seen in LL8, A should be preferred over E for these pts.

H03* Circulating-free tumor DNA as a surrogate for determination of EGFR status: the Italian experience within the ASSESS study

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Background: ASSESS (NCT01785888)is a non interventional, diagnostic study that aims to evaluate EGFR mutation status concordance between plasma-derived ctDNA vs tissue (as per local testing) in patients (pts) with advanced NSCLC (aNSCLC).ASSESS enrolled 1311 pts in Europe and Japan. Data from Italian patients are presented.

Material and methods: Newly diagnosed aNSCLC patients tested locally for EGFR status were enrolled. Extraction of ctDNA from plasma and determination of EGFRmutation status were performed in a central laboratorywith the Qiagen Therascreen EGFR RGQ PCR Kit. Tissue testing was performed in local laboratories with no restriction on method that could be used. Concordance, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) between tumour and plasma samples and EGFR testing practices were evaluated.

Results: 259 pts have been enrolled at 10 sites. Median age was 67years (range 26-86); M/F were 67/33% respectively. 235 pts had both tissue and plasma samples. 35 pts were EGFRM+ in tissue: between them, 22 were also EGFRM+ in plasma. Exon 19 deletion only was the most common mutation detected in tumour samples (50%), followed by L858R mutation only (14%). No T790M either alone or in combination was detected. In plasma, exon 19 deletion only was recorded in 66%, L858R mutation only in 23%. One L858R + T790M was detected. For local tumour analysis, Qiagen Therascreen EGFR RGQ PCR Kit was the most commonly used method (37%), followed by DNA Sequencing (23%) and Pyrosequencing (10%). Remaining samples were analysed with other methods, comprising Fragment Length Analysis in 9 pts and Sequenom in 1 pt. 89% of tumor samples had a number of tumour cells = 100. Median mutation test on tissue turnaround: 9 days. Mutation detection rate was 14.9%. Concordance of tumour vs plasma testing was 89% (95% CI 84, 93), sensitivity and PPV 63% (45, 79),specificity and NVP 94% (89, 97). In the 87 pts whose plasma and tumour were tested with identical highly sensitive methods, concordance increased to 94% (87, 98), sensitivity to77% (50, 93), specificity to 99% (92,100), PPV to 93% (66, 100) and NPV to 95% (87, 99).

Conclusion: These first real-world data suggest ctDNA is a suitable sample for EGFR mutation analysis when tumour samples are unavailable; robust/sensitive analysis methods should be used to reduce false negative results in both plasma and tumour.

H04* Update of REVEL: A randomized, double-blind, phase III study of docetaxel (DOC) and ramucirumab (RAM; IMC-1121B) versus DOC and placebo (PL) in the second-line (2L) treatment of stage IV non-small cell lung cancer (NSCLC) including subgroup analysis of histology

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Background: RAM is a human IgG1 monoclonal antibody that targets the extracellular domain of VEGFR-2. REVEL evaluated efficacy and safety of RAM + DOC vs PL + DOC (DOC) in patients (pts) with stage IV nonsquamous (NSQ) and squamous (SQ) NSCLC after platinum-based therapy.

Methods: Pts were randomized 1:1 to receive DOC 75 mg/m2 in combination with either RAM 10 mg/kg or PL every 21 days until disease progression, unacceptable toxicity, or death. Endpoints included overall survival (OS), progression-free survival (PFS), objective response rate (ORR), quality of life (QoL) as measured by the Lung Cancer Symptom Scale (LCSS), and safety profile. The primary LCSS analysis was time to deterioration (TtD). These endpoints were also evaluated by histology.

Results: A total of 1253 pts were randomized (RAM + DOC: 628; DOC: 625). 26.2% of the tumors were SQ; 72.8% were NSQ and 1% were unknown. The majority of NSQ were adenocarcinoma (79.5%). REVEL met its primary endpoint: the ITT population OS hazard ratio (HR) was 0.857 (95% CI 0.75, 0.98; P = 0.0235); median OS was 10.5 months (m) for RAM + DOC vs 9.1m for DOC. The HR for PFS was 0.762 (P < 0.0001); median PFS was 4.5m for RAM + DOC vs 3.0m for DOC. ORR was 22.9% for RAM + DOC and 13.6% for DOC (P < 0.001). Median OS was 9.5m vs 8.2m in the SQ population, 11.1m vs 9.7m in the NSQ population and 11.2m vs 9.8m in the adenocarcinoma subpopulation for RAM + DOC vs DOC arms, respectively. Other efficacy outcomes and safety profiles showed similar differences between treatment arms across histologies. No unexpected AEs were identified. Regarding QoL, TtD for all LCSS scores was similar for both treatment arms in both histological subgroups.

Conclusions: REVEL demonstrated significant improvements in ORR, PFS, and OS for RAM + DOC vs DOC in NSCLC pts in the ITT population. Benefits were similar in NSQ (including the adenocarcinoma subpopulation) and SQ pts; benefits from antiangiogenic therapy in SQ cell cancer patients have not been previously demonstrated, making RAM unique in this respect. QoL analyses suggest that there was no detriment in QoL by adding RAM to DOC 2L chemotherapy.

H05 Phase 1/2 study of nivolumab with or without ipilimumab for treatment of recurrent small cell lung cancer (SCLC): CA209-032

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Background: Patients (pts) with SCLC respond to initial platinum (PLT) based chemotherapy (CT), but rapidly progress. Combined blockade of PD-1 and CTLA-4 immune checkpoint pathways has anti-tumor activity with a manageable safety profile. Nivolumab (NIVO) is a fully human IgG4 PD-1 immune checkpoint inhibitor approved in the US & Japan. Interim safety and efficacy of NIVO ± ipilimumab (IPI), a CTLA-4 checkpoint inhibitor, in pretreated SCLC pts are reported.

Material and methods: Pts who were PLT sensitive or refractory and had progressive disease were enrolled regardless of tumor PD-L1 status or number of prior CT regimens. This open-label study randomized pts to NIVO 3 mg/kg IV Q2W or NIVO + IPI (1 + 1 mg/kg, 1 + 3 mg/kg, or 3 + 1 mg/kg) IV Q3W for 4 cycles followed by NIVO 3 mg/kg Q2W. Primary objective was overall response rate (ORR). Other objectives were safety, PFS, OS and biomarker analysis.

Results: Seventy-five pts were enrolled (NIVO, n = 40; NIVO + IPI, n = 35); 59% had ≥2 prior regimens. Drug-related adverse events (DrAEs) in ≥10% were fatigue (18%), diarrhea (13%), nausea (10%), and decreased appetite (10%) with NIVO; and fatigue (29%), diarrhea (17%), pruritus (14%), nausea, endocrine disorders, and rash (11% each) with NIVO + IPI. Gr 3–4 DrAEs in ≥5% included diarrhea and rash (6% each; NIVO + IPI). Drug-related pneumonitis occurred in 2 pts (1 per arm). One pt experienced a drug-related SAE of myasthenia gravis on study which was fatal. Of 40 evaluable NIVO pts, partial response (PR) was seen in 6 (15%; duration of ongoing responses [DOR] 80–251+ days); stable disease (SD) in 9 (22.5%); and progressive disease (PD) in 25 (62.5%). In 20 evaluable NIVO + IPI pts, 1 had complete response (CR) (5%; DOR 322+ days); 4 had PR (20%; DOR 41–83+ days); 6 had SD (30%), and 9 had PD (45%). In the NIVO + IPI arm, 12 pts had not reached first tumor assessment and 3 were not evaluable. Nine pts (23%) continue treatment with NIVO and 19 (54%) with NIVO + IPI.

Conclusions: In this PD-L1 unselected SCLC population with progression post-PLT, NIVO alone or combined with IPI was tolerable. ORR was 15% (NIVO) and 25%

(NIVO + IPI) for evaluable pts; durable responses were noted. Updated safety, clinical activity and biomarker analysis will be presented. Clinical Trial Number: NCT1928394.

H06 Advanced non-small cell lung cancer (NSCLC): the prognostic role of systemic Immune-Inflammation Index (SII)

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Background: The aim of the study was to assess the prognostic role of Systemic Immune-Inflammation Index (SII), obtained by analyzing the neutrophil, lymphocyte, and platelet counts, and to design prognostic models for patients with advanced non-small cell lung cancer (NSCLC) treated with first-line chemo- or targeted therapy.

Materials and methods: Patients with advanced NSCLC were treated with first line chemo- or targeted therapy till March 2015 at our Institution. Patients were stratified in two groups with SII =1270 (Group A) vs <1270 (Group B). Progression free survival (PFS) and overall survival (OS) were estimated using Kaplan-Meier method. The best SII cutoff was identified by X-tiles program. A Cox regression model was carried out for univariate and multivariate analyses.

Results: 311 patients were included in this analysis. At baseline, 179 patients had SII ≥ 1270 (Group A), whilst 132 had lower SII (Group B). The median OS was 12.4 months in Group A and 21.7 months in Group B ($p < 0.001$), whilst the median PFS was 3.3 months and 5.2 months, respectively ($p = 0.029$). At multivariate analysis, ECOG-PS ≥ 2, IV tumor stage and SII > 1270 were predictors of worst OS. On the other hand, only wild-type EGFR status and SII ≥ 1270 were independent prognostic factors for worst PFS. For OS, patients were stratified according to the absence of the 3 significant prognostic factors (13%), presence of 1 (44%), 2 (40%) and 3 factors (4%). In the 4 groups, the median OS was 47.0, 19.4, 10.2 and 4.0 months, respectively ($p < 0.001$). Similarly, patients were stratified for PFS based on the presence of 0, 1 or 2 factors. The median PFS was 8.7 months, 5.8 months and 3.3 months, respectively ($p < 0.001$).

Conclusions: Pre-treatment SII is an independent prognostic factor for patients with advanced NSCLC treated with first-line therapies. These prognostic models should be investigated and validated in prospective studies.

H07 Activity and Safety of Trabectedin in patients with Sarcomatoid / Biphasic Malignant Pleural Mesothelioma (MPM)

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Background: The efficacy of available therapies is poor in patients (pts) with sarcomatoid/biphasic MPM, and their prognosis remains dismal. The use of Trabectedin (T) in MPM is justified by its peculiar mechanism of action and the demonstrated activity against a range of tumours, including sarcomas. We studied its activity and safety in pts with MPM.

Methods: ATREUS, an Italian multicenter single arm phase II trial, evaluates T as second line therapy in pts with epithelioid histotype and as first/second line in biphasic/sarcomatoid pts. Seventeen evaluable sarcomatoid pts were needed in order to reject with a 10% one sided alpha error the null hypothesis that 12-week progression free survival (12w PFS) is ≤15% and an 85% power to show 12w PFS in =40% of pts. Overall survival and safety were secondary endpoints. Pts were treated with T, 1.3 mg/m^2, over 3 hours every 21 days, until progression or unacceptable toxicity.

Results: From July 2013 - March 2015 the study enrolled 68 patients (44 epithelioid and 24 biphasic/sarcomatoid). The latter cohort is now complete and results are reported below. Of the 17 evaluable pts (14 M and 3 F, median age 67.9 years), 10, 6 and one had stage IV, III and II disease, respectively. Seven (41.2%) were treatment naïve. Seven of 17 pts (41.2%, 95% CI: 18.4-67.1) obtained 12w PFS. Five (29.4%) had sustained response with PFS ≥18 weeks. By the time of analysis all pts interrupted treatment. Reasons were disease progression in 12 pts, death (4 pts) and consent withdrawal (one). The most frequent grade ≥3 treatment related toxicities were non febrile neutropenia (11.8%), nausea (17.6%), vomiting, mucositis and fever/infection (each observed in one patient, 5.9%). Two serious adverse events, classified as possibly related to T, occurred. One was fatal.

Conclusions: T demonstrated its activity and was well tolerated in these patients with advanced sarcomatoid/biphasic MPM. These optimistic results merit to be further investigated in a larger sample. ClinicalTrials.gov Identifier:NCT02194231).

H08 Sequential strategy with ALK-TKIs for ALK-positive advanced NSCLC: results of a multicenter analysis

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Background: We conducted a clinically oriented analysis of the effectiveness of ALK-TKIs in order to determine the relevance of sequential treatment strategy in a real-world clinical practice scenario.

Materials and methods: We reviewed the medical records of 3 Divisions of Medical Oncology (Perugia Hospital, Sant'Andrea Hospital, IRST Meldola) searching for the ALK-positive advanced NSCLCs who were treated with at least one line of ALK-TKI. The clinical outcome of treated patients was recorded and analyzed according to the type and sequential treatment strategy adopted.

Results: Sixty-eight ALK-positive patients received at least one ALK-TKI and were eligible for the analysis. Overall, 64/68 patients (94.1%) were pre-treated with chemotherapy, the median number of prior lines being 1 (0-5). Sixty-six out of 68 patients (97.0%) received crizotinib as 1st ALK-TKI, with the remaining 2 patients (3.0%) being treated with ceritinib as 1st ALK-TKI. Among patients who progressed on the 1st ALK-TKI (all on crizotinib), 22 patients were treated with a 2nd ALK-TKI in sequence. Of these, 19 patients (86.3%) went on to receive ceritinib, while 3 (13.7%) were treated with alectinib. Finally, 2 patients progressed on the 2nd ALK-TKI (all on ceritinib), being all treated with alectinib as 3rd ALK-TKI. Responses, disease control, PFS and OS to the 1st ALK-TKI were 58.8%, 83.8%, 10 months, and 33 months, respectively. The same features for the 2nd ALK-TKI were 77.2%, 90.9%, 6 months, and 22 months. Three-year survival seemed to favor the 22 patients who received at least 2 ALK-TKIs in sequence vs. the 46 individuals who received only one ALK-TKI (54.8% vs. 49.9%, P = 0.41). Of the 17 patients responding to the 2nd ALK-TKI given sequentially, only 14 (82.3%) had responded to the 1st ALK-TKI, while 2 (11.8%) and 1 (5.9%) had SD, and PD as best response, respectively. Also, of the 3 patients with SD to the 2nd ALK-TKI, 2 PRs and 1 SD was noted on prior ALK-TKI. Finally, of the 2 PDs to the 2nd ALK-TKI, all had experienced PRs on prior ALK-TKI.

Conclusions: Continuation of ALK inhibition with a different ALK-inhibitor despite progression on a prior ALK-TKI retains efficacy in ALK-positive advanced NSCLC. However, response to a 2nd ALK-TKI cannot be predicted solely on the basis of the efficacy of prior ALK inhibition, thus re-biopsy at progression for optimization of subsequent ALK-inhibition therapy should have a high priority in clinical trials.

H09 The role of health care professionals in smoking cessation among patients with pulmonary diseases: an Italian multicentric survey

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Background: Smoking causes many lung diseases, quitting this habit at any time provides positive results and gives the best chance for treatment all patients with pulmonary diseases, including lung cancer patients. Only few Italian centers offer counseling for smoking cessation in cancer patients.

Method: 408 patients with pulmonary diseases (293 with lung cancer) were evaluated from January 2013 to February 2015. An anonymous survey was developed with the aim to understand if current or former smoker patients had received information by health care professionals about smoking cessation before or after diagnosis. The survey was conducted in several Italian Thoracic Oncology Units and Pulmonology Divisions.

Results: After a pulmonary disease diagnosis, 72% of patients state to quit smoking, 20% to smoke less or not feel the same pleasure as before, 8% confirms to continue to smoke. Among 298 former smokers, 150 patients state how long they quitted smoking and 45% at the time of diagnosis or even later, about 35% 10 years before the diagnosis and 8% between 5 and 10 years earlier, while 12% more recently. Most of current smokers state continue to smoke because it helps them to control the stress or because they like it or because smoking is a repetitive gesture. Data show that 39% of patients did not receive information about smoking cessation by health professionals, 26% received it before the diagnosis, 12% after it and 23% received it both before and after diagnosis. Concerning the reaction to counseling, 53% considers positively the health care provider action, even if 28% hoped they could have helped them more quit smoking and 19% reports a warning and paternalistic attitude of them and also embarrassment. Only 23% of patients who attempted to quit smoking consider the gradual termination as the most effective measure. Regarding the smoking-cessation method or specific therapy adopted: 65% disclosed they simply quitted smoking overnight and 80% confirmed this as the most effective technique; 16% used electronic cigarettes, 8% a nicotine replacement treatment, 7% books and 4% attending a dedicated clinic.

Conclusion: The analysis of the results underlines that most patients quitted smoking after having received their diagnosis. Although many of them received advice by healthcare workers, the recourse to the use of techniques, drugs or access to specific clinic is still very low, especially considering that 50% of patients result highly dependent to nicotine.

H10 Mutational analysis of EGFR, c-KIT, PDGFRs, BRAF and KRAS, and expression of ALK and PD-L1 in a series of 103 thymic epithelial tumors with different histology

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Background: Thymic epithelial tumorsare unusual neoplasms with different prognosis, lacking consistent molecular alterations with therapeutic intent. A consecutive series of thymic epithelial tumors of various histologies were investigated for the mutational status of "druggable" genes (EGFR, c-KIT, KRAS, PDGFR-alphaand -beta, BRAF) and the expression of ALK and PD-L1. Immuno-molecular results were then statistically matched with clinico-pathologic characteristics.

Materials and Methods: One-hundred three cases of thymic epithelial tumorsand the relevant clinico-pathologic features (age, gender, histologic type, immunostains, tumor stage) were collected. Immunohistochemical expression of ALK (clone D5F3, Cell Signaling Technology) and monoclonal PD-L1 Ab (clone E1L3N, Cell Signaling Technology) were performed using an automated immunostainer (BenchMark XT, Ventana). Positivity for ALK and PD-L1 was quoted when at least 10% of tumor cells reacted with a moderate intensity staining (2+). Molecular analysis of EGFR (exons 18-21), c-KIT (exons 9,11,13,14,17), KRAS(exon 2), BRAF(exon 15) and PDGFR-alpha (exon 12) and–beta (exons 12, 14, 18)mutations was performed by direct sequencing.

Results: The case series included 57 male and 46 female, with a median age of 62 years (range, 19-84 years). Myasthenia was observed in 21 cases (20%) and 67 patients were surgically-treated (69%). According to Masaoka-Koga staging system, 25 (24%) were in stage I, 46 (44.5%) in stage II, 16 instage III and 16 instage IV. According to the WHO classification there were 76 (74%) thymomas (10 type A, 9 B1, 24 B2, 15 AB, 4 B1/B2, 5 B2/B3, 9 B3), 22 (21%) thymic carcinomas (type C) and 5 atypical carcinoids. At molecular analysis, there were 4 c-KITmutations (occurring in exon 11 V559A, L576P, Y553N, and exon 17 D820E) in thymic carcinomas (type C) but not in other tumor types ($p = 0.003$). No alterations were detected in EGFR, BRAF, KRAS, PDGFR-alphaand –beta. None case was positive for ALK. Fifty percent of thymic carcinoma (type C) and 17% of thymomasstained positive for PD-L1($P < .001$). A significant correlation was found between PD-L1 expression and c-KIT mutations ($p = 0.017$).

Conclusions: A subset of thymic carcinomas (18% of type C) harbor c-KITmutations and show consistent expression of PD-L1 (50%). The data suggest that PD-L1level and c-KITmutations represent "druggable" molecular targets of potential use for unresectable or relapsed thymic carcinomas.

H11 Hyponatremia normalization as an independent prognostic factor in patients with advanced non-small cell lung cancer treated with first-line therapy

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Background: The aim of the study was to assess, for the first time, the prognostic role of hyponatremia and sodium normalization in patients receiving first-line chemo- or targeted therapy for advanced non-small cell lung cancer(NSCLC).

Materials and methods: 433 patients with advanced NSCLC were treated with first line chemo- or targeted therapy between 2006 and 2015 at our institutions. Patients were stratified in two groups, with or without hyponatremia (group A and B, respectively). Progression free survival (PFS) and overall survival (OS) were estimated using Kaplan-Meier method. A Cox regression model was carried out for univariateand multivariate analyses.

Results: Sixty-nine patients (16%) presented with hyponatremia at the start of first-line therapy.The median OS was 8.78 months in Group A and 15.5 months in Group B ($p< 0.001$), while the median PFS was 4.1 months and 6.3 months respectively ($p= 0.24$). In Group A, median OS was significantly higher in patients who normalized their sodium levels (11.6 vs. 4.7 months, $p= 0.0435$). Similarly, the median PFS was significantly higher in patients who normalized their sodium levels (6.7 vs. 3.3 months, $p= 0.011$). At multivariate analysis, sodium normalization was an independent prognostic factor for both OS and PFS.

Conclusions: Sodium normalization during first-line therapy is an independent prognostic factor for OS and PFS in patients with advanced NSCLC treated with first-line therapies. Frequent clinical monitoring and prompt treatment of hyponatremia should be emphasized to optimize the outcome of these patients.

H12 Lume trial: searching for survival prognostic factors in malignant pleural mesothelioma

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Background: Malignant Pleural Mesothelioma (MPM) is a rare disease with limited therapeutic options. It is often highly aggressive but important differences in clinical evolution, including cases of prolonged survival, were reported. To date, no survival prognostic factors exist. LUME (Long sUrvivors in MEsothelioma) project aims to promote multidisciplinary collaboration at national level to improve clinical management of disease and identify long-term survival prognostic factors.

Methods: Patients (pts) with MPM treated at Fondazione IRCCS, Istituto Nazionale dei Tumori, Milan were retrospectively evaluated and divided into two groups, long and not long survivors, according to their Overall Survival (OS), longer than 36 months or not. We collected informations about disease characteristics, treatments and outcomes and we defined a panel of 22 genes to be sequenced by Next-generation sequencing on histological samples. We will correlate any gene alterations with disease clinical evolution and OS.

Results: From January 2002 to December 2011we selected 51 patients with MPM treated. Twenty-three pts, 12 men and 11 women, were long survivors and 28 pts, 21 men and 7 women, were not long survivors. In the first group 22 pts had epithelioid histology and only 1 mixed histology, 20 died and 3 are still alive. Ten pts were diagnosed in early stage (I-II) and 13 in advanced stage (III-IV). Median OS was 53.4 months (range 36-88 months). The second group included 24 epithelioid and 4 mixed histologies, all pts died and median OS was 15.0 months (range 1-30 months). Twelve cases had early stages at diagnosis, 16 advanced stages. Wide heterogeneity in management was highlighted in both groups: more or less extensive surgery, several lines, schedules and doses of chemotherapy and various volumes and doses of radiotherapy. Actually, gene assessing on histological samples is ongoing.

Discussion: Our genetic evaluations and their correlation with patient's outcomes are the first step of LUME project and will be presented at AIOM conference. Trial results will lay the basis for further and analysis on clinical data. Specific researchers could be performed on tissue samples collected by the network of referral centers for MPM. The closing goal is to maximize the management and improve outcomes of MPM in Italy.

H13 Vinorelbine as second or third-line therapy in pemetrexed-pretreated malignant pleural mesothelioma (MPM) patients

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Background: There is no standard therapy for patients (pts) with MPM progressing during or after pemetrexed/platinum-based chemotherapy (PBC). Single agent chemotherapy is often administered in everyday practice, although its use is poorly supported by clinical trials. The aim of this retrospective study was to analyze the efficacy and toxicity of second (2nd) and third (3rd) line vinorelbine (VNR) in a large cohort of PBC-pretreated MPM patients.

Methods: The clinical records of MPM pts consecutively treated at 8 Italian Centers with intravenous (iv) or oral (po) VNR as 2nd or 3rd line therapy following PBC were reviewed. Radiological response was assessed by modified RECIST criteria. Toxicity was reported according to CTCAEv4 criteria. Relative dose-intensity (DI) of VNR was calculated. Progression-free survival (PFS) and overall survival (OS) were estimated and correlated to clinical variables: age, gender, histological subtype, ECOG performance status (PS), line of VNR therapy (2nd vs 3rd) and outcome of first-line treatment.

Results: From August 2001 to September 2014, 161 pts (M/F 120/41) were treated, 128 with iv and 33 with po VNR. Most cases (92%) were treated after 2007. Histological subtype was epithelioid in 134, biphasic in 15, sarcomatoid in 8 and unspecified in 4 pts. Median age was 67 years (range 41-82). VNR was administered as 2nd or 3rd line treatment in 94 and 67 pts, respectively. Median number of VNR cycles was 3 (range 1-26), median relative DI was 88%. Main grade 3-4 toxicities were neutropenia in 9%, fatigue in 4% and constipation in 5% of pts. No toxic death occurred. A partial response was observed in 10 pts (6%), stable disease in 57 (35%), for an overall disease control rate of 41%. Median PFS and OS were 2.5 and 6.7 months, respectively. In multivariate analysis, only ECOG PS (0 vs 1-2) was significantly associated with improved PFS and OS. Median PFS and OS in pts with ECOG PS 0 were 3.3 and 8.5 months. An analysis of molecular predictors of VNR response is ongoing.

Conclusions: In this large retrospective patient cohort, 2nd and 3rd line VNR had modest but definite activity in PBC-pretreated MPM patients, with a good toxicity profile. Although inclusion in prospective clinical trials of new agents should be always considered in this setting, single agent VNR remains a reasonable option for palliation.

H14 Influence of dose adjustment on afatinib safety and efficacy in patients (pts) with advanced EGFR mutation-positive (EGFRm+) non-small cell lung cancer (NSCLC)

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Background: Afatinib 40 mg/day (oral) is approved for the treatment of pts with advanced *EGFRm+* NSCLC. Dose adjustment is recommended according to pre-defined tolerability criteria. We performed post-hoc analyses on the influence of afatinib dose reduction on adverse events (AEs), pharmacokinetics (PK) and progression-free survival (PFS) in the Phase III LUX-Lung 3 (LL3) trial.

Material (patients) and methods: All pts treated with afatinib in LL3 were included in the analyses (n = 229). Pts were initiated at the protocol-defined and approved dose of 40 mg. For pts experiencing drug-related grade 3 or selected prolonged grade 2 AEs, afatinib was dose reduced by 10 mg decrements to 30 mg or a final dose of 20 mg. Frequency and severity of the most common AEs before and after dose reduction were analysed. Final PK data collected as part of the standard visit schedule (Day 43) were used to compare plasma afatinib concentrations in pts who reduced to 30 mg versus those remaining at 40 mg. PFS was compared between pts who dose reduced within the first 6 months of treatment and those who did not.

Results: Dose reductions occurred in 53% (122/229) of pts; the majority (86%) within the first 6 months of treatment. In pts who dose reduced, decreases in the incidences of drug-related all grade (grade ≥3) AEs were 99.2% (20.5%) to 46.7% (4.1%) for diarrhoea, 88.5% (26.2%) to 38.5% (3.3%) for rash/acne, 77.0% (12.3%) to 27.9% (0%) for stomatitis, and 44.3% (16.4%) to 36.9% (4.9%) for nail effects. Dose reduction was more likely in pts with higher plasma concentrations of afatinib. On Day 43, pts who dose reduced to 30 mg ≥4 days previously (n = 38) had geometric mean plasma afatinib concentrations of 24.4 ng/mL versus 23.7 ng/mL in pts who remained on the 40 mg dose (n = 126). Median PFS was 11.3 months in pts who dose reduced during the first 6 months of treatment versus 11.0 months in pts who did not (HR = 1.25 [95% CI, 0.91–1.72]).

Conclusion: In LL3, tolerability-guided dose adjustment of afatinib was an effective measure to reduce treatment-related AEs without reducing therapeutic efficacy.

H15 Rare epidermal growth factor receptor (EGFR) mutations in a 425 patients population with non-small cell lung cancer (NSCLC): clinical, molecular and survival data. The IRCCS Candiolo experience

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Background: EGFR exon 19 deletion and exon 21 L858R mutations are well known to be associated with response to EGFR-TKI in NSCLC patients (pts). However, this response remains partly unclear due to EGFR complex alterations and rare mutations scattered throughout exons 18-21.

Patients and methods: Formalin fixed paraffin embedded sections (FFPEs) from 425 NSCLC pts were collected at IRCCS Candiolo Institute between 2005 and 2015. They were tested for exons 18-21 EGFR mutations by direct sequencing, pyrosequencing and a RealTime PCR approaches. Clinical and pathological data were available for 400/425 examined FFPEs and disease outcome data were available for 320/425 pts.

Results: Overall we detected 100 mutations (23.5% of the examined cases). They were mainly exon 19 (37/100) and 21 (51/100) mutations, but we also identified 6 mutations in exon 18 and 6 in exon 20. This high number of mutated cases compared to the national standard was due to a bias caused by the initial selection of non smokers women. Among these alterations, we found 17 rare mutations (17% of mutated pts and 4 % of screened pts): 2 exon 19, 4 exon 21, 3 exon 18, and 8 exon 20. Complex alterations were detected in 4 pts: ex 18 + 21; ex 20 + 21; de novo ex 20; T790 + 21; double mut of 19. All pts with rare EGFR mutations were Caucasian, none had received EGFR-TKI before DNA sequencing. Most of pts were smokers (10/17) and female (9/17).Clinical outcomes were observed to assess if there was a correlation whit pts mutations. Classic EGFR mutations were independent predictors of the increase in overall survival (OS) and were associated with a significantly higher progression free survival (PFS) in pts with common mutations than in pts with rare ones (PFS = 3 months for pts with exons18 and 20 rare mutations). Interestingly, rare mutations were frequently associated with high grade adenocarcinoma histology.

Conclusions: Our data suggest that only pts with rare mutations could receive platinum-based chemotherapy as 1° line treatment, due to their low response to EGFR-TKIs; EGFR-TKIs could be reserved as 2°or 3° line treatment unless in presence of T790 mutation, towards which new EGFR irreversible inhibitors have activity. Given that rare mutations occur with low frequency and tend to be heterogeneous, a meta-analysis would be useful to evaluate the relationship between the type of mutation and the response to EGFR-TKI therapy. This may guide the choice of treatment in this pts group.

H16 Clinical outcome of platinum/etoposide treated large cell neuroendocrine carcinomas of the lung according to the type of radiotherapy received: a single institution analysis

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Background: Large cell neuroendocrine carcinomas of the lung (LCNECs) belong to the class of poorly differentiated neuroendocrine tumors of the lung along with small cell lung cancers (SCLCs). Similarly to SCLCs, LCNECs seem to benefit from platinum/etoposide chemotherapy. However, recommendations on the use of radiotherapy in LCNECs is lacking.

Materials and methods: We reviewed the medical records of the Perugia Cancer Center searching for poorly differentiated neuroendocrine tumors of the lung that were uniformly treated with platinum/etoposide chemotherapy. For all patients, we recorded the type of radiotherapy received, either thoracic radiotherapy (TRT) and/or prophylactic cranial irradiation (PCI).

Results: One hundred thirty-eight patients were identified, of which 31 (22.5%) were histologically classified as LCNECs, while 107 (77,5%) were defined as having SCLCs. Overall, 16 out of 31 (51.6%) LCNECs and 33 out of 107 SCLCs (30.8%) had limited stage (LS) disease at diagnosis, with the rest having extensive stage (ES). When grouped according to disease stage, baseline clinical characteristics did not differ between LCNECs and SCLCs, except for median age, which was significantly higher in LS-LCNECs vs. LS-SCLCs [72 (50-88) vs. 65 (37-78), $P = 0.02$]. Significantly less LS-LCNECs received TRT, [8/16 (50.0%) vs. 27/33 (81.8%), respectively - $P = 0.04$] and PCI [2/16 (12.5%) vs. 18/33 (54.5%) - $P = 0.005$] compared with the SCLC counterpart. The same observation was carried out for PCI in ES patients who responded to platinum/etoposide and without brain metastases at baseline [1/11 (6.6%) vs. 19/40 (47.5%), respectively - P = NS). Median PFS and OS were generally found to be poorer in LCNECs vs. SCLCs, regardless of stage, though the difference reached statistical significance only for OS of LS patients (10.4 months vs. 16.3 months, respectively, $P = 0.05$).

Conclusion: Our analysis suggests that an underuse of TRT and/or PCI might account for the different clinical outcome observed for LCNECs vs. SCLCs, particularly in LS-LCNECs. Clinical trials of LCNEC should address prospectively this issue.

H17 Detection of secondary mutations associated with drug resistance in circulating tumor dna of patients with advanced ALK+ NSCLC

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Background: ALK translocation is present in about 5% of advanced NSCLC and is a predictive factor of response to ALK Tyrosine Kinase Inhibitors (TKI), such as crizotinib. Disease progression occurs after a median period of 9-10 months of treatment with crizotinib. Several mechanisms of resistance have been identified and include other mutations in ALK gene, ALK amplification, activation of bypassing signaling pathways involving EGFR, KRAS or c-KIT. Second-generation ALK-TKIs demonstrated an enhanced spectrum of activity in crizotinib-resistant ALK mutants. However, re-biopsy in NSCLC patients represents a critical issue and analysis of circulating cell-free DNA (cfDNA) has a promising role for identification of mechanisms of resistance to targeted therapy.

Patients and methods: Patients progressing during crizotinib were enrolled. After tumor progression, blood was collected and plasma isolated by centrifugation. DNA was extracted from plasma using QIAamp circulating nucleic acid kit (Qiagen®) and tested for ALK secondary mutations and KRAS exon 12 mutations using a Digital Droplet PCR (BioRad®).

Results: Twelve patients were studied:8 were female and 4 male. 6 were never-smokers and 6 former-smokers. Median age was 49 yrs (range 40-81) and all patients were stage IV adenocarcinoma. Eleven patients received crizotinib and only 1 ceritinib. ALK-TKIs was administered mainly as second-line, in 2 cases as first-line and in the remaining as third-line therapy.Ten patients had partial response and 2 stable disease. Median PFS was 16.9 months. In 10 cases brain was a site of progression while on ALK-TKIs. Only 5 patients presented a tumor site that could potentially undergo re-biospy. ALK secondary point mutations were identified in 3 patients. One showed p.L1196M and p. G1269A ALK mutations which levels decreased after 2 months of therapy with second generation ALK-TKI, along with tumor response. The second had p.L1196M alone while the third showed p.F1174L after initiation of second generation ALK-TKI. In a total of 9 patients, including those with secondary ALK mutations, KRAS mutation G12D or G12V appeared in blood samples at the time of resistance to TKI.

Conclusion: ddPCR can detect resistance mutations in cfDNA of ALK+ NSCLC and may represent an effective alternative to re-biopsy. Moreover, the assessment of mutated allele burden could be used for response monitoring during treatment. The development of KRAS mutations may play a role in resistance to ALK-TKIs.

H18 Tivantinib in combination with Carboplatin and Pemetrexed as first line treatment in patients with advanced non-squamous NSCLC or Malignant Pleural Mesothelioma: results of phase I trial

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Background: Preclinical data showed that MET inhibition blocks MPM and NSCLC cell growth and migration. Tivantinib (T) is a selective non-ATP competitive oral inhibitor of MET receptor. Adding Tivantinib (T) to standard first-line chemotherapy may improve efficacy. This trial is conducted to determine the maximum tolerated dose (MTD), safety/tolerability, pharmacokinetics and preliminary anti-tumor activity of escalating doses of Tivantinib in combination with standard fixed doses of Carboplatin and Pemetrexed.

Material and methods: Patients (pts) with advanced non-squamous NSCLC or MPM were eligible to be treated with escalating doses of T in combination with fixed doses of carboplatin (AUC 5 i.v. d1-q21) and pemetrexed (500 mg/m^2 i.v. d1-q21) delivered for 6 cycles as first-line treatment. T is continued as maintenance therapy until progression. Pts must have ECOG Performance Status <2 and adequate bone marrow, kidney and liver functions. A standard 3 + 3 dose-escalation design was employed starting from dose level 0 (T 240 mg BID). The primary endpoint of this part of the study is to assess the MTD, defined as the highest dose level at which no more than 1 of 6 pts experiences a DLT during the first cycle. Additional pts are now enrolled at the MTD in the expansion phase of the trial, to evaluate the anti-tumor activity (MPM pts: 3-month PFS%; NSCLC pts: 5-month PFS%).

Results: From April 2013 to September 2014, 12 pts were enrolled in this dose-escalation part of the study. Mean age was 69 years (range, 37-73 years), M/F: 9/3, MPM/NSCLC: 6/6, ECOG PS 0/1: 5/7. The MTD was reached at dose level 0 (T 240 mg BID). DLTs (2 neutropenia G4, 1 thrombocytopenia G4) were observed in 2 pts, both at dose level 1 (T 360 mg BID). The most common all-grade toxicities were nausea/vomit (67%), anemia (58%), neutropenia (50%), and asthenia (50%). The G3/4 treatment-related AEs were hematological (neutropenia, thrombocytopenia, anemia) and were reported in 6 pts (50%). All pts completed the six cycles of CT. Among 12 evaluable pts (2 ongoing), 1 had CR, 4 PR, 7 SD as best response.

Conclusions: The combination of T with first-line chemotherapy is safe with preliminary evidence of antitumor activity. T 240 mg BID combined with carboplatin (AUC 5 i.v. d1-q21) and pemetrexed (500 mg/m^2 i.v. d1-q21) represents the recommended dose for phase II trials. Updated clinical data will be presented at the meeting.

H19 Impact and prognostic role of single-neucleotide polymorphisms (SNPs) in thymic lesions

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Introduction: The thymus may present a large spectrum of morphological benign proliferative changes as thymic hyperplasia and malignant neoplasms, as thymoma and thymic carcinoma (Thymic Epitelial Tumors, TETs), that display significant heterogeneity. Angiogenesis has been highlighted as a needful component in development of thymic tumors. Therefore, the improvement of our knowledge of the molecular biology of thymic disorders represents a key challenge in the treatment of these rare diseases.

Patients and methods: The genomic DNA of 92 consecutive patients, undergone surgery or biopsy was extracted from paraffin-embedded tissue. We selected polymorphisms in the following genes involved in the angiogenesis mechanism: Platelet-Derived Growth Factor alpha (PDGFR-α: rs35597368T > C), Hypoxia Inducible Factor-1 alpha (HIF1-α: rs2057482C > T, rs1951795C > A, rs2301113A > C, rs10873142T > C, rs11158358C > G, rs12434438A > G, rs11549465C > T, rs11549467G > A), Vascular Endothelial Growth Factor-A (VEGF-A: rs2010963G > C, rs699947C > A). Gene polymorphisms were determined by Real-Time PCR using TaqMan assays.

Results: Ninty-two patients were included into the study, 57 females and 35 males. Eighty-seven patients underwent surgery (52 for thymomas or thymic carcinoma and 35 for thymic benign lesions), while 5 patients showed metastatic or locally advanced disease (3 thymomas and 2 thymic carcinomas). The frequency of rs35597368T allele of PDGFR-a was higher in TETs compared to general population ($p = 0.037$). The frequency of rs2057482C and rs11158358 C polymorphisms of HIF1-a resulted lower in TETs than in general population ($p = 0.011$ and $p = 0.012$, respectively). The frequency of 4 HIF1-a alleles was higher in general population than study groups: rs1951795C SNP ($p = 0.026$ for the benign lesions group and $p = 0.002$ for malignancy group, respectively), rs10873142T SNP ($p = 0.008$ and $p = 0.003$ respectively), rs12434438 A SNP ($p = 0.034$ and $p = 0.002$) and rs2301113A SNP ($p = 0.027$ and $p = 0.022$). The frequency of rs699947C polymorphism of VEGF-A was higher in patients with benign lesion in comparison with general population ($p = 0.012$).

Conclusions: To the best of our knowledge this is the largest monocentric study analyzing the angiogenetic variants in thymic benign lesions and thymic malignancies. The selection tool deriving from this analysis may allow an optimal use of innovative treatment strategies including targeted agents.

H20 Detection of EGFR alterations in circulating tumor DNA of non-small cell lung cancer by digital PCR and Next Generation Sequencing

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Background: Adenocarcinoma lung patients with *EGFR* sensitizing mutations receiving targeted agents develop resistance due to the onset of the additional activating *T790M* mutations in *EGFR* in up to 50% of cases. Proof of concept exist that circulating tumor DNA (ctDNA) could be used for the diagnostic molecular characterization and follow-up of cancer patients. Here we report the analysis of a series of matched tissue and plasma DNAs of 16 lung adenocarcinoma patients.

Methods: DNA from matched microdissected cancer tissue and plasma (6 ml) of 16 patients with advanced lung adenocarcinoma was assayed for *EGFR* mutations using next-generation sequencing (NGS) on Ion Torrent (Life Technologies) to sequence the coding regions harboring hotspot mutations of the gene and digital PCR (Bio-Rad) for three EGFR mutations (746-750del, L858R and T790M).

Results: Analysis of cancer tissues revealed that 6 of 16 cancers had EGFR mutations using both NGS and digital PCR analysis: five 746-750del and one L858R. The five deletions were also shown in plasma DNA by digital PCR while only three were detected by NGS. The L858R was not detected in plasma DNA. The 6 patients with EGFR mutations were treated with erlotinib and 5 of these were shown to harbor the *EGFR* T790M mutation by digital PCR, which was undetected in the original cancer tissue.

Conclusions: These data confirm that ctDNA holds important information for cancer diagnosis and disease monitoring. However, the question remains whether plasma DNA completely mirrors the genetic footprint of the primary cancer. Contradiction between digital PCR and NGS may originate from the different sensitivity of the 2 techniques requiring validation before clinical application.

H21 Effectiveness of somatostatin analogs plus prednisone in aggressive histotype and advanced stage of thymic epithelial tumors

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Background: Thymic epithelial tumors (TETs) are rare neoplasms characterized by histological variability. Several biological agents have been evaluated in TETs in small phase II trials. Efficacy of octreotide/lanreotide with or without prednisone in TETs OctreoScan positive has been widely demonstrated in thymoma, but no clearly in thymic carcinoma.

Material and methods: Twelve patients (five men, seven women; median age 47 years; range 27-70) with advanced stage disease according to the Masaoka-Koga staging system (seven with IVa stage; five with IVb stage), and aggressive histotype according to WHO classification, revised by central review (two B2/B3; five B3; one B3/thymic carcinoma; four thymic carcinoma) were enrolled in this monocentric referral study. All the patients showed a progressive disease according to RECIST 1.1 criteria to previous conventional chemotherapeutic regimens platinum or not platinum-based. All the patients performed OctreoScan. The schedule includes administration of long-acting analog octreotide (30 mg/every 28 days intramuscularly) plus prednisone 0.2 mg/kg/day until progression of disease was documented. Time to progression, Overall response rate and toxicity were evaluated.

Results: The median time to progression was 6 months (range 3-24), the overall response rate was 74.9%, particularly three patients (25%) obtained stable disease; four patients (33.3%) partial response; two patients (16.6%) complete response; three patients (25%) progression disease. One patient with Good Syndrome interrupted treatment after 6 months for infectious disease. One patient has been lost to follow-up after 24 months of treatment. One patient died after progression disease for Pure red cell aplasia. Treatment was generally well tolerated with acceptable toxicity: no symptomatic cholelithiasis (1 patient), Grade 1 diarrhea (two patients) hyperglycemia (1 patient). One patient with thymic carcinoma and IV b stage had PS improvement from 2 to 1 according to ECOG, and one patient had complete remission of pericardial and pleural effusion after six months treatment with symptomatic relief.

Conclusion: These results show that the association of somatostatin analogs plus prednisone is an effective treatment in aggressive histotype and advanced stage disease of TETs.

H22 Non Small Cell Lung Cancer (NSCLC) and Circulating Tumor Cells (CTCs): Could an implemented CTC assay reveal higher risk patients?

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Background: NSCLC is a major cause of cancer-related death in both men and women globally (Ferlay, Steliarova-Foucher et al. 2013). Despite recent advances in early tumor detection, surgical treatment, radio-chemotherapy, and targeted therapy, the NSCLC-related high mortality rate remains a daunting challenge (Jemal, Bray et al. 2011). Since predictive biomarkers are lacking so far, CTC assays have gained interest to assist clinicians in patient management. In NSCLC, CTCs show a different cytokeratin (CK) pattern and a lower expression of full-length Epithelial Cell Adhesion Molecule (EpCAM) compared to other carcinomas (Fong, Seeber et al. 2014). Indeed, 80% of patients were CTC-positive by the EpCAM-independent ISET compared to only 23% by standard CellSearch assay (Krebs, Sloane et al. 2011). We questioned whether we could detect a higher number of CTCs by implementing the standard CellSearch assay with an expanded CK pattern; secondly, we investigated if the implemented assay could better stratify patients' risk.

Methods: We evaluated 75 patients, enrolled from December 2012 to February 2015 in the trial no. NCT02407327 (http://www.clinicaltrials.gov). At baseline, we collected two blood draws for performing in parallel the standard and the CK-expanded CTC assay (including CKs 5, 6, 7, 14, and 17). Progression Free Survival (PFS) and Overall Survival (OS) between groups defined by CTC no. < or > 1 cells were compared with the Kaplan-Meier method, and differences were tested with the log-rank test for both standard and CK-expanded assays.

Results: We did not find a difference between the percentage of CTC-negative and CTC-positive patients depending on the assay, but, notably, the CK expanded panel identified a discordant CTC status in 21 out of 75 patients (28%) compared to the standard panel. At baseline, CTC-positive patients, as detected with expanded CK panel, had a significant lower median PFS (108 days) than CTC-negative patients (254 days; Kaplan-Meyer, Log-Rank test p = 0.017). Similarly, CTC-positive patients had a significant lower median OS (250 days) than CTC-negative patients (467 days; Kaplan-Meyer, Log-Rank test p = 0.033).

Conclusions: The interim analysis demonstrated that the expanded CK panel improves CTC detection and potentially discloses a more aggressive disease. Accrual is ongoing; we will present updated results at the meeting. * This work was supported by grants from Italian Ministry of Health, Proposal No: # GR-2010-2303193A (PI: E. R.).

H23 Absence of standard in the management of Thymic Epithelial Tumors

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Background: Thymic Epithelial Tumors (TETs) are a group of rare and heterogeneous neoplasms. Actually, according to the 2004 World Health Organization (WHO) classification, TETs are divided into thymomas (Ts – A, A/B, B1, B2, B3 subtypes) and thymic carcinomas (TCs - C). No validated and shared guidelines are available to manage TETs patients (pts).

Methods: We tested a preliminary database designed to share TETs pts data among TYME (TYmicMalignanciEs) members. This database includes information on disease histology, stage, diagnostic procedures, treatments, comorbidities and outcomes.

Results: Our database is in use at Fondazione IRCCS, Istituto Nazionale dei Tumori of Milan from March 2015.In this short period we added 29 pts (17 female, 12 male) from 11 different regions of Italy (5 B2, 7 B3 and 17 C pts). Radiologic staging were performed with Computerised Tomography (CT-scan) in 27 pts and Positron Emission Tomography (PET-scan) in 22 pts. Octreoscan or Nuclear Magnetic Resonance (NMR) were used in only 4 pts. Five pts had autoimmune disease. Clinical Masaoka stage at diagnosis was: stage III (5 pts), stage IVA (15 pts), stage IVB (9 pts). Seventeen pts underwent surgery, 13 radiotherapy. Ten pts, from 8 different hospitals, received neoadjuvant therapy with 5 different combinations of drugs. Three pts from 3 different hospitals were treated with adjuvant chemotherapy with 3 different regimens. The same scenario was found for first line treatment (28 pts from 22 different hospitals, treated with 10 different drug combinations); second line (22 pts from 18 different hospitals, treated with 8 different drug combinations) and third line (12 pts from 12 different hospitals, treated with 5 different drug combinations). Finally 22 pts have been included in a phase II clinical trial active at our center (17 in second and 5 in third line).

Discussion: This small test demonstrated the wide heterogeneous management of TETs in Italy, that only in small part can be justified by pts characteristics. The need to build a solid infrastructure and to share data among Italian centers is mandatory for these rare tumors. An efficient network as TYME may develop common clinical guidelines shared among members and their use may be recommended in all TYME centers. Through an hub and spoke network TYME should promote multidisciplinary web-discussion on clinical cases, create clinical register and virtual bio-bank useful to perform translational research.

H24 Single centre analysis of 132 pulmonary resections: can we overcome VATS limits?

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Background: Two decades have passed since video-assisted thoracic surgery (VATS) introduction in clinical practice in the surgical treatment of limited stage lung cancer. Purpose of the present study was to analyze our experience and point out feasibility and safety of this approach.

Matherials and methods: We analyzed our surgical practice with VATS anatomical pulmonary resection conducted in a 15-month period. Patients requiring anatomical pulmonary resections for lung neoplasms from 1/1/2014 to 31/3/2015 were treated with VATS procedure or open surgery. Group allocation was individually decided after multidisciplinary consultation aiming to anticipate possible technical difficulties in the case of VATS procedure. Data concerning the short outcome were prospectively recorded.

Results: 3 patients underwent pneumonectomy; one of them had a VATS procedure. A lobectomy was performed in 132 patients: 65 of them had a VATS procedure (Group A, 49.2%), this group included 3 patients who required the conversion to open; 67 patients had an open procedure (Group B). In whole population requiring lobectomy, pT1aN0 was the most representative stage (24.2%) followed by T2aN0 (15.9%) and T1bN0 (6.8%); there were no significantly difference in stage between the groups. The mean diameter of nodule was 2.0 cm in the Group A versus 2.8 (p = 0.002); on the contrary, the number of lymph-node harvested was similar in both groups (A = 15.5, B = 16.5; p = 0.4). Hospitalization was significantly shorter in the Group A (6.2 days versus 8.2; p = 0.0001). In this study are comprised patients treated with induction therapy and then operated with VATS including a pneumonectomy. Two patients had a hybrid procedure (VATS + open) for Pancoast tumors (Group B). Three patients had VATS sleeve lobectomy; one of them had induction therapy. Mean tumor size was statistically smaller in the Group A, but such group included tumor measuring 5.5 cm.

Conclusions: The proportion of patients requiring anatomical pulmonary resection for lung cancer and treated with VATS technique was progressively increased in our Unit; it seems possible that soon it could rise to a physiological plateau around 80%. If VATS lobectomy is coming to be the standard of care for T1-T2 lung cancers, the VATS limits are far to be determined. The analysis of our surgical practice for lung cancer confirmed that VATS will soon be considered the standard of care, but an extension of the VATS benefits to complicated clinical cases is possible.

H25 Immunohistochemistry (IHC) analysis with 3 different antibodies (Abs) and thymidylate synthase (TS) evaluation of FISH-positive ALK-rearranged (ALK+) lung adenocarcinomas (ADK)

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Background: ALK+ lung tumors are often diagnosed in young, never/light smokers, with ADK histology; these patients (pts) had good responses to pemetrexed (PEM)-based chemotherapy. ALK-kinase inhibition with 1st (crizotinib/CZT) and 2nd generation TKIs is the preferred treatment strategy. As several works support IHC as a sensitive and specific test, the European Medical Agency (EMA) approved CZT for 2nd-line treatment of ALK+ Non-Small-Cell Lung Cancers (NSCLCs) as detected by "an accurate and validated ALK assay", thus endorsing IHC for eligibility purposes as opposed to the FDA, which approved Vysis break-apart FISH probe as CZT-companion diagnostic test. We retrospectively performed ALK-IHC with 3 Abs in 28 pts with known FISH-positive ALK+ NSCLCs to assess IHC accuracy as compared to the FISH assay. We evaluated TS expression too, given the conflicting literature data on PEM sensitivity in those tumors.

Material and methods: FISH was performed with Vysis break-apart FISH probe. IHC was performed with 3 Abs: ALK1 (DAKO), 5A4 (Novocastra) and D5F3 (Ventana/Cell Signaling Technology). A positive or negative score was used with D5F3 and Ventana KIT; for ALK1 and 5A4 an IHC scoring value between 0+ and 3+ was used. TS gene expression was measured through Real Time PCR, TaqMan method.

Results: We evaluated 28 specimens of ALK+ ADK from 7 Italian Oncology Centres. Pts median age at diagnosis was 55 (range: 25-78),19 pts were males. 13/28 (46.4%) had 5A4 3+ score, 12 (42.8%) 2 + , 3 were 0+. 3/28 (10.7%) had ALK1 3+ score, 9 (32.1%) 2 + , 13 (46.5%) 1 + , 3 were 0+. 25/28 (89.3%) were D5F3 positive. 2 of 3 FISH-positive and IHC-negative pts received CZT, both progressing within 2 weeks; both had low percentage of rearranged tumor cells at FISH (16-20%). When considering 3+ and 2+ scores as positive, 12 specimens (42.8%) were positive with all the 3 Abs (3 strongly positive). TS gene expression median value on 25 cases was 6.27 (range 2,8-14-94). 65% of cases had low expression as compared to a population of ALK-negative(ALK-) lung ADK (personal data).

Conclusions: IHC, especially with D5F3 and 5A4 Abs, proved to be a reliable tool to diagnose ALK+ lung tumors. As the two IHC negative and FISH positive patients didn't respond to CZT treatment, IHC should be used as screening tool or a confirmatory test in low-rearranged FISH-positive cases. TS expression was lower in ALK+ as compared to ALK- lung ADK. Comparisons between clinical and molecular data are ongoing.

H26 EGFR-related miRNAs as potential biomarkers of response to Erlotinib in metastatic NSCLC patients

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Background: Epidermal growth factor receptor (EGFR) plays an important role in the therapeutic management of non-small cell lung cancer (NSCLC) patients. Erlotinib is a

EGFR tyrosine-kinase inhibitor prescribed in 2nd- or 3rd-line treatment for locally advanced or metastatic NSCLC patients, that have failed at least one prior chemotherapy regimen, including EGFR wild-type patients. MicroRNAs (miRNAs), a class of small non-coding RNAs, have emerged as critical players in cancer pathogenesis and progression by modulating many pathological aspects related to tumor development, metastasization, and drug resistance.Aim of the present study was to determine whether specific EGFR-related miRNAs (miR-133b, -146a, -7 and -21) are involved in therapeutic response of NSCLC patients.

Materials and methods: The study was conducted in a cohort of 36 lung cancer patients who received erlotinib in 2nd- or 3rd-line.The patients with disease stabilization on erlotinib for at least 6 months were considered responders. We analyzed the expression levels of miR-133b, -146a, -7 and -21 in 8 responder and 25 non-responder patients. Total RNA was isolated from formalin-fixed paraffin embedded (FFPE) sample by High Pure miRNA Isolation Kit (Roche). The levels of miRNAs were quantified using TaqMan microRNA Assay (Applied Biosystem) and normalized over an internal control (miR-191). Statistical significance was calculated using the Mann-Whitney U test (two-tailed) and the level of significance was set at $p < 0.05$. Statistical computations were performed with GraphPad v6.0.

Results: Three miRNAs showed a significantly different expression between responder and non-responder patients.The expression levels of miR-7 in responders resulted significantly lower than in non-responders (Mann-Whitney, $p<0.05$); in contrast the expression levels of miR-133b and -146a in responders resulted significantly higher than in non-responders (Mann-Whitney respectively, $p<0.01$ and $p<0.05$). MiR-21 expression levels were not significantly different (Mann-Whitney, $p>0.05$).

Conclusions: Our results suggest that miR-7, -133b and -146a might be involved in the response to treatment with Erlotinib. Despite the relatively small sample size, these results are very promising and confirmatory in vitroand in vivostudies are ongoing.

H27 Retrospective analysis investigating the correlation between ki-67 expression, the EGFR mutational status and histotype in a Non Small Cell Lung Cancer patient cohort

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Background: Ki-67 is a nuclear antigen, expressed by proliferating cells so that it is commonly used to quantify the proliferation rate in several tumor types (breast, neuroendocrine, etc). There is uncertainty in the ki-67 expression role in NSCLC although from few retrospective data it seems to have a negative prognostic value. Nevertheless the absolute cut-off levels have not been defined before and no available data describe its pattern in EGFR wild-type or mutated NSCLC or any correlation with EGFR mutational status. This retrospective study aims at identifying the ki-67 expression levels in a NSCLC population first and then to describe the correlation with EGFR, KRAS and BRAF mutational status.

Material and methods: After obtaining ethical approval, the analysis was conducted on a patient population that treated at the University Hospital Santa Maria della Misericordia and that was not treated or followed-up in other institution before or after. Patients will be considered eligible if they had a hystological or cytological diagnosis of NSCLC, a confirmed clinical stage IIIB-IV (7th TNM edition) and adequate or sufficient archival formalin-fixed and paraffin embedded (FFPE) tumor tissue for ki-67 immunohistochemistry (IHC) analysis and EGFR, KRAS and BRAF mutational status determination. FFPE samples were analysed to determine the ki67 IHC expression profile and EGFR, KRAS and BRAF mutational status.

Results: From June 2012 until June 2014, 227 patients were screened for the analysis. Patients had a median age was 59 years, were mainly males (n = 179, 65%), ex-smoker (n = 130, 57.3%), had a diagnosis of adenocarcinoma (n = 185; 81.5%) and were stage IV at the time of diagnosis (n = 221; 88.5%). The analysis of ki-67, EGFR, KRAS and BRAF is still ongoing and data will be presented at the conference.

Conclusion: This study describes the ki-67 IHC expression in the different subtypes of NSCLC. Final results will be presented at the conference.

H28 ROS1 rearrangement in lung adenocarcinoma: a retrospective cohort study

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Background: ROS-1 gene rearrangement has been described in 1-2% of NSCLCs, targetable by ALK inhibitors due to highly similar tyrosine kinase domains. We retrospectively identified ROS1- positive tumors, to describe their clinical and pathological characteristics, and to compare stage IV ROS1-positive patients (ps) with stage IV pts with other defined genetical predefined subgroups, regarding survival (EGFR, EML4-ALK).

Methods: ROS1 status was evaluable in 39 out of 274 (14%) pts, whereof 11 pts (28%) had a ROS1 rearrangement. The amount of cells showing aberrant signals ranged between 23% and 80%, with high concordance between IHC and FISH. 9 pts were female and 2 pts male with a median age at diagnosis of 56 years (range, 40–70). The majority of pts, presented with stage IV disease (n = 10), mainly solid cribriform and acinar poorly differentiated adenocarcinomas . Out of the cohort, 1 (10%) patient presented with brain metastases at diagnosis, while 3 (27%) developed during treatment. 8 (73%) pts were never-smokers, 2 active smokers (median of 20 pack-years) and a former one. Notably only one patient presented with K-RAS gene concurrent mutation. All the patients received both pemetrexed and crizotinib therapy: 9 (82%) pts have been treated with the TKI in the II line setting, 2 (18%) after at least 4 line of chemotherapy.

Results: The whole cohort was evaluable for outcome analysis: 9 pts achieved a partial response (PR) to pemetrexed, whether upfront or in subsequent lines, 2 pts disease progression (PD); all of them responded impressively to crizotinib monotherapy So far only one patient died under TKI therapy, whereas the remaining ten are still ongoing under crizotinib treatment. 2 pts with brain metastases received the TKI upfront, attaining a remarkable PR. Progression free survival (PFS) to pemetrexed therapy was 7 months (mo) [SD 13.6]. ROS1-positive pts were further compared with 95 EGFR mutated stage IV pts and 47 pts with ALK rearrangement, both treated with TKI. Median [CI 95%] overall survival (OS) for ROS1, ALK, EGFR positive was: 46.9 months (mo) [8.91-74], 74.6 mo [not reached], 43.6 mo [36.4-74.4].**Conclusions**: These data suggest that ROS1 rearrangement is not only a predictive marker for response to Crizotinib but also a prognostic one, with an interesting overall response rate and PFS to chemotherapy in stage IV disease.

H29 Correlation between circulating tumor biomarkers and positron-emission tomography in advanced non-small cell lung cancer

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Background: Circulating tumor cells (CTCs) and plasma circulating-free DNA (cfDNA) are promising prognostic markers in malignancies. Little is known about the relationship among such parameters and 18-fluorodeoxyglucose positron emission tomography integrated with computed tomography (PET/CT) in non-small cell lung cancer (NSCLC).

Methods: Peripheral blood from 28 patients (pts) with advanced NSCLC was collected before starting first-line chemotherapy. CTCs were filtrated and isolated (ScreenCell); cfDNA was isolated from plasma (QIAamp DNA Blood Mini Kit, Qiagen) and quantified by qPCR using human telomerase reverse transcriptase (hTERT). All pts underwent PET/CT (Biograph 16 Siemens) at baseline. Maximum diameter (dmax) of the primary lesion (T), of the greater lymph nodal (N), and metastatic (M) lesions were measured. Maximum and mean standardized uptake value (SUVmax, SUVmean) and size-incorporated SUVmax (SIMaxSUV) were computed; SIMaxSUV was calculated as SUVMax*dmax. The association among CTCs, cfDNA and PET/CT was evaluated through multivariate analysis. Differences of CTCs and cfDNA in pts with or without metabolically active bone lesions (bone mets) were analyzed by T-test.

Results: Median age was 66 years (range: 51-80); male/female ratio was 18/10; 15 pts were current smokers, 11 were former-smokers, and 2 were never-smokers. Histo-types were: adenocarcinoma = 22; squamous cell carcinoma = 5; not otherwise specified NSCLC = 1. 9/28 pts had bone mets. Median CTC count was 7 CTCs/3ml (range: 0-47 CTCs/3ml), while median HTERT copy number was 109.0 (range: 16.7-1405-5).

Table: H29

	PET/CT	Mean	Standard Deviation	P
T	Size	44.93	20.25	0.175
	SUV max	10.16	4.48	0.036
	SUV mean	10.6	3.4	0.994
	SIMaxSuv	487.7	333.5	0.472
N	Size	22.2	10.9	0.313
	SUV max	7.4	4.0	0.318
	SUV mean	5.8	3.0	0.294
	SIMaxSuv	172.8	158.1	0.231
M	Size	23.9	15.0	0.083
	SUV max	7.5	4.1	0.318
	SUV mean	7.4	1.2	0.307
	SIMaxSuv	216.4	206.5	0.463

At multivariate analysis, SUVmax of T was the only variable independently associated with cfDNA ($p = 0.036$). No correlations were highlighted between CTCs and any PET-derived parameter. A trend towards significance between high HTERT and the presence of bone mets was observed ($p = 0.058$).

Conclusions: The expression of cfDNA is apparently correlated with the metabolic activity of T. Since SIMaxSUV was not correlated with HTERT, the expression of cfDNA might depend from tumor metabolism rather than its size.

H30 Somatostatin Analogs as mainteinance therapy in heavily pretreated thymic epithelial tumors

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Background: Thymic epithelial tumors are rare neoplasms with a particular biological behavior, treated with a combination of therapeutic strategies such as surgery, chemotherapy, radiotherapy and target agents. No continuation maintenance therapy exists for these rare tumors. An high uptake of indium-labeled octreotide (111In-DTPA-D-Phe1-octreotide) and curative application of somatostatin analogs in thymic tumors have been widely demonstrated.

Material and methods: Eighteen patients (nine women and nine men, median age 54.5 years; range 32-78) with advanced thymic tumors (seven patients with stage III; seven with IVa; Four with IVb according to the Masaoka-Koga staging system), histotype sec WHO revised by central review (three AB, two B1, three B2, five B3, three B2/B3, two thmyc carcinoma) with a partial response or stable disease to conventional chemotherapeutic regimens platinum or not platinum-based, after performed OctreoScan, were enrolled in this monocentric referral center study. The schedule includes administration of long-acting analog octreotide (30 mg/every 28 days intramuscularly), until progression of disease was documented. Median time to progression and toxicity were evaluated.

Results: Median follow-up was of 43 months with a median time to progression of 14,5 months (range 77-2). Treatment was generally well tolerated with acceptable toxicity: Grade 1 diarrhea (5 patients), Grade 2 hyperglycemia (4 patients). No patients interrupted treatment because of toxicity.

Conclusions: The current study indicates that single-agent somatostatin analogs maintenance therapy is a potential treatment strategy for advanced TETs OctreoScan positive which respond to previous conventional chemotherapy. In particular, somatostatin analogs may provide an effective maintenance treatment duration regardless of histotype and stage of disease with an acceptable toxicity and an improved patients'compliance.

H31 KRAS and Ki-67 in Non Small Cell Lung Cancer

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Background: In non-small cell lung cancer (NSCLC) prognostic/predictive role of KRAS mutations is continuously debated. Potential association with levels of Ki-67 expression and different behavior of subtypes of KRAS mutations have been hypothesized.

Patients and Methods: We retrospectively analyzed consecutive patients (pts) with advanced NSCLC treated with a platinum-based chemotherapy at the Department of Oncology of Udine. Ki-67 has been assessed by immunohistochemistry and reported as Ki-67 average (Kia), Ki-67 hotspot (Kih) and Ki-67 heterogeneity values (I^2 Index). KRAS/EGFR mutational status and ALK rearrangement have been evaluated by Agena MassARRAY® Platform and fluorescent in situ hybridization, respectively. Univariate analysis was performed by Cox model for progression-free survival (PFS) and overall survival (OS) and by logistic regression for disease control rate (DCR). Survival curves were calculated with Kaplan-Meier method.

Results: From June 2012 to June 2014, 85 out of 227 screened pts have been analyzed: 48 were KRAS/EGFR wild-type/no ALK-rearranged (Rwt) whereas 37 were KRAS mutated/EGFR wt/no ALK-rearranged (Rmut). KRAS mutations occurred in 43% of pts and G12C (15 pts, 41%), G12V (7 pts, 19%) and G13C/D (6 pts, 16%) were the most frequent. Median value of Kia and Kih was 46% and 64% in Rwt and 41% and 55% in Rmut group. Pts in Rwt obtained 74.5% of DCR compared to 55.6% in Rmut (OR 2.43, 95%CI 0.93-5.88, p = 0.07); median PFS was 4.9 and 4.5 months (HR 0.88, 95%CI 0.55-1.39, p = 0.58) while OS was 11.3 and 8.0 months (HR 1.01, 95%CI 0.62-1.64, p = 0.96), in Rwt and Rmut, respectively. KRAS G13C/D mutations had a worse prognosis compared to wt group and G12V mutations for PFS (HR 0.28, 95%CI 0.08-0.96, p = 0.04 for wt and HR 0.13, 95%CI 0.03-0.59, p < 0.01 for G12V) and OS (HR 0.24, 95%CI 0.06-0.98, p = 0.05 for wt and HR 0.16,95%CI 0.03-0.81, p = 0.03). No interaction was detected among KRAS status, Kia or Kih (data not shown). Ninety-five percent of pts had an I^2 greater than 69.5%; DCR, PFS and OS improved increasing I2 value. (Table 1).

Conclusions: The study did not show any statistical interaction between all KRAS mutant pts and Ki-67 expression. Larger and better controlled studies are needed to confirm the absence of interaction, and verify prognostic role of KRAS mutation subtypes and I2 in NSCLC pts.

Table: H31 . I^2 and patients outcomes.

DCR			
	OR	95%IC	P
I^2*	1.46	0.98-2.16	0.061
PFS			
	HR	95%IC	P
I^2*	0.84	0.72-0.97	0.017
OS			
	HR	95%IC	P
I^2*	0.83	0.71-0.96	0.014

*OR and HR estimate for each 10% increase of I^2 index.

H32 In vitro and in vivo antitumor efficacy of the sequentially combined vinorelbine and gefitinib in Non-Small Cell Lung Cancer cell lines

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Introduction: The current standard of care for advanced NSCLC relies on systemic chemotherapy or epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) for patients with tumors harboring EGFR mutations. Preclinical studies suggest that the combination of chemotherapy and EGFR-TKI may increase the cytotoxic effect albeit influenced by the type of drug and the sequence of treatment. The aim of this study was to investigate *in vitro* and *in vivo* the antitumor efficacy of different combinations of gefitinib (GEF) and vinorelbine (VNB) in specific NSCLC cell-lines known to be poorly responsive to EGFR-TKIs, as a rationale to be potentially exploited in the clinical setting.

Material and method: *EGFR* wild-type A-549 and mutated H-1975 (exon 21 L858R/ exon 20 T790M) cell lines were used to evaluate the antiproliferative effects of three different treatment schedules: GEF followed by VNB, VNB followed by GEF and the two drugs given individually or concurrently (short-term). In addition, the efficacy of repeated weekly VNB doses along with sequential or continuous GEF administration for 21 days was assessed (long-term). Expression of EGFR and its downstream effectors AKT and ERK1/2 were investigated by western blot. The *in vivo* effects of single or combined treatments were studied using a xenografted nude mouse model (NCI-H1975). Cancer growth was evaluated by measurements of tumor diameters with a Vernier caliper every other day, while lesion glucose consumption was estimated by means of a dynamic micro-PET scans.

Results: *In vitro* short and long-term experiments demonstrated that the sequence of VNB followed by GEF was significantly more active in inhibiting the cell growth than GEF followed by VNB or the concurrent administration of the two drugs, especially in the *EGFR*-mutated H1975. Western blot indicated that the increased cytotoxic effect of the VNB and GEF sequence was accompanied by inhibition of p-EGFR, p-AKT and p-ERK1/2 expression levels, mainly in the H1975 cells. Moreover, the increased antitumor efficacy of the sequence VNB followed by GEF was also confirmed *in vivo* by a significant inhibition of the H1975 tumor growth (p < 0.0001) that was paralleled by a corresponding decrease in cancer glucose consumption (p < 0.05).

Conclusion: Our findings show that the sequential treatment with VNB followed by GEF might lead to a significant antitumor effect, advising clinical studies involving TKI-resistant NSCLC patients.

H33 Venous thromboembolic events in advanced adenocarcinoma of the lung: impact on prognosis according to platinum therapies and presence of driver mutations

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Background: The association of venous thromboembolic events (VTE) and lung cancer has a high prevalence. Limited data are available in the adenocarcinoma subtype population especially in relation to platinum based therapy and presence of driver mutations. We evaluated these aspects in our retrospective series.

Methods: We evaluated data of patients treated for advanced adenocarcinoma from January 2003 to July 2014 in our Institution. We conducted a subgroup analysis according to EGFR, KRAS and BRAF status defined by MassArray (Sequonom). Presence of EML4-ALK translocation was evaluated by FISH. Overall Survival (OS) and 95% Confidence Interval (95% CI) was estimated by Kaplan-Meier method and compared by logrank test.

Results: Among 289 evaluable patients, 62 (21.5%) experienced VTE. Median OS was 17 months (14.6-22.3): OS in VTE patients was 14.5 months (10.8-17.1) while in non VTE patients was 21.6 months (15.3-27.1) (p = 0.036). Forty-three (21%) of the 202 patients who received chemotherapy containing platinum in any line of treatment (188 in first line) developed TVE; a similar percentage of VTE was seen in those patients who never received platinum compounds. Among VTE patients, 45 (72.6%) didn't show driver mutations (p = 0.408). In the group of patients with driver mutations, 12 of 49 (24.5%) with EGFR mutation (p = 0.706) had VTE. Only 131 patients were evaluated for KRAS status: 50 presented KRAS mutation of which only 3 (6%) had VTE; occurrence of VTE was significantly higher in KRAS wild type patients (p = 0.032). Of 110 patients evaluated for EML4-ALK status only 2 of 6 (33%) with translocation had VTE (p = 0.276). No VTE were seen in 5 BRAF mutated patients.

Conclusions: Occurrence of VTE in lung adenocarcinoma in our series was higher than that reported in historical control of literature and is related with worsening of prognosis. No clear statistically significant relationship was seen between VTE and platinum based chemotherapy or presence of driver mutations. In particular the KRAS mutation seems to be not related with VTE. Prospective data in larger population are needed to confirm these findings.

H34 KRAS has a role in acquired resistance to EGFR-TKIs in NSCLC: an analysis on circulating tumor DNA

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Background: Activating mutations of *KRAS* oncogene drive resistance to EGFR inhibition by providing an alternative signal transduction pathway [1]. In non-small cell lung cancer (NSCLC), the efficacy of treatment with EGFR tyrosine kinase inhibitors (EGFR-TKIs) depends on activating *EGFR* mutations that are mutually exclusive with *KRAS* mutations. However, pharmacological inhibition of *EGFR* signaling has the potential to select cells whose growth may depend, at least in part, on alternative proliferation pathways or continued EGFR signaling due to the c.2369C > T (p.T790M) gatekeeper mutation within the ATP-binding pocket of EGFR. NSCLC heterogeneity can drive the therapeutic decisions; therefore, tissue availability is increasingly recognized as a crucial issue [2]. Unfortunately, the location of the tumor and the risk of complications are serious limitations to re-biopsies in NSCLC. Alternatively, the detection of somatic mutations in cell-free tumor DNA (cftDNA) released in plasma could be instrumental for a better understanding of the genetic modifications driven by the selective pressure of drug treatments on NSCLC [3].

Material and methods: This study used cell-free circulating tumor DNA (cftDNA) to evaluate the appearance of codon 12 *KRAS* and p.T790M *EGFR* mutations in 33 advanced NSCLC patients that progressed after an EGFR-TKI. Six ml of blood samples were drawn from patients at disease progression and cftDNA was extracted by Circulating Nucleic Acid extraction kit (Qiagen) and analysed by digital droplet PCR (BioRad).

Results: *KRAS* mutation at codon 12 alone or in combination with p.T790M was demonstrated in 3 (9.1%) and 13 patients (39.4%), respectively. p.T790M was detected in 11 subjects (33.3%) alone and in 13 patients (39.4%) with mutant KRAS. Six patients (18.2%) were negative for both *KRAS* and p.T790M. In 8 subjects paired tumor re-biopsy/plasma samples were available; the percent concordance of tissue/plasma was 62,5% for p.T790M and 37,5% for *KRAS*.

Conclusions: In conclusion, mutation of *KRAS* could be an additional mechanism of escape to EGFR-TKI and cftDNA is a feasible approach to monitor the molecular development of drug resistance. Therefore, the clinical relevance of this finding, expecially for what concerns ^{mut}*KRAS*, needs to be evaluated prospectively.

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H35 Predictive and prognostic value of early pet evaluation on disease progression of advanced non-small cell lung cancer

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Background: To evaluate the reliability of early PET prediction of disease progression after only the first cycle of chemotherapy by assessing the predictive and prognostic value of progressive metabolic disease (PMD), in patients with advanced non-small cell lung cancer (NSCLC) treated with standard doublet platinum-based chemotherapy.

Patients and methods: Patients with clinical stage IV chemotherapy-naive NSCLC were treated with a doublet platinum-based chemotherapy. A pre-treatment 18Fluoro-deoxy-glucose-positron emission tomography (PET) was performed before chemotherapy start (PET-0), and following the first cycle (PET-1). A pre-treatment CT scan was done before chemotherapy (CT-0), and following the administration of the third cycle (CT-3).PET-1 scans were compared with PET-0 scans, according to European Organization for Research and Treatment of Cancer (EORTC) and PET Response Criteria In Solid Tumors (PERCIST) classification criteria. CT-3 scans were compared with CT-0 scans (CT-3 versus CT-0), according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. The primary endpoint of this study was the positive predictive value (PPV) of PMD. Secondary endpoints included the prognostic value of PMD by PET-1.

Results: Among all 38 patients, 11 patients (29%) were in PMD by PET-1 and 15 (39%) in progressive disease (PD) by CT-3. The PMD by PET-1 was associated with a PPV of 100% (p-value =< 0.0001), according to the EORTC and PERCIST criteria (see Table). The median OS of patients with a PMD identified by PET-1 was 7.0 months versus 14.0 months of those without PMD, according to EORTC and PERCIST criteria (p = 0.04 and p = 0.09, respectively).

Conclusions: Early PET assessment may be a reliable tool for the identification of NSCLC patients whose disease does not benefit from chemotherapy.

Table: H35 . Diagnostic accuracy of early PET (PET-1) evaluation

EORTC	p-value (Fisher Test)	Spec. %	Sens. %	PPV %	NPV %
PMR vs SMD + PMD	0,68	83,3	23,1	**42,9**	66,7
PMD vs SMD + PMR	<0,0001	100	64,7	**100**	76,9
PERCIST					
PMR vs SMD + PMD	1,0	87,5	23,1	**50,3**	67,7
PMD vs SMD + PMR	<0,0001	100	58,8	**100**	74,1

EORTC, European Organization for Research and Treatment of Cancer; NPV, negative predictive value; PERCIST, PET Response Criteria In Solid Tumors; PMD, progressive metabolic disease; PMR, partial metabolic response PPV, positive predictive value; SD, stable disease; Sens, sensibility; SMD, stable metabolic disease; Spec, specificity.

H36 Mutations in main candidate genes (egfr, kras, braf) among patients with non-small-cell lung cancer from sardinia

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Background: Assessment of the mutational status in EGFR, KRAS, BRAF has become crucial in recent years for the molecular classification of patients with non small cell lung cancer (NSCLC). In this population-based study, we evaluated the incidence rates and distribution of such somatic mutations among NSCLC patients in genetically isolated population from Sardinia.

Material and methods: From July 2010, a total of 1,047 formalin-fixed paraffin-embedded tumor tissues from patients with NSCLC and ascertained Sardinian origin was prospectively collected at clinics across the entire island. Genomic DNA was isolated from tissue sections and screened for somatic mutations in EGFR, KRAS, and BRAF genes by automated DNA sequencing.

Results: Overall, 112 (10.7%) analyzed patients carried an EGFR mutation. Somatic mutations in EGFR gene were quite equally distributed between exon 19 (57/112; 51%) and exon 21 (52/112; 46%), with few mutations (3/112; 3%) in exon 18 of EGFR. No significant difference in distribution of EGFR mutations according to the age at diagnosis was observed [EGFR mutant: median age, 67 (range, 37-85); EGFR wild-type: median age, 65 (range, 35-89)]. Females presented a significantly higher frequency of EGFR mutations in comparison to males (23.6% vs. 5.7%, respectively] ($p = 0.003$). According to the smoking history, a significant preponderance of EGFR mutations were observed in never smokers (43.2%) as compared to former smokers (5.8%) and smokers (3.6%) ($p < 0.001$). Among 634 patients whose somatic DNA was available for further analyses [71 (11.2%) cases carried EGFR mutations], we detected 138 cases (21.8%) with KRAS mutations and 3 (0.5%) with BRAF mutation (V600E). KRAS and BRAF mutations were significantly more prevalent in males than females (22.4% vs. 10.3%, respectively; $p = 0.012$) as well as in smokers (31.8%) than in former smokers (17.6%) or never smokers (4.5%) ($p = 0.023$). In this series, no concomitant mutations in EGFR, KRAS, and BRAF genes were detected. Therefore, two thirds (422/634; 66.6%) of such patients lacked somatic mutations in all three analyzed genes.

Conclusions: Although the prevalence of mutations in the three main candidate gens among NSCLC patients from Sardinia was consistent with that reported in literature for Western populations, their distribution varied into the different clinical subgroups.

H37 Hot-spot Ki67 labeling index correlates with lymph-node status and prognosis in lung adenocarcinoma

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Background: Surgery is the treatment of choice in early stage NSCLC and lymph nodes status is the main prognostic factor. Aim of our study was the evaluation of cancer proliferation in resected lung adenocarcinoma (AD) using Ki67 labeling index and evaluation of Ki67 as a biomarker of lymph-node involvement and prognosis.

Material and methods: Patients that consecutively underwent surgery between 2004 and 2010 for pulmonary AD were included in the analysis. Exclusion criteria were palliative surgery or induction therapy. Records were available for all cases and included patient characteristics, tumor data and follow up informations. To evaluate intra-tumor heterogeneity of cell proliferation, five different tumor spots for each AD case were retrieved in donor blocks so that tumor periphery and central areas were represented in a tissue microarray platform (TMA). Tumor proliferation was then assessed in all TMAs by Ki67 staining using immunohistochemistry. The percentage of Ki67-immunoreactive tumor cells out of the total number of tumor cells (Ki67 labeling index) was scored for each core. Hot-spot Ki67 value was defined as the highest Ki67 value per case. Statistical analyses were performed using MedCalc sotware and p value less than 0.05 was considered statistically significant.

Results: In the 256 enrolled patients, we observed a heterogeneous Ki67 labeling index between central and peripheral areas. The hot-spot Ki67 value was correlated with overall survival ($p = 0.02$, HR = 1.01, 95%CI: 1-1.02), in the univariate analysis. Conversely the average Ki67 labelling index for each tumor was not associated to patients overall survival ($p = 0.1$, HR = 1, 95%CI: 0.9-1.02). The hot-spot Ki67 index lost its prognostic value in multivariate analysis. Ki67 was strongly associated to lymph-node metastases, tumor grade and smoking habit ($p = 0.01$, $p < 0.0001$, and $p = 0.0003$ respectively).

Conclusions: Heterogeneity in Ki67 staining reflects the histological and biological nature of AD that usually includes areas with different proliferation patterns, such as papillary, acinary, or solid type. Our study demonstrates that hot-spot Ki67 value correlates with overall survival in lung AD patients. If validated in independent cohorts, this result could be considered for follow up and adjuvant planning. Due to the strong association between Ki67 and nodal metastases, possible preoperative Ki67 detection could affect surgical lymphadenectomy strategy (sampling vs radical vs lobar specific).

H38 Prospective molecular profiling of lung cancer patients derived xenografts

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Background: The identification of "oncogenic drivers" and predictive factors both became a major research priority in thoracic oncology. A remarkable improvement in the outcomes of lung adenocarcinoma has been gained with EGFR or ALK directed targeted agents; for all other NSCLC cases the *"one-fits-all"* approach is the current standard of care. Most preclinical data are based on *in vitro* studies, but cell lines models do not entirely reflect tumour complexity and are hampered by genetic divergence. Patient derived tumour xenografts (PDTX) are a valuable tool to reproduce tumour biology and to characterize *in vivo* mechanisms of cancer growth and drug response. The project aims to confirm the reliability of such models in lung cancer and to prospectively characterize its biomolecular features.

Materials and methods: Metastatic and early stages lung cancer cases are considered for the enrolment. Written informed consent is requested from each patient. Fresh tumour tissue from lung biopsies or resections is collected and kept in serum free medium (4° C), embedded in 20% matrigel and subcutaneously engrafted into NSG and NOD SCID mice, within 24 hours from sample collection. Exponentially growing tumours are passaged subcutaneously to other mice for a second passage after which they are archived for subsequent analyses (formalin fixed, snap frozen and RNA later). Each sample from surgical resection is also stored to create a DNA lung cancer bank.

Results: Fourteen samples from TC-guided lung biopsies and 66 from radically resected NSCLC were engrafted in NSG and NOD SCID mice lineage, in a 1:1 ratio. Due to the low engraftment rate and high morbidity observed in NGS mice in the first 73 samples, subsequent engraftments and expansions were performed in NOD SCID mice only. The engraftment rate in biopsy samples was 0 % in NGS and 7.14 % in NOD SCID mice, as opposed to 0 % in NGS and 27,27 % in NOD SCID for surgical samples (50% adenocarcinomas, 44,45% squamous carcinomas and 5,55% sarcomatoid carcinomas). Nineteen samples underwent the second passage: of those, 10 samples have been archived after the second successful passage and will be used for further analyses.

Conclusions: The trial is still ongoing and a longer follow-up is needed. In biopsy-derived samples, engraftment is deeply limited by the paucity of tissue. This study will possibly confirm the reliability of PDTX in lung cancer and provide prospective biomolecular characterization for different histological types.

H39 Genetic polymorphism can help physician choosing the best lung cancer chemotherapy

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Background: Lung cancer is one of the most frequent malignancy with high mortality rate. Non small cell lung cancer (NSCLC) is the most common histological type, representing approximately the 85% of all lung cancers. Platinum-based chemotherapy

is the standard of care in the first line treatment for patients with advanced or metastatic NSCLC not carrying a driver mutation. Despite the recent advances, the overall survival (OS) of patients receiving chemotherapy remains exiguous, of approximately 8-10 months, with an high rate of toxicities. The new direction in personalization of care is to guarantee the best treatment, both in terms of outcome, and toxicities control. Therefore, the aim of our study is to identify some markers associated with toxicity, through the analysis of genetic polymorphisms involved in drugs metabolism.

Material and methods: We studied 41 chemo-naïve adult patients, with ECOG Performance Status 0-2, affected by NSCLC of all stages, underwent treatment with platinum-doublets, planned for at least 3 cycles. Through a peripheral venous blood sampling we genotyped them for selected polymorphisms using real-time PCR. We characterized Single Nucleotide Polymorphisms (SNPs) involved in detoxification (GSTP1), DNA repair (XRCC1, ERCC1), metabolism of anticancer agents (CYP3A4, CYP3A5, TSER, MTHFR, CYP2C9, CYP1A2, CYP2D6, UGT1A1) and in trans-membrane transport (ABCB1). The statistical analysis was conducted by MINITAB 16.2.3 software. A value of $p < 0.05$ was considered statistically significant.

Results: Toxicities and polymorphisms were prospectively evaluated in 41 patients (33 males and 8 females). Median age of patients was 66,6 (range 33-82). The statistical analysis showed a trend of greater toxicity in patients with polymorphisms leading to reduced metabolism, transport and DNA repair activity. Patient with lower detoxification capacity (homozygous genotype for GSTP1 A313G) showed a greater number of dose-limiting toxicity events ($p = 0.17$).

Conclusions: In this study we indentified an association with genetic polymorphisms and toxicities in NSCLC patients treated with platinum doublets. A larger cohort of patients must be investigated, in order to better understand the role of polymorphisms and to identify a signatures differentiating patients at higher or lower risk of toxicities and relative efficacy of platinum-based chemotherapy.

H40 Bone metastases (BMs) in patients with advanced non-small cell lung cancer (NSCLC): do they always correlate with poor prognosis?

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Background: The outcome of patients with metastatic non-small cell lung cancer (NSCLC) has improved in recent years. However, bone still represents an unfavorable site of metastasis for these patients. Aim of this study was to investigate for the presence of existing prognostic factors in patients with bone metastases (BMs) from NSCLC.

Material and methods: Data of patients with NSCLC were retrospectively collected. Survival estimates were quantified using Kaplan Meier curves, and comparisons were made using the log-rank test. Age (= 70y vs < 70y), gender, histology, Eastern Cooperative Oncology Group-Performance Status (ECOG-PS), smoking history and presence of BMs were included in the Cox analysis to investigate their prognostic relevance.

Results: Of 421 patients enrolled in this analysis, 288 (68%) were male and the median age was 68 y (23-86y). One hundred and eighty eight patients (45%) presented BMs, synchronous in 130 (69%) patients and metachronous in 58 (31%). Lung (66%), lymph nodes (53%), liver (30%), brain (27%) and adrenal glands (24%) were the most common concomitant metastases. Median overall survival (OS) was 19 months for patients without BMs, 11.7 months for patients with synchronous BMs and 12.3 months for patients with metachronous BMs ($p = 0.013$). Median progression free survival (PFS) was 6.2 months for patients without BMs, 4.7 months for patients with synchronous BMs and 5.4 months for patients with metachronous BMs ($p = 0.020$). At multivariate analysis in the overall study population, ECOG-PS = 2, non-adenocarcinoma histology and the presence of BMs were independent prognostic factors for worst OS. Independent prognostic factors for worst OS for patients with BMs were smoking history, IV tumor stage and metastases to liver or adrenal gland. A trend of worse OS was observed in hyponatremic patients with BMs even if the difference between hyponatremic and eunatremic patients was not statistically different (OS = 11.4 vs 12.3 months, $p = 0.220$). Furthermore hyponatremia was associated with a worse PFS (eunatremic patients = 5.36 vs 3.19 months in hyponatremic subjects, $p = 0.008$) in patients with BMs treated with first line therapy. No association was found between hyponatremia and the risk of BMs presentation ($p = 0.371$) or bone events ($p = 0.542$).

Conclusions: Our study suggests that smoking history and site of metastases should be necessary considered in order to optimize the management of NSCLC patients with BMs.

H41 Clinical features and systemic treatment outcome of diabetic versus non-diabetic non small-cell lung cancer patients

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Background: Diabetes (DM) and antidiabetic treatment (ADT) can influence non small-cell lung cancer (NSCLC) outcome.

Aim of the study: To compare clinical features and response rate (RR) to first-line systemic therapy of diabetic vs non diabetic NSCLC patients; secondary endpoint: to compare progression free survival (PFS) and overall survival (OS); exploratory endpoints: to investigate RR, PFS and OS in diabetic NSCLC patients according to ADT.

Patients and methods: Retrospective study on stage III-IV NSCLC patients with measurable disease evaluated for first-line systemic treatment between January 2010 and December 2013 at our Institution.

Results: 542 patients were included. Eighty-seven (16%) were diabetics: they were older, most frequently male and smokers, with worse ECOG performance status (PS) and more comorbidities; single agent chemotherapy was most frequently administered than in non-diabetics. Three-hundred eighty-seven patients were evaluable for RR assessment (61 diabetics, 16%). Median follow-up was 28.5 months. In diabetics we observed a trend toward a lower RR (26%) and a shorter PFS (4.8 months; 95%CI: 4.2–7.2 months) compared with non-diabetics (RR = 39%; $\chi 2 = 3.047$; $p = .0809$ and PFS = 6.7 months; 95%CI 6.3–7.6 months; $p = 0.0548$) with no difference in OS. Among diabetics, no significant difference in RR was found according to ADT; a trend toward a shorter PFS in patients treated with only insulin was observed (median 4,2 months; 95%CI 3,7 - 6,1 months vs 5,8 months; 95%CI 4,4 - 8,3 months; $p = 0.066$); this trend disappeared when insulin-dependent and insulin-metformin treated patients were considered together and compared with diabetics treated with other ADT. Multivariate analyses confirmed the correlation between PFS and DM, definitive locoregional treatment, epidermal growth factor receptor (EGFR)-inhibitor therapy and between OS and PS, definitive locoregional treatment, EGFR – inhibitor therapy and >1 further lines of therapy at progression.

Conclusions: A trend toward a lower RR and a shorter PFS in diabetics vs non diabetics and, in diabetics, a trend toward a shorter PFS in insulin-dependent diabetic NSCLC patients could be explained as a result of a long-term diabetes with prolonged exposure to cancer promoting events; metformin could mitigate a possible DM worse prognosis. Prospective studies are needed to confirm the prognostic role of DM and ADT in NSCLC, in particular in patients receiving metformin.

H42 Assessment of clinical outcomes and prognostic factors in patients (pts) with non-small cell lung carcinoma (NSCLC) and brain metastases (BM). Results from a single institution study

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Background: BM development, which is frequently observed in pts with NSCLC, is usually associated with a poor outcome. Systemic treatments and whole brain radiotherapy (WBRT) are widely used but increasingly, more aggressive local treatments such as surgery (S) or stereotactic radiotherapy (SRT) are being employed in selected cases. The present study is aimed to assess the factors affecting outcomes in NSCLC patients with BM.

Materials and methods: We retrospectively reviewed the clinical records of pts with NSCLC and BM consecutively treated in our Institution from October 2000 to December 2010. For each pt we recorded the clinical history and outcomes and collected the pt's, disease and treatment-related prognostic factors. Variables were examined in univariate and multivariate analysis.

Results: We collected data of 82 pts (87% male, 13% female) with a median age of 65 yrs (range 40-85). The histotype was squamous in 24%, non squamous in 54%, and NOS in 22% of the case, respectively. BM were diagnosed at the time of the diagnosis or thereafter in 63 % and in 37% of the cases, respectively. BM were managed by local treatments in 84 % of the cases (S 9 pts, WBRT 66 pts, SRT 4), with 17 pts receiving multiple local treatments. Chemotherapy after BM diagnosis was administered in 36 pts (44%), while a TKi was administered in 3 pts (4%). Median overall survival (OS) after BM diagnosis was 6 mos. The OS by variables which resulted statistically significant at Cox proportional hazards analysis.

Table: H42

			Univariate analysis			Multivariate analysis		
Variable	Value	Median OS	HR	95% CI	P value	HR	95% CI	P value
ECOG	0-1	8	0.322	0.176-0.588	0.0001			
	≥2	4						
Sincronous	No	14	0.402	0.192-0.845	0.016	0.254	0.102-0.634	0.03
	Yes	4						
Neurological symptoms	No	9	0.591	0.375-0.930	0.023			
	Yes	4						
BM number	1	8	0.534	0.297-0.963	0.032			
	> 1	5						
Bilaterality	No	8	0.586	0.356-0.964	0.035			
	Yes	4						
S or SRT	No	5	5.465	2.286-13.066	0.0001	5.468	1.469-20.358	0.011
	Yes	28						
Chemo post BM diagnosis	No	4	1.815	1.151-2.863	0.010	5.200	2.207-12.250	0.0001
	Yes	10						

Conclusions: From our preliminary results it appears that BM development after primary tumour diagnosis and the possibility to perform radical local treatments as well as chemotherapy after BM diagnosis are favourable prognostic factors in NSCLC patients with BM.

H43 ATREUS Trial: A Phase II Study On The Activity Of Trabectedin In Pretreated Epithelioid Or Biphasic/Sarcomatoid Malignant Pleural Mesothelioma (MPM)

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Background: Treatment options for patients (pts) with relapsing MPM are scarce. Moreover, the sarcomatoid and biphasic histotypes are generally resistant to treatment and outcome is poor. A viable regimen for 1st and 2nd line treatments is an unmet medical need. Trabectedin (T) is a natural marine compound that binds to the minor groove of DNA. It acts both directly on cancer cells and on tumor microenvironment, reducing the production of cytokines and chemokines and the number of tumor-associated macrophages. These features suggest a therapeutic potential for inflammation-related tumors, such as MPM. This study evaluates the activity and safety of T in pts with MPM.

Methods: ATREUS is an Italian multicenter single arm phase II not for profit trial of T as 2nd line treatment in pts with epithelioid MPM and as 1st or 2nd line in sarco/biphasic pts. The study aims to assess T's activity (in terms of progression free survival at 12 weeks (12w-PFS)) and its safety. The effect on several biological features of MPM, including miR profile, HMGB1 levels and monocyte/macrophage number and function, and on cancer related pain are also evaluated. Eligible pts receive T (1.3 mg/m^2 over 3 hours) every 21 days until progression or unacceptable toxicity. Treatment response is evaluated every 6 weeks using the Modified RECIST for MPM. Simon's optimal two-stage design was used for the epithelioid cohort. The first stage foresaw enrolment of 24 pts, and accrual extension in case of >6 responses. In the second stage, 12w-PFS should be observed in >19 of 62 pts to reject, with a one-sided alpha error of 10%, the null hypothesis that 12w-PFS is ≤25% and an 85% power to show a 12w-PFS of ≥40%. In the sarcomatoid/biphasic cohort, adopting the Fleming design with A'Hern's approach, >5 of 17 pts should report PFS ≥12w to reject, with a one-sided alpha error of 10%, the null hypothesis that 12w-PFS is ≤15% and to have 85% power to show 12w-PFS in ≥40% pts. To date, 64 patients were enrolled (41 epithelioid and 23 sarco/biphasic). Analysis of the first 24 epithelioid pts confirmed achievement of the first stage activity goal and enrolment continues. The sarcomatoid/biphasic cohort has completed accrual. ClinicalTrials.gov Identifier: NCT02194231).

H44 Epidermal Growth Factor Receptor mutational status predicts patterns of metastatic spread in treatment-naïve Adenocarcinomas of the lung

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Background: Oncogene addicted tumors, such as Epidermal Growth Factor Receptor (EGFR)-mutated Non Small Cell Lung Cancers (NSCLCs), may present peculiar patterns of metastatization compared with *wild type* tumors. Indeed, patients (pts) harboring EGFR activating mutations have been reported being associated with increased risk of developing brain metastases (BMs) during the course of their disease, as well as bone metastases. Moreover, the specific type of EGFR mutation may be associated with peculiar clinic-pathological features. The purpose of our study was to evaluate the impact of biomolecular factors at first clinical presentation in a cohort of lung adenocarcinoma (ADC).

Methods: Medical record of a total of 104 consecutive pts (60 M/44 F) with stage IV ADC and an EGFR mutation (25.9%), or *wild-type* (74.1%), treated at our institution from January 2012 to January 2015, were included. The incidence rates of metastatic spread at a given site between EGFR mutated and *wild type* were evaluated. Descriptive analysis was performed on these molecularly defined groups and associated clinical data.

Results: 37% of pts with EGFR activating mutations had bone metastases and 44% lung metastases. Moreover, BMs were reported in 18%. Lung metastases were more common among pts harboring exon 19 deletions (10/12 pts). In the subgroups of EGFR *wild type* pts, BMs were present in 15%, while bone and lung metastases in 17% and 22% of pts, respectively. The difference between the incidence of metastases in the different sites according to EGFR mutational status was not statistically significant. An interesting trend toward significance was observed in the incidence of lung metastases in EGFR mutated pts (p = 0.1).

Conclusion: Our results confirm the differential metastatic spread between EGFR mutated and *wild type* lung ADCs, suggesting that biomolecular characteristics rather than histology govern the metastatic process in lung carcinogenesis.

H45 Clinical applications of a next-generation sequencing panel in non-small cell lung cancer

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Introduction: Molecular markers have become important predictors of response to targeted therapies in non-small cell lung cancer (NSCLC), and Next-Generation Sequencing (NGS) has recently emerged as a cost-effective method able to provide more comprehensive genomic information with potential repercussions in clinical practice. The aim of this study was to identify potential actionable mutations in advanced NSCLC. Here we report the findings obtained for an initial group of patients screened in our Lung Cancer Unit.

Patients and methods: Twenty patients with advanced lung adenocarcinoma were evaluated. DNA was extracted from 4 cytological samples and 16 FFPE biopsies from primary or metastatic lesions. The specimens were analyzed for 22 cancer-associated genes using the Ion AmpliSeq Colon and Lung Cancer Panel *v.*1 (Life Technologies) and sequenced through Ion Torrent PGM™ (Life Technologies). Data were analyzed with the Ion Torrent Software Suite v.4.4 (Life Technologies) using the plugin Variant Caller (VC) *v.*4.4.2.1.

Results: Patients' characteristics: median age 65 (42-81); 30% males, 70% females; never smoker 60%, former smoker/smoker 40%. Data analysis reported an average of one genetic variant per patient annotated in the Catalogue of Somatic Mutation in Cancer (COSMIC database) (range 0-5). Twenty-one mutations were diagnosed in 12 patients (55%) in the following genes: *EGFR* (4), *KRAS* (1), *MET* (4), *TP53* (8), *NRAS* (1), *BRAF* (1), and *PI3KCA* (2). In addition to the known mutations in *EGFR*, we found a *BRAF* mutation resulting in an amino-acid substitution (K601E) potentially sensitive to BRAF or MEK inhibitors on the basis of preclinical studies on BRAF downstream signaling.. A potentially druggable mutation was found in *NRAS* gene (Q61R), which is sensitive to MEK inhibitors in *in vitro* models. Among *EGFR*-mutated patients, one case showed a *PI3KCA* missense mutation (E545K) synchronous with the *EGFR* exon 19 deletion (del746-750);notably, the E545K mutation has been described to activate EGFR downstream signaling pathway, resulting in TKIs resistance. Finally, 7 patients (35%) had a mutation of the gene

encoding for TP53, which is reported as a prognostic marker of poor outcome in advanced NSCLC.

Conclusion: Targeted NGS is a sensitive tool to screen multiple genes simultaneously and represents an attractive system to identify relevant mutations. The potential clinical significance of these variations needs to be elucidated in further studies.

H46 Molecular status of non squamous non small cell lung cancer: a restrospective study

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Background: Testing for EGFR mutations has become standard in managing advanced non-small cell lung cancer (NSCLC), because of its implication in first line therapy. Significant advances in clinical trial strong recommended molecular profiling for every patient with newly diagnosed NSCLC, including ALK and ROS1 rearrangement, BRAF mutation and evaluation of MET copy number gain. However, the really predictive and prognostic meaning of these mutations is not completely known. Aim of our study is to give an overview of molecular profile in Non Small Cell Lung Cancer, non-squamous subtype, and to describe potential role in the treatment decisions.

Materials and methods: We conducted a retrospective chart review of patients with advanced NSCLC referred to "Oncologia" of Novara Hospital. In this study, 70 sample non squamous NSCLC were screened for EGFR and BRAF mutation, ALK and ROS1 rearrangement, MET copy number gain, using both Fluorescence In Situ Hybridization e Real Time Polymerase Chain Reaction. Patients EGFR wild type harboring an other mutation (ALK or BRAF or MET positive) were defined "mutated"; patients negative for all tests were defined "all wild type". These patients were related to Time To Progression (TTP) to first line chemotherapy and to prevalence of brain metastases.

Results: Among 70 cases of non squamous NSCLC we detected 14 cases with EGFR mutations, 7 cases with ALK gene rearrangement, 1 BRAF mutation (V600E) and 8 MET copy number gain (4 amplification and 4 polysomy). No ROS1 gene rearrangement was detected. Median TTP was 14 months (95%CI 8–14 months) in mutated group and 6 months (95%CI 4–9 months) in all wild type group (log rank test 3.50 p = 0.061). Prevalence of brain metastases was 19% in mutated group and 25% in all wild type group (chi-square test 0.011; p = 0.915). Patients with EGFR wild type metastatic NSCLC received first line chemotherapy platinum based plus third-generation drugs; patients with locally advanced NSCLC were treated with concomitant radio-chemotherapy. Pemetrexed as first line chemotherapy proved to be more effective in patients with ALK rearrangement (TTP range 8–13 months in 7 patients).

Conclusions: Mutation status of NSCLC seems not to influence time to progression to standard first line chemotherapy and it is not predictive for brain metastasis. Further studies are required to clarify prognostic and predictive value of these mutations in real clinical practice.

H47 The role of second and third line tyrosine kinase inhibitor monotherapy in EGFR wild-type (and unknown mutational status) advanced non-small-cell lung cancer patients: Findings from a retrospective analysis

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Background: Second-line treatment for advanced non-small-cell lung cancer (aNSCLC) patients includes monotherapy with a third generation cytotoxic drug (CT) or with the tyrosine kinase inhibitor (TKI) erlotinib. These options are the actual standard treatment for EGFR gene wild-type (WT) status, as patients with EGFR mutations achieve greater benefit by the use of TKI in first-line treatment. Some prospective clinical trials and meta-analyses investigated the comparison between CT and TKI in second-line, but data are conflicting.

Methods: We designed a retrospective trial to gather information about TKI sensitivity in comparison with CT. We selected from clinical records data of patients treated with at least 1 line of CT and at least 1 line of TKI. We collected information about age, sex, performance status, comorbidity, smoking status, histotype, metastatic sites, EGFR mutational status, mutation type, treatment schedule, better response and time-to-progression (TTP) for each line of treatment and overall survival (OS). Statistical analysis was performed by MedCalc version 14.12.0. Survival measures and comparisons were evaluated by Kaplan-Meier method. Results: We identified 118 patients who met the selection criteria. Mean age 64,63 (range: 32-84). M/F ratio: 73/45. EGFR non-mutated (41 WT and 54 unknown): 95. All EGFR WT/ patients received erlotinib or gefitinib as second-line or third-line TKI. Median TTP at second-line: 4 (TKI) vs 4 (CT) months, p = 0,64, HR: 0,91 (TKI vs CT), 95%CI: 0,57-1,44. Median TTP at third-line: 2 (TKI) vs 3 (CT) months, p = 0,59, HR: 1,14 (TKI vs CT), 95%CI: 0,65-2,00. Median OS: 22 (third-line TKI) vs 15 (second-line TKI) months, p = 0,09, HR: 0,67 (third-line vs second-line TKI), 95%CI: 0,42-1,06.

Conclusions: This study explores the role of TKIs in EGFR non-mutated aNSCLC patients. The data about the comparison of TKI with CT show no difference in TTP for both second-line and third-line treatment. The analysis of OS highlights a trend to a benefit in the group of patients who receive TKI in third-line, even if this result is not statistically significant. Further analysis are needed to find an explanation for this observation.

H48 Retrospective evaluation of chemotherapy options in non-squamous non-small cell lung cancer (non-Sq NSCLC) patients (pts) unfit for standard platinum-based chemotherapy in clinical practice

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Background: In clinical practice, major challenge in non-Sq NSCLC pts unfit for standard platinum-based chemotherapy, due to age and/or comorbidities, is the selection between mono- or doublet-chemotherapy properly weighing expected clinical outcome and safety profile in the individual patient.

Patients and methods: Consecutive pts *EGFR* wild-type and mutant unsuitable for anti-*EGFR* were treated in clinical practice. Conventional or modified (schedules and/or dosage of doublets, or mono-chemotherapy) first-lines were selected according to fitness, defined by age (non-elderly, young-elderly YE ≥65 < 75 y, old-elderly OE ≥75 y), performance status (PS), and comorbidity (Cumulative Illness Rating Scale). Activity and efficacy were evaluated, and compared by log-rank. Limiting toxicity syndromes (LTS) were used to evaluate individual safety.

Results: From November 2009 to February 2015, 45 pts were treated: 21 fit (46.6%) with conventional and 24 (53.4%) unfit with modified regimens; specifically 14 (31.1%) fit standard platinum/pemetrexed (sPP) and 10 (22.2%) unfit modified PP (mPP). Unfit were prevalently YE/OE, PS 1-2, CIRS secondary. Overall, objective response rate (ORR), progression-free survival (PFS), overall survival (OS) were 47.7%, 7 and 13 months. Among fit and unfit, respectively: 61.1% and 30%, 8 and 6 months (p 0.935), 15 and 13 months (p 0.963). Among all PP, 60%, 8 and 15 months. Among sPP and mPP, respectively: 66.6% and 50%, 5 and 8 months (p 0.247), 15 and 13 months (p 0.816). In PP pts, no significantly different cumulative toxicities were reported among sPP and mPP; LTS were 6 (25%): only 1 (4.1%) single-site (LTS-SS) in fit, all 5 (20.8%) multiple-site (LTS-MS) in unfit, with cardiovascular comorbidities, and represented by neutropenia, thrombocytopenia, asthenia, hypertransaminasemia, hypoalbuminemia, atrial fibrillation, and arrhythmia. In mPP received dose-intensities (rDIs) were ?80% of projected standard doses. Overall, among unfit pts, 12 (26.6%) were treated with modified platinum-based doublets and 12 (26.6%), prevalently OE, with mono-chemotherapy; ORR, PFS and OS were: 50% and 10%, 8 and 3 months (p 0.008), 15 and 13 months (p 0.360), respectively.

Conclusions: mPP schedules (rDIs ≥80%) may be a therapeutic option for unfit pts, due to not significantly different efficacy and cumulative toxicity compared to sPP, but individual unfit pts prevalently show LTS-ms. Unfit pts treated with mono-chemotherapy show significantly worse PFS.

H49 Effectiveness of direct egfr mutations research at time of diagnostic biopsy for lung cancer: a single institution outcome research

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Background: The majority of NSCLC are diagnosed at an advanced stage. It is crucial, in the metastatic disease, to obtain sufficient material to carry out molecular testing. EGFR activating mutations and ALK translocation are the most important predictors of clinical response and outcome using specific tyrosine kinasi inhibitors (TKI). In our institution we implemented a virtuous path to accelerate routine EGFR somatic mutation testing and ALK rearrangement testing in order to offer the best first line therapeutic option to the Patients (Pts). Effectiveness of the process was studied in this outcome study focusing on EGFR mutations.

Material and methods: All the Pts presented with advanced lung disease from March 2014 to March 2015 underwent tumor biopsy in the pulmonary division by Broncoscopy or TAC-guided biopsy. At the time of biopsy the pulmonologist obtained patient's consensus for molecular markers testing and sent the request to the pathologist. All diagnosed non-squamous NSCLC were directly tested for EGFR mutations. EGFR mutations of exon 18-21 were detected by Real-Time PCR (Rotorgene) using the therascreen EGFR RGQ PCR Kit, (Qiagen, Germany). Data of the Pts and test results were consecutively introduced in a clinical database. Effectiveness of the process has been established in a rate of test execution >90% and in a median time of attendance for the result less then 2 weeks.

Results: 110 Pts have been included. Diagnosis was adenocarcinoma in 99 pts (90%), NSCLC NOS in 11 Pts (10%). Median age was 67 years. We found 16 patients with EGFR mutation (14,5%); 10 Pts with exon 19 deletion, 4 Pts with exon 21 point mutation (L858R),1 Pt with exon 20 insertions and 1 Pt with exon 18 mutation (G719X). Biopsy material was appropriate for molecular testing for 109 Pts (99%) and median time of reporting was 11 days. Molecular tests were ready for the firt contact with the Oncologist for all the Patients. All mutated Patients received a first line TKI treatment except for the Patient with the exon 20 insertions.

Conclusions: In our institution the introduction of a virtuous path for direct molecular testing in advanced disease has showed high effectiveness in this cohort study that reflects our day by day routine. We strongly support outcome research to optimize clinical pathways of lung cancer Patients.

H50 Clinical and pathological predictors of outcome for malignant pleural mesothelioma

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Background: Although worldwide use of asbestos has decreased, the incidence of Malignant Pleural Mesothelioma (MPM) is expected to increase over the next few decades. A number of scoring systems have been proposed to assess clinic-pathological features and to predict the prognosis. We assessed the relationship between patients' features and disease evolution in order to choose the best treatment able to prolong overall survival (OS) and progression free survival (PFS).

Material and methods: We retrospectively analyzed patients with locally advanced or metastatic MPM, treated at the Department of Medical Oncology - Università Politecnica Marche in Italy, from January 2003 to September 2013. Data on age, gender, smoking history, asbestos exposure, performance status (PS), tumor stage, histology, type of treatment and routine laboratory tests including complete blood count panel, date of death or censored status were collected. OS and PFS were estimated using Kaplan-Meier method and Cox analysis was performed to analyze the prognostic relevance of clinical parameters.

Results: We enrolled a total of 62 patients. Univariate analysis showed that histological type, performance status, response to first line therapy, pre-treatment haemoglobin levels and plasmatic Ca125 were significant prognostic factors. Conversely, no significant correlation was found between age, gender, smoking history, reported exposure to asbestos, stage at diagnosis, treatments and overall survival and progression free survival.

Conclusions: Our results showed that anaemia and increased Ca125 might be considered negative prognostic parameters in MPM patients and confirmed the prognostic role of histotype, performance status and response to first line chemotherapy.

H51 Oral Vinorelbine as single agent in the treatment of poor Performance Status (pPS) metastatic Non Small Cell Lung Cancer (NSCLC): a single institution experience

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Background: Vinorelbine is a consolidated treatment for advanced non-small cell lung cancer(NSCLC),both as single and in combination with other chemotherapeutic drugs. Oral vinorelbine (OV) has demonstrated an important activity in different NSCLC settings with results in terms of overall survival(OS)and progression free survival(PFS) similar to intravenous(i.v.) formulation.There are multiple advantage of this formulation for example the patient's compliance to the treatment, the absence of venous irritation and the possibility to take the treatment at home.Adverse events are similar between OV and i.v.formulation.Moreover pharmacokinetic studies demonstrated that OV have 40% bioavailability and a dose of 30 mg/m^{2}intravenously is the equivalent of 80 mg/m^{2}orally.In our study we evaluated single-agent OV therapy in pre-treated advanced NSCLC patient with poor Performance Status(PS).

Patients and methods: Sixteen pre-treated advanced NSCLC patients with median age of 70 years(range 65-75 yrs)were enrolled at University Oncology Unit of Aprilia (Latina).All elderly patients recruited,with a PS of two or more and good functional status, received OV at the dose of 60 mg/m^2 once a week every 3 weeks until disease progression or development of unacceptable toxicity.Primary end points were PFS,OS and safety.The secondary end point was the quality of life(QoL)evaluated with FACT-L v4 scoring questionnaire.

Results: OV was administered as second-line in seven patients(43%) and as third-or further-line in nine(57%)patients.Median PFS was six months(range 2-16)and median OS 13months (range 3-52).Treatment was well tolerated.We observed grade 3/4 neutropenia in 2/16(12,5%)patients. Regardless non-hematologic toxicity, grade 3/4 fatigue was the most common severe adverse event observed in 68% of patients, followed by nausea in 31%,vomiting and diarrhoea in 18% of patients.The questionnaire were distributed to all patients and FACT-L v4 scores did not significantly change during treatment.

Conclusions: In conclusion vinorelbine can have a role as a single-agent treatment and represent a valid option for elderly patients with advanced NSCLC and poor PS.OV appears to be a reasonable alternative to i.v. formulation, both in terms of efficacy and safety.The oral administration is feasible and associated with manageable toxicity in pre-treated NSCLC patients.Furthermore its route of administration is generally preferred by patients with a consequent best compliance and reasonable QoL.

H52 Pemetrexed maintenance therapy in advanced non-squamous NSCLC: a single institution experience

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Background: Pemetrexed (Pem) monotherapy continued after four cycles of Cisplatin-Pem doublet (continuation maintenance strategy), in patients (pts) with advanced non-squamous Non-Small Cell Lung Cancer (NSCLC), demonstrated an advantage, in comparison to placebo, in terms of progression free survival (PFS): 6.9 months (mos) vs 5.6 (p = 0.00006); and overall survival (OS): 16.9 vs 14 mos (p = 0.019).

Patients and methods: Here we describe our experience of Pem continuation maintenance in pts with advanced non-squamous NSCLC. We retrospectively analyzed data of pts who received Pem continuation maintenance since January 2011 until April 2015. The efficacy parameters were median PFS and median OS, calculated from the beginning of first line chemotherapy. We included in the analysis pts who received Carboplatin and Cisplatin with Pem for a total of 4 or 6 cycles and we analyzed data of these subgroups.

Results: We reviewed a total of 36 pts with a median age of 68.5 years (range 35.0-79.8); 52.8% were women and 47.2% men. The majority (75%) of pts had a Performance Status (PS) of 0 (ECOG classification) and 25% had PS 1. Only 5.6% of pts were in IIIB stage (TNM classification) whereas the remaining 94.4% were in stage

IV. Half of pts were treated with Cisplatin and 50% with Carboplatin; 16 pts received 4 cycles of first line chemotherapy and 20 received 6 cycles. A median number of 4 cycles of maintenance chemotherapy was administered with a range of 1-15 cycles. PFS was 9.7 and OS was 13.8 mos. A total of 9 pts (25%) experienced a long survival beyond 24 mos. Pts treated with Cisplatin achieved PFS of 13.8 mos and OS of 19.1 mos, whereas pts treated with Carboplatin had PFS of 8.5 mos and OS of 12.7 mos. We also analyzed PFS and OS of patients who received 4 and 6 cycles of doublet chemotherapy: in particular PFS was 8.4 mos and 10.9 mos respectively and OS was 11.2 mos and 14.5 mos. No toxic deaths were observed.

Conclusions: Our experience confirm the efficacy of Pem maintenance therapy for advanced non-squamous NSCLC in unselected pts, not progressing during Pem-platinum induction therapy. These results were consistent even in pts treated with carboplatin or those who have received up to 6 cycles of induction therapy.

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Session L. Gastrointestinal (noncolorectal) cancer

L01* Age subgroup analysis of efficacy and safety data from two phase 3 studies of second-line ramucirumab (RAM) versus placebo (PL) in patients (pts) with previously treated gastric or gastroesophageal junction (GEJ) adenocarcinoma (RAINBOW and REGARD)

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Background: From 2009–2012, 1020 pts with metastatic gastric or GEJ adenocarcinoma were enrolled in two phase 3, randomized, double-blind studies of RAM following progressive disease on first-line platinum- and/or fluoropyrimidine-containing combination therapy: the RAINBOW and REGARD studies.

Methods: In RAINBOW, 665 pts were randomized to RAM (8mg/kg) + paclitaxel (PTX; 80 mg/m^2) vs PL + PTX; in REGARD, 355 pts were randomized to RAM (8 mg/kg) + best supportive care (BSC) vs PL + BSC. We examined outcomes by age (<65 and ≥65 years [y]). Overall survival (OS) was the primary endpoint; secondary endpoints included progression-free survival (PFS), objective response rate (ORR), and safety.

Results: In RAINBOW, 416 pts were aged <65y and 249 were ≥65y. In REGARD, 227 pts were <65y and 128 were ≥65y. Outcomes are summarized in the Table; RAM efficacy was similar in younger and older patients in both studies. The incidence of Grade ≥3 adverse events in RAINBOW was higher in the RAM + PTX arm for both age groups and similar across age groups. The incidence of Grade ≥3 adverse events (AE) in REGARD was similar between treatment arms for both age groups (see Table).

Conclusions: RAM conferred similar improvements in OS and PFS for pts aged <65y and ≥65y in both studies; AE profiles were similar for pts aged <65 and ≥65y.

L02* Multicenter randomized study of Gemcitabine and Oxaliplatin (GEMOX) +/- Panitumumab as First Line Treatment in K-Ras Wild type Advanced Biliary Tract Cancer; the VECTI-BIL study

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Background: Biliary tract cancer (BTC) is a rare and lethal disease with very few therapeutic options. Preclinical data suggest that Epithelial growth factor receptor (EGFR) pathway activation could be involved in BTC pathogenesis, envisaging a potential role of anti-EGFR monoclonal antibodies.

Methods: Eighty-nine patients (pts) with advanced BTC harboring wild-type KRAS status, ECOG PS 0-2, without prior systemic therapy, were randomized to receive gemcitabine and oxaliplatin (GEMOX) with (arm A, 45 pts) or without (arm B, 44 pts) panitumumab (6 mg/kg), every 2 weeks for up to 12 cycles. In arm A maintenance therapy with panitumumab was allowed in case of clinical benefit after 12 cycles. Randomization was stratified for ECOG status (0-1 vs 2) and histology (intrahepatic-IHC vs extrahepatic-EHC) cholangiocarcinoma and gallbladder carcinoma-GB). Primary endpoint was progression free survival (PFS); secondary ones were response rate (RR) (RECIST v1.1), overall survival (OS) and safety.

Table: L01*

Study	Rainbow				Regard			
Age group	<65 years		≥65 years		<65 years		≥65 years	
Median age (range)	56 (25–64)		70 (65–84)		54 (24–64)		71 (65–87)	
Treatment Arms	RAM + PTX	PL + PTX	RAM + PTX	PL + PTX	RAM + BSC	PL + BSC	RAM + BSC	PL + BSC
N	204	212	126	123	156	71	82	46
			Outcome Measures					
Median OS (m)	9.3	7.1	10.7	8.7	5.3	4.1	5.2	3.8
HR (95% CI)	0.753 (0.604–0.939)		0.861 (0.636–1.165)		0.846 (0.611–1.171)		0.722 (0.471–1.106)	
p value for interaction	0.37				0.18			
Median PFS (m)	4.3	2.8	4.6	2.9	1.9	1.3	2.8	1.4
HR (95% CI)	0.572 (0.460–0.711)		0.673 (0.506–0.894)		0.450 (0.327–0.620)		0.490 (0.319–0.752)	
p value for interaction	0.56				0.94			
ORR	28%	14%	27%	20%	NA	NA	NA	NA
Safety								
Grade ≥3 adverse event incidence	79%	64%	85%	60%	55%	57%	60%	60%

NA, data not available.

Results: After a median follow-up of 10.1 months (mo) and 86 PFS events (radiological progression or death), median PFS was 5.3 mo in Arm A (95% CI 3.3–7.2) and 4.4 mo (95% CI 2.6–6.2) in Arm B (p = 0.27). No survival differences were observed, being median OS 9.9 mo (95% CI 5.4-14.3) in Arm A and 10.2 mo in Arm B (95% CI 6.4-13.9, p = 0.42). Median PFS for IHC patients was 5.7 mo in Arm A (95% CI 2.7–8.7) and 6.2 mo in Arm B (95% CI 3.1–9.2). Median PFS for EHC and GB was 4.9 mo in Arm A (95% CI 2.4–7.4) and 3.8 mo in Arm B (95% CI 2.3–5.3). However, pts with IHC treated with panitumumab had an improvement in OS of 3.3 mo compared to control group (15.1 vs 11.8 mo; p = 0.13). Among patients evaluable for response (84/89) RR was 26.6% in Arm A and 18.1% in Arm B, with DCR favoring the experimental arm (75.5% vs 68.1%, p = 0.99). As for safety, skin toxicity was the main adverse event in arm A, affecting up to 80% of pts. Neurotoxicity, constitutional and gastrointestinal symptoms were equally common in both arms, but a higher incidence of diarrhea (55.5 vs 31.8%), mucositis (22.2 vs 13.7%) and constipation (24.4 vs 15.9%) was seen in patients treated with panitumumab.

Conclusions: The study did not meet its primary endpoint. A trend toward better RR was observed in pts treated with panitumumab. Pts with wild-type KRAS IHC may receive greater benefit from P-GEMOX treatment. Further analyses on potential markers of response/resistance are currently ongoing.

L03 Ramucirumab (RAM) as Second-Line Treatment in Patients with Advanced Hepatocellular Carcinoma (HCC) Following First-Line Therapy with Sorafenib: Analyses from the Randomized Phase III REACH Study

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Background: REACH was a global, multicenter, double-blind, phase 3 study evaluating the efficacy and safety of RAM as a single agent for patients (pts) with advanced HCC after prior sorafenib.

Methods: Eligible intention-to-treat (ITT) population included: Child-Pugh (CP) A; advanced HCC; Barcelona Clinic Liver Cancer stage C or B refractory or not amenable to locoregional therapy; Eastern Cooperative Oncology Group performance status 0–1; prior sorafenib; and adequate hematologic and biochemical parameters. Pts were randomized 1:1 to receive RAM (8mg/kg IV) or placebo (PBO) every 2 weeks until progression, unacceptable toxicity, or death. CP B pts were enrolled initially; analyses in this population are exploratory. RAM treatment efficacy and safety data are presented for the ITT (CP A) and CP score 7 + 8 (CP B) populations, and for the pre-specified subgroup of pts with baseline alpha-fetoprotein (AFP) ^{3} or <400 ng/mL. Analyses compared overall survival (OS) using stratified or unstratified log-rank tests. Hazard ratios (HR) were generated using a corresponding Cox regression model.

Results: The OS HR for the ITT population (RAM 283; PBO 282) was 0.866 (95%CI 0.72–1.05; $p = 0.1391$); median OS was 9.2m for RAM vs 7.6m for PBO. The observed safety profile of RAM in the ITT population was consistent with advanced HCC and the previously demonstrated safety profile for single-agent RAM. In ITT (CP A) pts with baseline AFP ≥400 ng/mL (RAM 119; PBO 131), OS HR was 0.674 (95%CI 0.508–0.895; $p = 0.0059$); median OS was 7.8m for RAM vs 4.2m for PBO. In CP B pts (RAM 39; PBO 39), OS HR was 0.998 (95%CI 0.623–1.599; $p = 0.9946$). In CP B pts with AFP ≥400 ng/mL, OS HR was 0.674 (0.332–1.368; $p = 0.2756$). The safety profile in ITT pts with baseline AFP ≥ or <400 ng/mL was consistent with the overall ITT safety population. Detailed quality-of-life (QoL) analyses and safety results will be presented.

Conclusions: A statistically significant improvement in OS was not met in REACH using single-agent RAM. However, a consistent and clinically meaningful improvement in OS was observed in pts with baseline AFP levels ≥400ng/mL who received RAM, warranting further investigation. In the ITT population with baseline AFP ≥400ng/mL, a trend for delay in symptoms and performance status deterioration was observed. The safety profile of RAM in the ITT population is considered manageable, regardless of baseline AFP.

L04 Angiogenesis polymorphisms profile in the prediction of clinical outcome of advanced HCC patients receiving sorafenib: combined analysis of VEGF and HIF-1a. Final results of the ALICE-2 study

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Background: Tumour cells adapt to hypoxia via the activation of numerous molecules, among which hypoxia inducible factor 1-α (HIF-1α) is the most important. HIF-1α plays a crucial role in tumour angiogenesis triggering the transcription of several genes including the vascular endothelial growth factor (VEGF). The overexpression of HIF-1α in hepatocellular carcinoma (HCC) is significantly associated with tumour angiogenesis, invasion, metastasis, treatment resistance and poor prognosis. Currently the therapeutic stronghold of advanced HCC is the antiangiogenetic TKI sorafenib. In our previous report (ALICE-1 study) polymorphisms (SNPs) rs2010963 and rs4604006 of VEGF have been shown to predict clinical outcome in HCC patients treated with sorafenib.

Methods: 210 patients from a multicentre database were eligible for our analysis. Tumour histologic or peripheral blood samples were tested for 8 different HIF-1α SNPs. Patients progression free survival (PFS) and overall survival (OS) were analysed.

Results: At univariate analysis CC > AA + AC of rs1951795, TT > CC + CT of rs10873142, AA + AG > GG of rs12434438 SNPs of HIF-1α were statistically significant for PFS and OS. The extended analysis of VEGF and VEGFR SNPs confirms the results of ALICE-1 study. At multivariate analysis rs12434438 of HIF-1α, rs2010963 of VEGF-A and rs4604006 of VEGF-C have been confirmed as independent factors. At the combined analysis of significant SNPs the presence of 2 favourable alleles of rs2010963 and rs4604006 of VEGF compared to only 1 or to none favourable alleles, identifies three populations with different PFS (respectively: 10.8 vs. 5.6 vs. 3.7 months, p < 0,0001) and OS (respectively: 19.0 vs. 13.5 vs. 7.5 months; p < 0,0001). Furthermore the presence of GG genotype of rs12434438 (HIF-1α) select a population with a particularly poor outcome independently from the clinical effect of the two VEGF SNPs (PFS: 2.6 months, p < 0,0001; OS: 6.6 months, p < 0,0001).

Conclusions: This investigation on HIF-1α SNPs, following our previous discoveries on VEGF and VEGFR, may represent a clinical tool to identify patients with favourable response to sorafenib. In the presence of a favourable genotyping, clinicians would administer sorafenib as soon as clinically indicated, instead of delaying it with other treatments. Conversely patients with unfavourable genotyping may not be optimal candidates for sorafenib. These patients should be preferably included in clinical trials exploring new treatment modalities.

L05 eNOS polymorphisms in relation to outcome in advanced HCC patients receiving sorafenib. Final results of ePHAS study

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Background: Sorafenib, an oral multikinase inhibitor, represents the standard care for advanced hepatocellular carcinoma. Sorafenib, by blocking the vascular endothelial growth factor receptors (VEGFRs), could induce an inhibition of endothelial nitric oxide synthase (eNOS) activity with a consequent decrease of the production of nitric oxide (NO). The NO produced by eNOS mediates a variety of physiologic functions including neovascularization, regulation of blood vessel tone, platelet aggregation vascular permeability and leukocyte endothelial interaction. In our study we analysed the role of *eNOS* polymorphisms in relation to clinical outcome in patients with HCC treated with Sorafenib.

Methods: One hundred and twenty eight patients from a multicentric database were eligible for our study. A peripheral blood sample or formalin fixed paraffin embedded

(FFPE) tumor tissue was collected for each patients and submitted to genomic DNA extraction. Two *eNOS* polymorphisms (*eNOS* + 894G > T and *eNOS* -786T > C) were assessed by a Real-Time PCR method while *eNOS* VNTR 27bp intron 4a/b was analysed by direct sequencing. These polymorphisms were assessed in relation to progression-free survival (PFS) and overall survival (OS) (log-rank test).

Results: With regard to *eNOS*-786 the presence of the C allele both in homozygosity (CC) and in heterozygosity (TC) was associated with a statistically significant longer PFS [6.2 months (range 5,3-10,8) versus 2,1 months (range 1,8-2,5); $p < 0.0001$)] and OS [15.1 months (range 12,4-19,5) versus 5,2 months (range 3,2-7,5); $p < 0.0001$], than those with TT genotype, respectively. With regard to *eNOS*-VNTR the presence of the 4a allele both in homozygosity (4aa) and in heterozygosity (4ab) was associated with a statistically significant longer PFS [6,2 months (range 5-10,8) versus 2,6 months (2,3-3,9); p =0,001)] and OS [15,1 months (range 11,8-20,6) versus 9,7 months (range 6,6-12,5); p =0,024], than those with 4bb genotype, respectively. Moreover, patients carrying T allele for *eNOS* + 894 both in homozygosity (TT) and in heterozygosity (GT) showed a better PFS respect to patients with the GG genotype [6,2 months (range 4,7-8,7) versus 2,6 months (2,1-3,4); p = 0,0002)]. Haplotype subgroups correlations are under statistical analyses.

Conclusions: *eNOS*-786, *eNOS* VNTR and *eNOS* + 894 polymorphisms could represent prognostic markers in patients with advanced hepatocellular carcinoma treated with sorafenib.

L06 Impact of age, ECOG PS and type of treatment on progression-free survival and overall survival in second-line therapy for advanced gastric cancer: analysis on 709 cases

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Background: Although second-line therapy is considered a reasonable option for advanced gastric cancer (AGC) patients with good performance status (PS), the optimal candidates are not well-defined. Retrospective studies suggest that different clinical variables may have a prognostic role in this setting.

Patients and methods: To describe the most frequently used second-line regimens and define possible prognostic factors, we retrospectively identified 709 AGC patients treated with second-line therapy at 15 Italian Institutions. Cross-tables and $\chi 2$ test were used to analyze and describe categorical characteristics. To predict the impact of clinical data on progression-free survival (PFS) and overall survival (OS) we performed Kaplan Meier and Cox Regression analyses with IBM SPSS Statistics 20 software.

Results: 47.4% of patients received a single-agent therapy, 41.6% a doublet, and 8.4% a triplet chemotherapy. Fluoropyrimidines were the most frequently used agents (44.7%), followed by taxanes (43.7%), irinotecan (38.4%), platinum salts (15.5%), and anthracyclines (6.1%). Only 4.7% of patients received a biological drug in second-line. The median number of administered cycles was 4 (range 1-20). At the time of analysis, we reported 689 second-line progression events and 647 deaths. Median PFS was 2.73 months (95% CI 2.57-2.89), median OS was 5.85 months (95% CI 5.29-6.41). Patients treated with a triplet regimen had longer median PFS compared with either doublet (HR 1.36, p = 0.037) or single agent (HR 1.49, p = 0.009). Accordingly, being exposed to second-line triplet regimen significantly impacted on median OS when compared to single agent therapy (7.26 months vs 5.88 months, HR 1.36, p = 0.046) or doublet (7.26 months vs 5.68 months, HR 1.36, p = 0.042). Baseline ECOG PS positively influenced both median PFS (4.04 months for PS 0 vs 2.83 months for PS 1 vs 1.45 months for PS 2, p < 0.001) and median OS (8.61 months for PS 0 vs 5.85 months for PS 1 vs 2.46 months for PS 2, p < 0.0001). No outcome differences were observed between younger (<70 years) and elderly (≥70 years) patients (median PFS 2.63 vs 2.99 months, p = 0.113; median OS 5.55 vs 6.47 months, p = 0.095, respectively).

Conclusions: Treatment intensity and favorable ECOG PS at the time of treatment start may influence survival outcomes of AGC patients receiving second-line treatment, regardless of age. These findings might help clinicians to better identify who may benefit the most from a second-line therapy.

L07 Baseline characteristics and survival outcomes of advanced gastric cancer patients treated with two or more lines of chemotherapy: results from a large Italian cohort

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Background: Second-line therapy is a valuable option in ECOG performance status (PS) 0-1 advanced gastric cancer (AGC) patients who have failed first-line treatment. Since limited real-world data are available,we investigated the characteristics and outcomes of a large Italian patients' cohort.

Methods: Medical records of approximately 2,000 AGC patients from 15 Italian centers were reviewed to select eligible cases. Demographic, pathological, and clinical data were reviewed and anonymously collected. Categorical characteristics were analyzed and described using cross-tables and $\chi 2$ test. Survival analyses were performed using Kaplan Meier methods with IBM SPSS Statistics 20 software.

Results: A total of 709 patients were included, 492 were male (69.4%). Tumor location was:15.3% esophagogastric junction,19.8% cardia,13.4% fundus, 29.8% gastric body, and 21.7% pylorus. Intestinal histotype accounted for 63.7% of the cases whereas 68.1% had moderate-to-poorly differentiated tumors. HER-2 status was positive in 16% of tested cases. 60.3% of patients presented with stage IV at diagnosis. 396 cases (55.8%) had previous total gastrectomy (191), partial gastrectomy (172), or other palliative intervention (33). When performed, lymphadenectomy was most frequently D2 o D3 (88%). All patients received a first-line treatment, except those who developed metastatic disease while on perioperative or adjuvant therapy. First-line median progression-free survival (PFS) was 6.15 months (95% CI 5.77-6.52). At the time of second-line therapy start median age was 64.4 years (range 26-86), and ECOG PS was 0 in 28.9%, 1 in 51.8%, and 2 in 17.8% of the patients. The median follow-up was 18.6 months (range 17.6-19.6).Response rate was overall low (11.4%, with 9.7% of partial responses). Stable disease and progressive disease were reported in 24.2% and 57.3% of treated patients, respectively. No information on response was available for 7.1% of the cases. Second-line median PFS was 2.73 months (95%CI 2.57-2.89). At the time of analysis, 647 out of 709 patients (91.3%) had died with second-line median overall survival of 5.85 months (95%CI 5.29-6.41). 271 patients (38%) of those who progressed on second-line treatment received a third-line therapy.

Conclusions: Our study provides detailed information about the baseline characteristics of patients with AGC who received a second-line therapy as well as useful data on survival outcomes, depicting a real-world insight of the Italian scenario.

L08 A Single Arm Clinical Trial to Assess the Efficacy and Safety of Panitumumab (Vectibix®) in combination with FOLFOX4 Chemotherapy as 1st line treatment in Subjects with Metastatic Gastric or Gastroesophageal Junction adenocarcinoma (VEGA trial). A multicenter Phase II SICOG trial 0802

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Background: EGFR overexpression occurs in 27–55% of gastroesophageal adenocarcinomas, and correlates with poor prognosis. We aimed to assess the efficacy and safety of the anti-EGFR antibody Panitumumab (PANIT) in addition to

Oxaliplatin, 5-FU and Leucovorin (FOLFOX 4) as front-line treatment in patients (pts) with metastatic gastric or gastroesophageal –junction (GEJ) adenocarcinoma. Primary endpoint was response rate (ORR); secondary endpoints were duration of and time to response (DoR and TTR), safety, PFS and OS.

Patients and methods: Between October 2009 and July 2013 we enrolled 65 pts with untreated metastatic gastric(80%) and GEJ (20%) adenocarcinoma at 8 referral SICOG centers. Eligible pts were 69% males, median age 62 years (y) (33-82), 60% and 40% ECOG PS 1 and 0, respectively; 72% and 28% presented with synchronous and metachronous metastases, respectively; 69% had nodal plus visceral metastases. Pts received FOLFOX 4 for a maximum of 12 cycles plus PANIT (6 mg/Kg) for a minimum of 4 cycles or until progression or unacceptable toxicity, q1-14. Response was evaluated every 4 cycles according to modified-RECIST criteria, in intention to treat population . Gene expression profiling studies are ongoing.

Results: Eleven and 54 (83%) pts received < and = or > than 4 cycles, respectively. Median number of administered FOLFOX cycles was 8 (1-12) and 43% of pts received all 12 planned cycles; median number of administered PANIT cycles was 8 (1-28) and 43% received 12 or more PANIT cycles. ORR was 42%, median TTR was 2 months (m) (1-11); median DoR 8 m(2-19); median PFS 5.6 m (0.6-16.2); median OS 11 m (0.6-46.3); 1 y PFS and 1y OS rates were 11.4% and 42.7%, respectively. Most frequent PANIT-related AEs were skin toxicity, asthenia, diarrhea and mucositis; 3 pts discontinued PANIT, 1 for infusional reaction, 1 for rash G3, 1 for mucositis G3. No PANIT-related deaths occurred.

Conclusions: Addition of PANIT to FOLFOX 4 in gastric and GEJ cancer patients seems to be effective and safe, however ongoing tissue gene expression profiling analyses would identify subpopulation of pts benefiting more from anti-EGFR target therapy in this setting.

L09 Mismatch repair protein expression and Hedgehog signalling pathways in human pancreatic cancer

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Background: Pancreatic ductal adenocarcinoma (PDAC) is thought to develop primarily due to an accumulation of genomic mutations, which would be monitored and repaired by the mismatch repair (MMR) system in the normal cells. The Hedgehog (HH) signalling pathway has been shown to regulate the expression of several genes in a variety of PDAC cell processes. Recently, preclinical studies have suggested that Gli-1 may interfere with MMR in PDAC, suppressing MMR activity through the inhibition of mutL homolog 1 (MLH1). In this study, we analyzed the relationship between MMR protein and HH signalling elements in samples from resected PDAC patients.

Methods: Tissue samples from 91 PDAC were subjected to immunohistochemical staining to assess the expression of MLH1, MSH2 and MSH6. Gene expression analysis was performed to evaluate the expression of HH signalling pathway elements (SMO, SHH, DHH, IHH). KRAS mutation status was assessed by DNA sequencing. Expression of MMR proteins was correlated with HH signalling pathway elements by chi-square test.

Results: At immunohistochemistry analysis, 42.2% of samples were negative for MLH1 expression, while 27.7% were negative for MSH2 and 34.4% for MSH6. Thirty-four patients (37.4%) expressed both MSH2 and MSH6. Nineteen patients (20.9%) were found to present loss of at least two MMR proteins. MMR protein expression was not related to clinical characteristics, as pathological stage or grading, or to clinical outcome in terms of overall survival (OS). MMR expression was not correlated with KRAS mutation status. Expression of SMO was significantly correlated with loss of MLH1 expression ($p = 0.018$) but not with MSH2 or MSH6 expression.

Conclusions: Our results suggest that Hedgehog signalling pathway may suppress MMR activity through SMO, one of HH principal effectors. This observation confirms what observed in preclinical studies also in PDAC patients and gives new insights on HH signalling contribution to PDAC development and progression.

L10 Final results of the gideon study according to patient etiology: The italian experience

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Background: Sorafenib is the only targeted agent indicated for the treatment of hepatocellular carcinoma (HCC). The global, prospective, non-interventional GIDEON (Global Investigational of therapeutic DEcisions in HCC and Of its treatment with sorafeNib) study enrolled over 3200 patients (pts) with unresectable HCC (uHCC) treated with sorafenib in real-life clinical practice conditions. The primary objective of the study was to evaluate the safety of sorafenib in HCC patients in clinical practice. Secondary objective was efficacy. We report the final analysis of the Italian subgroup of patients according to etiology.

Material and methods: Patients with uHCC for whom the decision to administer sorafenib was taken were eligible for enrollment. Disease and patients characteristics were assessed at baseline. Sorafenib dose, adverse events (AEs) and disease assessments were reported at follow-up.

Results: Of 278 pts enrolled in Italy, 274 were evaluable for efficacy and 271 for safety analysis. The median age was 70 years (range: 44-90), 227 pts (83%) were male, 266 pts (97%) caucasian and disease stage was BCLC-B in 87(32%) and BCLC-C in 142(52%) pts. The etiology of the underlying liver disease was recorded as hepatitis B (hep-B) in 58(21%) pts, hep-B only in 39(14%) pts, hepatitis C (hep-C) in 157(57%), hep-C only in 119(43%) pts, alcohol use in 112(41%) pts and nonalcoholic steatohepatitis (NASH) in 7(2.6%) pts. Overall adverse events were slightly more frequent in pts with hep-B (88%) than those with hep-C (75%) or alcohol use (75%). The type and incidence of AEs were consistent among all subgroups, the most frequent being gastrointestinal (diarrhea/ascites), dermatologic (hand-foot skin reaction/rash) and fatigue. There were no new unexpected AEs. Median OS in days (months) in pts with hep-B, hep-C, alcohol use, NASH, hep-B only and hep-C only were 351(11.5), 617(20.5), 402(13.1), 211(6.9), 351(11.5) and 633(20.7) respectively.

Conclusion: The most frequent etiology was hep-C followed by alcohol use and hep-B. Safety was consistent with the known profile of sorafenib. Overall survival was longer in the subgroup of hep-C pts than in the other etiology subgroups. This has also been reported in previous analyses.

L11 Hepatocellular Carcinoma In Elderly Patients: final results of The Italian Cohort Of GIDEON (Global Investigational of therapeutic DEcisions in HCC and of its treatment with sorafeNib) Study

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Background: GIDEON is a global, prospective, non-interventional study in unresectable HCC (uHCC) patients (pts) receiving sorafenib. Over 3200 pts were enrolled worldwide. Elderly pts are often underrepresented in clinical trials and thus related data are limited. The aim of this analysis was to evaluate the tolerability and efficacy of sorafenib in pts 70 years of age or older in the Italian cohort of the GIDEON study.

Material and methods: Patients with uHCC candidates for systemic therapy in whom a decision to treat with sorafenib was taken, were eligible for enrollment. Patient and tumor characteristics, safety and efficacy were analyzed by age. The median age of 70 years was chosen as the cut-off to define the elderly patient subgroup. As an observational study, all results are descriptive in nature.

Results: In Italy, 278 pts were enrolled overall, of which 271 valid for safety and 274 valid for efficacy analysis. Median age was 70 (44-90) years. Of the total of 274 pts, 141 were = 70 years. Performance status (ECOG PS 0,1,2) were 65/26/9% respectively for younger and 58/35/6% respectively for the elderly subgroup. Stage of disease (BCLC) was 11/24/62/2% (A,B,C,D) for the younger and 14/39/42/1% for the elderly. Macroscopic vascular invasion and extrahepatic spread were 33% and 29% respectively in the younger age group and 19% each in the elderly. Child-Pugh A was present in 73% in the younger and 83% in the elderly. Median OS was 10 (8-18) months in the younger and 20 (12-23) months in the elderly pts. The median TTP was also longer in the elderly than in the younger, 7.6 and 5 months respectively. The median duration of treatment was similar in both subgroups: 4.2 and 3.5 months respectively. The type and incidence of adverse events (AE) (serious and non-serious) were similar in the younger and the elderly subgroups and in line with the known sorafenib safety profile. The most frequent AEs were gastrointestinal (diarrhea), dermatologic (hand-foot skin reaction/rash) and fatigue.

Conclusion: In the Italian cohort of the GIDEON study sorafenib showed to be well-tolerated and an effective treatment option in both younger and elderly pts. Elderly had longer OS than younger possibly because of more advanced disease in the younger. However due to the limitation and potential bias of an observational non- randomized study it is not possible to attribute this difference to a different treatment effect.

L12 Association with programmed death ligand-1 (PDL-1) expression and Helicobacter Pylori infection in patients with non-diffuse type gastric carcinoma

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Background: Gastric cancer (GC) develops through a multistep process. Helicobacter pylori (HP) is a strong risk factor, and PDL-1 on epithelium was suggested as a contributor to the chronic process of HP infection. The present study evaluates the association of HP infection, PDL-1 expression, and tumour-infiltrating lynfocytes (TIL) in tumour samples of radically resected non-diffuse-type GCs.

Material and methods: We included patients enrolled in the ITACA-S phase III study and for whom both normal gastric mucosa and tumor tissue was available. All patients received adjuvant chemotherapy according to the protocol design. The istological type was classified by WHO classification system. Gastric mucosa samples were investigated by the presence of the HP by Giemsa and anti-HP antibody immunostain. The expression of PDL-1 was detected by immunohistochemistry stain using anti-PDL-1 (Anti-B7-H1, Anti-CD274 molecule) antibody. Two independent observers, blinded to any prior information, examined the immunohistochemical slides. Percentage of PDL-1 positive tumour cells and staining intensity was scored as negative for <5% of stained tumour cells and as positive for 5%-100%.The binary associations were tested using the exact chi-square test or the chi-square for trend test (the latter for PDL-1 vs T- and N-stage).

Results: A total of 55 samples were analysed (N+ in 93%; gastric origin in 71%, gastroesophageal junction in 9%, multiple sites in 20%). HP was positive in 42% and negative in 58%. PDL-1 was negative in 33% and positive in 67%. There was a statistically significant higer prevalence of HP infection when comparing PDL-1 positive samples as compared to PDL-1 negative ones (54% vs. 16%; $p = 0.010$). PDL-1 was not significantly associated to TIL (61.8% vs 76.2% $p = 0.377$) and to N-stage ($p = 0.452$). As regards the latter, no clear trend was observed for the percentage of positive PDL-1 at increasing N-stage. On the other hand, the percentage of PDL-1 positive cases decreased at increasing grading or T-stage, however such an association was not statistically significant ($p = 0.152$ and 0.180, respectively).

Conclusions: Our data document for the first time an association between HP+ GC and PDL-1 expression. This represents the proof of well a known biological rationale to investigate new targeted approaches in this patients' population.

L13 Capecitabine, oxaliplatin and irinotecan (COI regimen) as perioperative treatment of resectable gastric or gastroesophageal junction (GEJ) cancer

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Background: Perioperative strategies represent a challenge in the treatment of resectable gastric cancer (GC). The combination of capecitabine, oxaliplatin and irinotecan (COI regimen) has beenstudied in the treatment of metastatic colorectal cancer and GC, achieving promising response rates and manageable toxicity profile. In this monoistitutional prospective phase II trial,we aimed at assessing the activity and safety of COI regimen as perioperative treatment for resectable gastric or GEJ cancer.

Methods: Patients with resectable locally advanced (T3-4 and/or N + , M0) adenocarcinoma of the stomach or of the GEJ were staged with CT scan and EUS. Patients were treated with COI regimen (irinotecan 180 mg/m2on day 1, oxaliplatin 85 mg/m2on day 2 and capecitabine 2000 mg/m2/day from day 2 to 6 of a biweekly schedule). The protocol schedule consisted of four preoperative cycles followed by restaging with the same techniques used at baseline, gastrectomy with standard D2 lymphadenectomy and additional four postoperative cycles. Tumor samples before chemotherapy were collected to evaluate exploratory biomarkers in all cases.

Results: From 1/2011 to10/2014, 30 patients were enrolled. Adenocarcinoma pf the GEJ was documented in 8 cases (27%) and 90% had clinical involvement of regional lymph nodes. All patients completed the preoperative phase and underwent surgery, whereas 22 (73%) completed all the postoperative cycles. No progressive disease was observed during preoperative phase. Clinical response rate occurred in 70% of patients. Radical R0 resection was performed in 90%, but a pathologic complete response (pCR) was documented in only 7%. At a median follow-up of 30 months, the median disease free survival (DFS) was 14.2 months. The 1-year and 3-year DFS rates were 62% and 40% respectively, the 2-year and 3-year overall survival rates were 63% and 56%, respectively. The 3-year DFS in patients with pCR was 100%. The most common G3/G4 toxicities during chemotherapy were fatigue (23%), diarrhea (17%) and neutropenia (10%).

Conclusions: Perioperative COI regime is active with manageable toxicity in patients with resectable gastric or GEJ cancer. The results of the traslational biomarkers substudy will be presented at the Meeting.

L14 Second-line chemotherapy (CT2) in advanced biliary tract cancer (aBTC) patients (pts) progressed to first-line chemotherapy (CT1) with gemcitabine plus platinum: where are we now?

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Background: The role of CT2 after progression to CT1 with gemcitabine plus a platinum derivative in aBTC has not been established. We aimed to refine the role of CT2 after standard CT1 in a large retrospective pts cohort and by pooling our results with the available literature evidence.

Patients and methods: We collected the clinical records of aBTC pts treated with CT2 after progression to a first-line gemcitabine plus cisplatin or oxaliplatin regimen. We then performed a pooled analysis of published data: eligible studies were identified by the Medline database and the on-line abstract datasets of the Annual Meeting of the American Society of Clinical Oncology, the biannual European Society of Medical Oncology Congress since 2002 and the annual World Gastrointestinal Congress since 2006.

Results: A total of 174 pts were included in the survey: CT2 demonstrated low response rate (RR: 3.4%), with median progression-free (mPFS) and overall survival (mOS) of 3.0 and 6.6 months, respectively. Comparing different CT2 regimens, combination chemotherapy demonstrated a slight increase in disease control rate compared to monotherapy (32% vs. 21%, $p = 0.140$), as well as modestly improved mPFS (3.1 vs. 2.9 months; $p = 0.072$) and mOS (7.1 vs. 5.0 months; $p = 0.006$). An Eastern Cooperative Oncology Group (ECOG) performance status of 0 and low pre-treatment CA19.9 levels were associated with better prognosis at univariate analysis ($p < 0.0001$). Data from other five series were identified by literature search, for a total of 499 pts analyzed. Types of CT2 used were the following: fluoropyrimidine plus platinum (FOLFOX, XELOX, 5-fluorouracil plus cisplatin) in 138 pts, FOLFIRI in 92 pts (in 13 of whom in combination with bevacizumab), 5-fluorouracil or capecitabine monotherapy in 88 pts, gemcitabine plus cisplatin or oxaliplatin in 30 pts, and other regimens in 151 pts. The results of the pooled analysis confirmed low RR (10.2%; 95%CI 7.3%-13.1%) and limited efficacy of CT2 in unselected pts populations (mPFS: 3.1 months, 95%CI 2.9-3.4; mOS: 6.3 months, 95%CI 5.6-7.0).

Conclusions: Our analysis confirms the limited value of CT2 after a standard CT1 in aBTC pts. Randomized trials are needed to definitively assess the benefit of CT2 over best supportive care in this setting. In the meanwhile, CT2 may be offered to aBTC pts selected on the basis of several clinical prognostic parameters.

L15 Effects of metformin on clinical outcome in advanced hcc patients receiving sorafenib

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Background and aims: Several studies reported an association between type 2 diabetes mellitus (DM2) and hepatocellular carcinoma (HCC). Data from several retrospective studies and meta-analysis have demonstrated a risk reduction of about 50% of developing HCC in cirrhotic patients treated with metformin for DM2. Several in vitro studies have shown anti-tumor activity of metformin (M) in HCC. The aim of this study is to evaluate the different outcomes of patients that have received or not metformin during treatment with sorafenib (S).

Methods: From 257 patients diagnosed with HCC from 2004 to 2014, 93 patients consecutively treated with sorafenib were analyzed. Of these, 42 patients (45.2%) were diabetic and 31 (33.3%) of these have received M for DM2. Progression-Free Survival (PFS), Overall Survival (OS) and their 95% Confidence Interval (95% CI) were estimated by Kaplan-Meier method and compared with log-rank test.

Results: The concomitant use of S and M was associated with a median PFS of 2.6 months (95% CI 1.9-3.3) compared to 5.0 months (95% CI 2.5-8.2) for patients who have not received M ($p = 0.029$). The concomitant use of S and M was associated with a median OS of 10.4 months (95% CI 3.9-14.4) compared to 15.1 months (95% CI 11.7-17.8) for patients who have not received M ($p = 0.014$).

Conclusions: These findings could be explained by an increased tumor aggressiveness and resistance to S in patients treated with M. M usually enhanced the activity of S, but probably molecular alterations in transporter genes or transcription factors involved in M molecular action and pharmacokinetics could contribute to a different response to these drugs combination. Further studies are needed to confirm the data and to identify possible mechanisms of resistance that may occur during treatment with S.

L16 Prognostic model for patients (pts) with advanced pancreatic cancer (aPC) receiving first-line modified FOLFIRINOX (mFOLFIRINOX)

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Background: FOLFIRINOX is a standard first-line treatment for aPC. We aimed to explore putative prognostic factors in pts treated with mFOLFIRINOX at our institution.

Patients and methods: 137 consecutive aPC pts treated with mFOLFIRINOX between 2008 and 2014 were identified. Clinical, laboratory and pathological data were collected and their association with activity, progression free survival (PFS) and overall survival (OS) were investigated by chi-square and log-rank test. A two-sided $p < 0.02$ was selected at univariate analysis to account for multiple testing. Multivariate analysis was carried out using Cox regression modelling.

Results: Baseline characteristics were: male/female, 48.2%/51.8%; median age, 60 years (range: 33-75); ECOG performance status (PS) 0/1, 67.2%/32.8%; histology ductal /IPMN-derived, 89%/11%; grade 1/2/3/x, 0.7%/32.1%/1.9%/63.5%; site head/body-tail/multifocal, 53.2%/45.3%/1.5%; stage III/IV, 40.9%/59.1%; previous surgery, 10.9%, adjuvant chemotherapy, 8%; sites of metastases $<3/\geq 3$, 89.1%/10.9%; median Ca19.9, 603 U/ml (range: 1-75000); neutrophil-lymphocyte ratio (NLR) <4/>4, 82.4%/17.6%; platelet-lymphocyte ratio (PLR) <150/150-300/>300, 70.1%/28.2%/1.7%; LDH $<225/\geq 225$ U/l, 63%/27%. Median PFS and OS were 8.0 months (95%CI 6.2-9.8) and 12 months (95%CI 9.7-14.2), respectively. Response rate was 38.7%, while disease-control rate (DCR) was 72.3%. DCR was significantly associated with NLR <4 ($p = 0.021$), stage III ($p = 0.025$) and absence of liver metastases in stage IV pts ($p = 0.014$). At multivariate analysis, liver metastases, PS 1 and NLR > 4 were associated with poorer outcome in terms of PFS (Liver metastases: $p = 0.036$; HR 0.51, 95%CI 0.27-0.95; PS 1: $p = 0.001$; HR 2.29, 95%CI 1.43-3.67 and NLR > 4: $p = 0.019$; HR 2.03, 95%CI 1.12-3.69) and OS (Liver metastases: $p = 0.019$; HR 0.59, 95%CI 0.38-0.92; PS 1: $p = 0.001$; HR 2.26, 95%CI 1.42-3.59 and NLR > 4: $p = 0.002$; HR 2.42, 95%CI 1.38-4.26). We categorized 119 pts with complete data as good-risk (0 factors, 38 pts), intermediate-risk (1 factor, 49 pts) and poor-risk ($\geq$2 factors, 32 pts). Median OS for good, intermediate and poor-risk groups were 17.6, 11.1 and 7.4 months, respectively ($p < 0.001$).

Conclusions: Prognosis of aPC pts undergoing mFOLFIRINOX is influenced by easily available clinical and laboratory factors: our analysis revealed ECOG PS, liver metastases and NLR as the most important predictors of survival. These factors could be helpful for treatment decision and clinical trial design.

L17 Safety and efficacy of sorafenib in stella study, a Multicenter, Observational, Phase IV Study In Italian Centers

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Background: Sorafenib, a multikinase inhibitor, is the only systemic treatment approved for hepatocellular carcinoma (HCC). Data collected on sorafenib in routine clinical practice provides valuable information on patient characteristics, etiology,

pattern of disease and treatment modalities in a specific geographical area. This helps to better understand the use of sorafenib in order to maximize its safety and efficacy.

Materials and methods: STELLA (Sorafenib Treatment modalities for HEpatoceLLular Carcinoma patients in ltAly) is a phase IV, prospective, non-interventional, Italian, multicenter study, aiming to evaluate the efficacy and safety of sorafenib (400 mg/bid) in terms of overall survival (OS) rate at 12 months (primary endpoint) in patients (pts) with HCC under daily-life treatment conditions. Additional objectives were safety and OS. Pts with HCC in whom a decision to treat with sorafenib has been made, were enrolled. The observation period for each patient is the time from the start of sorafenib to withdrawal of consent, death, or the last visit.

Results: A total of 234 pts were enrolled. Of these 224 received sorafenib and were valid for the intention-to-treat (ITT) analysis and 214 pts for safety. Male 79%, median age 70 years, hepatitis C virus infection in 115(51%)pts, followed by alcohol abuse in 58 (26%)pts and hepatitis B virus infection in 42(19%)pts; ECOG performance status 0/1/2 in 143(64%), 69(31%) and 11(5%) respectively; Child-Pugh class A/B/C in 179(80%), 34(15%) and 2(1%) respectively. The distribution per BCLC stage A/B/C: 10(4.5%), 67 (30%) and 146(65%) respectively. The OS rate at 12 months was 54% [90% CI: 48-60%]. Adverse events (all grades) in 176(82%)pts whereas drug-related adverse events (all grades) in 151(71%), most of which were grade 1 or 2 (11% and 29% respectively). The most frequent drug-related AEs were gastrointestinal (33%), dermatologic (30%), fatigue (27%) and anorexia (13%). Drug-related AEs resulting in permanent study drug discontinuation in 31% of pts.

Conclusion: The STELLA study provides additional insight on the use of sorafenib in Italian clinical practice. The OS rate at 12 months compares favourably with that observed in the phase III SHARP study. This may be explained by a lower percentage of BCLC C pts than in SHARP (65% and 82% respectively). The safety profile was comparable in nature and frequency to that seen in other studies under real-life conditions, with no new safety signals observed.

L18 Long non-coding RNA HSAT II as a new biomarker for the identification of high risk intraductal papillary mucinous neoplasms (IPMNs)

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Background: Satellite repeat RNAs HSAT II belongs to an heterogeneous group of non-coding transcripts, namely long non-coding RNAs. HSAT II transcripts, recently found in pancreatic ductal adenocarcinoma (PDAC), reflect global alterations in heterochromatin silencing and could potentially useful in tracking malignant progression in IPMNs.

Methods: We retrospectively evaluated 37 patients (median age 69y, range: 43y-83y) with histological diagnosis of IPMN (2010-2013) obtained from Pathology Departments of Campus Bio-Medico University of Rome. 19 were associated with PDAC, 8 with biliary tract cancer, 2 with colloid adenocarcinoma, 1 with neuroendocrine tumor, 1 with ampullary adenocarcinoma (intestinal-histotype). In 6 cases, IPMN was not associated with invasive carcinoma. Patients were divided into: low (n = 15), moderate (n = 13) and severe grade dysplasia (n = 9) IPMN. For statistical analysis (Fischer exact test), moderate and severe grade dysplasia were grouped as high grade dysplasia. A semiquantitative evaluation of HSAT II status was performed using RNA in situ hybridization (QuantiGene ViewRNA Assays, Affymetrix). The sections underwent RNA-ISH were compared with consecutive section stained in H&E. HSAT II expression were classified in: score 0, no staining; score 1, faint staining; score 2, moderate staining and score 3, intense staining. Invasive neoplastic tissue was used as positive control while normal pancreatic duct epithelia as negative control.

Results: Normal pancreatic ducts resulted negative for HSAT II expression. Significant positive correlation between grade of dysplasia and HSAT II expression was found. High HSAT II levels were identified in 20% (3/15) of low grade IPMN and in 86% (19/22) of high grade IPMN lesions ($p < 0.001$) (RR: 5.867; 95% CI: 1.989 to 17.31). The sensitivity and specificity of HSAT II expression for high grade IPMNs were 80% and 86%, respectively. Positive correlation between HSATII transcript level and association with PDAC was also found ($p = 0.038$).

Conclusions: High HSAT II expression is strongly associated with malignant progression in IPMN acting as a totally new biomarker useful for the identification of high-risk disease.

L19 Natural history of skeletal disease in primary biliary cancers. National survey on behalf of GICO group (Gruppo Italiano Colangiocarcinoma – Onlus)

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Introduction: In literature few data on the natural history of bone disease in Biliary Cancers are available. We conducted a national multicenter retrospective survey to explore the impact of bone metastases in this setting of tumors.

Patients and methods: Data on clinical-pathology, skeletal outcomes, skeletal-related events (SREs), and bone-directed therapies were collected from 110 patients affected by biliary cancer with bone metastasis.

Results: Intrahepatic Cholangiocarcinoma was the most common primary tumor (75 patients, 68%), followed by Gallbladder carcinoma (14%), Extrahepatic Cholangiocarcinoma (9%) and Klatskin's tumors (8%). 58% of patients developed bone metastases during the course of the disease, in the remaining cases skeletal disease was just evident at the time of biliary cancer diagnosis. The axial skeleton was the most common involved site (76%). SREs were experienced by 47 patients (42%), 32 of them experienced one SRE, 13 two SREs, only 2 at least 3 SREs. The necessity for radiotherapy was the most common first SRE (62,5% of patients). Bisphosphonates were administered in 47% of patients; zoledronic acid was the most used (98%). 18 patients experienced at least one SRE during treatment with biphosphonates (36%). Median time to first SRE from bone metastases diagnosis was 1,2 months (Cl 95% 0,5–1.8 months) and median survival was 6,5 months (Cl 95% 4-9 months). Survival analysis showed that, among the clinical and tumoral features considered, only ECOG PS correlates with survival after bone metastases diagnosis. The use of zoledronic acid seems to correlate with longer survival (p 0,007, Cl 95%): the median survival in patients treated with bisphosphonates was 9 months (Cl 95% 7,2-11,3 months) versus 5 months of untreated patients (Cl 95% 3,4–6,4). Among patients who received zoledronic acid before the first SRE, the median time to appearance of first SRE was significantly prolonged compared to control (6 months vs 1 month for control; p: 0.05).

Conclusions: This study demonstrates that bone metastatic biliary cancer patients are a heterogeneous population in term of skeletal events and of survival. Moreover for the first time in literature it documents the role of bifosphonates in delaying time to the first SRE and increasing the median survival. These data may support the beneficial effects of ZOL in patients affected by biliary cancer metastatic to bone.

L20 Geographical spread of gastric cancer incidence in cremona: spatial analysis of cancer registry data

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Introduction and purpose: Gastric cancer (GC) exhibits a wide variation in incidence rates worldwide. Many etiological factors have been suggested, including Helicobacter pylori prevalence, as well as dietary and genetic variations [Babaei 2011]. Possible associations are also emerging between GC risk and environmental factors, like exposure to contaminated water and pesticides [Barry 2012]. The province of Cremona exhibits a particularly high GC incidence. The most recent data from the 2014 AIRTUM Report indicate prevalence per 100,000 people of 228 for Cremona, vs 126

for pooled Italian Registries. This higher risk currently remains unexplained. In Cremona, a population-based GC Registry is active since 2010; preliminary analysis has hinted to differences in GC incidence between municipalities within the Province. If confirmed with the appropriate statistical methodology, this information may allow to identify areas at greatest risk and investigate possible causes.

Objectives: This study aims to: 1) describe the geographical spatial patterns of gastric cancer incidence based on cancer registry data and, 2) determine whether geographical clusters of statistical significance exist.

Methods: The population–based, specialized gastric cancer Registry of Cremona, which includes the three districts of Cremona, Crema and Casalmaggiore (total population = 363606), will be used to identify gastric cancer cases. Age standardized incidence ratio (SIR) of each municipality for each sex will be calculated. Spatial autocorrelation indices, hierarchical Bayesian Poisson models, and spatial scan statistics will be used in measuring the geographic pattern and clusters. In the case of sampling uncertainty due to small numbers of cases, SIR crude estimates of underlying ward-specific relative risks will be calculated using the autoregressive conditional model.

Results: From 2010 to 2014, data on 744 patients have been entered in the Registry. The spatial analysis is currently underway and findings will be presented at the AIOM conference.

Conclusion: If interesting spatial distributions are found, we will investigate whether geographical patterns may be related to information on water sources, as the literature suggests that one important source of exposure to potential carcinogens in agroechosystems is through water contamination by agrichemicals [Van Leeuwen 1999], and that there is a big possibility for Helicobacter Pylori to be transmitted via drinking water [El Sharouny 2015].

L21 An updated overall survival analysis with correction for protocol-planned crossover of the international, phase III, randomized, placebo-controlled trial of regorafenib in advanced gastrointestinal stromal tumors after failure of imatinib and sunitinib (GRID)

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Background: The GRID study showed that regorafenib improves progression-free survival compared with placebo in patients with advanced GIST after failure of at least imatinib and sunitinib (HR 0.27; 1-sided $p < 0.0001$; Demetri 2013). At the time of the primary analysis, no significant difference in the secondary endpoint of overall survival (OS) was observed (HR 0.77; $p = 0.199$), but this result may have been confounded by the high rate of crossover to regorafenib (85%) of placebo patients at progression. We conducted exploratory analyses of updated OS data to assess the effect of correcting for this protocol-planned crossover.

Methods: The data cut-off for this updated OS analysis was 31 January 2014 (2 years after the primary analysis). OS was corrected using two randomization-based methods: rank preserving structural failure time (RPSFT) and iterative parameter estimation (IPE); both methods are considered as best choice among all correction analytics. Hazard ratios and 95% CI were derived using the Cox model.

Results: A total of 139 deaths had occurred at the time of data cut-off: 91 events (68.4% of patients) in the regorafenib group and 48 (72.7%) in the placebo group. A total of 22 patients remained on regorafenib treatment (median duration 2.1 years, range 0.9–2.4). The updated hazard ratio for OS favored regorafenib (0.85, 95% CI: 0.60 - 1.21; $p = 0.18$). Median OS was estimated as 17.4 months in both groups, with crossover from placebo. The corrected HRs for OS are less than the uncorrected HR (Table).

Conclusions: The updated analysis of OS in the GRID trial is consistent with the primary analysis. An exploratory analysis correcting for the impact of cross-over on OS suggests a survival benefit for regorafenib in GIST. Clinical trial information: NCT01271712

Table: L21

OS crossover correction method	Hazard ratio	95% CI
ITT, uncorrected analysis	0.85	(0.60-1.21)
RPSFT	0.39	(0.26-0.58)
IPE	0.51	(0.35-0.73)

L22 Retrospective analysis of the role of adjuvant chemotherapy and microRNAs expression in resected cholangiocarcinomas (CCAs)

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Background: Surgery is the only potentially curative treatment for CCAs. Although potential benefit of adjuvant chemotherapy (CT) was suggested in R1 disease, international guidelines recommend adjuvant CT only within clinical trials. Objective of this study was to analyse the effect of adjuvant CT and the prognostic role of microRNAs in a retrospective cohort of CCAs.

Material and methods: Clinical data were retrospectively collected from 42 patients who underwent surgical resection for CCA within Humanitas Cancer Center between 1999 and 2014. FFPE tissues were retrieved and subjected to RNA extraction after macrodissection of tumoural and adjacent counterpart. MicroRNA expression was assessed by Taqman assays.

Results: Analysis was limited to 31 patients who didn't receive treatment (n:16) or adjuvant CT for >3 months (n:15). These included 15 extrahepatic, 6 intrahepatic and 10 gallbladder cancers. Median follow-up was 22.1 months. Adjuvant CT included single agent gemcitabine (n:6) or combination CT (n:10). Relapse Free Survival (RFS) did not differ according to tumour type ($p = 0.9$). Patients treated with adjuvant CT had longer median RFS compared to non-treated (22.5 vs 10.4 months, $p = 0.0034$). Advantage in RFS was maintained in R0 resections ($p = 0.0017$). We didn't observe differences in RFS according to type of CT (single agent, gemcitabine- or fluorouracil-based). Single agent gemcitabine prolonged median RFS vs no treatment (17.9 vs 10.4 months, $p = 0.04$). *In vitro* findings suggested that miR-1249 modulates response to CT in CCA. We observed over-expression of miR-1249 in tumour vs adjacent normal tissues in 36% of cases. Strong expression of miR-1249 in tumour tissues was confirmed in a second cohort of CCA (n:35) by In Situ Hybridization. When miR-1249 tumour expression was considered as a binary predictor, we noticed an association between high miR-1249 expression and shorter RFS ($p = 0.05$). MiR-1249 was correlated with RFS also in the two subgroups of non-adjuvant ($p = 0.0013$) and adjuvant CT ($p = 0.05$). In patients with highmiR-1249 tumours adjuvant CT improved RFS (19.9 vs 3.1 months, $p = 0.0003$). With multivariate analysis, adjuvant chemotherapy ($p = 0.0096$) and elevated miR-1249 expression ($p = 0.0026$) maintained a prognostic role.

Conclusions: We showed a significant advantage of adjuvant CT in patients with resected CCA, which was also maintained in R0 resection. In addition we identified miR-1249 as a potential prognostic factor that may identify candidate patients for adjuvant CT.

L23 Second line treatments in metastatic, pre-treated gastric cancer. pooled analysis of randomized clinical trials

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Background: To assess the role of Second Line Treatments (SLTs) in the treatment of metastatic, pre-treated gastric cancer we have recently concluded a systematic review of literature with meta-analysis of randomized clinical trials.

Methods: A systematic review of literature in the MEDLINE and EMBASE data bases from 1966 to 2014 was independently performed by two authors (DT and ET) All the randomized phase III trials comparing SLTs with Best Supportive Care (BSC) in the treatment of metastatic, pre-treated gastric cancer were considered eligible and included into the pooled analysis. Overall Survival was the primary end point of the analysis; overall survival in the groups of patients treated with chemotherapy (CHT) or biological agents (BA) as SLTs were the secondary ones. Primary and secondary end points were assessed as Hazard Ratio (HR) and 95% Confidence Interval (95CI). Heterogeneity between the trials was assessed using the I^2 test; the outcome analysis was performed using a random effects model with an alpha error of 5%. The quality of the selected trials was assessed using the Jadad and Nicolucci scores.

Results: Five trials met the selection criteria and were included into the pooled analysis. Three trials compared CHT (docetaxel or irinotecan) vs BSC and 2 trials compared BA (ramucirumab or everolimus) vs BSC. The outcome of 1417 patients included into the 5 trials was analyzed. 911 patients were treated with SLTs and 506 with BSC. 236 patients were treated with CHT and 675 with BA. The pooled HR for

the entire population was 0.78 (95CI: 0.565-0.99, p = 0.043) in favour of SLTs and it was 0.642 (95CI: 0.522-0.79, p < 0.001) and 0.855 (95CI: 0.738-0.991, p = 0.039) respectively for the subgroups of CHT and BA. I^2 for the entire population was 39.5%, and the quality of all the selected trials was high-to-moderate using the Jadad and Nicolucci scores.

Conclusion: Our analysis confirms that SLTs have to be considered the standard treatment in metastatic, pre-treated gastric cancer. Nevertheless, till today no definitive data exist to identify the better approach (if CHT or BA) to be used as SLT in patients with metastatic, pre-treated gastric cancer, and further trials are probably needed to better define what kind of treatment has to be used in this class of patients.

L24 Intermediate and advanced hepatocellular carcinoma management in four Italian centers: patterns of treatment and costs

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Background: Hepatocellular carcinoma(HCC) is the fifth most common malignancy worldwide and represents a severe health condition imposing high hospitalizations and mortality rates, and consequently a relevant economic burden.

Purpose: Objective of the present analysis is to investigate treatment pathways and related healthcare costs for intermediate and advanced HCC patients(Barcelona Clinic Liver Cancer Classification(BCLC) stage B and C respectively).

Patients and methods: Structured interviews with gastroenterologists and interventional radiologists were performed in four Italian centres experienced in HCC management. Information on disease stage, diagnostic procedures, treatments performed and healthcare resource consumption related to HCC were included in the questionnaire. Direct healthcare costs per patient associated with relevant treatments (sorafenib, Transarterial chemoembolization(TACE), transarterial radioembolization (TARE) systemic treatment) were evaluated.

Results: Between 2013 and 2014, 285 patients(pts) with HCC(mean age 66 years, 74% males) were treated in the 4 participating centres; of these, a total of 80 were classified in the intermediate stage B and 57 pts were BCLC stage C. TACE was the most frequent first-line treatment in intermediate stage HCC(63%), followed by sorafenib(15%), radiofrequency ablation(14%) and TARE(1,3%). In the advanced stage of HCC the most frequently used first-line therapy was sorafenib(56%), followed by best supportive care(21%), TACE(18%) and TARE(3,5%). The mean duration of treatment with sorafenib(137 pts with intermediate and advanced HCC) was 6.1 months(all treatment lines combined); the average number of TACE sessions was 2.5 procedures/patient, while pts treated with TARE received an average of 1.5 procedures/patient The total costs of treatment per patient amounted to 12,215€ for sorafenib, 13,419€ for TACE and 26,106€ for TARE. Both in the intermediate and the advanced stage of the disease, variability in treatment patterns among centres was observed.

Conclusion: The present analysis raises for the first time the awareness of the overall costs incurred by the Italian National Healthcare Service for different treatments used in intermediate and advanced HCC highlighting the need for future research and analysis of the cost- effectiveness of TACE alone or combined with sorafenib, in the treatment of HCC.

L25 A systematic review and meta-analysis of randomized trials on the role of targeted therapy in advanced pancreatic cancer

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Introduction: Despite in the past several clinical trials have attempt to clarify the role of targeted therapy in the treatment of pancreatic cancer, at present its real impact is still controversial. To shed light on this relevant issue, a systematic review and meta-analysis of literature was performed.

Methods: By searching different literature databases and major cancer meetings, we collected data from all randomized clinical trials designed on targeted therapy in advanced pancreatic cancer. The time-frame between January 2007 to March 2015 was selected. Data on predefined end-points, including overall survival, progression-free survival in terms of Hazard Ratio and response rate were extracted using a random effects model.

Results: Twenty-seven randomized clinical trials for a total of 8205 patients were selected and included in the final analysis. In particular a significant benefit was demonstrated for anti-EGFR agents on overall survival (HR 0.880; 95%CI 0.797-0.972; p = 0.011). In the pooled analysis, no benefit on overall survival (HR 0.957; 95%CI 0.900-1.017; p = 0.153), or progression-free survival (HR 0.908; 95%CI 0.817-1.010; p = 0.075) for targeted-based therapies as compared to conventional treatments was observed.

Conclusion: These results do not demonstrate clinical benefit. Therefore, our work highlights the need to identify predictive factors for patient selection and rationally design of clinical trials.

L26 Second-line chemotherapy after disease progression following first-line FOLFOXIRI in advanced pancreatic cancer patients

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Background: Second-line (2L) doublet chemotherapy (CT) resulted superior to mono-CT after progression to first-line (1L) gemcitabine in advanced pancreatic cancer (aPC); however, no standard 2L treatment has been yet identified after 1L combination CT as FOLFIRINOX. The aim of our analysis is to describe the 2L treatments used in this setting and to explore possible prognostic factors.

Material and methods: We collected data from patients (pts) with histologically proven aPC treated with 2L CT after progression to 1L FOLFOXIRI at our institution from 2011 to 2014. We reported data on response rate (RR), progression-free (PFS) and overall survival (OS) with 2L CT. Survival was evaluated according to Kaplan-Meier method. The associations between clinico-pathological factors and OS were investigated by log-rank test and Cox model.

Results: From a total of 108 pts progressed after 1L FOLFOXIRI, 71 received 2L chemotherapy and have been included in the analysis. Median age was 59 years (range 41-76); M/F:38/33. ECOG PS was 0 in 27 pts, 1 in 42 and 2 in 2 pts. RR with 1L FOLFOXIRI was 35.2% with a median PFS of 6.4 months. 2L CT consisted of: gemcitabine in 32 cases, gemcitabine plus nab-paclitaxel in 13 pts, gemcitabine plus capecitabina in 9, GEMOX in 5, FOLFIRI in 4, retreatment with FOLFOXIRI in 3 and other regimens (XELOX, FOLFOX, nab-paclitaxel alone, paclitaxel, gemcitabine plus carboplatin) in 1 patient each. Four partial responses (5.6%) and 18 stable diseases (25.4%) have been observed with 2L CT; 6 pts are still not evaluable. Median PFS was 2.8 months (95% confidential interval, CI: 1.8-3.7) and median OS from the beginning of 2L CT was 6.2 months (95% CI:5.6-6.8). There were no major differences in RR, PFS and OS according to the number of drugs used in 2L (combination vs. monotherapy: RR: 8.3% vs. 2.9%, p = 0.11; PFS: 2.8 vs. 2.5 months, p = 0.684; OS: 6.3 vs. 5.9 months, p = 0.104). At univariate analyses the following factors resulted associated with better OS: fluoropyrimidine-based regimens (p = 0.042), ECOG PS 0-1 (p = 0.015), first-line PFS > 6months (p = 0.003) and Ca19.9 ≤ 59UNL (p = 0.011). At multivariate analyses only Ca19.9 ≤ 59UNL remained associated with improved OS (OR: 3.794, 95% CI1.39–10.33, p = 0.009).

Conclusions: 2L CT after FOLFIRINOX has limited activity but a group of pts could benefit from treatment. The analyses of prognostic factors might be helpful to guide patient selection and trial design for the development of new drugs in this setting.

L27 MiR-21 expression as prognostic biomarker in extrahepatic but not intrahepatic radically resected cholangiocarcinomas

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Background: Cholangiocarcinoma (CCA) is an aggressive malignant tumor affecting the biliary tree**.** Increasing evidence suggests the importance of key microRNAs (miRNAs), such as miR-21, in CCA pathogenesis and progression, but previous reports demonstrated the pathological and molecular heterogeneity of intrahepatic (ICC) and extrahepatic cholangiocarcinomas (ECC). Therefore, the aim of our study was to evaluate the prognostic role of miR-21 expression in ICC and ECC.

Patients and methods: RNA isolated from 69 paraffin-embedded ICC and ECC tumors was used for expression analysis of mir-21 by quantitative Real-Time PCR. Comparison of clinical information and miR-21 expression was made using the Mann-Whitney U nonparametric test. Disease-free survival (DFS) and overall survival (OS) curves were constructed using Kaplan-Meier method, and differences were analyzed using log-rank test. A Cox proportional hazards model analysis was performed to determine the joint association of all ten clinicopathological factors investigated.

Results: ECC patients showed significantly worse median OS compared to ICC (i.e., 32.5 vs. 47 months, respectively, p = 0.047). ICC and the ECC showed also differences in the occurrence of lymphatic and perineural invasion (p = 0.043 and p = 0.010) and miR-21 expression (p = 0.037), which was significantly higher in the ECC. Strikingly, Cox proportional hazards model analysis in the subgroup of ECC patients (N = 41) showed that higher than median miR-21 expression was associated with a significantly higher hazard ratio (HR) for both death (HR = 4.95; 95%CI = 1.07-22.98; p = 0.041) and recurrence (HR = 6.21; 95%CI = 1.29-29.89; p = 0.023). Moreover, miR-21 expression emerged as the single most predictive biomarker for DFS and OS among all the clinicopathological factors evaluated in ECC, while not significant association with prognosis was detected in ICC patients.

Conclusions: Several clinicopathologic diversities between ICC and ECC tumors exist. MiR-21 expression might be considered a prognostic factor in ECC, but not in ICC tumors. ECC patients with worse prognosis have high miR-21 expression which therefore represents a promising target for prognostic and therapeutic approaches, suggesting a certain similarity with pancreatic cancer. These results prompt further prospective studies on the prognostic *vs.* predictive role of miR-21 in larger cohorts of radically resected CCA/ECC patients, including patients who were not treated with adjuvant chemotherapy.

L28 Central Nervous System metastastasis in gastric or gastro-esophageal junction cancer, correlation with human epidermal growth factor 2 (HER-2) status

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Background: Central nervous system (CNS) metastases from the gastrointestinal tract (GIT) cancers are relatively rare, and occur in 0.16–0.69% of the patients with gastric cancer. Overexpression of the human epidermal growth factor 2 (HER2) is associated with a aggressive metastatic phenotype poor prognosis, in the absence of HER2 targeted-therapy, and increased incidence of CNS metastases in patients with breast cancer. However, the role of HER2 overexpression in CNS metastatizing is not so well-characterized in gastric, or gastroesophageal adenocarcinoma. The purpose of this retrospective study is to assess the incidence of CNS metastases in patients with gastric cancer and to evaluate the relation of CNS metastases with HER2 status.

Patients and methods: Between 2007 and 2013, 300 patients with gastric cancer were admitted to the general hospital of Piacenza (Italy). These cases were retrospectively analyzed to evaluate CNS metastases. The metastases were diagnosed on imaging techniques performed in symptomatic patients. Histological samples of patients with CNS metastases were reviewed and tested for HER2, and patients were considered to have HER2 positive gastric cancer if the their tumor samples were scored as 3+ on immunohistochemistry or if they were fluorescence in situ hybridization (FISH) positive performed in case with 2+ on IHC.

Results: Seven of 300 patients (2.33 %) with gastric cancer were found to have CNS metastases on imaging studies and six out of seven (85.71 %) patients with gastric cancer and CNS metastases, had HER2 positive disease. These patients showed also an advanced initial disease, a more aggressive behaviour and poor prognosis with a median overall survival of 4.1 months (range 2.1-6.6 months).

Conclusion: Despite the limitations of a retrospective study, these results suggest that there is a CNS recurrence susceptibility in patients with HER2 positive gastric cancer. To the best of our knowledge this is the first report that correlates CNS metastases and HER2 status in gastric cancer.

L29 Palliative gastrectomy in asymptomatic metastatic esophagogastric cancer (EGC): does it make sense?

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Background: Surgery is effective as palliative procedure in esophagogastric cancer (EGC) patients in case of major symptoms such as bleeding or obstruction. In other malignancies (like colorectal, breast and kidney cancer), resection of the primary tumor seems to confer a better outcome even in presence of metastatic disease in pauci-or asymptomatic patients and randomized trials are ongoing.

Material and methods: We retrospectively collected the clinical data of EGC patients treated from 2009 to 2014 at our Institution. Selection criteria were the following: histologically confirmed gastric or gastroesophageal junction adenocarcinoma, metastatic disease and treatment with at least one line of systemic chemotherapy. Primary end point was overall survival (OS) from the start of first-line chemotherapy, estimated using the Kaplan-Meier method. Two-tailed log-rank test was used for survival comparison between groups: statistical significance was set at $p < 0.05$.

Results: We identified 148 patients eligible for analysis (gastroesophageal junction cancer: 26 patients; stomach cancer: 122 patients). Of these, 62 (42%) underwent primary tumor resection. There was no difference in terms of median OS between resected and not resected patients (10.4 and 10.7 months, respectively; p= 0.523, HR 1.13, 95%CI 0.779-1.630). The difference was not significant even when resected patients with synchronous metastases (i.e. with metastatic disease ab initio or developing distant metastases within 3 months after an apparently radical intervention) were compared with those who did not undergo surgery (median OS: 12.3 and 10.7 months, respectively; p = 0.596, HR 0.87, 95 CI 0.532-1.437). When the analysis was restricted to the 121 patients treated with doublet or triplet first-line chemotherapy, median OS did not differ between resected and not resected patients (11.9 and 10.7 months, respectively; p = 0.744, HR 0.93, 95%CI 0.608-1.426) and between resected patients with synchronous metastases and not resected patients (13.8 and 10.7 months, respectively; p = 0.458, HR 0.82, 95%CI 0.494-1.375).

Conclusions: In the absence of impelling symptoms related to primary tumor, our analysis does not support the usefulness of palliative surgery in metastatic EGC patients treated with first-line chemotherapy.

L30 Possible predictive role of the soluble cd40 ligand (scd40l) in metastatic pancreatic ductal adenocarcinoma (PDAC) patients (pts) treated with first line folfirinox or gemcitabine/ nab-paclitaxel combination

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Introduction: PDAC is projected to become the second leading cause of cancer death by 2030 in the absence of either significant improvement in treatment or predictive biomarkers of response and resistance. CD40, a member of the TNF superfamily, is wildly expressed in cells of the immune system. CD40-sCD40L interaction is considered to contribute to the promotion of tumor cell growth and angiogenesis for different malignancies. In particular, sCD40L is a promising diagnostic/prognostic biomarker superior to CA19.9 and CEA. The aim of the present study was to investigate the possible predictive role of sCD40L in metastatic PDAC.

Patients and methods: We evaluated 26 consecutive PDAC pts treated with FOLFIRINOX (22 pts) or a gemcitabine/nab-paclitaxel combination (4 pts). The sCD40L level was measured in serum by ELISA. Venous blood was drawn at baseline, after 3 months (all pts) and after 6 months (8 pts). Radiological response was evaluated according to the RECIST 1.1 criteria (partial response, PR; stable disease, SD; progressive disease, PD). To assess the comparison between sCD40L levels pre-post treatment with respect to clinical response, the paired t-test was used. The correlation between sCD40L and CA19.9 in terms of pre-post treatment variation was tested using Pearson's Correlation Coefficient (PCC).

Results: We observed a statistically significant reduction of sCD40L level after 3 months of treatment in patients with PR (7886.95 ± 3770.16 pg/mL versus 3259.74 ± 4176.21 pg/mL; $p < 0.05$). Conversely, in patients with PD the biomarker statistically increased in the same time (6861.64 ± 4928.13 pg/mL versus 14599.08 ± 7227.92 pg/mL; $p < 0.0001$). No differences were reported within the SD group (Table). This trend of sC40L was confirmed in the 8 pts after 6 months of therapy. Moreover, there was a positive correlation between the sCD40L and CA19.9 pre-post treatment variation percentage (PCC = 0.68; $p < 0.05$).

Table: L30

Response	Number of pts	sCD40L *basal* (mean ± sd)	sCD40L *after 3 months* (mean ± sd)	P-value
PR	8	7886.95 ± 3770.16	3259.74 ± 4176.21	< **0.05**
SD	8	7034.11 ± 4649.63	6938.72 ± 4472.04	NS
PD	10	6861.64 ± 4928.13	14599.08 ± 7227.92	< **0.0001**

Conclusions: Our data suggest a possible predictive role of sCD40L in PDAC, similarly to CA19.9. The recruitment of patients in this study is ongoing as well as the evaluation of other possible pathogenic mechanisms involved in the intracellular pathway downstream to the CD40-sCD40L interaction.

L31 MiRNAs modulate gastric cancer drug response by affecting hypoxia signaling

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Introduction: Multiple drug resistance (MDR) confers cancer cells resistance to a broad range of chemotherapeutic agents. It constitutes a major obstacle for successful treatment in cancers and is one of the main cause of a poor outcome of gastric cancer (GC). The overexpression of the membrane transporter P-glycoprotein (P-gp) encoded by the *MDR-1* gene is one of the common forms of MDR and its deregulation seems to be also associated with hypoxia signaling. Recently, the ability of microRNAs (miRNAs) to modulate the MDR by affecting the expression levels of target proteins involved in several cell signaling pathways has been described. The tumor suppressor homeodomain-interacting protein-2 (HIPK2) in counteracting hypoxia-induced chemoresistance was reported. Because of these genes involved in multidrug resistance resulted validated target of miR-27a, miR-181a and miR-20b, our aim was to investigate whether these 3 miRNAs could be involved in GC multidrug resistance by affecting the expression of HIPK2, HIF1α and MDR-1.

Materials and methods: A total number of 21 advanced GC patients treated with chemotherapeutic regiments based on epirubicin and platin were enrolled in this study. The expression of miR-27a, miR-181a, miR-20b and of HIPK2, HIF1α and MDR-1 genes were detected by real-time PCR while the expression and the subcellular localization of all proteins were assessed by immunohistochemistry. Computational tools were used to identify miR-27a, miR-181a and miR-20b target genes.

Results: Higher median expression level of HIF1α and MDR-1 genes was observed in GC patients who showed a progression disease (n. 15) compared to those with disease control rate (DCR; n. 6). This result has been also confirmed at protein level. Higher expression of HIPK2 was found in GC patients with progressive disease with an higher protein amount in cytoplasmatic rather than nuclear compartment in all samples. Finally, lower miR-27a, miR-181a and miR-20b expression were found in GC patients with progressive disease. A negative correlation between all miRNAs and their validated target genes was also found.

Conclusions: Our results highlighted the role of miR-27a, miR-181a and miR-20b in GC multidrug resistance by affecting genes involved in the hypoxia-mediated chemoresistance. Furthermore, despite higher expression of HIPK2 in GC patients with progressive disease, its citoplasmatic localization could suggest an oncogenic rather than tumor suppressive role in GC multidrug resistance.

L32 Single-centre experience with third-line chemotherapy with irinotecan plus 5-fluorouracil and leucovorin (FOLFIRI) in metastatic gastric cancer patients

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Background: Selected patients (pts) with metastatic esophagogastric cancer (mEGC) progressed after two lines of chemotherapy (CT) are fit enough for a third-line treatment (CT3). We retrospectively evaluated the activity of the combination of 5-fluorouracil/folinic acid and irinotecan (FOLFIRI) as CT3 in mEGC.

Methods: We retrospectively collected the data of mEGC pts treated with FOLFIRI CT3 at our Institution. Eligible pts had received a fluoropyrimidine-platinum first-line CT and a subsequent taxane-based second-line CT. FOLFIRI consisted of irinotecan 180 mg/sqm and leucovorin 200 mg/sqm (administered concomitantly as 90-minute iv infusion on day 1), followed by 5-fluorouracil 2800 mg/sqm (administered as 48-hour iv continuous infusion from day 1 to day 3). Cycles were repeated every 2 weeks. Response rate (RR) was evaluated according to RECIST v. 1.0 every 8 to 12 weeks, while progression-free (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method.

Results: A total of 33 ptswere included. Main pts characteristics are the following: male/female, 25/8; esophagogastric junction/gastric cancer, 1/32; median age, 62 years (range 38-84); ECOG performance status 0-1/2, 32/1; previous surgery on primary tumor yes/no, 7/26; previous adjuvant CT yes/no, 4/29; number of metastatic sites 1/ > 1, 14/19; median PFS to first-line CT, 5.2 months (range: 0.5-23.4); median PFS to second-line CT, 4.4 months (0.5-31.1). 2 ptsexperienced an objective response (RR: 6%), with other 14 ptsachieving disease stabilization (disease-control rate: 42%). Median PFS and OS from the start of CT3 were 3.3 months and 7.5 months, respectively. Hematological and non-hematological grade 3-4 toxicities were uncommon, and included neutropenia (6.1 %), diarrhea (9.1%), vomiting (3%) and asthenia (3%). Febrile neutropenia was not reported.

Conclusions: CT3 with FOLFIRI may be an option in heavily pretreated mEGC pts with good PS. This regimen has a favorable safety toxicity profile and signs of activity have been observed after standard first- and second-line CT.

L33 LDH serum levels as prognostic and predictive factor in advanced biliary tract cancer patients treated with first line chemotherapy

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Background: Previous data suggested that LDH serum levels may be associated with tumour hypoxia and VEGFA and VEGFR-1 overexpression. LDH may represent an indirect marker of neo-angiogenesis and worse prognosis in many tumour types. In our analysis we assessed the role of LDH serum levels in predicting clinical outcome for biliary tract cancer (BTC) patients treated with first-line chemotherapy, to individuate a potentially reliable and useful marker for patients stratification.

Methods: 114 advanced BTC patients treated with first-line chemotherapy with gemcitabine and platinum compounds were included. LDH values were collected within one month before and after treatment end. Patients were divided into two groups (low vs. high LDH), according to pre-treatment LDH cut-off value determined by ROC curve analysis. Patients were also classified according to pre- and post-treatment variation in LDH serum levels (increased vs. decreased). Survival distribution was estimated by Kaplan-Meier method and disease control rate (DCR) was assessed by chi-square test.

Results: Patients proved homogeneous for all clinical characteristics analyzed. Median progression free survival (mPFS) was 5.0 and 2.6 months respectively in patients with low and high pre-treatment LDH levels (p = 0.0042, HR = 0.56, 95% CI:0.37-0.87). Median overall survival (mOS) was 7.7 and 5.6 months (low vs. high LDH) (p = 0.324, HR = 0.81, 95% CI:0.54-1.24). DCR was 70% vs. 43% (low vs. high LDH) (p = 0.0166). In 35 patients with decreased LDH values after treatment, PFS and OS were respectively 6.2 and 12.1 months, whereas in 79 patients with post-treatment increased LDH levels, PFS and OS were respectively 3.0 and 5.1 months (mPFS: p = 0.0009; HR = 0.49; 95% IC: 0.33-0.74; mOS: p < 0.0001; HR = 0.42; 95% IC: 0.27-0.63).

Conclusions: Our data seem to suggest a prognostic role for LDH in BTC patients and show improved PFS and DCR in patients with low pre-treatment LDH serum levels, thus suggesting a possible predictive role in patients treated with first-line chemotherapy. After further confirmation in larger trial, these results may be relevant for a better patients' stratification and selection.

L34 Baseline neutrophil-lymphocyte ratio as a prognostic factor for patients with resectable gastric cancer undergoing adjuvant chemotherapy

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Background: A high neutrophil/lymphocyte ratio (NLR) in peripheral blood has been shown to be a strong negative prognostic factor in several types of tumors, such as colorectal, breast, pancreatic and lung cancers, while the results in gastric cancer are still controversial. The aim of our study was to define the prognostic value of pre-surgery NLR in an Italian population of resectable patients with gastric adenocarcinoma (GC).

Methods: We retrospectively collected the data for 139 patients (pts.) with histologically confirmed GC who underwent curative resection between April 2006 and December 2014. All pts had a complete blood count record prior the surgery and the NLR was calculated from neutrophil and lymphocyte on this routine test. The survival was calculated by Kaplan-Meyer analysis and Cox regression was used to evaluate the prognostic value of NLR. Software SPSS 16.0 was used for statistical analysis.

Results: From April 2006 to December 2014, we analyzed NLR in 139 pts with GC who had undergone curative surgery followed by adjuvant chemotherapy with Folfox-4 regimen. Patients characteristics were the following: median age was 62 years (range 22 - 87), the male/female ratio was 88/44, ECOG PS was 0 in 94.7% pts and 1 in 5.3% pts; the stage at diagnosis was Ib: 6.7%, IIa: 14.4%, IIb: 30.3%, IIIa: 23.5%, IIIb: 18.2%, IIIc: 6.8%.The median preoperative NLR was 1.81 (range 0.29-12.68) and pts were divided into two groups according to this cut-off value. In the whole group of 132 pts, 42 pts died, while 90 pts are still alive; in this group the 1-, 3-,5-year survival rate was 94.7%, 73.5% and 68.9% respectively. In the 65pts with low NLR the 1-, 3-, 5-year survival was 98.5%, 76.9% and 72.3% respectively, while in the 67 pts with high NLR was 89.5%, 70.1% and 65.7%. On multivariate analysis, no statistically significant differences were observed between OS in pts with low and high NLR (p = 0.069).

Conclusions: Based on this study carried out in a caucasian population, we can affirm that NLR isn't a prognostic factor in resectable gastric cancer patients underegoing

adjuvant chemotherapy. Further studies in larger reports are required to evaluate the prognostic meaning of NLR in gastric cancer.

L35 Metronomic capecitabine and bevacizumab is an active combination in patients with relapsed peritoneal pseudomyxoma

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Background: The standard treatment of peritoneal pseudomyxoma (PMP) is based on cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC). The establishment of newer systemic treatments is an unmet clinical need for unresectable or relapsed PMP, traditionally considererred chemoresistant. We previously published data on promising activity and efficacy of FOLFOX-4 regimen in this disease, highlighting that modern chemotherapy may improve outcomes. The aim of the study was to assess the efficacy and safety of metronomic capecitabine combined with bevacizumab in relapsed PMP.

Material and methods: Patients were included in an open-label, monoinstitutional study and treated with metronomic capecitabine at the daily oral dose of 625 mg/mq b. i.d. and intravenous bevacizumab at the dose of 7,5 mg/Kg every 3 weeks, until progressive disease or unacceptable toxicity. All patients were relapsed after CRS and HIPEC; six (43%) received one prior treatment line with FOLFOX-4 regimen. Ion Torrent® next generation sequencing technology ("Hot-spot Cancer Panel") was used to obtain most of the molecular data. MGMT and MET status were determined by methylation-specific PCR and in situ hybridization respectively.

Results: Fourteen patients were included from February 2014 up today. Two patients are too early for response assessment. Partial response was observed in 3 (25%) patients, progressive disease in 2 (17%), while radiological stable disease in all remaining 7 (58%). Treatment was associated with a significant decrease of sierological markers (CEA, Ca19.9, and/or Ca125) in all the evaluable patients except for the two who had progressive disease. Median PFS was 7.3 months, while OS data are not mature. Safety data were consistent with the literature. Next generation sequencing was performed in 14 samples. *KRAS* mutations were found in 13 (92%) cases; *GNAS* mutations in 7 (50%), always coupled with *KRAS* mutation. Rare mutations were discovered: HNF1A in one case, FGF3 and LKB1 mutations in another case, TP53 mutation in two cases. MGMT promoter methylation was found in 3 patients (23%). MET amplifications were never observed.

Conclusions: Metronomic capecitabine and bevacizumab combination is tolerable and active in patients with PMP when disease is relapsed after CRS and HIPEC. The identification of predictive biomarkers is a priority for the development of evidence-based treatment strategies for this orphan disease.

L36 Second line chemotherapy for gastric cancer: a single center experience

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Background: Gastric cancer is a very aggressive tumor, most patients are often not fit enough to receive second line chemotherapy, and even in this case results are dismal with poor response rate and short survival

Matherials: We retrospectively reviewed data about patients with metastatic gastric cancer receiving second line chemotherapy from January 2012 to February 2015 at Oncology Unit of Humanitas Gavazzeni

Results: Among 52 patients with progressive disease after first line chemotherapy, 24 (46%) received second line treatment. Patients characteristics were: male/female 18/6; median age 63.2 years (37-76). Hystological type was adenocarcinoma/mixed adenoneuroendocrine tumor in 22/2 cases. ECOG performance status was 0/1/2 in 13/9/2 cases. Metastatic site of disease were: peritoneum/liver/nodes/lung/bone/other in 16/6/13/3/3 cases. First line chemotherapy regimen were mainly platinum (cisplatin and Oxaliplatin) based (22 patients), 5 patients had received trastuzumab. Best response to first line was PR/SD/PD in 9/7/8 cases, with a median PFS of 5.57 months (2-52 months weeks), 11 patients had a PFS longer than six months. Second line chemotherapy regimen was: 12 (50%,)docetaxel, 3 (12.5%) paclitaxel (2 with ramucirumab), 4 (16.6%) FOLFIRI and 4 (16.6%) FOLFOX; median number of chemotherapy courses was 3 (range 1-12). Best response to chemotherapy was RC/RP/SD/PD in 1(4.7%)/4(16.7%)/1(4.5%)/14(58%); in 4 (16.7%)patients response has not been evaluated yet; with ORR 21,4% and DCR 25.9%. PFS to second line chemotherapy was 2.9 months (range: 1.2-22.9), with a median OS (second line) of 9.8 months (range 1.3-41.7) and a global OS of 22 months (range 5.7-253). Results according to duration of first line PFS: second line PFS was 24 vs 10 months for patient with PFS > 6 months and < 6 months respectively (p = 0.17; HR 2.01); second line OS was 22 vs 3 months for patients with PFS longer and shorter than 6 months (p 0.02; HR 3.4). Adverse events were mild, and consisted mainly in grade 1-2 leuco- and neutropenia, anemia, asthenia and nausea. Only 1 patient had a G4 neutropenia, thrombocytopenia, and G3 anemia. Among patients with progressive disease 9 (37.5%) received further treatment.

Conclusion: These results confirm that second line chemotherapy in gastric cancer is feasible, with a low toxicity profile. We observed that patients with a first line PFS longer than 6 months had higher probability of benefit from second line chemotherapy.

L37 Mast Cells (MCs) Infiltration Affects Pancreatic Cancer (PC) Response To Gemcitabine Based Chemotherapy: In Vitro New Insights

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Background: MCs are critical components of the tumor stromal microenvironment in a number of human malignancies. Tumor-infiltrating MCs are associated with worse prognosis in PC; however their role in tumor response to therapy is completely unknown. Actually, a new therapeutic choice for first line treatment in PC is the combination of gemcitabine with nab-paclitaxel. In this study we focused at evaluating in vitro, whether MCs affect the response to gemcitabine, and abraxane in PC models with the aim to assess the role for MCs infiltration in tumor in response to therapy.

Methods: We utilized four PC cell lines: Capan-1, MiaPaCa-2, AsPC-1, Panc-1. The antitumor effectiveness of the drugs was evaluated by cell counting and MTT assays after 72 hrs of drugs exposure. The effects on cell cycle progression were determined after 24 hrs by staining treated and untreated cells (control) with propidium iodide and analysis by flow cytometry. The phosphorylation status of H2AX, utilized as a pharmacodynamic indicator of DNA damage induced by the drugs, was evaluated through flow cytometry procedure. To test the effects of MCs in all experiments, the drugs were administered in the presence or absence of MCs conditioned medium (HMC-1-CM).

Results: Cell proliferation after gemcitabine and nab-paclitaxel, alone or in combination, was assessed in all cell lines. Interestingly we observed that HMC-1-CM reduced drug effectiveness; however the extent of such effect varied among cells; from no modulation in AsPC-1 to a "protection" from drug cytotoxicity of 20-40% in the other cell lines, mainly when the treatment included gemcitabine. As expected, cell cycle analysis evidenced the S-phase arrest induced by gemcitabine and the G2/M phase arrest induced by nab-paclitaxel. Both drugs induced phosphorylation of H2AX, a marker of DNA damage. Accordingly with cell proliferation results, when drugs were administered in HMC-1-CM, we observed the recovery of cell cycle arrest, mainly after gemcitabine and a concomitant increase of H2AX phosphorylation which are consistent with an abrogation of S-phase checkpoint, increased DNA damage accumulation and cell proliferation recovery.

Conclusion: MCs infiltration in PC could affect the effectiveness of treatment with gemcitabine perhaps through increasing DNA damage and by abrogating the S-phase checkpoint.

L38 Tumor burden reduction between primary and metastatic sites in advanced pancreatic cancer patients (pts) undergoing chemotherapy with nab-paclitaxel (Nab-P) and gemcitabine (Gem)

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Background: In the phase III MPACT trial, *nab*-P + Gem was superior to Gem alone for treating metastatic pancreatic cancer (MPC) for all endpoints examined, including overall response rate (ORR; 23% vs 7%; $P < 0.001$) and overall survival. Nab-P resulted in stromal depletion, increased the blood vessel diameter and the expression of mNestin (an endothelial cell marker) in the tumour, and improved the delivery of gemcitabine. We present tumor burden reduction with the combination of *nab*-P and gem according to the site of the tumor (primary vs metastatic lesions) in pts with MPC.

Methods: From January 2012 to January 2015, 47 previously untreated pts with MPC received *nab*-P 125 mg/m^2 + Gem 1000 mg/m^2 days 1, 8, and 15 every 4 weeks and were evaluated for the burden reduction according to tumor location. All pts underwent spiral CT imaging at baseline and after three cycle of chemotherapy. Changes in the sums of target lesion diameters from baseline were evaluated separately for pancreatic and non pancreatic lesions. We used histograms and box plot, for the

graphical representation of the data and we considered as significant response a reduction of the lesions of 30% evaluated by RECIST criteria.

Results: Primary tumor was located to pancreatic head or body-tail in 28 (60%) and 19 (40%) pts respectively. At diagnosis, 66% of pts have liver metastasis, 13% have lung and liver metastasis, 6% have lung metastasis, 4% have peritoneum metastasis, 4% have peritoneum and liver metastasis and only 2% of pts have liver and bone . At the first evaluation, the median response of the pancreatic tumor was 34% (range 20/44%); in particular 61% of pts achieved a response ranging between 20 and 40%; 15% of pts achieved the response between 40 and 50%; 8% of pts achieved the response between 60 and 70% and 5% of pts achieved the response between 0 and 10%. The median response of metastatic lesions was 12% (range 45% /-75%); in particular 33% of pts scored a response between 0 and 20%; 22% between 21 and 40%; 22% between 60 and 75% and the 23% showed, instead, a progressive disease on metastatic sites. Using a cut-off of 30%, 54% of pts had a response on the primary lesion> 30% while only 30% of pts had a response> 30% on metastatic lesions.

Conclusion: *Nab*-P + Gem was associated with a greater reduction in primary tumors than secondary sites. These data support the evaluation of this drug combination as primary treatment in locally advanced pancreatic cancer.

L39 Prognostic value of blood neutrophil-to-lymphocyte ratio (NLR) in advanced pancreatic cancer patients treated with Nab-paclitaxel and Gemcitabine: our experience

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Background: A high neutrophil to lymphocyte ratio (NLR) is a strong predictor of poor survival in many tumors.Therefore in our study we have valuated the prognostic value of pretreatment NLR in a cohort of patients with advanced pancreatic cancer treated with Nab-paclitaxel and Gemcitabine.

Methods: From January 2012 to January 2015, 47 patients with metastatic pancreatic adenocarcinoma (mPDAC) were evaluated for analysis. NLR was calculated from lymphocyte and neutrophil counts on routine blood tests taken before chemotherapy. Survival analyses were generated according to the Kaplan-Meier method. Univariate and multivariate analyses were carried out by the Cox proportional hazard model.

Results: Median age of patients was 67 (range 41-77), 11 pts had an age ≥ 70 and, ECOG PS was 0-1 in 32 pts and 2 in 9 pts. Primary tumor was located to pancreatic head or body-tail in 24 (58.5%) and 17 (41.5%) pts respectively. Metastatic sites were represented by liver (60.9%), nodes (24.3%), lung (21.9%), peritoneum (9.75%) and bone (2.4%). Nine patients had received biliary stent implantation before starting chemotherapy. Median CA19.9 levels at baseline was 469 U/I (range 17,4–61564 U/I). These patients were divided into two groups according to NLR cut-off of 5: high (≥5.0) and low (<5.0). A low NLR pre-treatment was observed in 29 patients while high level of NLR was observed in 12 patients. Median Progression free survival (PFS) of patients with low NLR *was* 8 months (95%CI: 6.9-9.0) compared with 3 months of patients with a high NLR(95%CI: 0.8-5.1) (*p*: 0.005). Median Overall survival (OS) was 12 months (95%CI: 9.3-14.6) in patients with low NLR compared with 7 months (95%CI: 3.8-10.1) of patients with high NLR (*p: 0.0001)*. On multivariate analysis, after adjusting for other clinic-pathologic factors, high NLR turned out to be an independent risk factor for poor survival (p = 0.001).

Conclusions: Our results suggest that an elevated pre-treatment NLR (≥ 5) is an independent prognostic factor correlated to a poor PFS and OS in metastatic pancreatic cancer treated with Nab-paclitaxel and Gemcitabine. Furthermore these results justify the use of NLR as a prognostic factor for risk stratification in future studies.

L40 Locoregional treatment for advanced biliary tract cancer (aBTC): evaluation of efficacy and safety

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Background: In most cases biliary tract cancers present as unresecable liver-dominant disease, associated with poor prognosis and clinical outcome. Locoregional treatments, such as transarterial chemo-embolization (TACE) and radioembolization (TARE), might be helpful in improving the outcome of these patients (pts). The aim of our analysis is to map TACE/TARE use in 8 Italian Institutions and explore their safety and efficacy in aBTC.

Methods: We retrospectively analyzed the outcome of 73 pts with histologically-proven unresectable aBTC treated with TACE/TARE. Pts' data, treatments and tumor characteristics were collected and evaluated. TACE and TARE were performed according to the standard of practice.

Results: From August 2011 to March 2015 73 pts underwent a total of 113 TACE (median 2, range 1-7) and 23 TARE (median 1, range 1-2). Pts' characteristics were as follow: M/F: 36/37; median age: 63 years (range 31-77); ECOG PS 0/1/2: 41/30/2; intrahepatic cholangiocarcinoma 64 (88%), extrahepatic cholangiocarcinoma 6 (8%), gallbladder cancer 3 (4%); unilobar/bilobar: 30/35. 29 pts (40%) presented liver-predominantly disease with extrahepatic localizations. TACE used doxorubin (n = 30), oxaliplatin (n = 6), irinotecan (n = 8) as active drugs. 2 pts received TACE as neoadjuvant therapy to improve resectability and 20 pts as first line treatment; additional 16 pts received TARE as first line for a relapse after adjuvant gemcitabine-based chemotherapy (n = 3) or as consolidation strategy after a partial response (PR) or a stabilization (SD) to systemic chemotherapy (n = 8). 35 pts received TACE/TARE in second or later lines. According to RECIST criteria 3 pts had a complete liver response, 19 a PR, 39 a SD and 11 progressive disease, one is not evaluable yet. 27 out of 39 RECIST SD showed an increase in the lesions central necrosis configuring a morphological response. 2 pts became resectable and underwent surgery. No hepatic progression was observed within 4 weeks after procedures. Treatments were well tolerated with no deaths or acute liver failure within 30-days. Grade 1-2 toxicities occurred in 21% of pts: abdominal pain (n = 5), fever (n = 5), fatigue (n = 2), liver infection (n = 2), hypertransaminasemia (n = 1); 2 pts had an hepatic abscess as major complication. At a median follow-up of 10 months, 28 out of 73 pts are alive.

Conclusion: TACE and TARE showed favorable toxicity profile and promising results. Larger studies are necessary to confirm their role in aBTC management.

L41 Phase II study of Gemcitabine and Curcumin (Meriva®) as first line treatment for locally advanced or metastatic pancreatic cancer: preliminary results

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Background: Gemcitabine (GEM) was the first drug to demonstrate survival advantage and improvement in quality of life (QoL) in advanced pancreatic cancer (PC). Improvement in response rate (RR), progression free survival (PFS) and survival were obtained with newer combination treatments but at the expense of increased toxicities. Thus, GEM still represents one of the standard treatment for PC. Curcumin has demonstrated antinflammatory, antioxidant and potential antitumor properties in different solid tumors. Therefore, we evaluated the possibile synergistic activity of curcumin extract coniugated with phospholipids (MERIVA®) to enhance bioavailability, and GEM in advanced PC.

Patients and methods: This was a single center, single arm prospective phase II trial. Inclusion criteria were: previously untreated patients with histologically confirmed metastatic or locally advanced PC, ECOG performance status of 0-2, adequate organ function and written informed consent. The patients received GEM (1000 mg/mq in 100 minutes on day 1,8,15 every 28 days) and Meriva® (2000 mg/die, continuously) until progression, unacceptable toxicities or patients refusal. Primary endpoint was RR (according to RECIST criteria version 1.1), secondary endpoints were PFS, OS, tollerability and QoL. Serum samples collection for inflammatory biomarkers was also performed.

Results: Between October 2012 and February 2015 a total of 57 consecutive patients were enrolled. Forty patients (14 females and 26 males; 14 patients locally advanced disease and 26 metastatic) are at present suitable for primary endpoint evaluation. Median age was 66 years (range 42-87); all patients except one had ECOG performance status 0-1. The median number of treatment cycle was 4 (range 1-14). The overall RR was 27,5% (all partial responses), stable disease (SD) was reported in 32,5% of cases with a disease control rate (RR + SD) of 60%. Grade 3/4 hematological toxicities included neutropenia (40%, but no febrile neutropenia were observed) and anemia (7,5%). No grade 3/4 non-hematological toxicities nor treatment-related deaths were reported.

Conclusions: The addition of Meriva® to GEM was safe and translate in good disease control rate in first line therapy of advanced PC. Treatment was well tolerated, but we observed a higher than expected rate of hematological toxicities. No treatment-related deaths were observed. Biomarker analyses are ongoing to identify potential patients whi canc get more benefit with this combination.

L42 The potential predictive role of nuclear NHERF1 expression in advanced gastric cancer patients treated with epirubicin/ oxaliplatin/capecitabine first line chemotherapy

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Background: Gastric cancer (GC) is the second leading cause of mortality worldwide. 65% of patients with GC present a locally advanced or metastatic stage at diagnosis. In these settings, Her2-neu positive patients receiving regimens containing Trastuzumab showed a median overall survival of 13.8 months, whereas Her2-neu negative patients treated with chemotherapy alone have a survival of less than 12 months. For this latter group of patients the gold standard includes treatment with epirubicin, oxaliplatin, and capecitabine (EOX). There is much evidence of progression under one year of diagnosis due to resistance to chemotherapy, which remains the major obstacle to treatment success. Cellular resistance in advanced GC might be related to function of multidrug resistance (MDR) proteins. The adaptor protein NHERF1 (Na + /H+ exchanger regulatory factor) is an important player in cancer progression for a number of solid malignancies, even if its role to develop drug resistance remains uncertain. We aimed to analyze the potential association between NHERF1 expression and P-gp, sorcin and HIF-1a MDR-related proteins in advanced GC patients treated with EOX regimen, and its relation to response.

Patients and methods: Total number of 28 untreated patients were included into the study. Expression and subcellular localization of NHERF1 expression and P-gp, sorcin and HIF-1a were assessed by immunohistochemistry on formalin-fixed paraffin embedded tumor samples.

Results: We did not found significant association between NHERF1 expression and the MDR-related proteins. A trend was observed between positive cytoplasmic NHERF1 (cNHERF1) expression and negative nuclear HIF-1α (nHIF-1α) expression (68.8% versus 31.3% respectively, $P = 0.054$). However, cytoplasmic P-gp (cP-gp) expression was positively correlated with both cHIF-1α and sorcin expression ($P = 0.011$; $P = 0.002$, respectively). Interestingly, nuclear NHERF1 (nNHERF1) staining was statistically associated with clinical response. In detail, 66.7% of patients with high nNHERF1 expression had a disease control rate, while 84.6% of subjects with negative nuclear expression of the protein showed progressive disease ($P = 0.009$). Multivariate analysis confirmed a significant correlation between nNHERF1 and clinical response (OR 0.06, $P = 0.019$).

Conclusion: These results suggest that nuclear NHERF1 could be related to resistance to the EOX regimen in advanced GC patients, identifying this marker as a possible independent predictive factor.

L43 Advanced pancreatic ductal adenocarcinoma in daily clinical practice: a single center experience

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Background: The aim of this outcome study was to evaluate the oncological approach to advanced pancreatic ductal adenocarcinoma in a real world clinical practice; few experiences like the above were reported in literature.

Material and methods: A retrospective analysis of all consecutives patients with advanced pancreatic ductal adenocarcinoma followed at the Our Medical Oncology Unit between January 2003 and December 2013 was performed. A univariate analysis for OS was estimated according to the Kaplan-Meier method with statistical significance ($p < 0.05$) of differences evaluated by log-rank test. The multivariate analysis was executed with Cox regression model.

Results: We evaluated 78 patients, 50 (64.1%) with metastatic and 28 (35.9%) with locally advanced disease. Median follow-up time was 10.77 months, with 74 patients (94.9%) deceased, 3 patients (3.8) alive with metastases and 1 patient (1.3%) NED at the last follow-up time. Median OS was 8.29 months. Median age was 67 years (range: 41-83). At the univariate analysis, the presence of pain at the onset ($p = 0.020$), ECOG PS ($p < 0.001$), stage ($p = 0.047$), first-line chemotherapy ($p < 0.001$), second-line chemotherapy ($p < 0.001$) and a weight of loss ≤ 10 Kg at the diagnosis ($p = 0.029$) have demonstrated a statistical positive impact on OS. At the multivariate analysis, the presence of pain at the onset ($p= 0.043$), stage ($p = 0.003$) and second-line chemotherapy ($p = 0.004$) have confirmed as independent prognostic factors. In particular, concerning second-line chemotherapy, this difference was confirmed with a statistical significance ($p = 0.010$) for patients that showed PR as their best response to first-line treatment (OS = 23.09 months) vs. patients that showed SD (OS = 10.56 months) or PR (OS = 5.66 months) as their best response to first-line treatment.

Conclusions: We are aware of the limitations of a retrospective study, but, studies like the above, though the analysis of not selected case study, are able to evaluate the oncological approach to advanced pancreatic cancer in a real world clinical practice. Moreover the patients were treated over a 11-year period (2003-2013) during which the use of the new combination therapies in first-line, such as FOLFIRINOX and nab-paclitaxel plus gemcitabine, were not routinely used and this could be carried improve survival results. In addition, the identification of whole-genome sequencing may be directed more and more towards a "tailored therapy".

L44 Second-line chemoterapy in advanced gastric cancer patients

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Background: At the time of diagnosis 80% of gastric cancer patients present an inoperable, locally advanced or metastatic disease. In this setting first-line chemotherapy have shown to relieve symptoms and to improve quality of life and survival when compared to best supportive care alone. Instead, the role of a second-line chemotherapy in not still encored. The purpose of this study was to evaluate the efficacy and toxicity of a second line-mono -chemoterapy with Taxane (Paclitaxel or Docetaxel) in pre-treated pts with locally advanced or metastatic gastric cancer.

Methods: A total of 44 patients (Male 70%, Female 30%, median age 64 years, PS 0 10%, PS 1 45 %, PS 2 45%) who progressed after a first line chemotherapy (Al-Sarraf, FOLFOX 4, EOX, Trastuzumab) were enroled. Paclitaxel was administered at a dose of 80 mg/m2 repeated once a week for 3 consecutive weeks followed by a 1 week rest period (1 cycle). Docetaxel was administered at a dose of 30 mg/m2 repeated once a week for 3 consecutive weeks followed by a 1 week rest period (1 cycle). Pts were evaluated for tumor response every 12 weeks. Therapy was continued for a maximum of six cycle in pts showing tumor response or stable disease.

Results: We observed 13% of major response (RC + RP) and 26% of stable disease with a 39% of tumour control. Grade 3-4 toxicities were mild. No treatment-related death were observed. The median survival with 8.1 months with Paclitaxel and 8.5 months with Docetaxel.

Conclusions: Second-line chemotherapy in advanced gastric cancer patients can represent an important option respect to a best supportive care in terms of relieving symptoms, improving quality of life and overall survival.

L45 Efficacy and safety of combined sequential treatment with radiofrequency ablation and sorafenib in patients with hepatocellular carcinoma in intermediate stage ineligible for tace: a prospective randomized open study

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EuDRACT number: 2014-003925-16 Protocol Code Number: 054

Introduction: TACE is considered the gold standard for patients (pts) with Hepatocellular Carcinoma in Intermediate Stage (BCLC-B HCC). Pts with contraindications or ineligible for TACE are candidates for Sorafenib (S). Aim of the present study is to verify efficacy and safety of a combined treatment Radiofrequency Ablation (RFA)and S in pts with BCLC-B HCC ineligible for TACE. Primary Endpoint: Overall Survival in both groups. Secondary Endpoints: validation of CEUS for evaluation of RFA efficacy; safety and efficacy of combined RFA + S.

Methods: A prospective randomized open-label study is expected to enroll during 12 months 124 pts with BCLC-B HCC (3-5 HCCs nodules ≥ 3cm≤ 5 cm), not eligible for TACE or who refused TACE. Pts will be randomized 1:1 into two arms: Group A: S 400 mg bid; Group B: combined sequential treatment RFA + S. In Group B S will be administered for 2 weeks; then S will be stopped from 15th to 19th day to perform RFA scheduled on day 17. CEUS to assess the extent of necrosis and biochemical tests will be performed 24 hours after RFA. In case of complete necrosis, pts will re-take S 2 days after the RFA and will be followed-up . In case of incomplete necrosis, 2 days after RFA, pts will start again S at full dosage for 11 days, then drug will be stopped 2 days before the 2th RFA and resumed 2 days after procedure (up to 3 sessions of RFA; up to 2 nodules or a single nodule up to 5 cm, for session). Seven days after the last RFA therapeutic efficacy will be evaluated with CEUS and three-phase contrast-enhanced (CE- CT) shows the follow-up flow-chart.

Results: From December 2014 up to March 2015, 18 pts for group were enrolled. To date, statistical evaluation in terms of survival, safety and efficacy of treatment in the 2 group is impossible due to the too small sample size and the short time of observation.

L46 Exploratory study of histopathological characteristics of Hepatocellular carcinoma (HCC) in African (Tanzania) and Caucasian (Italian) population

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Background: HCC is a primary malignancy of the liver. HCC is now the third leading cause of cancer deaths worldwide, with over 500,000 people affected. Pathogenesis of HCC is different between Caucasians (C) and African (A) population. Infection with HBV and aflotoxin are most frequent in A while HCV infection are most frequent in C. These etiological differences are reflected in a different biological behavior of HCC. The aim of the study is to evaluate different pathways among the various types of HCC. Currently we speak of HCC, clinically we know that there are different subtypes, but these differences have not been identified at the molecular level.

Case series: 6 Tanzanian and 6 Caucasian patients with HCC in the Biosciences Laboratory at IRST (Meldola, Italy) as part of a global cancer control project currently being carried out in close cooperation with the Bugando Medical Center (Mwanza, Tanzania) were analyzed.

Materials and methods: Immunohistochemical analyses were performed by using the Benckmark XT (Ventana Medical Systems) with Cox 2(Cell Signaling), Hsp27(Cell Signaling), c-fos (Thermo Fisher) antibodies diluted 1:600, 1:100, 1:300 respectively. Samples were evaluated as positive in the presence of cytoplasmatic immunopositivity for Cox2 and Hsp27 and in the presence of nuclear immunopositivity for c-fos.

Results: All A cases were negative for Cox 2 expression while only one C case presented immunoreactivity 1/6 (16.6 %). C-fos is expressed in 83% of C cases and only in 50% of A cases. Hsp27 is expressed in 100% of C cases and only in 50% of A.

Discussion: These are the preliminary results of an ongoing study. In literature, there are few studies that evaluate differences of HCC insurgents between A population and C population. The initial data obtained show a difference in the expression of Hsp27. HCV infection could be correlated with the expression of this protein. HSP27 has also been object of research in order to elucidate its possible contribute to invasion and metastasis cascade affecting the overall survival of the patients. Overexpression of HSP27 was found to be associated with poor prognosis in different tumors. Other researchers report that HSPs in general and especially HSP27 can also represent the ideal target for cancer therapy treatment with appropriate drugs, as well as the target for the immune system. If the preliminary results are confirmed, HCC could be the ideal cancer to test these drugs.

L47 Osteopontin (OPN) and interleukin-6 (IL-6) as predictive biomarkers in HCC receiving loco-regional treatment: preliminary results

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Background: OPN, a potential diagnostic biomarker and therapeutic target, is a multifunctional protein involved in the carcinogenesis, neoangiogenesis and metastasization in many solid neoplasms. IL-6 is a mediator of the immunologic response involved in the hepatocyte proliferation and carcinogenesis. The aim of our study was to analyse the potential correlation between blood levels of OPN, IL-6, IL-2, VEFG and clinical outcome in HCC patients receiving RFA.

Methods: 14 patients diagnosed HCC and candidate to loco-regional treatment (RFA) with curative intent have been included in this study. Main inclusion criteria were: a solitary HCC smaller than 5 cm in diameter or multiple (no more than three) HCC smaller than 5 cm in total diameter; no extrahepatic metastasis; no radiologic evidence of invasion into the major portal/hepatic vein branches; good liver function with Child-Pugh Class A or B, with no history of encephalopathy, ascites refractory to diuretics or variceal bleeding; no previous treatment of HCC. Plasma levels of OPN, IL-6, IL-2, VEGF have been estimated through ELISA test in d0, before the loco-regional treatment and after 30 days. Patients with progressive disease at the first revaluation after RFA (15%), including local and new HCC sites in other hepatic segments, have been considered early progressors.

Results: A statistically significant correlation between the basal levels of OPN and IL-6 ($p = 0,001$) has been observed, while there was no correlation between the IL-2 levels and VEGF. The levels of OPN and IL-6 resulted not significantly modified after the regional treatment compared to the basal. Levels of OPN and IL-6 increased significantly ($p = 0,022$ and $p = 0,013$) in patients showing early progression after RFA

Conclusions: Although the limited sample size, we suggest that OPN IL-6 may be effective biomarkers for patients undergoing loco-regional treatment: OPN and IL-6 seemed in fact to able to predict response to treatment and to early identify the patients who may benefit from other anti-cancer treatments.

L48 Tolerability of FOLFOXIRI regimen after surgical resection for pancreatic cancer

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Background: The are no data at our knowledge about the tolerability of FOLFOXIRI schedule in patients (pts) who underwent resection for pancreatic cancer. The aim of this retrospective analysis is to investigate the safety profile of FOLFOXIRI in resected pts for pancreatic cancer.

Patients and methods: We retrospectively analyzed tolerability of FOLFOXIRI regimen in selected pts who had received surgical resection for pancreatic cancer within 12 months before start of chemotherapy.

Results: A total of 12 pts were included in the analysis: 8 male and 4 females received surgical resection from 2009 to 2014; two pts had metastatic disease at the time of resection; all pts had ECOG PS 0 at the start of chemotherapy. Six pts received a left pancreatectomy, 4 a pancreaticoduedenectomy e 2 a total pancreatectomy. In 11 out of 12 cases FOLFOXIRI was used as a first-line treatment for metastatic disease, in one case it was used in adjuvant setting in GIP-2 trial. A median of 6.5 cycles were administered. FOLFOXIRI doses were: 5-fluorouracil (5FU) 2800 mg/mq c.i.48h and Irinotecan (CPT-11) 150 mg/mq iv day1 in 4 pts, 5FU 2800 mg/mq c.i.48h and CPT-11 165 mg/mq iv day1 in 1 pt, 5FU 2400 mg/mq c.i.48h and CPT-11 150 mg/mq iv day1 in 3 pts, 5FU 3200 mg/mq c.i.48h and CPT-11 165 mg/mq iv day1 in 4 pts; the dose of oxaliplatin was 85 mg/mq in all pts. Dose reduction at 75% were necessary in three cases, in one case treatment was interrupted after two cycles due to deterioration of general conditions. Doses were delayed once in 4 pts. Four pts (33.3%) experienced = grade (G)3 neutropenia (3 pts G3 and 1 G4), but only in one case the use of G-CSF was necessary, while no thrombocytopenia was reported. Other grade 3 toxicities were experienced by 3 patients (25%). The detailed nonhematologic toxicities were: diarrhea in 7 patients (3 pts G1, 3 G2 and 1 G3); nausea/vomiting was present in 9 pts (3 G1 and 6 G2); 7 pts experienced mucositis (3 G1, 3 G2, 1 G3). Both fatigue and anorexia were present in 3 pts (2 pts G1-G2 and in one both were present as G3). Neurotoxicity was reported in 6 cases, all grade 1.

Conclusions: In this small cohort of patients the treatment with FOLFOXIRI seems to be feasible and safe even after pancreatectomy. Although nonhematologic toxicities were common, the majority of them were grade 1 or 2 and hematologic toxicity was not more relevant than those reported in metastatic disease.

L49 Ante mortem diagnosis of intracardiac metastases from known esophageal cancer: a case report and literature review

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Introduction: Metastatic spread to the heart from neoplasms are very rare, often silent and usually caused by direct invasion.Here we report a case of an asymptomatic cardiac metastases (CM) from esophageal carcinoma and a review from the literature.

Case report: In late July 2014, a 73-year-old woman diagnosed with locally advanced esophageal squamous cells carcinoma was admitted to our institution.Symptoms included dysphagia and right shoulder blade pain. No cardiothoracic metastases were detected at basal CTscan.Transthoracic echocardiography was normal with a LVEF of 60%.The patient was submitted to concurrent Cisplatin and Radiotherapy. On October, a CTscan and an endoscopy showed a reduction of both the esophageal mass and nodes.Before surgery, a new CTscan revealed 2 metastases in the right ventricle and in the interventricular septum.USS confirmed the 2 CM.An endomiocardial biopsy confirmed the diagnosis of squamous cell carcinoma from esophageal origin. Surgery and radiotherapy were not considered as therapeutic options.As the patient asked for a treatment, in February chemotherapy was started, but after two courses of Gemcitabine a pulmonary embolism and then a congestive hearth failure conducted to death on April 2015.

Discussion: As more of 90% of CM are silent, diagnosis is often difficult and in most cases it is discovered at necropsy.Symptoms or signs are often overshadowed in the metastatic disease. The patients usually die from other metastatic lesions.Intracavitary

or endocardial metastases occur in less than 6% of cases.In the literature,12 cases with ante mortem diagnosis of CM from esophageal cancer are reported. Patients main characteristics are:median age 61.8 years;male (66.6%);squamous cell carcinoma (91%). The median time to the onset of CM is 5.1 months; the method of choice to detect recurrence is echocardiography in 100% of cases; the right heart is more involved (58.3%); the structure primarily affected is myocardium (60%). Treatments used are best supportive care (33.3%), chemotherapy (25%), radiotherapy (16.6%) and 1 case of surgery before concurrent chemo-radiation; the median time to death from CM discovery is 3.7 months with an OS of 9.1 months.Our case is in agreement with these data with a median time to death from CM and an OS respectively of 4 and 8 months.

Conclusions: Our case reinforces the importance of the fact that undetected CM may exist.Accumulation of reports may help clarify the natural course of CM and how to treat them.

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Session M. Oncology nursing

M01* Propolis for prevention of chemo-induced oral mucositis in breast cancer patients: A randomized controlled trial

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Background: Oral mucositis is a major side effect of cytotoxic treatments associated with significant symptoms and increased costs. The incidence of oral mucositis in patients receiving standard chemotherapy regimens for breast cancer ranges 31-70%. Evidence-based guidelines cannot recommend effective prophylaxis for this population. Propolis is a natural substance with many biological properties, and relatively non-toxic. A dry extract of Propolis reduced severity of oral mucosa diseases and ulcers for recurrent aphthous stomatitis.

Materials and methods: This study aimed to evaluate safety, tolerability and efficacy of a dry extract of propolis with a minimum 8% of galangin for the prevention of chemo-induced oral mucositis in patients diagnosed of breast cancer. Adult patients scheduled to receive doxorubicin and cyclophosphamide in a Teaching Hospital were recruited. Patients recently diagnosed of stage I, II or IIIA breast cancer were included. Exclusion criteria were: allergy to propolis or pollen, poor oral health, recent therapy with antibiotics, steroids or immune-suppressor drugs. Randomization was managed by an external centre. Patients were randomized to receive a dry extract of propolis with a minimum 8% of galangin 8-10 mg/kg/day plus mouth rinsing with sodium bicarbonate (intervention group) or mouth rinsing with sodium bicarbonate (control group). Prophylaxis with sodium bicarbonate was routinely used where the study took place and was not withheld. The intervention lasted 15 days starting on the first day of chemotherapy. Incidence and severity of oral mucositis were evaluated using the NCI-CTCAE v4.0 at baseline, after 5, 10, 15 and 21 days of treatment.

Results: 60 patients were randomized to experimental (n = 30) and to control group (n = 30). All were female, mean age: 51 years (range: 26-75; SD: 11.4). The incidence of oral mucositis higher than G1, in the control group was 16.67%. No patient in the experimental group developed oral mucositis graded more than G1, while 5 patients in the control group developed mucositis grade G2 or G3 (p = 0,02; chi-square test = 5,455; df:1). Two patients (6.7%) manifested suspected skin reaction to propolis. Most patients wished to continue propolis also during the next chemotherapy cycles.

Conclusions: This study showed that propolis was effective in the prevention of oral mucositis. Propolis resulted well tolerated and safe. Multicentre studies should test the efficacy of propolis on bigger samples.

M02* Scalp cooling to prevent chemotherapy-induced hair loss

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Background: Since about 1970 scalp cooling has been used to reduce chemotherapy-induced hair loss, a well documented common cause of distress to patients undergoing cancer treatment,with negative effects on body image and quality of life. We prospectively collected data to evaluate efficacy and safety of this technique, side effects and satisfaction of women receiving chemotherapy as a form trestment for breast cancer.

Methods: The scalp cooling, by using a Paxman machine,it is composed of a refrigeranting unit whic is connected to a helmet of silicon. Inside flows a liquide which keeps the temperature at -4° C. Was offered to breast cancer patients starting chemotherapy containing anthracycline and/or taxanes;patients could be chemonaive or pretreated. Infusion times vary according to the schedule. Between june 2013 and december 2014 eightynine patients have been utilized pax in our hospital.Nurses completed questionnaires on patients,chemoterapy and scalp cooling characteristics during each session.Results were evaluated indicating the severity of hair loss according to CTCAE 3.0 during each chemoterapy session and taking into account patient's satisfaction during the last treatment.

Results: All patients werw women (one man) with breast cancer who were mainly treated in the adjuvant setting (80%) and are chemonaive. The mean age was 53 years (range 35-72). The median number of cooling session was 5 (1-12). 70% of patientsreceived anthracycline-based polichemotherapy (ac or fec 75 every three weeks) and 30% received monotherapy with taxanes on weekly schedule. Alopecia G0 and G1 were registered at the end of chemoterapy in 62% of the patients,irrespective of the type of treatment . 100% of these patients reported to be satisfied in terms of hair preservation during their last session. 27% of patients discontinued scalp coolingtreatment because of severe alopecia (G2); all these patients were receiving anthracycline. Scalp cooling was stopped because of intolerance in 11% of patients mainly due to discomfort and longer time of infusion.

Conclusion: The Paxman scalp cooler was found to be an effective technique with moderate side-effects for patients treated with commonly prescribed alopecia-inducing chemotherapy drugs.Lengthening infusion time seems to be the main limit of this system.

M03* Safe chemotherapy (CT) administration and impact on nurses' workflow of a mobile health (mHealth) information technology system

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Background: A *Safe Therapy Mobile (STM) System,* fully integrated with the electronic oncological patient record (eOPR), has been developed for the safe delivery of intravenous CT, from prescription to administration and reporting.

Materials and methods: At the moment of the CT prescription, the STM system automatically associates specific barcodes with the patient and each Ct and ancillary drug. At the patient bedside, a barcode reader checks the patient, nurse, infusion bag, drug sequence and time of infusion, in order to monitor and trace the entire administration process, which is then automatically reported in the eOPR. The usability and acceptability of the STM was investigated by means of a modified questionnaire administered to nurses, which explored the three dimensions of the *quality of working life*, the *perceived usefulness* and *ease of use of the system*. The questionnaire was administered to all 15 nurses in both Day Hospitals after each had used the STM system for at least two months.

Results: In February 2014, STM system was introduced into a Day Hospital with limited daily activities. Two months later, at the end of the testing period, it was adopted for routine chemotherapy administration in the larger Day Hospital of the Medical Oncology Unit of Trento. The STM never failed to match the patient/nurse/drug sequence/timing association correctly, and proved to be accurate and reliable in tracing and recording the entire administration process. The questionnaires revealed that the users were generally satisfied (86.66%), particularly concerning the perceived usefulness of the system when managing therapy administration (86.66%), the improvement in information sharing (93,33%) and the general perception of greater safety when administering the therapies (86.66%). The system was perceived as helping to associate the prescribed drugs with the right patient (73.33%) and respect the correct sequence of administration (93.33%), speeding up recording the details of the administered therapies in the eOPR (80%), although it appeared to slow down bedside operations (60%). No significant objective differences in the duration of CT administration however were found after the system was introduced.

Conclusions: It appears from these data that the STM system may effectively ensure a safer in-hospital delivery of infusion chemotherapy with a positive impact on nurses' workflow.

M04* Peripherally inserted central venous catheters (PICCs) in cancer patients placed by specialist nurses. A prospective observational study of 817 consecutive catheterizations

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Background: A central venous catheter (CVC) currently represent the most frequently adopted intravenous line for patients undergoing infusional chemotherqapy and/or high-dose chemotherapy with hematopoietic stem-cell transplantation and parenteral nutrition. Unfortunately, CVC insertion in subclavian or internal jugular vein represent a risk of pneumothorax, nerve puncture or major bleeding. The aim of this prospective observational study was explore the safety and efficacy of peripherally

inserted central venous catheter (PICC) and to confirm its utility in clinical practice in cancer patients.

Methods: Consecutive adult patients attending the oncology-hematology department hospital of Piacenzawere elegible if they had solid tumors or hematological malignances and required CVC insertion. Four types of possible complications were defined a priore: mechanical, thrombotic/hemorrhagic, Infection and malfunctioning. Operators included a group of four nurses (PICC-Team) with specific experience with ultrasound guided vein catheterization. All PICCs were inserted in a dedicate room, with US-guidance using an US-machine exclusively dedicated for PICC insertion (SONOSITE, NANO MAX, Milan). The catheter was inserted into the basilic or the brachial vein and the appropriate central position of the catheter tip was always verified either by the intracavitary electrocardiography during the procedure and by chest-X Ray at the end.

Results: From April 2012 to April 2015, 817 PICCs were applied in 787 patients. The procedure was performed 146 times in hematological malignances and 671 times in solid tumors. The procedure was efficacious in 98,3% of cases and failed in 1,7%of cases. No bleeding, no nerve punctures and no hematomas were reported. Symptomatic vein thrombosis developed in 2,57%of cases, mainly in the first 15 days of implantation, no pulmonary embolism was recorded. Catheter-related infections occurred in 1,36% of the PICCs inserted. The Insertion of PICC allowed the delivery of the planned therapy in 96,7% of the cancer patients.

Conclusion: This study represent a large series of consecutive patients with cancer undergoing PICC insertion successfully performed by specialist dedicated nurses. The procedure allowed completation of the therapeutic program for the 96,7% of the patient with catheter inserted.

M05* Efficacy of cryotherapy in paclitaxel-induced nail toxicity: sperimental study Phase II

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Background: Taxanes are cytotoxic agents that induces nail toxicity in several or all nails. Toxicity may be asymptomatic and limited to cosmetic concern but other severe effects like pain and discomfort can occur. The physiopathology is uncertain. A successful approach in preventing nail changes is cryotherapy that temporarily causes vasoconstriction. In literature of last 10 years not many studies describe cryotherapy and his effects on nails. Frozen gloves and socks used in these studies reach a temperature from -25°C to -10°C and are often refused because of discomfort.

Materials and methods: This study is a sperimental Phase II and will be performed in Multidisciplinary Day Hospital of CRO Aviano starting from May 2015 for a Year. It investigates all patients treated with cryotherapy on nails during infusion of paclitaxel to evaluate effectiveness in prevention, reduction or delay toxicity. Other objectives are to evaluate: time of occurrence and grade of toxicity, tolerance and compliance. The study will enroll 62 patients to estimate a 15% reduction in nail toxicity (i.e., from 40% to 25%) fixing the a priori probabilities alfa 0.05 and beta 0.20. Criteria for inclusion are: patients diagnosed for breast cancer, treated with weekly chemotherapy containing hourly paclitaxel for the first time for 3 cycles with no previously nail disease and collaborating to the treatment. Exclusion criteria: Raynoud's syndrome, poor collaboration and no previous treatment with taxanes. Partecipants will wear frozen bags of a temperature from -5°C to 0°C on hands and feet nails during drug infusion for a total of 70 minutes. Nail condition is assessed every week by the nurse. Every kind of nail change, including pain, is evaluated using CTCAE 4.02 grades and through photographs. At the end of the treatment we will explore satisfaction.

Results: Results of our study aim to demonstrate efficacy of cryotherapy in reducing nail toxicity in patients treated with paclitaxel. We expect a reduction of 15% from incidence from literature, a raise of occurrence time of toxicity, a reduction of pain and a good level of compliance.

Conclusion: As reported in scientific literature an important limit in cryotherapies compliance is the low temperature of frozen glove and socks. The use in our study of a temperature from -5°C to 0°C will allow a better compliance to the treatment and consequently a reduction of nail toxicity using frozen and a raise of time of occurrence.

M06 Descriptive study for the prevention of Hand-foot syndrome in oncologics patients who undergoing cycles with 5 FU, sorafenib and capecitabine

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Introduction: Hand Foot Syndrome (HFS) and Hand Foot Skin Reaction (HFSR) are the manifestation of painful erythematous lesions that are located on the palmar plantar region. There are no clear guidelines for implementing an optimal preventive behavior.

Objective: To compare the effectiveness and appropriateness of Urea 5%, cream based moisturizer and Holoil® in injury prevention in patients with high risk of developing HFS and HFSR HFSR because undergoing chemotherapy cycles with sorafenib, capecitabine and 5-FU.

Materials and methods: Descriptive study between January 2014 and February 2015. The inclusion of patients in the study was carried out through randomized method Inclusion criteria: 1. Age greater than 18 years; 2. Capability of discernment intact; 3. good understanding of the Italian language; 4. favorable opinion in accordance with the privacy policy; 6. cancer patient at the first cycle of chemotherapy with Sorafenib, 5FU and Capecitabine in monotherapy or combination chemotherapy. Exclusion criteria: 1. lesions overt arrival of the patient in the structure; 2. Diabetes mellitus treated and / or neuropathy diagnosed.

Results: 70 patients enrolled, the moisturizing products were assigned in numerically comparable proportions. The drugs most frequently are 5FU and capecitabine. 14 patients developed the lesion, the statistical analyse is not statistically significant (p = 0.3493, Degrees of Freedom: 2) in terms of effectiveness in the prevention of injury. The incidence of injury within the sample appears to be decreased compared to the literature: 52% Capecitabine, 40% Sorafenib, 35% 5FU. The timing of the onset of the injury appears to be dilated compared to literature, most markedly for Sorafenib which is the chemotherapy drug with which the injury occurs more belatedly: (median days of onset: 85). Urea 5% is the product emollient with which the lesion develops earlier (median day of onset: 21).

Conclusions: The incidence of lesion was decreased compared to literature. What appears to be positively incisive is the adoption of preventive measures rather than the use of an emollient product compared to an else. The percentage of patients not adequately informed about HFS and HFSR turns out to be large and the use of an informational interview devoted to this has proved to be a valuable tool for passing information as preventive behavior, often, is not put in act for lack of information and education to the patient.

M07 Tunnelled peripherally Inserted Central Catheters

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Background: The patientcare requires frequently the availability of a reliable long-medium term venous access, due to the particular complexity ofthe chemotherapy regimens, the frequent need for a nutritional or transfusional support and for periodic blood sampling. Peripherally Inserted Central Catheters (PICC) are an important innovation technology that has substantially changed the approach to the venous system. Usually they are inserted ad the middle third of the arm at an equal distance between axilla and elbow. Sometimes it could be requested an implantation more proximal to the axilla so the realization of a tunnelled device may be needed.

Methods: After careful ultrasonographic evaluation of both arms and of all veins, we proceed to the implantation of PICC in respect to the current international guideline with the Seldinger technique. Whenever it is impossible to maintain the insertion at the middle third of the arm, we proceed positioning the device more proximal to the axilla and then realizing a tunnel; this allows us to obtain an exit site congruent with the middle third of the arm.

Results: From January to September 2014, 343 procedures were applied for 290 onco-haematologic patients (84.5%) and 53 internistic patients (15.5%). In two cases since the basilica vein of our patients was too small at the middle third of both arms, we decided to insert the PICC proximal to the axilla. Subsequently the insertion we proceeded realizing a tunnel and creating an exit site at the middle third of the arm. The procedure was in both cases without complications such as pain, malposition or increase of the time for insertion. In both the cases the PICC had a long life, exactly 10 months for the first and 15 for the second.

Conclusions: In experienced team, a tunnelled PICC or midline could be an option whenever it is impossible to maintain the insertion at the middle third of the arm. This technique can allows operator to guarantee a stable and safe vascular access. Moreover, the procedure is simple, does not extend the time of insertion and does not create discomfort for the patient.

M08 The experience of nurses facing death of cancer patient in Hospice: a qualitative study

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Background: Death is an event that, by its nature, has acquired different peculiarities, until arriving at its current medical meaning. In fact, today special emphasis is placed, on the management pain and all the symptoms related to terminal illness, by definition, no longer treated by curative approaches but by palliative interventions. The latter treatments are increasingly being provided in specific structures, the Hospice,

within which health care providers, and firstly among them nurses, are in continuous contact with the event Death. Even though described in literature, it is evident how much that experience could be hard and stressful. In fact, the goal of this study is to evaluate the experience of nurses facing death of cancer patient in Hospice.

Materials and methods: This is a qualitative descriptive study. The purposeful sample is represented by the nurses working at the Hospice San Marco of Latina. Data were collected by semi-structured interviews featuring three questions, audio recorded, produced through focus groups, between September and November 2014. The interviews were then transcribed "word by word" and analyzed using the Framework Analysis as a methodology for the identification of themes that capture the meaning of unity and global experience described by each nurse.

Results: A total of four focus groups were conducted (medium number: 4/5 nurses participating for each group). By this analysis, among the data obtains three themes: death is a natural event; the dying creates the pain of separation; death determines the need for a network of psychological, relational and spiritual relief.

Discussion: Based on these data, death is considered a natural occurrence especially when it concerns the older individuals, which always causes the pain of separation, not only in the relatives of patients, but also in nursing staff. In order to improve the comparison of the nurse with the event death, it is necessary to create experiential groups conducted by a psycho-oncologist and training courses, in order to improve not only technical skills, but also tools capable of moving more delicate resources.

M09 Nurses and Clinical Research Coordinators (CRCs) collaboration to improve quality in clinical trials

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Background: Collaboration between team members is essential in order to improve clinical effectiveness and care quality in cancer clinical trials, as they have become increasingly complex and require a fully integrated multidisciplinary team. There is no sufficient knowledge of neither the interactions and communication strategies between nurses and CRCs in cancer centers nor the communication strategy enhancement to achieve optimal conduction of clinical trials in the healthcare setting. Nurses and CRCs of IRST scheduled a series of meetings to improve care quality for patients involved in CTs and promote the integration between professionals.

Methods: Based on a previous survey that had highlighted this lack, a series of meetings was scheduled to improve the exchange of knowledge and skills, define operative procedures to ensure a correct and complete data collection, identify paths and tools to facilitate the conduct of clinical trials. During the meetings participants also provided an update of ongoing studies, discussed any relevant issue, proposed actions for improvement, presented the results of the studies already completed and published.

Results: From March 2010 to March 2015, 11 meetings were held and attended by an average of 15 nurses (of the ward and day hospital) and 8 CRCs of the Biostatistics and Clinical Trials Unit. A meeting report was compiled and participants' attendance was recorded in each meeting. All items showed a trend of improvement, with significant reduction in the number of missing data and protocol violations reported to the Ethics Committee and the Principal Investigator. New procedures have been produced for the collection and management of hematologic samples for centralized laboratories, the recording of vital signs, the devices utilization and the sharing of trial documents in e-medical records, such as protocol, informed consent and information for patients and GPs. The presence of a nurse at the Selection Visit (SV) and at the Initiation Study Visit (SIV) was introduced.

Conclusions: Optimal integration between different professionals requires personal motivation, organization, sharing of common goals. Multidisciplinary meetings to discuss, plan together and share knowledge improve collaboration among professionals and help to increase the quality of clinical research and to ensure the patients receive the best care.

M10 A computerized approach for the management of peripheral and central venous accesses

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Background: In the last years in our Department it was created a team specialized in positioning and management of peripheral and central vascular access. This team is composed of six nurses and only an oncologist. With the increase of patients, the elaboration of a structured pathway has become our priority in order to guarantee a more efficient and effective performance.

Methods: We proceeded with a careful revision of our actual service in order to identify possible critical points and bottlenecks for the patients.

Results: We identified four critical points, named number of daily appointments and subdivision in peripherally or central inserted catheter; number of inpatients and outpatients; management of complication. We redesigned our service by creating a computerized system aimed to receive and manage requests and appointments as well as manage complications such as thrombosis. This system allowed us to define a fixed number of daily appointments of which 30% were reserved to outpatients and 70% to inpatients; moreover, for each day a fixed number of appointments for each type of vascular access was established. The computerized system was implemented also with an application for the management of thrombosis; this application consists in a flow-chart that guides the clinician in selecting the more efficient and effective therapy and automatically organizes the subsequent follow-up. Finally, the system was completed with a computerized form reporting the type and characteristics of the implanted device, vein, ultrasonographic guide, number of venipunctures, name of operator and date of positioning. Furthermore, with this computerized support we were able to create a data- base.

Conclusions: The critical revision of our service appeared a very useful strategy, being able to identify our organizational weaknesses. In this way we have organized a computerized system that allowed us to better manage not only appointments but also the complications. This in turn, is resulted in a reduction of waiting times and in a benefit also in terms of costs containment.

M11 Falls in hospice: analysis of the problem through the method of clinical audit

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Background: Fall of hospitalized patients represents the most relevant adverse event reported in clinical settings, since the resulting consequences affect both patient and sanitary system by economical and organizational mean. Falls risk factors vary according to patients clinical status and increase with the presence of frailty factors. Patients hospitalized in hospice are among those most frail due to the simultaneous presence of advanced/terminal stage neoplastic disease, comorbidities, pharmacotherapies. Falls rate observed in the hospice of Rimini is higher compared to other divisions of the Oncology department. We conducted an audit in patients hospitalized in hospice in 1year period in order to analyze the fall event and its management in prevention, identification of risk factors and at its occurrence.

Materials and methods: The director of Oncology department in Rimini Hospital commissioned the audit on 132 randomly selected clinical charts. They have been analyzed for adherence to selected indicators and collected data include evaluation of risk factors, prevention and management of falls, adherence of medical and nursing staff to specific sanitary procedures.

Results: Regarding fall event, there was moderate compliance in the use of medical chart: excellent/good medical evaluation of fall risk was present in 74,5 % of cases, while nursing evaluation is of same level in 60% of cases. Falls risk factors were identified in 66% of charts (58% in the appropriate "fall risk evaluation form", 8% deducible by an extensive reading of the clinical diary completed by medical and non medical staff) and they are typical for this setting of patients, including anamnestic (50%), pharmacological (20%) and comorbidities (9%). Preventive measures were planned in 39% of cases and executed in 45% of cases. A sub-analysis conducted on 9 fall events (6,8%), showed that reporting was not always accurate, thus resulting in a significant underestimation of risk factors. Management of falls, when Occurred, was conducted appropriately. A final report was presented in a closing meeting and actions to be implemented have been discussed and agreed by all the division's operators.

Conclusions: Fall rate observed in the hospice of Rimini was confirmed higher compared to other oncology's divisions, but in line with what observed in similar settings. Education to patient and caregiver and a more consistent and homogenous use of clinical chart are expected to be easily improved.

M12 Analysis of the experiences, needs and difficulties experienced by oncological patient's caregiver: a quanti-qualitative survey

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Background: In the last decade the incidence of cancer diagnosis has increased significantly and the assistance of cancer patients was mostly given to informal caregivers, often lacking in the knowledge and skills needed to cope with the responsibilities arising from that role.

Objectives: To analyze the experiences, difficulties, emotions and needs of the cancer patient's informal caregiver, to investigate the level of satisfaction in the relationship with doctors and nurses of the C.O.E.S. and to contemplate the possibility to create some focus groups with caregivers and nurses.

Materials and methods: The study involved 350 caregivers of patients being under treatment at the C.O.E.S. of City of Health and Science hospital of Turin in the period between October 2013 and July 2014. The evaluation was carried out by distributing a questionnaire consisting of 16 items.

Results: Over half of the caregivers were female (71%), patient's spouse (52%) with a mean age of 56 years, while cancer patients were mostly male (54%), retired (52%) with a mean age of 64 years. The majority of caregivers surveyed admitted that the caregiving activity has had a big impact on their daily lives (94%), work (38%) and finances(61%). Many of them often felt unprepared for this role and tried feelings of sadness (53%), impotence (46%), fear (39%) and anger (36%). The main difficulties experienced at home were help the patient in the activities of daily living (61%), understand his/her needs (38%), help him/her and in the management of pain (29%) and communicate feelings and fears (15%). Some caregivers revealed also positive aspects of the caregiving role: being helpful (49%), taking care of their loved ones (36%), sharing new experiences and emotions (22%), rediscover the value of little things (19%). The results showed high levels of satisfaction with the medical and nursing staff (99%), even if the psychological support was a little insufficient (92%). Many caregivers wouldn't take part in a focus group as sharing their personal experience and emotions with strangers would be too difficult and painful (69%).

Discussion and conclusions: A greater support should be provided to cancer patient's informal caregiver. Nurses need to ensure that caregivers receive a psychological support and an adequate training to face the caregiving role and avoid strain and burden.

M13 Nursing assessment of constipation in surgical oncological patients: a retrospective descriptive study

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Background: Constipation is a problem characterized by a set of symptoms defined by the Rome III criteria. Is particularly present in oncological subjects undergoing abdominal surgery or in oncological patient who receive chemotherapy. Variations depending on concurrently risk factors or the used diagnostic criteria. The nurse are guided in risk assessment, prevention and treatment of constipation process by the Evidence Based Nursing raccomandations.

Objectives: Describe, according to the RNAO 2011 Guidelines, used criteria for risk assessment, prevention and treatment of constipation and compare them with practice inside some departments of surgical oncology.

Materials and methods: Retrospective descriptive study. The study population is represented by 100 cancer patients from two departments of surgery of AOU "Città della Salute e della Scienza" of Turin, which will undergo surgery during the observation period between May and September 2014. Data contained in the medical and nursing records were reviewed in order to detect the degree of compliance with the RNAO recommendations. The data related to quantitative variables were analyzed reporting cumulative and percentage frequencies; for qualitative variables simple and percentage frequencies; the obtained data were compared using "Chi-square test" and "Fisher's exact test".

Results: Among the approximately 100 specific items which should be gathered by nurses in the process of constipation risk assessment, the data that occur frequently are:

- Acceptance: frequency of bowel movements (55%), incontinence (70%), diet (59%), mobility (83%);
- Postoperative: channeling in gas and feces (70%), nutrition and hydration (80%), early mobilization (96%), hygiene (98%), bowel movements (76%);
- Discharge: diet (59%), mobility (63%).

Conclusion: From the study's results can be assumed that nurses focus on the acute phase; during the acceptance, risk assessment and prevention are not taken into account and during discharge seems to lack a personalized educational project. The amount of information that nurses collects according to the RNAO 2011 Guidelines, seems to be inadequate for a complete bowel evaluation; this argument is supported from data on alterations of bowel motions reported during follow-up visits. Is reasonable to assume that the introduction of standardized tools for data collection could increase the level of attention of nurses during the process of evaluation and data logging.

M14 The Nutrition of a Cancer Patient: Perspective Cohort Study on The Variation of the Consume of Meals by Location and in Caregivers Presence

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Background: To evaluate the intake of food that oncology patients hospitalized in the ward are taking in during the three different meals of the day (breakfast lunch and dinner) and observe how their dietary behavior changes according to the place where they eat their meal (in the dining room or hospital room) and in the presence of a caregiver.

Materials and methods: It was done a prospective cohort study for a period of 65 days in the oncology ward of a hospital located in the northeast of Italy. To collect all the data the patients filled an ad hoc questionnaire. The variables regarding the meals were described in three forms (breakfast lunch and dinner): place where the meal was eaten, presence of other patients eating, presence of caregivers, consumption of snacks between meals, discomfort conditions, type and amount of food eaten. For the analysis of the data were used Wilcoxon Signed-Rank Test, Wilcoxon Rank Sum Test and Chi Squared Test. The statistical significance was calculated on a value of $p < 0.05$. The software used were Microsoft Excel 2007 and 2010, XLSTAT Ver. 2012.6.06.

Results: The questionnaire was filled by 41 patients and 522 meals forms were taken in consideration. The consumption of meals was evaluated and obtained by averaging the percentage of amount of food eaten and calories consumption. Lunches and dinners taken in the dining room are consumed 14.9% more ($p < 0.0001$). Patients who eat their meal with other patients who were also eating have a food consumption of 5.8% higher than those who eat with other patients who are not eating ($p = 0.026$). Eating with a caregiver rather than alone leads to increase the food consumption of a 10.7% ($p = 0.048$).

Conclusions: Eating in the dining room leads to a higher consumption of food: a cozy and familiar room is a favorable factor; it is conceivable that the patients who eat in the dining room with other people feel better and this could lead to a higher food consumption. The phenomenon of the social modeling that brings people to mimic the eating behavior of their pals is confirmed in this study. The presence of a caregiver increases the food consumption because it helps to create a positive environment and increases the time dedicated to the meals. It is essential to encourage oncology patients to eat their meals in the dining room. This implies looking for solutions for those who cannot leave the room. For the patients' welfare it is important to encourage the presence of a caregiver during meals.

M15 Experimentation of a nursing record in Oncology, in printed and digital formats, according to Gordon model with classification Nanda-I, NOC and NIC : analysis and comparison with the nursing documentation department

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Introduction: During the training of the third year of the Nursing Degree of the University of Trieste, at the Oncology Hospital Maggiore of Trieste I observed the organizational model of care implemented and the tools used by the team to provide nursing care to the client, such as nursing record noting that was built on a physiological model, incomplete and unclear among the health needs of the person. On the strength of my university experience, that over the 3 academic years included the use of the 11 functional health models of Gordon and taxonomies NNN (NANDA-I, NOC, NIC) for care planning, I decide to experience the process of nursing in printed and digital formats.

Objective: The primary aim of the thesis was to document the individual oriented nursing and results of health of the person. The secondary objectives were: firstly sensitize the nurses and nursing students using a standardized nursing language in the paperwork and digital process nursing care; secondly implement within the clinical information systems with the purpose of recording the data clearly care and reduce the time required for document management and dedicate them to the planning and management of the person.

Materials and methods: The experimentation of nursing record occurred in Oncology, from 13/10 to 23/10/2014. Enrolled in the trial: 6 assisted present in the ward within 24 hours of admission. Exclusion criterion: the presence of the assisted before the beginning of the trial. The nursing record proposal for the collection of data regarding the medical history of the person was structured on the 11 models of Gordon and taxonomies NNN.

Results: The investigation carried out by the nursing record experimented has allowed to evaluate the holistic health needs of the people seen at the Oncology, to highlight the problems with the definition of nursing diagnosis NANDA-I, to fix the results NOC and to choose NIC interventions most appropriate to meet the care needs of the clients.

Conclusions: The use of a classification recognized at the international level would lead to a standardization of the nursing language in the worldwide. The use of a Gordon digital nursing record would brought a great evolution of the nursing profession, a better organization of the nurse's work, save resources and increase the quality of care of people assisted.

M16 Improving cancer patients' information about ports

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Background: Cancer patients requiring intravenous chemotherapy are often exposed to totally implantable access ports (TIAP). Most cancer patients wish to receive as much information as possible, but more than 50% are not satisfied with the amount of information received. Patients may need information about TIAP structure, management, complication signs and phone contacts in case of problems. Booklets are recommended informational aids. The aim of this study was to evaluate the effectiveness of an information booklet in improving cancer patients' knowledge about TIAP.

Methods and material: This pre-post study was conducted between August and September 2012 in a teaching hospital in Rome. Adult cancer patients with a TIAP since at least 6 months were recruited. Participants completed a 7-item test assessing knowledge about TIAP, together with a 7-items questionnaire regarding information needs and preferred sources of information (T0). Patients were provided with a booklet and asked to read it before completing again the test of knowledge about TIAP, and a 8-item scale investigating opinion about the booklet (T1). Pair t-test was used to evaluate the change between T0 and T1 in knowledge about TIAP.

Results: The 129 patients with cancer enrolled in the study were quite balanced in gender (51.2% female), with a mean age of 59 years (SD = 12; range = 34-81), and with an average level of education (16.3% completed elementary school; 27.1% middle school; 37.2% high school; 15.5% university; 3.9% post-degree). At baseline, 42,6% of the participants reported having received little information about TIAP, and 95,3% wished to receive information before TIAP implantation. ANOVA at T0 showed that patients who desired as much information as possible (n = 39) scored higher in knowledge about TIAP than patients who desired just a lot or enough information (n = 90) about TIAP (mean = 5.15; SD = 1.5 vs mean = 4.54; SD = 1.2; $p < 0.05$). Change in knowledge about TIAP was significant between T0 and T1 ($p < 0.001$; effect size = 0.689; power = 1). Patients improved their knowledge from 4.72 (S.D. = 1.28) at T0, up to 6.53 (SD = 0.65) at T1. More than 75% reported that the booklet was very useful and 76.2% that it decreased their level of anxiety.

Conclusions: The study supports the provision of written information materials about TIAP to all patients, if possible before TIAP implantation. Booklets can facilitate patients to absorb, retain and recall information about TIAP.

M17 The prevention of malnutrition in a person with the disease cancer: application of a format verification, model of nutritional-metabolic according to Functional Gordon, with NANDA-I NOC and NIC

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From the data of the literature, it appears that approximately 69% of people with malignant disease showed a weight loss of more than 5% of their usual weight already in the 3 months prior to the diagnosis, with a higher frequency in cases of cancers of the digestive tract.
Given the situation, the person has difficulty coping with the disease and its treatment. The consequences of malnutrition on these subjects occur influencing both the psychological and the physical stability and modify the therapy compliance.
Also cachexia secondary to malnutrition is, directly or indirectly, cause of death in one third of deaths from malignant disease and its presence already predicts a decreased response to chemotherapy.
For the prevention of malnutrition in oncology, it is proposed to establish a card-based Model Nutritional Metabolic according to Gordon, that allows you to analyze the eating habits of the patient considering: the consumption of food and fluids, metabolic needs, the objective and subjective difficulties in feeding. The parameters of the investigation include: eating habits, the rating scale Must (with their weight, height and BMI index), the conditions of the skin, mucous membranes and teeth, measuring the body temperature, allergies and food intolerances, the presence of pressure sores.
Following detection and related diagnostic reasoning can formulate the Nursing Diagnosis, setting the objectives and related care interventions according to taxonomy NANDA-I, NIC and NOC.
The statement accompanies the person from the first access to the facility to periodically re-evaluate the nutritional status.
The objective of this study are the early prevention of malnutrition, to improve the state of well-being, to decrease side effects related to treatment and to decrease the number of hospitalizations due to malnutrition.

M18 Patient adherence to oral therapy in oncology. Measuring instruments and strategies for improvement: literature review

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Background: Currently, only 5% of anticancer drugs is available in oral formulation, while 20-25% of the chemotherapy drug under development have an oral formulation. This means that these chemotherapy drugs will be commonly used in cancer treatment. Many studies have observed that the adherence to oral cancer therapy is decisive for treatment effectiveness. The lack of adherence to treatment, according to WHO, can be linked to various factors.The review aims to identify the best valid measurement tools and strategies to promote adherence to oral chemotherapy.

Materials and methods: We have been performed several literature research by the following internet databases: PubMed, The Cochrane Library, CINAHL and the magazine of Asco Educational Book of 2013. The search was performed linking search headings "medication adherence," "adherence assessments tools," with "oral antineoplastic agents" and "oral cancer therapy". For the fulfilment of this review it has been possible to formulate the question with 2 Pico models.

Table 1: M18 First PICO

PATIENT	Cancer patients who take oral therapies
INTERVENTION	Identify strategies to increase adherence
COMPARISON	/
OUTCOME	Increase therapeutic adherence

Table 2: M18 Second PICO

PATIENT	Cancer patients who take oral therapies
INTERVENTION	Identify the tools to assess the adhesion
COMPARISON	/
OUTCOME	Select the most effective tools in adherence assessment

Inclusion criteria: We have been included full-text and abstract, between 2000 and 2014 to detect assessment tools and strategies to increase adherence, in patients who take oral therapy with biological drugs and / or chemotherapy.

Exclusion criteria: We have been excluded all articles aimed to indentify assessment tools and strategies to increase adherence in patients with non-neoplastic diseases.

Results: This review identified 61 articles with inclusion criteria and we selected 14 articles. Non-adherence in medication can considerably compromise the effectiveness of oral cancer therapies. Many methods have been used to measure adherence to oral therapies in cancer patients, each of which is limited by methodological faults and distortions. A major problem is the lack of a standard measurement tool. At present the association of multiple instruments is the best choice.

Conclusions: Nurses play a key role in the monitoring of adherence. They should ensure understanding of the treatment aims, promoting the management of side effects, identifying the barriers to adherence with a suitable measuring instrument.

M19 Hyponatremia in cancer patients

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Background: Hyponatremia is a condition characterized by a concentration of serum sodium below 135 mEq/L. Several conditions can cause hyponatremia through various pathophysiological mechanisms: among the others it can be induced by drugs, including chemotherapy, diuretics and antidepressants, or it can be determined by the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Material (patients) and methods: We analysed 423 patients with non-small cell lung cancer (NSCLC) treated at the Department of Medical Oncology of our institution, between 2006 and 2014. Of each patient we collected demographic, clinical, haematological and biochemical data. Serum sodium levels before starting treatment, during treatment and at the end of treatment were also were included.

Results: All patients were interviewed by a nurse before, during and after chemotherapy. From these interviews is showed that hyponatremia, even modest, was associated with walking instability, falls and increased risk of fractures. Approximately 60% of patients with hyponatremia, although mild, experienced neurological symptoms including lethargy, headache, impaired memory. Furthermore, in our series of patients we observed an increase in the number of falls.

Conclusions: This study underlines the impact of hyponatremia on patients' quality of life and well being. A correct diagnosis and therapy of hyponatremia can help to improve quality of life and patients' well being. In this context, nurses may have an important role to identify early symptoms and to contribute to monitor serum sodium levels.

M20 The quality of information received by women with breast cancer treated with surgical and medical therapy in Breast Care Unit: a descriptive survey

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Background: Information is one of the most important needs for the patients after diagnosis of cancer. Many studies have shown that informational and emotional support leads women with breast cancer diagnosis to manage the disease in complete autonomy and awareness. Medical doctors and their staff have to manage this type of needs in order to increase the compliance of the patients. The aim of this study was to assess the quantity and the quality of information. Moreover, it was shown the most utilized sources of information and the favorite way of support.

Material and methods: A questionnaire of 23 items was submitted to 150 women with breast cancer after surgical procedure (one between quadrantectomy and mastectomy) and treated with at least one adjuvant therapy between chemotherapy, radiotherapy, hormonal therapy, biological therapy and target therapy. The study was conduct at A. O.U. Città della Salute e della Scienza of Turin between December 2013 and May 2014.

Results: The level of information was medium/high for the 94% of the women. The 76% of the sample felt well involved in the decisional process of therapy and 84% of women were satisfied of information about surgical procedures. The 63% of the patientswere informed of psycho-oncological support but only 28% of the sample was aware of counseling groups. Women preferred medical doctors (47%) and nurses (18%) as the most important sources nevertheless the 81% declared that information exchange between women is important, as well.

Conclusions: Information is one of the cures to tackle cancer and the study showed that the quality and the quantity of information were relevant and satisfying. However, nurse could play an important informational role to increase knowledge and awareness of women with breast cancer in order to decrease the weak points.

M21 The ZIM method: study of complications associated with PICC insertion site selection

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Background: The ZIM method is a method to locate the ideal area for the insertion of PICC. This method detects a specific pattern of areas that offer a variety of risks and benefits for the insertion of the device and its management taking into account the characteristics of the musculo-skeletal tissue, skin and vessels. It has been conducted a longitudinal observational study of comparative complications developed following the implant of the PICC according to the ZIM method and by the traditional method. Does the choice of the PICC insertion site with the ZIM method reduce the incidence of catheter-related complications than the traditional method? By which percentage the PICC inserted without following the ZIM method are still positioned in the area of the arm considered ideal?

Materials and methods: The sample was composed by 84 patients in which it has been placed a PICC between June 17th and November 4th 2014 at the Oncology of Novara. The patients was randomized in: Group 1: Zim method insertion (42) Group 2: Traditional method insertion (42) About patients belonging to Group 2, after the insertion it has still measured the point of insertion of the PICC in the arm, for to see in which area of the ZIM method it has been implanted

Results: On 84 PICC placed 92.8% no complications (64 PICC in use, 5 removed and 9 patients are died) and the remaining 7.14% developed some complication.: Complications reported by the ZIM method insertion: Breaking the outer tract of the catheter, secondary dislodgement Complications reported by the traditional method insertions: Dislodgement, loop of the catheter, 2 breakages of the outer tract of the catheter, deep vein thrombosis This initial observation shows that the ZIM method is an optimal way to reduce the incidence of the post-insertion complications.

Conclusions: Compared to the evaluation parameters established by Robert Dawson the Deep Vein Thrombosis is the only complication associated with the choice of the insertion site; other complications are associated with the device management, so only apparently the ZIM method can be considered valid. Although it hasn't verified the validity or not of the ZIM method, this study revealed three interesting data:

- 88% of PICC belonging to Group 2 have been placed in the green area according to guidelines of the ZIM method.
- A good management of the device by the nurses is essential to prevent the development of late complications.
- The ZIM method could be used for training.

M22 Observational study on the actual flow rate of 5-fu filled elastomeric pumps in comparison to what declared by the producer

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Background: In the course of our experience of infusional therapy in the Department of Medical Oncology of the Sant'Antonio Abate Hospital in Trapani we have detected frequent differencies between the actual emptying times of elastomeric pumps containing 5-FU in saline and those declared by the producer in the technical details.In order to further explore the entity of these differencies we have designed an observational study fulfilled between October 2014 and March 2015.

Material and methods: We have evaluated two lots (CT14EDH88 and CT14DDH48) of Accufuser Elastomeric Pumps used for a total of 92 5-fluorouracil infusion therapies. The staff of the department of medical oncology has developed a form containing the necessary information to conduct this study such as the date and time of start of the infusion and the date and time of complete emptying of the pump as reported by patients. In order to calculate the density of the solution the amount of the drug was also recorded in the form.Emptying times, average infusion rate and density of the solution were calculatedand compared to look for a possible relationship of proportionality and to understand the reasons for the significant differences in declared andactual flow rate.The elastomeric pumps were filledup to a volume of 89 ml to obtain an emptying time of 44 hours, for a rate of 2.02 ml /hour according to the technicals details.

Results: Out of 92 therapies, 3 have reported emptying times one hour longer than the time declared in the technical details, therefore they had a flow rate slightly lower than expected. 3 therapies (3.2%) reported emptying times exactly equal to the declared technical details; 7 therapies had a variation percentage of emptying rate between 2 and 5%; 2 therapies between 5 and 10%; 12 therapies between 10 and 20%; 15 therapies between 20 and 40%; 35 therapies between 40 and 60%; 15 therapies had percentage differencies of emptying timeshigher than the60%, and a patient showed a percentage variation of 238% (emptying time: 13 hours).

Conclusions: This study highlights a wide variability of the flow rate of two lots of Accufuser Elastomeric Pumps filled with 5. FU in saline. We didn't find any proportionality (direct or inverse), between the concentration of the infused solutionand the infusion rate. Furthermore we didn't find any toxicity due to the variation of the flow rate.

M23 A Prospective Observational Study of Oral Mucositis in Oncology Patients Receiving Cancer Therapy

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Background: Oral mucositis (OM) is the most frequent oral complication in oncology patients receiving cancer therapy, especially due to an increasing use of targeted therapies. OM can require amendment of the original treatment plan with the risk of compromising the patient's therapeutic response.

Table: M23 Correlation between degree of OM and oncology disease

	BREAST	H&N	LYMPHOMA	ABDOMEN	OTHER CANCERS	TOTAL
G2	37	26	14	15	16	108
G3	1	22	2	1	10	36
G4	0	6	0	0	0	6
TOTAL	38	54	16	16	26	150

The objectives of the study are to:

- Identify patients (PT) with OM grade (G) ≥2 in the National Tumor Institute of Milan;
- Identify therapeutic regimes that can lead to severe OM, necessitating suspension of treatment or reduction of dose.

Materials and methods: From February to October 2014 a prospective observational study was carried out involving PT with OM G ≥2 as a direct result of cancer therapy. Data was collected by nurses of different departments via compilation of a case report form(CRF). Parameters included: OM assessment (WHO scale), pain levels (NRS scale), stage of disease and associated therapies.

Results: The study featured 150 PT with OM, subdivided as follows: 72% G 2, 24% G 3, 4% G 4. OM was observed in 36% of PT with head-neck (H&N) cancer treated with radiotherapy alone orconcomitant chemoradiotherapy and in 25% of PT with breast cancer: about half of the latter received adjuvant polychemotherapy and about 1/3 was treated with targeted therapy. 14,7% of PT required therapy reduction or suspension because of OM.

Conclusions: The scientific literature features many articles on OM and correlated therapies. Identifying which drugs can lead to the onset of OM is undoubtedly important but it's more constructive to focus on the correlation between various therapeutic regimes and oncological conditions to be treated. In the study, OM was observed primarily in PT with H&N and breast cancer in specific therapeutic regimes; this latter group represents over half of the total cases examined. Future healthcarestrategies should focus on the prevention of OM and adequate support to specific groups of PT with high risk of OM's onset because of their disease and type of treatment.

M24 Evaluation on the perceived quality, perception and information received during the first visit at the Reception and Service Centre (C.A.S.) at the Hematology and Oncology Units (C.O.E.S.) of the University Hospital Città della Salute e della Scienza in Turin

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Introduction: The Quality is a central aspect in the system of health protection of citizens / users.

Objectives: To evaluate the perceived quality, perception and information received by patients during the first visit to the Reception and Service Centre of the Hematology and Oncology Unit of the University Hospital Città della Salute e della Scienza in Turin.

Materials and methods: 112 patients who took part in the first visit at the CAS, period between December 2013 and July 2014, were involved. The evaluation was conducted administering a structured telephone questionnaire with 18 item.

Results: The results show overall good levels of satisfaction about the organization's service, the overall assessment of the information received, the role played by the nurse and the overall service provided. The majority of patients say they feel calm after the visit, although there are not significant correlations between the emotional state of the patient and other aspects investigated. The organizational aspects and the relationship

Table: M24

	Easy access	Waiting time	Time spent by operators	Complete information's	Clear information's	Ability to orient	Overall satisfaction	Critically
Easy access							Pearson's r = .415 P < .01	
Waiting time							Pearson's r = .483 P < .01	
Time spent by operators							Pearson's r = .524 P < .01	
Complete information's						Pearson's r = .586 P < .01		
Clear information's						Pearson's r = .645 P < .01		
Ability to orient					Pearson's r = .715 P< .01			
Overall satisfaction				Pearson's r = .691 P < .01	Pearson's r = .577 P < .01	Pearson's r = .433 P < .01		
Critically	Pearson's r = .187 P < .05	Pearson's r = .246 P < .01	Pearson's r = .289 P < .01	Pearson's r = .356 p < .01	Pearson's r = .193 P < .05			

	Nurses' courtesy and helpful	information about service organization	Information on the path to follow	information useful to face difficulties	Availability nurses to answer questions	Importance about nurses participation
Nurses' courtesy and helpful						Pearson's r = .427 P < .01
information about service organization	Pearson's r = .437 p < .01					Pearson's r = .806 P < .01
Information on the path to follow	Pearson's r = .372 P < .05					Pearson's r = .853 P < .01
Information useful to face difficulties						Pearson's r = .734 P < .01
Availability nurses to answer questions	Pearson's r = .315 P < .05					Pearson's r = .574 P < .01
Importance about nurses participation						

with the operators are areas where is important to intervene to improve the perceived quality.

Conclusions: The results of this study indicate high patient satisfaction. An issue is the limited availability of nurses to take part in the first visit at the CAS.

M25 Oral candidosis in the oncology department of the University Hospital in Pisa: prospective observational study

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Oral mucositis (OM) is a major dose-limiting toxic effect of cancer chemotherapy leading to dose reductions or delay in further cancer treatment. Furthermore painful OM greatly impairs quality of life in cancer patients, but its diagnosis, and consequent treatment, are often delayed due to scarce consideration of referred symptoms by oncologists.
In our department (15 beds, shared among oncology (10) radiotherapy (4), and gynecology-oncology -1) nurses assessed oral mucosa in every admitted patient by physical exam, and, when appropriate, mucosal tampons looking for mycosis and bacterial infections, between January 1st and march 30th, 2014. Objective of the prospective observational study was to estimate the number and degree of OM in our patient population. All patients signed an informed consent. 67 patients entered the study (male/female: 38/29), median age was 65 (range 37-86), median ECOG PS: 0 (range0-3). 82% of patients were admitted in the oncology unit. All cancers were equally represented in the population. 77% of patients had either lung or liver metastases. Cardiovascular disease and diabetes affected 50% of the population under study. Chemotherapy, either with single agent (30%) or with drug combinations (46%) was administered in the majority of patients and 33% of patients were receiving the second or third cycle of chemotherapy. In ¼ patients OM was detected even before Chemotherapy treatment began. More than 80% of patients received corticosteroids (mainly dexamethasone) either chronically or occasionally. OM was detected in 20 patients (30%) and in 13 (65%) of them oral tampon documented the presence of C. subspecies (52%) or bacterial infection. C. albicans was detected in 37% of patients. OM was Grade 1 and 2 in 80% of patients and resolved completely after treatment in about 3 weeks. All patients had WBC in the normal range. In 3 patients OM recurred, in 3 patients more than 1 pathogen was detected. OM deserves further consideration since it affects 1 in 3 patients admitted in the oncology department. OM diagnosis can easily be suspected and graded by trained nurses which can alert doctors on patients' discomfort and advice patients on appropriate preventive measures.

M26 Midline for apheresis of peripheral blood stem cells

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Background: The apheresis is a crucial phase in the stem cell donation in that it allows clinicians to obtain an adequate number of stem cells for bone marrow transplantation. When using peripheral blood stem cells, the apheresis process is possible only through a vascular catheter, usually inserted into a large vein in the arm of the donor. Then the blood goes through a machine that remove the stem cells and returns the blood to the donor. In this way, the stem cells can be collected and frozen until they are infused to the recipient. The apheresis process typically takes four to six hours and it need a large vein and a stable venous access in order to guarantee the adequate stem cells collection.

Methods: After a careful revision of the literature on the best available venous access for apheresis of peripheral blood stem cells from the donor, we decided to use a peripheral venous access such as a midline.

Results: During the mobilization phase, two midlines were placed one in each arm of the donor, into the basilica vein. The two peripheral inserted catheters were 5 French midlines placed in the upper third of the arm; in the left arm was placed a midline 10 cm in length and in the right arm a midline with a length of 12 cm. The first was used to collect the peripheral blood stem cells and the last one to return the blood to the donor. In a few hour we were able to collect an adequate number of peripheral blood stem cells without any complication or discomfort for the donor.

Conclusions: We think that midline could be a valuable and cost-effective device when projecting apheresis of peripheral blood stem cells. In our opinion further research will be crucial in establishing the preferable gauge as well as the best length of the midline in order to guarantee the adequate collection of peripheral blood stem cellsand to reduce the discomfort for the donor.

M27 The role of research nurse in translational studies: LUCAS experience

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Background: During the last few years, the role of research nurse (RN) has emerged as key player to ensure complete adherence to clinical trial and to make patients informed about all study procedures. In addiction, RN is encharged to correctly process biological samples and administer anti-neoplastic drugs. Aim of the present study is to assess the role of RN in LUCAS trial, a phase II study evaluating in *in vitro* drug-sensitivity of cancer stem cells (CSCs) obtained from pre-treated non -small cell lung cancer (NSCLC) patients.

Material and methods: CSCs were isolated from fresh tumor tissue or metastatic lesions or were derived from malignant effusions. Fresh cancer tissue were placed in saline, with no additional additive. After collection, pleural, peritoneal or pericardial effusions were distribuited in about 16-20 tubes without additives, each containing 6ml. Tubes were then centrifugated at 3000 rpm for 20 minutes in order to separate the supernatant from cells.The supernatant was removed and separately collected in 6ml tubes. An amount of 5-6 ml of saline was added to the remaining cells layer. Finally, all tubes and fresh tumor isolated in saline, were sent to centre laboratory within one day.

Results: Currently, the study enrolled 31 adavanced NSCLC patients. Fiftheen patients underwent to biopsy of primary or metastatic lesions, whereas 13 individuals underwent thoracentesis and only one patient paracentesis. Two patients withdrew informed consent.

Conclusion: Procedures for tissue or tumoral cells collection were feasible. All biological samples were sent to centre laboratory within established time. RN activity is essential to finalize this translational study. Currently LUCAS trial is still ongoing and it could be offer a real personalized therapy in pre-treated NSCLC patients.

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Session N. Simultaneous care

N01 Integration of medical oncology and palliative care to improve the appropriateness of antitumor therapy near the end of life in advanced cancer patients: first evidences of the prospective sequential MIRTO study. (Supported by "Programma di Ricerca Regione Emilia-Romagna-Università 2007-2009 Area 2 - Ricerca per il Governo clinico")

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Background: Recently the use of antitumor therapy (AT) near the end of life when the efficacy is almost nil and high the risk of toxicity, was reported in a significant proportion of advanced cancer patients (22.7% in a our previous study). The insistence in potentially inappropriate prescribing of AT in this clinical setting can find a viable alternative in the earlier activation of palliative care programs. This study aims to assess the impact of a new model of integration between oncologist and multi-professional team with expertise in palliative care.

Methods: This is a prospective sequential study enrolling advanced cancer patients with estimated life expectancy < 6 months: in the phase I the "natural" policy of the Medical Oncology unit in the prescription of AT was recorded. In the phase II the oncologist was supported in the decision making by a multi-professional team operating in homecare or hospice setting, consisting mainly in a palliativist and a psychologist. In both phases, the oncologist filled a form where he motivated prospectively the therapeutic choice (AT or supportive care) for each patient. Later, after the death of the patient, a follow-back survey was carried out. The interval between last dose of AT and patient death was considered a major indicator of therapeutic appropriateness. The analysis involves comparison between the two sequential cohorts of patients.

Results: Currently 111 and 122 patients are evaluable in the phase I and phase II, respectively. GI tract and chest tumours were the most represented. At the time of enrolment the median age was 68 and 71 years and median KPS was 70 and 80, respectively. The decision by the oncologist was prescribing AT in 49.5% and 61.5% of patients, respectively. The activation of a palliative care program represented mainly by home care (ADI-ANT, ADI MMG) at the time of therapeutic decision increased from 59.5% to 87.7%, respectively. The median time between the last dose of AT and the patient death increased from 62.5 (2-663) to 77.5 days (2-703), respectively. The AT was administered in the last month of life in 20 cases in both cohorts corresponding to 20.2% in phase I and 18.2% in phase II. The median survival in the two cohorts was 56 and 99 days, respectively.

Conclusion: Enhancing integration between Medical Oncology units and home Palliative Care programs in advanced cancer patients is associated with a trend in reducing the use of AT near the end of life without survival compromising.

N02 Emergency department as place of end-of-life care and death in cancer patients

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Background: Place of death is an important issue in palliative care: many studies showed that patients (pts) prefer to die outside of the acute care setting (e.g. at home or in a hospice setting). However, the proportion of deaths in the emergency department (ED) remains high.To better evaluate the characteristics and care of cancer pts using acute care resources at the end of life, we conducted a retrospective analysis of a cohort ofpts who died at the ED of IRCCS AOU San Martino – IST in Genoa (Italy) over a one year period.

Material and methods: This is a population-based descriptive study. All cancer pts who died at the ED of our Institution in 2013 were identified through Hospital Discharge Records. Cases were excluded if the pts died in another department even with a prior admission to the ED. Primary data were collected from pts' hospital charts focusing on reasons for admission and care in the ED.

Results: Out of 381 cancer inpatients who died at our Institution in 2013, 254 had prior admission to the ED. Among these pts, 108 (45.4% females and 54.6% males) died at the ED and were included in the present analysis. Median age was 78 years (IQR = 69–86). There were 53 pts admitted with red-code, 48 with yellow-code and 7 with green-code. The most common cancer diagnoses were: lung (25.9%), breast (9.3%) and liver (9.3%). Median time in the emergency department was 23.5 hours (IQR = 10–58.3). Among pts with available information on the use of chemotherapy or radiotherapy, median time from the last chemotherapy cycle was 41 days (IQR = 19–91), and from the last radiotherapy 201 days (IQR = 23–312). The main reasons for admission to the ED were: shortness of breath (54.6%), pain (16.7%) and cachexia (14.8%). A total of 135 imaging procedures were performed: the most common were chest X ray (56.3%) and body CT scan (19.3%). The most common treatments administered were: antibiotics (17.6%), pain killers (10.2%) and sedatives (8.3%). A total of 5 patients underwent resuscitation procedures. The awareness regarding the end-of-life stage of the disease in doctors and nurses was not present for 7.4% and 8.3% of pts, respectively. For 18.5% of pts, no meeting with pts' care giver was performed.

Conclusions: Cancer pts are heavy users of acute care resources at the end of life. Additional investigations are needed to better assess both the reasons for pts' access to the acute care setting and the appropriate use of resources during this time.

N03 Active treatment near the end-of-life in metastatic cancer patients

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Background: For the majority of cancer types, overall survival of patients with metastatic disease has increased overtime. This is probably due to the introduction of new effective therapeutic agents that are often safe, well tolerated, and may be administered also in advanced stage of disease. However, if compared with best supportive care, benefit of systemic anticancer treatment near the end-of-life is uncertain, and the corresponding toxicities are not justified. In this study we evaluated the percentage of patients that received active treatments in the last 30 and 15 days of life in a single institution. We also explored the association between clinico-pathological factors and treatment near the end-of-life.

Patients and methods: We analyzed a retrospective series of 425 patients, deceased between January 2013 and September 2014 and treated for metastatic disease at the Department of Oncology of Udine, Italy. We evaluated the percentage of patients that received anticancer treatments in the last 30 and 15 days of life. Logistic regression analysis tested the association between clinico-pathological factors and death within 30 days from the start of the last treatment.

Results: Anticancer treatment was administered in 77 (18.12%) patients in the last 30 days of life and in 41 (8.47%) patients in the last 15 days. Last line was chemotherapy for 312 (73.58%) patients, biological therapy for 72 (16.99%), and endocrine therapy for 40 (9.43%). The last anticancer treatment was stopped because of: deterioration of clinical status in 193 cases (45.84%), disease progression in 169 (40.14%), death in 35 (8.31%) and completed treatment in 24 cases (5.70%). A shorter interval between last-line treatment and death was associated with a better ECOG performance status, younger age, and lesser number of concomitant diseases. On multivariate analyses, ECOG performance status was the stronger predictor of anticancer treatment in the last month of life (ECOG 0-1 *vs* 2-3: OR 4.53, 95% C.I. 2.69-7.93).

Conclusions: This study showed a limited use of active treatments near the end-of-life, within the range of literature data. ECOG performance status, younger age, and small number of comorbidities were found to be predictive factors of treatment in the last month of life. However, treatment's withdrawal remains a difficult decision; in order to reduce futile treatments, informed discussion with patients and their caregivers should be encouraged.

N04 Appropriateness and cost analyses of anticancer treatments (at) in the last 3 months of life: a retrospective single center cohort study

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Background: The appropriate time to stop AT represents a controversial issue. The development of new agents improving survival and the difficulties in managing end-of-life (EOL) discussions leads to overtreat patients (pts) in clinical practice, with debatable benefits. In addition, AT may impair quality of life, increase the costs of cancer care and impact upon the overall financial sustainability. Thus, we aimed to evaluate the AT appropriateness, the costs of treatment and hospitalization (H) in the EOL context.

Methods: A retrospective database from medical records of all pts referring and deceased at the Oncology Ward of University Hospital of Verona in 2013 was developed. Included variables were clinico-pathological data, age at death, length/cost of the last H, lines of AT, cumulative doses and costs of AT in the last 3 months, rate and start of a new AT at 12, 4 and 2 weeks before death. Descriptive statistics was used.

Results: A total of 113 pts were included. Median age at the time of death was 69 years (range 27-92). Among these pts, 81 (71,7%) received AT with a median of 2 lines of therapy (range 1-7). AT was received 12, 4 and 2 weeks before death by 79%, 44% and 17% of all the treated pts, respectively. Among pts treated in the last 3 months of life (64 pts), a new AT regimen was started 12, 4 and 2 weeks before death by 59,4%, 23% and 9% of pts, respectively. 26/64 pts (40%) received high-cost drugs. Overall AT cost in the last 12 weeks of life was 77.106 €. Mean length H was 10,6 days (22,1% £ 2 days), with a total cost of 437.198 €.

Conclusions: The appropriate discontinuation of chemotherapy in EOL may represent an important Quality Oncology Practice Initiative assessment measure. In our analysis, 79%, 44% and 17% of treated pts received AT in the last 12, 4 and 2 weeks of life. Cost of AT and H in the EOL are relevant. Further analyses are currently ongoing to identify predictors for major intensity of care in the EOL in order to improve appropriate decision making about discontinuing futile and unsustainable treatments.

N05 The G8 screening as a tool for malnutrition risk

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Background: Incidence of cancer increases with age. In older cancer patients, important information may be missed without a Comprehensive Geriatric Assessment (CGA). A validated screening instrument is needed to identify patients for whom a CGA would be beneficial. G8 is a screening tool (8 questions) for older cancer patients in need of a CGA, it explores functional, cognitive, nutritional status and it takes 5 minutes; a score of ≤14 is considered abnormal.

Objectives: To test the performance of the G8 ≤14 in older patients with solid cancer; to identify those who would benefit from a nutritional support when a reduced MNA in the Mini Nutritional Assessment in the CGA was found.

Methods: Between January and April 2015, G8 was performed in 488 consecutive patients aged ≥70 years diagnosed with solid cancer at Vito Fazzi Hospital for a total of 963 G8. The G8 was administered 3 times in 78 patients and in 54 with G8 score <14, CGA (including MNA) were completed. MNA involves anthropometric measurements, global assessment, dietary questionnaire, a subjective assessment and it enables a subject to be categorized as normal (adequate nutrition), borderline (risk of malnutrition) or undernutrition. MNA is an 18-item questionnaire comprising anthropometric measurements (BMI, mid-arm/calf circumference, weight loss) combined with a questionnaire regarding dietary intake (number of meals consumed, food-fluid intake, feeding autonomy), a global assessment (lifestyle, medication, mobility, acute stress presence, presence of dementia/depression) and a self-assessment (self-perception of health and nutrition). Patients aged 70 years or older treated with chemotherapy for solid tumor and at risk of malnutrition (MNA) received Nutritional Advice.

Results: 54 patients with 76 years median age were included; 31,4% (N = 17) had an abnormal MNA <24, risk factor of malnutrition (5 female, 12 male) for each of them Clinical Nutrition Unit adopted an individualized nutrition program with oral nutritional supplements (ready-made liquids) or in 2 patients parenteral nutrition. In these patients there was an improvement of the G8 due to the increase of the MNA to start the chemotherapy.

Conclusion: G8 can be used in order to identify those patients who would benefit from a CGA and those who have a malnutrition risk. The results show that it is important to implement and develop strategies for individual nutritional care, in order to prevent and treat malnutrition in elderly people.

N06 Chemotherapy near end-of life: aiming for appropriateness at the Cancer Institute of Romagna (IRST IRCCS)

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Background: The administration of chemotherapy near the end-of-life is still an open question and, despite position statements in this field from ASCO and ESMO, the lack of detailed guidelines makes the decision to stop a specific treatment in favour of the best palliative care an incredibly difficult one. Proposed quality indicators of cancer care for external benchmarking include <10% of cancer patients receiving chemotherapy (CT) in the last 14 days of life and < 2% starting a new CT regimen in the last 30 days of life (Earle C, 2005). However, with respect to these indicators, populations of interest often differ among studies which have measured them. A monitoring project to routinely measure these indicators in our Institute was planned for all tumor types to evaluate how cancer patients are managed in the last days of life.

Materials and methods: A retrospective analysis based on the electronic medical records of patients with metastatic cancer who were candidates for CT was carried out at IRST IRCCS. Residents in the Local Health Authority (AUSL) catchment areas of Forlì and Cesena who started CT between 1.01.2007 and 30.06.2014 and died before 15.11.2014 were included. Overall (OS) and progression-free survival (PFS) between first- and second-line treatment was calculated for gastric and colorectal cancer patients who started first-line treatment for advanced disease during the same period. The two above indicators of cancer care quality were also measured.

Results: During the period studied, 367 patients died from metastatic colorectal cancer and 227 from advanced gastric cancer. In the last 14 days of life, 27 (7.4%) colorectal cancer and 21 (9.3%) gastric cancer patients underwent CT. Thirty-eight (10.4%) colorectal and 36 (15.8%) gastric patients started a new CT regimen in the last 30 days of life. At a median follow up of 48 months, median OS and PFS for colorectal patients (n = 424) receiving first-line CT were 21 and 10.8 months, respectively, while those of gastric patients (n = 238) were 8.6 and 6.3 months, respectively.

Conclusions: A permanent program to monitor the appropriateness of CT prescriptions and clinical outcomes is now considered mandatory. Our preliminary data show substantial appropriateness in the management of end-of-life patients for the indicators in question. However, it is clear the percentage of patients starting a new CT regimen in the last 30 days of life should be reduced.

N07 Adherence to WHO pain guidelines in a community hospital

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Background: In the last years the attention to pain and supportive care have been implemented in our Hospital through "Comitato Ospedale Senza Dolore" program. This comitate has the aim to evaluate, systematic recording, correct guidelines application and standardization of treatment among clinicians. Among these activities, a quantitative and qualitative evaluation of pain medicaments have been performed by the pharmacists.

Material and Methods: Opioids and non-opioids drugs prescriptions into our hospital during a decade has been performed. Specific calculation of oral morphine milligrams (mg) provided by the local pharmacy to hospital departments has been done. Similarly, calculation of equivalent morphine dose of other opioids used, as well as of weak opioids, FANS and paracetamol has been elaborated trough tabular and graphical tools using Microsoft Excel software. All clinical departments and general medicine departments separately were considered. Years considered started from 2002 to 2013.

Results: In the whole hospital, use of oral morphine (or equivalent) almost doubled from 2003 to 2013 (749.077 to 1.409.724 mg). In particular oxycodone consumption raised dramatically from 2006 (+350%), conversely morphine sulfate (-60%) and tramadol prescription (-45% fell in the same years). Fentanyl patch remained similar in a decade. Buprenorphine and hydromorphone have a low rate of usage. Interesting data were observed for paracetamol and FANS. The first drug observed an important growth as a first step for general and oncological pain (+330%); FANS remained stable with a low rate of diclofenac use. Among weak opioids, the combination of codeine/paracetamol reduced hospital utilization by a 40%.

Conclusion: Opioids use increased 2 folds in last decade and consequently weak opioids, commonly used as second step of analgesic scale (e.g., tramadol and codeine/paracetamol) were significantly less incorporated in the treatment of chronic pain for hospitalized patients. Use of paracetamol as the first step of the analgesic scale was the preferred agent. Oxycodone replaced almost entirely oral morphine that was 60% less

prescribed. Use of FANS remained stable, mainly required for chronic and benign pain of not oncologic reasons. In summary, in our general hospital, consumption of analgesic drugs has changed dramatically in last decade justly in agreement to WHO guidelines for pain treatment.

N08 Taking care for the patients from hospital discharge to home assistance: 5-year experience from a single Institution

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Background: Patients suffering from neoplastic disease need to be taken in charge by an experienced Palliative Care Team (PCT) before the clinical deterioration could evolve dramatically in the last days of life, trying to minimize the discomfort and the physical and psychological distress imposed to the patients and their families.

Patients and methods: The 5-year activity of the San paolo Hospital PCT was analyzed in order to evaluate the cliinical outcomes of the patients taken in charge and assisted at home from 2010 to 2014. Data were reported in a dedicated register.

Results: A total of 477 patients has been followed at home, coming from a hospital discharge in 96% of the cases. Among these patients 380 (79.6%) died at home while 97 (20.4%) were transfered to Hospice or returned back to hospital. The PCT provided the first home visit in the first day in 93% of the cases. In 5 years of activity the total number of domiciliary visits was 13.560, 30% assolved by doctors, 65% by nurse staff and 5% by the psychologist involved in the assistance to the patients, the care-givers or their families. Some of the most relevant activities were pain measure and treatment. The great effort of the PCT was to register and document pain according to the scoring systems in use: the Visual Analog Scale and mainly the Verbal Numeric Rating scale. About 60% of the patients experienced some form of pain needing treatment. In this group 98% have been evaluated during any home access and treated. Therapies for pain control were administered in all cases and opioids were employed in 100% of the patients. The coefficient of assistance intensity, a measure of a single case complexity, has always been between 0.6 and 0.7, in line withe the literature and the activity of The Palliative Care Units operating in Lombardy. The median hospitalization at home was 32 days. Before death at home the last visit was made within 48 hours in 96% of the patients. Terminal sedation was carried out in 180 patients (37.7%) for refractory dyspnea and severe psycho-physical distress.

Conclusions: Patients affected by neoplastic diseases in their end of life should be followed by en experienced PCT with the competence to take care of all the complex and articulate aspects of such a stressful event, from pain control to psychologial assistance and terminal sedation. The care-givers and the families should also find in the PCT the right answer to all their needs.

N09 "Comitato ospedale senza dolore": a successful strategy

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Background: Quite all cancer patients experience pain and also non oncological patients often have the same problem. The pain's evaluation and treatment are relevant for the management of hospitalized patients both in Medical and Surgical Department (Dep). In 2010 in our hospital "Comitato Ospedale senza dolore" was founded with the aims of correctly evaluate and treat pain, both acute and chronic pain, above all when the patients experienced a chronic illness. To achieve this purpose the Committee coordinated training program for nurses and phisicians. The aim of our study was to evaluate if this program obtained an improvement in the management of hospitalized patients.

Patients and methods: From January 2012 to December 2014 a questionnaire for pain survey was delivered to all hospitalized patients (Medical and Surgerical Dep). 11 items was measured. The results were pooled into 6 semesters (two for each year considered). 3841 questionnaires were filled: 1477 (38,4%) in Medical Dep, 2364 (61,6%) in Surgical Dep. We consider for the analysis 6/11 items; see items considered in the first line of Table 1. For each question the patient gives a score from 1 to 10, that is "at all" to "a lot". For the first and second item the score is the pain intensity.

Results: In Table 1 we show the median score for the six items considered, pooled in six semester for Medical and Surgical Dep.

Table: N09

Year a: first semester b: second semester	pain score at admission	pain score at discharge	pain reduction after treatment	information about pain treatment during hospitalization	patients satisfaction about pain management	information about pain management at home
Medical Department						
2012a	5,23	3,25	7,33	7,75	8,48	7,79
2012b	5,00	2,88	7,42	7,99	8,52	7,94
2013a	4,48	2,72	7,16	7,67	8,47	7,65
2013b	5,64	2,89	7,33	7,66	8,74	7,92
2014a	4,75	3,11	7,09	7,71	8,37	7,73
2014b	4,49	2,42	6,77	7,66	8,24	7,89
Surgical Department						
2012a	3,34	2,73	7,63	8,23	8,89	8,31
2012b	4,30	3,48	7,30	8,23	8,78	8,20
2013a	3,79	2,82	7,06	8,04	8,61	7,82
2013b	3,56	2,96	7,31	8,11	8,64	8,04
2014a	3,61	2,93	7,22	7,89	8,47	8,09
2014b	3,64	2,80	7,14	7,97	8,66	7,99

Conclusion: The "Comitato Ospedale senza dolore" program reached in all patients considered both for Medical and Surgical Dep a reduction of pain score from admission to discharge. In all patients there is a good level of satisfaction about pain treatment, pain management and informations obtained. These results were maintained along three years.

N10 A preliminary validation of an Italian version of the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF-I)

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Background: Fatigue is one of the most common and distressing side effects of cancer and its treatment. The National Comprehensive Cancer Network defines Cancer-Related Fatigue (CRF) as a persistent, subjective sense of physical, emotional and/or cognitive exhaustion that is not proportional to recent activity. It can range from mild to severe, and may be either temporary or a long-term effect. Percentages of patients who experience CRF vary across studies from 25% to 100% according to the type of cancer, treatments, and method of assessment. Screening for fatigue before, during and after cancer treatment is today a core part of clinical evaluation and quality of life assessments.

Material and methods: The aim of this study was to report the preliminary validation results of an Italian version of the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF-I), one of the most used and validate CRF-assessing tool. A total of 121 cancer patients (44 men and 77 women) were recruited to this study from the outpatient oncology clinic at the Santa Maria Annunziata Hospital in Florence. The Italian version of the MFSI-SF was developed through a forward-backward translation procedure, according to the EORTC Quality of Life Group Translation Procedure. We estimated internal consistency using Cronbach's α and split-half technique. Test-criterion validity was evaluated through ANOVA. The convergent validity was evaluated by estimating the Pearson's r correlation with the Italian version of the Brief Fatigue Inventory (BFI-I).

Results: This Italian version of MFSI-SF revealed adequate internal consistency ($\alpha = .919$) and convergent validity ($r = .683$; $p < .01$) and confirmed the original unidimensional structure (explained variance = 51%). More than the 50% of participants showed a significant CRF. Patients in the adjuvant and first line setting showed a lower level of fatigue as compared to more advanced lines of treatment ($p < .05$), although with a significant higher score ($F = 3.844$; $p < .05$) at the item 17 ("I feel sluggish"). Moreover, patients with low scholarization rate (primary and secondary school degree) showed a significant higher score ($F = 3.829$; $p < .05$) at the item 19 ("I ache all over").

Conclusions: While further studies are needed in order to extend the sample size ($n \approx 300$) and verify the validity and the sensitivity of this Italian version of MFSI-SF, it seems a reliable tool to detect clinically significant fatigue in cancer patients.

N11 A single institution survey on prevalence and management of severe cancer pain in patients with cancer of different sites

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Background: Pain is one of the most frequent and disabling symptoms of cancer especially in advanced stage. This survey focused on prevalence and management of severe cancer pain in patients (pts) referred to Medical Oncology Unity of Cagliari, ESMO designated center of integrated oncology and palliative care.

Patients and methods: From June 03 2014 to July 03 2014, we conducted a single institution survey in pts with cancer of different sites. The study's main objective was the evaluation of severe pain prevalence in pts receiving opioid treatments, secondary objectives were: evaluation of clinical characteristics of pain, therapies for chronic and breakthrough pain, pain therapy efficacy. For pain assessment we used a numeric rate scale.

Results: We enrolled 1382 pts (1255 inpatient and 127 outpatient). Pts with severe pain treated with opioid were 78/1382 (5.6%) with the following clinical characteristics: mean age 65.2 years (range: 37-84), M/F: 38/40. Site of cancer were: colorectal (29.4%), urogenital (19.2%), breast (17,9%), lung (17.9%), gastro-intestinal-pancreatic (12.8%), soft tissue and head-neck (1.2%), respectively. Ninety-four percent of pts had stage IV disease with the following metastatic sites: lung (47.4%), bone (43.6%), liver (41.0%) and lymph nodes (29.5%). Nociceptive and neuropathic pain were both reported by 44.9% of pts, nociceptive alone in 51,3% (23.1% somatic, 15.4% visceral, 12.8% somatic/visceral) and neuropathic alone in 2.6%. Opioid therapy for chronic pain was administered with oral (66.7%), transdermal (30.8%) and subcutaneous (s.c.) (1,3%) formulation and in the 60.2% of pts it was associated with adjuvant drugs (psychotropic/ neuromodulators, anti-edema). Breakthrough pain was reported by 58.9% of pts and treated with trans mucosal fentanyl (23.9%), oral, s.c. and intravenous morphine (23.9%) and 9% with non-opioid drugs (NSAIDs, acetaminophen). Twenty-four percent of pts underwent local therapies for pain: 84.2% radiotherapy; 10,5% celiac plexus block; 5.3% bone surgery. Forty-two percent of pts reported inadequate pain control and uncontrolled pain was the main reason hospitalization for 12.8% of them.

Conclusions: This study shows a high prevalence of severe cancer pain in our pts. Nearly half of them don't reach adequate pain relief despite of tailored pain treatment. These data are in agreement wiht literature and suggest the need of new clinical research to improve pain management and patient's quality of life.

N12 An innovative program of integrative rehabilitation based on promoting healthy lifestyles for cancer survivors. Preliminary results of an experimental study

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Background: Nearly 3 million of Italian people survive cancer (Airtum 2014). Even if survivor quality of life is often seriously compromised, our National Health Service shows a relative lack of rehabilitation programs concerning mental, emotional, physical and social issues. However, several international studies prove the efficacy of the mind-body interventions in enhancing the quality of life of cancer survivors. Specifically, meditation, yoga, and relaxation with imagery are recommended practices for routine use for common sympthoms, including anxiety and mood disorders.[1] Taking account of international and national guidelines, we designed a program of integrative rehabilitation based on promoting healty lifestyles including: nutritional counselling, 3 months Yoga Lessons, psychological group support, acupuncture and Physiotherapy on demand. The aim was to prove the efficacy of such a program on the quality of life of cancer survivors.

Material: A group of 30 cancer survivors that, in the follow-up phase, suffering from psycho-physic symptoms not curable by a pharmacological approach. People in the group had different types of cancer (breast, colon, prostate, ovary, etc).

Method: Admininistration of specific questionnaries at beginning and at the end of the rehabilitation program in order to evaluate the effects of an integrative rehabilitation on the patient quality of life (POMS- Profile of Mood States-McNair et al. 1981; ESAS-Edmonton Symptom Assessment Scale - Bruera et al. 1991; BPI- Brief Pain Inventory Short Form – Cleeland, 1991).

Results: We found a significant improvement in two areas: tension-anxiety ($p < 0,012$) and Fatigue ($p < 0,015$). Moreover, in 15 pts (50%) we found pain improvement, with complete pain remission and consequent withdrawal of analgesics in 4 pts. Finally, 84% of partecipants shows a significative amelioration of quality of life.

Conclusions: Our study confirm that yoga can enhance quality of life of cancer survivors. Moreover, the life style change can have positive effects on different type of cancer survivors. We hope that such type of complementary intervention, quite inexpensive and with strong scientific evidence of efficacy, will soon became a standard for oncological follow up. [1]Greenlee H et al., Clinical Practice Guidelines on the Use of Integrative Therapies as Supportive Care in Patients Treated for Breast Cancer, J Natl Cancer Inst Monogr, 2014 (50): 346-358. doi: 10.1093/jncimonographs/lgu041.

N13 Clinical nutrition can improve outcame in cancer treatment?

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Background: Good nutrition during cancer treatment can be a challenge. Instruct patients to consume the right foods, in appropriate during drug treatment, can help to minimize the side effects of chemotherapy as well as to help reduce the risk of weight loss and malnutrition, as well as improve the set immunological ensuring better general well-being.

Materials and methods: From October 2014 in Oncology-Unit of Cosenza, we have started a "Service of Nutrition" with the collaboration of Association ONLUS ONCOrosa and Human Nutrition. To cancer patients receiving chemotherapy, we administered a "nutritional regime" with a wide variety of nutrient-rich foods with proven anti-tumor activity in vitro, as well as by the high antioxidant power, In 6 months of activity we observed 59 cancer patients (20 colorectal, 19 breast,11 ovary and uterus, 3 stomach, 3 lung, 1 bladder, 1 esophagus,1 pancreas). 20 pz. (33.8%) had started chemotherapy prior to insertion of the nutritional regimen. All patients were also subjected to a panel of clinical chemistry tests, a test of motivation and psychological stress as well as an initial training of the preparation and cooking of food.

Results: The nutritional regime was welcomed by patients of both sexes, in older subjects was more frequently expressed some concern to eliminate foods considered important for nutritional value as meat and dairy products. Remissions and improvements were observed for constipation (11), constipation alternating with diarrhea (13), swelling (26), stomach pain (15), nausea (5). All 20 pz. having introduced the nutritional regimen in chemotherapy treatment already begun reported greater well-being.

Conclusion: The study, still preliminary, will demonstrate the importance of taking food and phytonutrients for therapeutic purposes and define the importance of nutrition during the drug treatment that could also prove therapeutic control in vivo disease progression.

N14 The clinical governance model (UFA-ONCO-EMA model) for anticancer drugs delivering of the ARNAS Garibaldi: third year experience

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Background: The ARNAS Garibaldi of Catania is a third-level hospital Institution the whom Department of Oncology administer more than 25 thousands of anticancer therapies per year. In the aim to standardize the interaction of all the actors of the process of prescription, preparation and administration of anticancer therapies and in reference to the Ministerial Recommendation 14 and to the DA 10/2012 of the Sicilian Region we developed a model of inter-departmental functional integration between the Anticancer Drugs Unit, the Medical Oncology Unit and the Ematology Unit that we called "UFA-ONCO-EMA model".

Methods: With the economical support of Novartis and the collaboration of OPT agency we developed a clinical governance model the whom main objectives are to promote a positive culture among the components of all the staff, ensuring a robust quality governance framework and deriving the best levels of quality and safety of the treatments. The entire process were organized according to the complete national regulatory context; the model defines protocols and behaviors for managing clinical and therapeutic appropriateness, monitoring and prevent drugs toxicities and manage the entire clinical course of the patients.

Results: The UFA-ONCO-EMA model of the ARNAS Garibaldi was certified in july 2013 by a National Certifing Body and the Regional Health Department recognized the model as a unique example of integrated clinical governance system in the Sicilian scenario and declared by law its adoption by the all oncological units of the Region. Is actually active the second phase of the project aimed at the formation of the teams of internal auditors who will assess the correct application of procedures in the oncology regional structures. We also selected the process' indicators of performance for the 2015, so we chosen: six indicators for the procedure for taking care of the patient; two indicators for the procedure of antitumoral drugs prescribtion; two indicators for the process of preparation of anticancer drugs; two for the distribution of anticancer drugs;

three indicators for administration of the drugs; two indicators for the distribution of oral drugs; three indicators for handling procedure extravasation.

Conclusions: to our knownledge the UFA-ONCO-EMA model of ARNAS Garibaldi is the first example of law-based adoption of a clinical governance system in a regional context and is actually ongoing its second phase.

N15 Osteonecrosis of jaw (ONJ) with and without bone exposure in patients receiving antiangiogenic agents (+/- bisphosphonates or denosumab)

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Osteonecrosis of Jaw (ONJ) definition is controversial. The "classical" definition by AAOMS (American Association of Oral Maxillofacial Surgeons), clinically based on bone exposure lasting at least 8 weeks, is too much restricted, even if recently a bit enlarged to include cases with an intraoral or extraoral fistula (Ruggiero S et al, JOMS 2014). A large part of ONJ cases actually shows symptoms and signs without clear bone exposure (so-called "stage 0" according to the contradictory AAOMS 2009 definition and staging system). Computed Tomography (CT) scan could be of value in differential diagnosis (Bedogni A et al BJOMS 2014, Fedele S et al BJOMS 2015). Alternative definitions based on clinical and radiological criteria have been proposed (Campisi et al, Future Oncology 2014; Schiodt et al, OOOE 2014). ONJ has been reported since 2003 in patients receiving Bisphosphonates (BPs) or more recently receiving denosumab. ONJ cases have also been reported after antiangiogenic drugs: on 2010, alerts were released by EMA (European Medicine Agency) about bevacizumab and sunitinib. Methods: we reviewed charts of all patients with diagnosis of ONJ observed between August 2005 and April 2015 at our centre and analyzed cases diagnosed after antiangiogenic treatment. Results. We registered 54 ONJ cases: 27 were patients from our hospital Oncology-Hematology Department and 27 were referred to our ONJ multidisciplinary team by other hospitals or by dentists. Seven cases of ONJ in patients receiving antiangiogenic agents were observed: 2 cases after bevacizumab alone (1 colorectal cancer, 1 ovary cancer); 2 after sunitinib alone (both renal cell cancer); 3 after sunitinib and BPs (all renal cell cancer). Out of 4 ONJ patients receiving antiangiogenic drugs alone, only 2 showed short-lasting bone exposure; all the patients complained episodes of infections, with remission after antibiotic therapy and/or antiangiogenic drug holiday (as already described by Brunello et al, Bone 2009). CT scan jawbone alterations suggestive for ONJ (without bone metastasis) and bone scintigraphy uptakes were observed in the implicated sites. Conclusions. Antiangiogenic drug-related ONJ cases can be challenging for diagnosis and management: oncologists have to be alerted of potentially difficult ONJ adjudication, of possible successful imaging study of suspected ONJ cases, and of atypical clinical behavior of disease.

N16 GelX Oral Gel and GelX Oral Spray (GOG&GOS) pain relief for oral mucositis

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Oral Mucositis (OM) is a painful condition affecting the mucosa of the mouth and throat.OM refers specifically to toxicity associated with chemotherapy and radiation therapy for cancer. Approximately 40% of pz receiving chemotherapy as part of their cancer treatment will develop some degree of Mucositis. The process of oral mucositis involves not only the epithelium, but also includes multiple cellular processes of the lamina propria and sub-mucosa. Inflammation is a complex biological event; a loss of mineral homeostasis contributes to the destructive effects of this process. Current treatment for OM is largely palliative and no adequate treatment with conclusive evidence exists.
GOG&GOS are novel muco-protecting products utilizing the bioactive Zinc-Taurine complex, designed to resolve the underlying inflammatory signaling pathways that cause OM while providing anti-bacterial, anti-fungal and analgesic relief for patients with OM. Zinc and Taurine exert anti-microbial, anti-inflammatory, free radical scavenging and analgesic effects when topically applied; Zinc-Taurine complex demonstrated enhanced biological activity compared to its individual components. GOG&GOS are viscous products in two different delivery systems (rinse and spray) designed to coat the oral cavity with a film-like barrier which protects and insulates against stimulants capable of causing mouth pain and irritation. This study wants to assess the ability of GOG&GOS to delay the onset of OM, reduce pain and severity of oral mucositis and decrease the time to resolution of OM. We evaluated 40 pz with solid tumors and who underwent cisplatinum/5FU containing chemotherapy, chemo-radiation therapy and radiation therapy . Each patient utilized: GOG as prevention 2 times per day ten days before starting cancer treatment; GOS as therapy 3 times per day during cancer treatment. OM were evaluated by physician and pz using RTOG scale at the beginning of prevention, after one month of treatment, at the end of treatment, one month after the end of treatment. After 1 month from the end of treatment 30 pz had completely resolution of pain and swelling alteration; 8 pz no pain but loss of swelling, 2 pz had mild pain and loss of swelling. GOG&GOS is safe and active and could be new approach in management and prevention of OM. Phase III study is ongoing vs preference physicians therapy.

N17 An interdisciplinary early simultaneous palliative approach in metastatic non-small cell lung cancer: preliminary data in outpatient setting

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Background: Non-small cell lung cancer (NSCLC) is mostly diagnosed in advanced stage. In addition, patients affected with advanced NSCLC are very often characterized by a high tumor burden with a complex symptomatology that goes along with some comorbidities frequently related to smoking history and to elderly. Thus, the global approach to these patients requires different skills. Some landmark experiences have demonstrated that patients with advanced lung cancer achieve a better outcome by providing a simultaneous palliative care in a early phase of the treatment plan. An interdisciplinary palliative approach has been proposed for patients with advanced NSCLC that referred for the first time to the Thoracic Oncology outpatient' department of a National Cancer Institute.

Patients and methods: From September 2014 to 31 March 2015 a total of 25 patients with stage IV disease, receiving first-line therapy,have been enrolled into the program. The equipe comprises medical oncologysts, a palliative care specialist, a nutritional expert and a research nurse. A complete evaluation of the status of disease, as well as the needs of the patients and comorbidities,have been performed. The assessment included a nutritional, psychosocial and pain evaluation. Smoking habits were also recorded and information about smoking cessation programs were provided. A survey about the grade of satisfaction of patients during this muiltimodal approach has been conducted in the first group of patients.

Results: The main patients' characteristics were: 20 male, 5 female, Histotype (Adenocarcinoma 12, squamous carcinoma 6, large-cell/undiffererntiated 5, neuroendocrine 2), median age 67 (range 41-82), ECOG Performance Status 0:4 patients, ECOG 1:18 patients, ECOG 2:3 patients, current/former smokers 21, never smokers 4.

Conclusions: These very preliminary data suggest that a interdisciplinary palliative approach is feasible in a outpatient' setting with a good compliance and satisfaction of patients as well as of their caregivers. Furthermore, the different professional figures involved could usefully carry out an approach very simple but essential in a disease with multiple needs. To anticipate the simultaneous palliative care could be a very important tool in advanced NSCLC patients while receiving cancer treatments.

N18 Consolidation of the use of early palliative care in cancer patients: rationale and barriers. a review of the literature

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Background: One of the most controversial aspects of modern palliative care is the correct integration with the standard therapies aimed to neoplasia treatment. As outlined by the World Health Organization (WHO), palliative care should be applied to improve the quality of life of all patients with life-threatening disease and their family, and should start during the treatments intended to prolong life and be extended as a continuum care throughout the course of the disease and not limited to the terminal end-of-life period. Despite this assertion and although palliative care services are rapidly increasing worldwide, it is well known that patients diagnosed with cancer in advanced stage, continue to be sent to palliative care too late, thus resulting in an inadequate and inhomogeneous use of these therapies. The aim of our review of literature has been to identify and analyse in depth the rationale of early palliative care in cancer patients and the main barriers hindering its use.

Materials and methods: The research has been carried out consulting the MEDLINE database since January 1970 to October 2014, inputting the terms "early", "palliative", "care","palliative care", "palliation". The application of broader selection criteria has been due to the assumption of a high sensitivity in primary research, at the expense of a low specificity, that was then improved during the analysis of the various works. We have analysed the abstracts sorted out through the search string, selecting the articles available both in English and Italian, deemed potentially useful to the review.

Results: Our review has detected and explored four main achievable goals, through the use of concurrent palliative oncology care: improving the control of physical and psychological symptoms, improving the communication of prognosis and the decision-making process, the proper use of resources and the improvement of survival, as a further potential achievable goal, resulting from the upgraded quality of life. The main barriers identified and analysed have been classified as terminological,

communicative, methodological, psychological and cultural, resource-related and organizational.

Conclusions: This review of the literature outlines that there is a strong rationale for the consolidation of early palliative care in patients with advanced cancer state and highlights the barriers to overcome to reach this important goal.

N19 Efficacy and tolerability of oxycodone-naloxone prolonged release tablets (o/n –prt) for moderate to severe bone pain in cancer patients (pts) bone metastases (bm): data from a single-centre experience

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Background: Bone pain still represents a major issue in cancer pts with bone metastases. Mild to moderate bone pain can be efficiently controlled using NSAIDs +/- weak opioids +/- adjuvant drugs whereas strong opioids are needed to control moderate to severe pain. Due to its unique mechanism of action, O/N-PRT can achieve a satisfactory control of pain with less side effects in terms of constipation. In our center we have evaluated efficacy and safety of O/N-PRT in cancer pts with symptomatic BM.

Patients And methods: From March 2013 to November 2014, we evaluated efficacy and tolerability of O/N-PRT in 203 consecutive cancer pts with painful BM. Median age was 62.4 years (range: 37-86 yrs); all pts had moderate to severe bone pain despite analgesic treatment with NSAIDs +/- weak opioids +/- adjuvant drugs. Median pain intensity (assessed on a 10-point NRS) at baseline was 6.9 (range: 6-9). After discontinuation of weak opioids, O/N-PRT was administered at dose 20/10 mg bid; after baseline, pain intensity was evaluated at day 1, 3, 5 and 7 whereas adverse events and QoL scores were daily assessed for 7 consecutive days.

Results: Efficacy and safety of O/N-PRT were assessed in all recruited pts. Median pain intensity progressively decreased as follows: at day 1 a median NRS of 4.8 (range 3-6) was detected; at day 3, 5 and 7 median NRS values were 3.6 (range 3-5), 3.1 (range 2-5) and 2,2 (range 1-4), respectively. During the entire period of evaluation no modifications of QoL scores were reported; adverse events were modest: only 43 pts experienced mild constipation easily treated with common laxatives.

Conclusions: In our experience, O/N-PRT confirmed its satisfactory efficacy and tolerability in cancer pts with moderate to severe pain due to BM: it represents an effective therapeutic option in cancer pts with symptomatic BM.

N20 Impact of cannabinoids on the Quality of Life in Oncology: Prospective Observational Study

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Background: In Italy, the use of derivatives of Cannabis in oncology is being inserted in clinical practice. In particular, the mention of these substances is oriented within relieving emesis and pain, and their prescription is presenting various aspects that deserve to be explored.

Patients and methods: The aim of our study was to evaluate the efficacy in clinical practice of inflorescences of cannabis for pain control and emesis in cancer patients. The secondary endpoints are the appetite, quality of life and toxicity. From January 2014 to now, we enrolled 18 patients with different oncological diseases who have started treatment with cannabinoids for pain and / or chemotherapy induced nausea and / or vomiting. Efficacy data are collected every three weeks of treatment through NRS scale to quantify pain and emesis. The evaluation of appetite is measured through a NRS scale, too; for measuring the quality of life is used QoL Index and the test for the toxicity psychiatric PROD-Screen. The anamnestic interview and physical examination were practiced in all cases.

Results: All patients received inflorescences of cannabis with THC to 19%, in the form of an infusion, one or two times a day, at doses ranging from 14 to 264 mg per day. The control of the emetic symptomatology was achieved in all cases. The pain was not controlled significantly. Patients enrollment showed appetite or sleeping hours decreased or anxious or depressive symptoms have reported clinical improvement. QoL Index score rose for all patients. There were neither significant changes in the PROD-Screen nor any relevant toxicity except mild epigastralgia in three cases during the administration of the infusion.

Conclusions: From obtained data, the use of inflorescences of cannabis in cancer patients appears to be useful for the control of emesis, while it seems insufficient to relieve pain. The formulation in infusion appears to have a high compliance. The ability of the derivatives of Cannabis in improving the quality of life through better control of the anxious / depressive symptoms and an increased appetite and hours of sleep should best be studied in a larger number of cases.

N21 A prospective observational study on quality of life (qol) questionnaire reliability in oncology (x-life study)

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Background: Patient-reported health related-outcomes may help inform treatment choice in advanced/metastatic cancer, particularly between approved targeted therapies with similar efficacy. There is a large body of evidence supporting the validity and utility of EORTC QLQ-C30 across a wide range of clinical research contexts, and it is also available in many languages. Despite this fact, recent concerns have focused on the quality of reporting of Health Related Quality of Life data (HRQoL). Several factors such as patients compliance and modality of administration might reduce their reliability and their reproducibility. These limitations will need to be addressed if HRQoL data are to be used to successfully support clinical decision-making, treatment options and labelling claims in oncology.

Patients and methods: This is a prospective monocentric observational study approved by Ethical Commitee. 150 patients with solid tumors receiving antineoplastic treatments will be consecutively enrolled. EORCT QLQ-C30 paper questionnaire will be self administered twice to patients in the oncology setting. The research nurse will be available just for purpose of helping in collecting and preventing missing data.

Aim: to verify the test and re-test realibility of EORTC QLC-C30 administered before and after oncologic visit.

Results: 150 patients have been enrolled since February 2015. Median age is 69 years (30-84). Men and women are equally distributed. More than 90% of patients have good performance status (PS ECOG 0-1) despite the fact that 108/142 (76%) patients are receiving treatments for metastatic disease. Only 5% of patients have refused to answer to the questionnaire.

Conclusions: Analysis of the patient responses is ongoing. We hope that our observational study will add some evidence to quality of life trial methodology and to the potential value of the information provided by HRQOL data, especially when used in comparative effectiveness reaserch.

N22 Quality of care, patient needs and health-care profile in cancer inpatients: prospective observational clinical trial

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Background: Patients with advanced cancer have reduced quality of life, which tends to worsen towards the end of life. Many patients are hospitalized in the last moths of life and the referral to palliative care occurs late in the trajectory of illness at an average of 30 to 60 days before death or at all. Aim of this study was to analyzed the factors (relating illness, individual characteristics, health-care input and social support) concerning hospitalization, and to evaluate the impact of health services on patient's needs.

Patients and methods: This trial included all adult inpatients with a solid tumor of Local Health Authority No.5, Veneto region, between June and November 2014. Demographics, clinical, pathological and health-care variables and reason(s) for hospital admissions were all recorded. Recurrent event survival analysis was used to evaluate the relation of potential predictors to hospital admission and death during hospitalization. Independent prognostic value of increase/decrease of Glasgow Prognostic Score/Glasgow Prognostic Score modified (GPS/mGPS) and the Palliative Prognostic Score (PaP Score) was evaluated. A stratified Cox proportional hazard model was used.

Results: Of 150 patients, 39 (26%) died during hospitalization. The main reason of hospital admission was low/absent control of cancer-related symptoms (76%). 71 (47.3%) inpatients were in terminal stage and 135 (90%) had a metastatic illness with a performance status (PS) ≤50 (Karnofsky); overall survival was 69 days (CI95% 46-91). Only 31 (20.6%) inpatients had a palliative home care high intensity. No difference was found for palliative home care high intensity post admission (20.7%). Pain ($p = 0.03$), dispnoea ($p = 0.01$), confusion/delirium ($p = 0.001$), nausea/sickness ($p = 0.06$), lack of appetite ($p = 0.04$), PS > 50% ($p < 0.0001$) or worsening PS ($p = 0.001$) were all predictors for poor prognosis. Increased PaP Score and GPS/mGPS had independent

prognostic value (HR 3.34 95% Cl 2:04 to 5:48, p and lt; 0.0001 and HR 1.37 CI 95% 1.14-1.65, p-0.001, respectively).

Conclusions: This trial shows that cancer inpatients are frail patients with advanced disease, poor PS and several unmet needs. Moreover medical staff's prognostication (general practitioners, oncologists and internists) is inaccurate. PaP Score and GPS/mGPS are simple validated instruments which permit a more accurate quantification of expected survival and therefore may be used in the routine clinical assessment of patients with cancer.

N23 Palliative care and palliative sedation

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Introduction: The goals of palliative care at the end of life include relief of pain, suffering and also reaching adequate control of symptoms of the patient. In case the symptom is not controllable it can be used sedation. It's an accepted option for relieving pain and suffering at the end of life and it can spark a great deal of emotion and debate for all that are involved. It is therefore an intervention implemented by the team physician and decided in accordance with the patient or with his family in order to alleviate the sufferings, whether physical, psychological or social (total pain) when the interventions applied have not led to an adequate control of symptoms.

Objective: To assess which were the conditions and the reasons that have led to a predominantly sedation in the last days of life and, if possible, identify situations, moods, diseases that may be predictive for a greater chance of having performed palliative sedation.

Materials and methods: We took in analysis 160 patients who died in our hospice between January 2014 and March 2015. Among these we selected the patients who required a sedation in the days before the death and studied the reasons and the symptoms that led to this decision. The choice of criteria and the drugs used for sedation followed the internal protocol in use in line with the indications of SICP.

Conclusions: During the period questioned, there were admitted 160 patients (53% males and 47% females). The 93% of patients suffered from oncological disease while 7% had benign. Of these 30% was subjected to palliative sedation due to the presence of symptoms refractory to treatment implemented. The symptom of pain needed more often sedation (45% of sedated patients) followed by dyspnea (25%),emotional-distress agitation-anxiety-fear (20%),gastrointestinal symptoms(10%). An interesting fact showed that a large proportion of patients who were sedated for uncontrolled pain had an emotional distress associated (15%). The presence of emotional disorders or situations of distress might influence the subjective perception of symptoms making it difficult to control and could be a condition for a predictive palliative sedation.

N24 Hospitalization and rehabilitation service through an oncological support PROJECT S.O.R.R.I.S.O (Service of Hospital and Rehabilitation through Integrated Network Supportfor Cancer)

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S.O.R.R.I.S.O. was born to favorish the global take in charge of the oncological patient to guarantee a therapy continuity and the quality of life.
One of the elements characterizing this intervention model is the multidisciplinary equipe work where each member has his own specific role in a reciprocal confrontation and integration. The innovation of the project is the offer of a psycho – social assistence for oncological patients of the department who could take advantage of social operators work coordinating their work to the medical activities and favorishing the integration between sanitary and socio-assistential prestations. This objective, realised thanks to the global patient's take in charge researches and evaluating healthy, psychological and assistential needs, probable obstacles to social and/or work re-integration assures the necessary suppor eat through the definition of assistence personalised planes and favorishing the integration between territorial and hospital services. The intervetion implies also a net coordination of the oncology activities of the place with other specialised assistance and research structures for oncological deseases, and the integration between socio-sanitary services with the definition of routes and direction to guarantee the continuity of oncological patient's assistence.

Form the analyses of the preliminary dates this integrated care model for the oncological patient for other patients is:
- A real possibility to re-integrate, in a more global and unitary dimension the divided parts of the self and of the same desease;
- A sensible reduction of the anxiety with a major satisfaction for the assistence quality both for patients and for their families.

N25 Tapentadol PR in the treatment of cancer pain

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Background: 50% of cancer patients suffers from pain whose nociceptive or neuropathic etiopathology could be considered very complex. Recent studies show that bone metastasis pain is a mixed one (nociceptive and neuropathic). Tapentadol has a dual action - opioid and noradrenergic (MOR-NRI) - which is achieved without activation and that explains the effectiveness in chronic and mixed pain. The lower contribution of the opioid component also allows a reduction in adverse events μ-related. Tapentadol has a low risk of drug interactions (low protein binding and metabolism for glucuronidation). As tapentadol differs from traditional opioids we have evaluated its efficacy and tolerability in patients with cancer pain.

Patients and methods: An observational study was conducted in adult patients, of both sexes, suffering from moderate to severe cancer pain (NRS baseline ≥5). The initial dose of tapentadol PR was 50 or 100 mg BID, in case of ineffectiveness the dosage was gradually increased up to 250 mg BID. The observation period was 4 months and 5 visits were performed. Pain intensity (NRS 0-10), pain relief (NRS 0-10), quality of sleep (4-point scale), overall efficacy (4-point scale), number and reason of drop-out were considered for the evaluation of effectiveness. All adverse events was registered and an the PGIC was recorded (7-point scale).

Results: 30 patients (15M/15F, mean age 65.9 years) suffering from cancer pain with NRS between 6 and 8 (Karnofsky average 66.7; metastasis in 23 cases) were enrolled. Due to tapentadol PR the reduction of pain intensity was clinically (-3.7 points NRS) and statistically significant ($p < 0.01$). Patients have recovered a night's rest and got a sharp pain relief. At the end of the study, treatment with tapentadol PR was judged effective in 27 patients and the tolerability was good in all cases. These results were obtained with doses of tapentadol PR between 200 and 400 mg / day, stable after titration.

Conclusions: Tapentadol PR was effective and well tolerated in patients with cancer pain: the reduction in pain intensity was strong and tolerability, even gastrointestinal, was good.

N26 Diffusion of biosimilar hemopoietic growth factors use in oncology practice

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Background: Hemopoietic growth factor biosimilars present an important pharmacoeconomic opportunity. However, while pharmacologists are aware of their potential benefits, biosimilars are under-used clinically in Italy, with marked differences among regions. Poor knowledge of marketing authorization processes and lack of guided clinical experience are probably mostly responsible.

Methods: The study involved the Oncology Unit at the San Matteo Hospital and the Local Health Care Authority in Pavia. The primary aim of the project was to promote the introduction of biosimilars of hemopoiesis stimulating agents in the clinical practice. The target was set to reach 90% of all naïve patients treated with biosimilars in one-year period of time (2013). The change in management strategy included a formal lesson on biosimilar biotechnology and authorization practices at the start of the project, and a second meeting held approximately 6 months later, at the time of the first assessment, aimed at identifying difficulties and differences from expected results. To follow-up drug prescription, the clinician filed an electronic therapeutic planning record for each patient that was submitted to the Local Health Authority. The number of patients and drug prescriptions were analyzed on a monthly basis. Use of biosimilars vs originators and use of biosimilars vs total relevant drug market were recorded. Yearly average expenditure for each treated patient was recorded during the project time (2013) and during the following year (2014). Results were compared with prescriptions for all *naïve* patients treated by San Matteo oncologists in the year before the project (2012).

Results: At the end of the period of study (2013), a dramatic relative increase in biosimilar drug prescription was noted, with virtually 100% of new patients receiving biosimilars 4 months before project ending, with a positive pharmacoeconomic impact (31% saving). Active pharmacovigilance did not report any serious adverse drug

reactions and, although the project was not designed with this aim, no activity issues were apparent. Analysis of the year following the end of the project, 2014, showed persistent prescription change and additional savings (46% with respect to 2012).

Conclusions: This pilot project demonstrated that specifically designed pragmatic interventions focused on local learning and monitoring may be extremely effective in promoting the use and acceptance of biosimilar drugs in the clinical setting.

N27 New trends in prevention and detection of falls: preliminary results

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Background: Falls often causes serious injury to cancer patients (PTS) and hospital costs account for two thirds of the total. Fall prevention and detection (FAPRE) project was planned to develop a new technology in three steps: first to identify potential high risk fallers (HRF) by Timed Up and Go (TUG) test; second to compare TUG with Conley Scale and third to hospitalize HRF in monitoring room equipped with a network of smart sensors that can identify person's location, fall or lack of balance and posture connected by smartphone alerting watch nurse. Aim of this study is to describe general characteristic of HRF and to determine if new test instruments can identify them. Aim of this study is to describe general characteristic of HRF by TUG and to determine how new test instruments can identify them.

Methods: A nurse performed TUG in ambulatory room equipped with pressure sensors on the floor (intelligent carpet), webcam, home gateway, WI-FI router and smartphone. PTS were required to sign informed consent. HRF were identified by TUG test >12 seconds.

Results: From January to March a series of 99 consecutive PTS enter the trial, performance status ECOG < 2, age: median 73, range 34-87, 50 males and 49 females. All PTS underwent TUG and were evaluable. There were 11 hematologic (H) and 88 solid tumors (ST); 45/88 ST had metastatic disease; 97/99 were treating by chemotherapy, 2 by palliative care. Six PTS had brain metastasis and 9 bone; 33/99 had previous pathological fractures. Comorbidity: 14/99 diabetes and 33/99 hypertension 10/99 were taking psychoactive drugs, 22 were treated with opiate and 5 both. HRF identified by TUG were 44%; there were 27% H, 46% ST and 75% were older then 70 years. Previous pathological fracture in long bone were 14/33; bone metastasis (BM) 7/9; brain metastasis 3/6. HRF taking only psychoactive drugs were 50% and 72% opiate; 100% both.

Conclusions: TUG detected HFR more frequently in ST, elderly with BM and previous long bone fractures treating by opiate and hypertension. Identify HRF by new integrated room automation FAPRE infrastructure seems a simple, reliable and manageable approach at preliminary data. Trial is ongoing and carrying on next step.

N28 The use of denosumab in treating bone metastases from breast and prostate cancer: a Single- Institution Experience

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Background: Denosumab (DEN), a human monoclonal antibody resembling natural IgG2 immunoglobulin, has antiresorptive activity and is distinguished from other antiresorptive drugs. It mimics osteoprotegerin (OPG) that binds to receptor-activator natural Killer-ligand (RANK-L) not allowing RANK-L to bind with RANK receptor. It inhibitis osteoclast differentiation, activation and survival exerting primarily antiresorptive action. In phase III studies denosumab was superior to zoledronic acid in reducing skeletal-related events (radiation to bone, pathologic fracture, surgery to bone, or spinal cord compression) in metastatic breast and prostate cancer (PC) patients (pts).

Patients and methods: The purpose of this study was to evaluate the toxicity profile and activity of denosumab in bone metastatic prostate and breast cancer (BC) pts. DEN was administered as a single sub-cutaneous dose of 120 mg repeated each four weeks. Every pts received calcium/vitamin D integration.

Results: From December 2013 to February 2015 we treated 32 pts. 24 pts (75%) had a diagnosis of BC and 8 pts (25%) had a PC. Median age was 55 years (range 30-80). 27 pts (83,5%) had a performance status (PS) of 0 and 5 pts (16,5%) were in PS1. 23 pts (71,8%) received at least 1 line of chemotherapy for metastatic disease (MD) and 28 pts (87,5) a median of 1 line of hormanal therapy (range 1-3). All 32 pts had a MD to bone with a median number of metastatic sites of 2 (range 1-4). Pts received a median number of administrations of 8 (range 1-16). For 24 pts (75%) treatment with DEN is still ongoing. We observed 3 (9,2%) Grade 1 (G1) ipocalcemia and 1 (3,1%) renal ipofuncion requiring treatment discontinuation. We interrupted treatment in 1 pt (3,1%) for pathologic fracture. Any G2-4 toxicity was observed.

Conclusions: Treatment with DEN showed in our series a good activity and safety profile when administered a calcium – vitamin D implementation.

N29 Biosimilar epoetin alfa in the management of chemotherapy-induced aneamia: results from ANEMONE observational study

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Background: A large proportion of patients with solid tumours or non-myeloid haematopoietic tumours develop symptomatic anaemia, with relevant impact on quality of life (QoL).The efficacy of erythropoiesis-stimulating agents (ESA) in improving QoL and reducing blood transfusions has been widely demonstrated. Several biosimilar epoetins have been approved by the European Medicines Agency. Biosimilar is a regulatory term used to describe medicines with similar properties to that of an approved biological medicine for which the patent has expired. Binocrit® is a biosimilar epoetin alfa approved by EMA in 2007 for several indications, including the treatment of chemotherapy-induced anaemia (CIA). The aim of this retrospective study was to verify, in the Italian clinical practice, the trend of haemoglobin (Hb) levels in anaemic cancer patients for whom physicians deemed to use Binocrit®.

Patients and methods: The ANEMONE study was a national, longitudinal, retrospective, multicentre observational study. Patients had to be 18 years or older, presenting solid tumour or non-Hodgkin's lymphoma, Hodgkin's disease or multiple myeloma, receiving chemotherapy, treated with Binocrit® to manage CIA. The primary outcomes were the proportion of patients with an increased level of haemoglobin ≥ 1 g/dL during the first 4 weeks and with an increased level of Hb ≥ 2 g/dL during the first 12 weeks.

Results: 245 patients were enrolled and 215 patients were evaluable for statistical analysis. In the first 4 weeks, 49.3% of patients showed increased Hb = 1 g/dL: 45.5% in patients with solid tumours, 52.1% in patients with haematologic malignancies. In the first 12 weeks, 51.6% of patients showed increased Hb = 2 g/dL (48.4% solid tumours, 54.2% haematologic malignancies). Treatment with Binocrit® was well tolerated and no unexpected adverse drug reactions were reported. Interestingly, iron supplementation was adopted less than expected according actual guideline indications.

Conclusions: Despite the fact that, to date, biosimilar epoetins are widely used at European level, few publications currently have reported data about their efficacy and safety in real world clinical practice. This multicentric study represent, therefore, an important step to create and increase awareness of biosimilar epoetin clinical data. These results confirm efficacy and safety on biosimilar epoetin alpha (Binocrit®) for the treatment of CIA in routine practice in patients with solid tumors,lymphoma and myeloma.

N30 The role of medical department in the management of Breast Cancer patients: a series review

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Background: Patients (pts) affected by breast cancer, in the course of their disease often need to be admitted to Hospital because of various conditions, frequently not directly related to cancer. Literature data about rates and causes of hospitalisation are generally poor. Aim of this study was to evaluate the number and reasons of hospital admissions in a population of breast cancer pts, in order to define the real impact and need of inpatient management.

Patients and methods: All admissions of breast cancer pts to Internal Medicine Unit at our hospital between January, 1st 2012 and December, 31st 2014 were reviewed by electronic research according to the DRG system. One to 6 diagnoses, codified for each hospital admission, were considered for the analysis.

Results: One hundred twenty seven pts (F/M = 125/2, mean age = 73yrs, median = 74yrs, range 33-99yrs) were admitted to the Internal Medicine Unit. Mean duration of hospitalization was 15 days (median = 12, range = 1-62). In 6 (4,7%) pts an ex novo diagnosis of breast cancer was reached according to physical examination and subsequent biopsy. When evaluating all the diagnoses related to the hospitalization, in 73 pts (60%) there was at least one diagnosis related to cancer or cancer treatment; the

most represented were: symptoms related to metastatic disease (N = 24), cancer pain (N = 7; 6%), anemia (N = 21), neutropenia/thrombocytopenia (N = 4), radiation therapy (N = 14; 12%), and chemotherapy (N = 3; 2%). Concomitant medical problems conditioning hospital admission were: infections (N = 53), pulmonary embolism (N = 7), cardiovascular diseases (N = 35), diabetes (N = 16), kidney/electrolytes alterations (N = 19), liver and GI diseases (N = 16).

Conclusions: The small number of hospital admissions for ex novo diagnosis, chemotherapy, radiation therapy and cancer pain control, suggests that a good outpatient management was performed. Nevertheless, the availability of a Department, where a multidisciplinary approach is feasible, allowed to take care of "pts" and not only of "cancer".

N31 Redefining the pathways of care: the patient journey

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Background: The process mapping is for healthcare providers, a new important form of clinical audit that examines how they manage the patient journey. By using the patient's perspective, it identifies problems and suggests improvements.

Methods: We used a planned approach in order to identify value and non-value steps in the patient's pathway. We identified a team including a psychologist with experience of lean thinking transformation, an oncologist, a nurse specialised in oncology and a clinician specialised in Internal Medicine. The project and its scopes were planned and the pathways was visualized through a flow diagram. Data collection has included information on each step under routine clinical circumstances in the usual clinical environment; waiting episodes and bottlenecks were collected. We used the technique of walking the patient journey through interviews with patients and team and through direct observation of the patient journey and the clinical environment.

Results: We planned to improve patient pathway to our services (first access, diagnostic and therapeutic phases, follow-up, palliation, terminal phase). The team analysed the actual patient journey, drafted a map, and identified key factors to the patients experience including time spent waiting, time to discuss the findings with the oncologist, quality of time spent with nurses and team-patient interaction. The clinician specialised in Internal Medicine has observed the patient journey from the team and patient's perspectives and for each step possible notes for bottlenecks and patient's waits were entered. Each step was mapped on a paper with coloured markers and additional information were added in different colours. The time spent waiting the results of biochemical analysis was deemed as critical; time to discuss with oncologist, quality of time spent with nurses and team-patient interaction where shown to add value to our services. The patient journey was redesigned including a clinician specialised in Laboratory Medicine so optimizing the time to obtain biochemical analysis.

Conclusions: Improving the patient pathway involves the coordination of multidisciplinary practices, aiming to maximise clinical efficacy and efficiency by eliminating both ineffective and unnecessary care. The process mapping can be used to redesign the patient journey in order to improve the quality or efficiency of clinical management and to alter the focus of care towards activities most valued by the patient.

N32 Denosumab after bone progression with zoledronic acid: a single center experience

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Background: Bone involvement is associated with increased risk of developing skeletal-related events (SREs). Bone-targeted pharmacological treatments aim to prevent complications, reduce pain and improve quality of life. Bisphosphonates have been the main pharmacological treatment option for patients with bone metastases until a few years ago. Recently, osteoblast-released receptor activator of nuclear factor kappa-B ligand (RANKL) was identified as a new target for bone health. Denosumab, a fully human monoclonal antibody against RANKL, demonstrated superiority as compared with zoledronic acid (ZA) in terms of SREs postponement and treatment in solid tumors. To date very few data are available on the role of denosumab in patients who already received ZA. Based on the different mechanism of action, we hypothesized the absence of cross resistance between biphosphonates and anti RANKL drugs.

Patients and methods: We retrospectively identified 12 consecutive patients with bone metastases from solid tumors who received denosumab after prior treatment with ZA. Patients were treated at our Institution between November 2013 and April 2015. Descriptive statistical analyses was used with the aim of investigating bone response and the incidence of SREs and adverse events (AEs).

Results: Among our cohort of patients (5 female and 7 male), the median age at cancer diagnosis was 54 years (range 39-76); patients were affected by breast (3), prostate (4), kidney (1), colon (1), gastric (1) and thyroid (2) cancer. The median number of ZA infusions was 17 (range 4-44). A patient experienced osteonecrosis of the jaw and 3 had SREs during ZA treatment. At the time of bone progression, 5 had concomitant extra-osseous disease progression while 7 had stable disease. A concomitant change in systemic therapy occurred in 5 patients. The median number of doses of denosumab was 8 (range 2-16). Radiological assessments were available in all but 2 patients: 6 patients experienced stable disease, 3 patients had partial response and we observed 1 complete response. Treatment was well tolerated and we reported only a case of asymptomatic grade 2 hypocalcaemia, that was resolved with oral calcium supplementation. No SRE occurred.

Conclusions: The analysis suggested that denosumab is efficacious and well tolerated in patients with bone metastases previously treated with ZA. Therefore, denosumab can be considered as second line therapy for patients progressing with ZA.

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Session P. Psychological and psychosocial aspects

P01 Psychosocial distress and individuals needs: a HuCARE-based mediation moderation analysis in oncological population – a preliminary study

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Background: In last few years, there was an increasing attention to the psychosocial sphere of oncological patients (*e.i.*: project HuCARE). Despite of this carefulness – however – psychological distress still has a severe impact on medical care treatments. Several studies have identified different predictors of distress in oncological population; such as: aging, number of patients' needs and the degree of hospitalization. The present study – carried out within project HuCARE – aimed to test the psychological process in which the number of needs may mediate the relationship between aging and distress; in conjunction with the degree of hospitalization.

Methods: Using an observational research design, oncological patients ($N = 110$) were consecutively enrolled at the "Presidio Ospedaliero" of Saronno, Saronno (VA) in conjunction with "Ospedale di Busto Arsizio", Busto Arsizio (VA). During the first oncological examination, participants were split according to the degree of hospitalization required for their oncological care (low vs. high); afterward, patients were tested with PDI (Cronbach's Alpha = .80) and NEQ (Cronbach's Alpha = .87).

Results: Mediation moderation analysis (Hayes, 2013) shows statistical significance for the expected model [$F = 7.98$, $p < .001$; $R^2 = .22$]. The relationship between age and distress (*path c*: *beta* = .576; $p = .001$; *CI*95%: .233, .921) was partially mediated (*path c'* : *beta* = .417; $p = .016$; *CI*95%: .078, .756) by the number of needs (*path a*: *beta* = .317, $p = .004$; *CI*95%: .101, .534; and *path b*: *beta* = .503, $p < .001$; *CI*95%: .225, .781). Moreover, this psychological process was partially moderated by the degree of hospitalization (*interaction on path a*: $F = 8.14$, $p = .005$, $\Delta R^2 = .063$; and *interaction on path c'*: $F = 5.17$, $p = .024$; $\Delta R^2 = .035$).

Conclusion: These results showed a mental process based on both physical and psychological variables. These findings points out a possible way in order to investigate the psychosocial process that leads the oncological patient to experiencing distress. Moreover, these promising results suggest a mode for the implementation of psychological intervention in order to reduce physical and psychosocial distress and to improve health and quality of life in oncological treatments.

P02 Sexuality in cancer patients: a study on female sexual dysfunctions in women with breast cancer

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Background: Breast cancer (BC) is the most common cancer among women. The diagnosis and treatments of breast cancer negatively affect quality of life (QL) and sexual functioning (SF). The aims of this study were to evaluate QL and SF in BC patients during chemotherapy and follow-up.

Materials and methods: All patients with BC during chemotherapy or follow-up with regular sexual activity before BC diagnosis were eligible. SF was evaluated using FSFI (Female Sexual Function Index). FSFI dysfunctional cut-off was ≤ 26.55. FSFI evaluated six items (desire, arousal, lubrication, orgasm, satisfaction, pain) and the dysfunctional cut-off of each item was ≤ 6. Test was practiced once in outpatient.

Results: One-hundred patients were eligible: 60 patients accepted to complete the study tests and 40 were excluded due to refused to talk about sexuality. Mean age was 49.6 years, 72.5% were married; 55.1% had early breast cancer and 31.9% metastatic disease. Overall 57% and 23% of women were respectively sexually active or inactive 12 months before FSFI and 20% did not complete this test. Thirty patients completed the questionnaire during chemotherapy (group A) and 30 during follow-up (group B). Both groups obtained FSFI score lower than cut-off (18.08) without statistically significant differences between groups (FSFI score Group A: 17.28; Group B: 17.93; p: NS). The main causes of sexual dysfunctions were in group A lack of arousal (2.33) and lubrication (2.42) while in group B lack of sexual desire (2.62) and arousal (2.35).

Table: P02

FSFI SCORE

Items	Group A	Group B	p < 0.05
Desire	2.57	2.62	n.s.
Arousal	2.33	2.35	n.s.
Lubrication	2.42	2.82	n.s.
Orgasm	2.76	2.74	n.s.
Satisfaction	3.14	3.95	n.s.
Pain	3.00	2.70	n.s.
Total score	17.28	17.93	n.s.

Conclusions: This study shows that QL and sexual functioning of BC patients are heavily compromise during treatment and follow-up. The main causes for low FSFI were similar in both groups and were represented by arousal, sexual desire and lubrication. Oncology clinicians may monitor these sexual aspects particularly during follow-up to improve QL of BC survivals. The real impact of psychological aspects or therapy on female sexual functions should be prospectively studied.

P03 Quality of life as a crossroad between patients and professionals: a pilot study about cancer narratives

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Background: Health-Related Quality of Life (HRQOL), a ubiquitous construct, has proven difficult to define. It covers the subjective perceptions of the positive and negative aspects of patients' symptoms, including physical, emotional, social, and cognitive functions and, specifically, disease symptoms and side effects of treatment. Despite the difficulty in defining such a construct, it has been recognized as a basis for approval of new anticancer drugs and a common indicator of research. As the EORTC Quality of Life Group pointed out, collecting HRQOL data in a clinical trial can be complicated. It requires resources and surveys through the patients' own language and meanings. At the same time it requires to confront such meanings with the ones professionals use and agree on.

Methods: The aims of this study were:-to explore the personal narratives of patients and professionals about HRQOL, cancer illness and therapy;- to analyze differences in the narratives between patients and professionals;-to explore the correlations between such differences and the distress and social support of patients. All the subjects (51 patients and 21 professionals) were recruited at the Oncological Department of Florence. They all completed a written survey. The patients fulfilled two questionnaires about distress (Distress Thermometer, DT) and social support (Norbeck Social Support Questionnaire, NSSQ). All the narratives were analyzed through a Computer Aided Qualitative Data Analysis Software (CAQDAS). We explored occurrences and co-occurrences of words and themes and performed correspondence and cluster analysis. CAQDAS results were finally confronted, through Pearson's *r* correlation and Student's *t* test, with patients' scores at the DT and NSSQ.

Results: Patients described HRQOL in terms of psychological and social effects of cancer, whereas professionals usually talked about side effects and physiological response to treatment. Both the subgroups find difficult to hypothesize the narratives of the other subgroup. Patients who showed different themes in describing HRQOL from those of professionals, exhibited a significant higher distress($t = 2.06$; dof = 51; $p < .05$) as compared to the other patients.

Conclusions: For both patients and professionals it was difficult to define how the others perceive HRQOL: Differences in narratives seem to affect the distress of patients. Further studies are needed in order to confirm the results and estimate possible effects of confounding variables.

P04 Body Mass Index (BMI) e quality of life (QoL) in cancer patients – the 'Tor Vergata' Observational study in oNCOlogy– TV-ONCO study

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Background: Obesity has been consistently linked to an increased risk of developing cancer. A recent retrospective study on > 8000 pts has found longer survival in pts with metastatic cancer and high BMI (Martin.J Clin Oncol. 2015). Data on the effect of BMI on the Health-related quality of life (HRQoL), are scarce. The purpose of this study was to evaluate the effect of BMI on QoL in pts with metastatic or inoperable cancer.

Methods: We prospectively evaluated the association between baseline BMI and the HRQoL among 136 pts with metastatic or inoperable cancer. Quality of life was measured through the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30, version3.0). Associations between BMI and QoL were determined by means of univariate and multivariate analysis. We classified our patients on the basis of their BMI status (underweight <18.5 kg/m2, normal weight 18.5-24.9 kg/m2, overweight 25–29.9 kg/m2, obese > 30 kg/m2), sex, number of sites of metastases (inoperable or one site, two sites, more than two sites), cancer primary site (breast, lung, upper GI, colorectum, GU, other).

Results: Among recruited pts 5 were underweight (3.7%), 59 normal weight (43.4%), 46 overweight (33.8%) and 26 obese (19.1%). Male 56 (41.1%) and female 80 (58.9%). Pts inoperable or one site of metastases 26 (19.1%); pts with two and more than two sites of metastases were 63 (46.3%) and 47 (34.6%), respectively. Primary sites were GU (n 20, 14.7%), upper GI (n 18, 13.2%), colorectum (n 46, 33.8%), breast (n 25, 18.4%), lung (n 17, 12.5%), or other (n 10, 7.4%). Median Global Health Status (GHS) score was 50 for underweight pts, 50 for normal weight pts, 58 for overweight pts and 67 for obese pts. By dividing pts in BMI quintiles, we found that pts group with lowest BMI category (BMI<18) had a significantly lower median GHS score as compared with the pts group with highest BMI category (BMI>31), 50 vs 75, p 0.02. Other significant differences between these two extreme BMI categories were in Physical Functioning (median score 67v90, p 0.01), Role Functioning (67v100, p 0.02), Emotional Functioning (67v91, p 0.02) and Social Functioning (67v100, p 0.02).

Conclusion: Our results show that better HRQoL is associated with higher BMI possibly owing to additional energetic reserve counteracting cachexia. Further studies will need to address whether intensified nutritional support to achieve weight gain is warranted to improve HRQoL.

P05 Health Literacy: application of the principles in the context of ASMN-IRCCS and AUSL Reggio Emilia

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Background: Health Literacy indicates the ability of people to obtain, process and understand the basic health information to make appropriate decisions about health. The application of the Health Literacy principles is very important and now both nationally and internationally recognized. Using Health Literacy skills improves relationships and activates partnership to ensure the best outcomes of care. Low Health Literacy is associated with a lower health level and a higher mortality, especially in elderly people.

Objective: On this basis, the Emilia Romagna region established a working group in order to make the health care professionals more conscious about this issue. The project was particularly accepted in oncology, where communication is very important.

Methods: The project started in 2013 with a 4 day-course with Professor Rima Rudd, (Senior Lecturer on Health Literacy, Education and Policy, Department of Social and Behavioral Sciences, HarvardUniversity) addressed to a large number of health operators working at Arcispedale Santa Maria Nuova-Istituto di Ricerca e Cura a Carattere Scientifico (ASMN-IRCCS) and Azienda Sanitaria Locale (AUSL) of Reggio Emilia. After their training, some of them were designated to explain and spread the Health Literacy expertise to all the health care workers of ASMN-IRCCS and AUSL. Different workshops, lasting2 days each, were planned and adjusted according to the different professional fields. Questionnaires were designed and supplied to the professionals who had taken part to the workshops toevaluate the degree ofawarenessand competence, before andafter the course.

Results: The project lasted two years. Duringthe first year, 75 professionals completed their training and 4 professionals attended only one of 2 days scheduled meetings. The results of the questionnaires showed that most of the partecipants appreciated the course, and acquired specific communication techniques, like "teach me back" and "ask me 3". They also learned the importance of creating a "shame free" setting in every part of the patient-professional relationship.

Conclusions: According to our experience, the Health Literacy education of professionals improves the communication with patients, and allows a better therapeutic compliance. Health Literacy should be always part of the "know how" of every health care professional.

P06 Psychological well-being, acceptance and psychological flexibility, in breast cancer patients undergoing mastectomy or lumpectomy

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Background: Female patients with breast cancer are in a context with a strong emotional impact that requires adaptability and resilience. The psychological well-being and psychological flexibility and the ability of acceptance, may be considered protective factors. The aim of this study is to evaluate the psychological well-being (Ryff, 1989), and the acceptance and psychological flexibility in the ACT model (Hayes, 1999), in patients undergoing mastectomy, or lumpectomy or patients that have not performed interventions.

Methods: Patients were asked to complete questionnaires on clinical state (RSCL, GHQ, Distress Thermometer (DT)), eating behaviour (TFE.Q-51), body image acceptance (BIAAQ), psychological flexibility and acceptance (AAQ-2) and psychological well-being (PWBQ). The patients were divided into two groups: 1- patients without surgery and patients with breast-conserving surgery (lumpectomy) and 2- patients with mastectomy.

Results: Fifty consecutive patients (mean age = 54 years (SD 9,28)), have completed the questionnaires; t-test showed significant differences in two groups (group 1: M 55,22; SD 9,22; groups 2: M 49,57; SD 7,89). Both groups of patients showed high psychological distress (GHQ - group 1: M 4,08; SD 2,5; BIAAQ- groups 2: M 4,45; SD 3,7); (DT - group 1: M4,87; SD 2,19; DT - groups 2: M 5,15; SD 2,44), and high physical distress (RSCL - group 1: M 17,97; SD 10,54; BIAAQ- groups 2: M 25,32; SD 20,35). The data show a high well-being (PWBQ - group 1: M 75,98; SD 11,07; PWBQ- groups 2: M 79,50; SD 11,27) and a high acceptance and psychological flexibility (AAQ-2 - group 1: M 43,54; SD 11,16; AAQ-2 - groups 2: M 46,61; SD 11,01).

Conclusion: Our study shows a good level of general well-being for both groups. However, a very interesting aspect is that women without surgery and with breast-conserving surgery (groups 1), have lower levels of acceptance and less psychological flexibility. At the same time, this outcome shows that psychological flexibility is independent from suffering. We believe that this finding is relevant for clinical practice. It suggests that acceptance and then psychological flexibility, are independent factors to be evaluated in the assessment process of cancer patients.

P07 Maintenance Therapy (MT) for non-squamous advanced NSCLC: a multicenter Italian survey about patients (pts)' perspectives and physicians' awareness

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Background: Pemetrexed MT after induction chemotherapy (CTX) has become a concrete strategy of treatment for advanced non-squamous NSCLC, by extending survival, delaying disease progression, and maintaining quality of life. However, the benefit of the MT has also to be planned on the basis of pts' perception and preferences.

Material and methods: After conducting a focus group with 8 physicians concerning their clinical and emotional opinions about MT, a 12 questions-anonymous survey has been fulfilled in 13 Italian Oncological Institutions and supported by WALCE (Women Against Lung Cancer in Europe). The aim is to evaluate patients' attitude toward the MT, the benefit they expected and to provide data on physicians awareness about

patients' inclinations. The Distress Thermometer Questionnaire has been employed to perform a holistic assessment of patients. Patients' evaluations have been performed at the beginning of chemotherapy (T0) and of MT (T1), while physicians fill the survey just once.

Results: The survey has been prospectively administered to 92 newly diagnosed pts (58,7% male, median age 63,9 years), EGFR wild-type, consecutively enrolled and suitable for first-line platinum/pemetrexed-based CTX, and to 37 referring physicians (51,3% male, median age 41 years). To date, after platinum-based induction CTX, 26,1% of pts enrolled have already started pemetrexed MT. 73,9% of pts are in favor of MT. Until life expectation is over 3 months, data show agreement between pts' and physicians' perceptions of patients. When Overall Survival (OS) benefit drops at 1 month the two perceptions split: a lower percentage of pts (44,5%) would perform MT. By contrast, even without OS benefit, 71,3% of patients accept MT if it can increase symptom control (Tab 1).

Table: P07 Pts' attitudes and physicians' perceptions about MT at T0

	NSCLC pts**			Physicians		
Compliance to MT*	Yes %	No %	Unsure %	Yes %	No %	Unsure %
	73,9	1,2	23,9	97,3	0	2,7
Expected benefits from MT*	Yes %	No %	Unsure %	Yes %	No %	Unsure %
1 year OS	85,8	1,08	10,9	100	0	0
6 months OS	73,9	6,5	17,4	89,1	0	10,9
3 months OS	59,8	13	26,1	62,1	8,1	29,7
1 months OS	44,5	29,3	22,8	59,4	10,8	29,8
No OS difference but symptom control	71,3	5,4	19,5	78,4	13,5	8,1

* Possibility of multiple choices.
** Some pts did not answer to the question proposed.

Conclusions: The present study is still ongoing; preliminary data suggest the importance to stress the symptoms' control more than the survival benefit from MT, when physicians propose this strategy of treatment to NSCLC pts.

P08 Anxiety and depression: risk and resilience factors in a population of cancer patients in active treatment

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Background: Scientific literature recognizes unanimously that anxiety and depressive disorders can interfere significantly with the adherence to treatment and with the quality of life of cancer patients. To our knowledge, no studies have been conducted in Italy with high sample size, aiming to describe the presence of these psychological problems, in order to identify risk and resilience factors in a psychosocial and clinical perspective.

Method: From 2004 to 2010, during 30 consecutive days each year, 765 patients attending the outpatient ward for anticancer therapy took part in the survey. Overall, the average age was 63.10 years (from 23 to 87). 59% were female and 41% male. The majority was born in Biella, with a low level of education (77.5% had an education of less than 9 years). Breast and gastrointestinal cancer are the most frequent in our sample (35.3% and 34.5% respectively). Almost one third of the patients (31.5%) are metastatic. All patients were administered a socio-demographic and clinical questionnaire along with the Hospital Anxiety and Depression Scale (HADS, Zigmond & Snait, 1983; Costantini et al. 1999).

Results: 34.1% of our sample reported an anxious or a depressive symptomatology (8% only anxiety, 14.6% only depression and 10.5% both anxiety and depression). Participants with both anxiety and depression were more likely to be divorced and with a low level of education. Anxiety condition is associated with a younger age and with the family status, while female gender, widowhood and living alone seem to be risk factors in developing a depressive symptomatology. A higher degree of education and living only with a partner are resilience factors in developing significant clinical level of anxiety, depression or both. We found that patients with metastasis are overrepresented in the depression and anxiety-depression groups and patient undergoing further lines of therapy are at risk of developing both conditions.

Discussion: Receiving a cancer diagnosis challenges our own vulnerability and mortality, facing also physically demanding therapies, often painful and debilitating. In order to ensure the patient a holistic care process, the early detection of cases at greater risk can help the multidisciplinary team in terms of identification and planning of an effective and personalized psychological support.

P09 Second-opinion. Impact on Italian Oncologists

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Background: Cancer is a confusing and frightening diagnosis, and it may be hard to makedecisions about treatment options. Many patients (pts) seek the knowledge and advice of more than one Oncologist to confirm a diagnosis and evaluate treatment options. This is called "Second Opinion" (SO).

Materials and methods: Our research want to understand Italian incidence of SO, Oncologists' perception of SO development and how they emotionally feel, how they react facing SO, and how they behave, both when they are the first or the second opinioners.We developed a questionnaire that sought Oncologist's characteristics and reactions. 104 italian oncologists answered; 67,3 males. 51% were directors of Oncologic Unit, mean age was 48 years. An important data is that 97% of Oncologists gave a SO. This data underlines the habit of SO.

Results: Oncologists think that pts ask SO:
- 68,2% because of their emotional problems, such as fear and anxiety
- 65% for seeking reassurance that the diagnosis or treatment already suggested was appropriate;
- 25% because they need a real confirmation of a diagnosi; Oncologist consider SO:
- 75% important to calm pts fears and anxiety
- 60% a way to improve knowledge about diagnosis and available treatment
- 57% helpful to make some patients feel more comfortable with decisions. 53% pts tell Oncologist that they want to have a SO. 70% Oncologists think pts are reluctant to seek a second opinion because they are afraid they will offend their doctor and somehow it will interfere with their subsequent doctor-patient relationship. None Oncologist report negative feelings when their pts ask a SO. A problem that 63% Oncologists report and feel is the absence of communication between first and second opinioners. 10% complain about unfair collegues. Only 6% first opinioner has received a call or a letter from second opinioner.

Conclusions: SO is considered important in Italy, both by pts and oncologist.The problem is the lack of communication and cohoperation beetwen first and second opinioners and patients. Our data can give a starting point for a debate in order to think about etical and clinical guidelines that could create a bridge between patients and oncologists.

P10 Predictive Features of Resilience in Early Breast Cancer Young Patients : experience in Real Life

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Background: In clinical practice the breast cancer diagnosis represents traumatic event in women life. Despite the early intensive emotional impact, women show different psychological reactions: some patients seem more resilient than others. The resilience is defined as: no evidence of protracted psychological or somatic distress in the 12 months following treatment completion. Aim of the study was to examine the resilience in young patients with diagnosis of early breast cancer.

Material and methods: The study was conducted on 54 young breast cancer patients (mean age 45.0 sd 3.9; range 30-50 years). Women were recruited after surgery for early-stage breast cancer but before starting adjuvant treatment. Self-reported validated questionnaires assessed were PDI (Psychological Distress Inventory), BDI (Beck Depression Scale; Beck, 1967), STAXI (State-Trait Anger Expression Inventory-2; Spielberg, 2002) AND STAI-Y(State-Trait Anxiety Inventory –Y; Spielberg, 2002) at baseline, during adjuvant endocrine therapy or at the end of adjuvant treatment during follow-up.

Results: Among 54 evaluated women, 31,4% presented no signs of psychological distress, 24,0% mild distress, 16.6% moderate distress and 27.7% severe distress. High level of distress was associated with high level of anxiety and angry ($F = (9,112) = 4.49$; $p0 < 0.001$); depression condition wasn't relevant. Life factors (as education, marital status, maternity and occupation) and typology and/or timing treatments variables did not correlate with the psychological distress.

Conclusion: Our data confirm no predictive outcomes of clinical or treatment variables; patient's resilience to breast cancer diagnosis is a predictive factor related more to emotional features than to any other examined variable. Our results suggest the strong influence of internal positive adaptation during the stressing life events. More, the major compliance to pharmacological treatments seems to be related to a positive psychological condition of patient, strongly associated to an exhaustive communication by the medical staff in the early phases of the care process.

P11 The "Bandalarga" project: School's concerts in oncology

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Background: Music finds various application fields in medicine, especially in Oncology, where it can be used to relieve physical and mental pain and to induce relaxation as some studies showed.The National project "Donatori di Musica" proposed by AIOM has inspired the creation of a network of musicians that work inside different Oncology wards. The "Bandalarga" project aims to introduce music at the Oncological Day Hospital (DH) in Guastalla with the contribution of young students of the various music schools of this area.

Materials: January 2015 the physicians of the oncological DH took contact with 9 music Schools in Reggio Emilia area. After joining the project, the headmasters organized training meetings with the young students, to prepare them to the strong emotional impact that could come from getting in touch with the hospital and with oncology patients.

Methods: February 23, 2015 at 4 p.m., the Boretto Musical School hold the first concert of "Bandalarga". After this first appointment, everymonth, a concert has taken regularly place at the oncological DH, performed by different schools: Guastalla Musical School, Luzzara Musical Schooland Dosolo Musical School. The artistic program will end in June 2015 with Brescello Musical School and start again with the monthly shows on 23 Sept 2015. The designate school provided the basic staging and equipment for them show. A various number of young musicians played a large inventory, including Italian folk songs, foreign rock and blues pieces, supervised by their teachers. Every concert lasted about 120 minutes. Patients of the oncological Day Hospital, volunteers, families and hospital professionals were invited to participate at the events. The wide appeal of "Bandalarga" was possible also thanks to Emilia Romagna Project "The open Hospitals", a regional project that aims to use some hospital spaces for social and cultural activities.

Results: An increasing audience are taking part in each appointment. The events are having a positive feedback both from patients and hospital staff. Also the young students are appreciating more and more the value of the project.

Conclusions: In order to create a socializing moment, "Bandalarga" offers monthly concerts to oncological patients, letting them benefit of the positive effects of music on health. Its aims is to create a link between the local health system and the local education system and allow young students to get in touch with hospitals in a different way.

P12 Distance as a barrier to cancer diagnosis and treatment: review of the literature

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Background: The burden of travel from a patient's residence to health care providers is an important issue that can influence access to diagnosis and treatment for cancer. Though several studies have shown that travel burden can result in delays in diagnosis and treatment of many common cancers, its role appears underestimated in the management of patients in clinical practice.

Material and methods: Therefore we review the literature on the role of travel burden in delay of diagnosis, in adequate treatment, in outcome and in the quality of life of cancer patients.

Results: Forty-six studies, published up to December 2014, were analyzed. Twenty studies were excluded because they did not regard specifically the objects of the review. Twenty-six studies form the basis of this study, which included 611,423 patients. The association between travel burden and a) cancer stage at diagnosis (12 studies), b) appropriate treatment (7 studies), c) outcome (4 studies), and d) quality of life (1 study) were analyzed. In the remaining two studies, the relation between travel burden and compliance to treatment was examined. The results of this review show that increasing travel requirements are associated with more advanced disease at diagnosis, and with inappropriate treatment, worse prognosis and worse quality of life.

Conclusion: These results suggest that clinical oncologists should keep in mind the specific travel burden problem for cancer patients, who often need health care services every week or every month for many years, and should inform policy makers, service providers and health care professionals on this important issue.

P13 The unrepresentable body: a pilot study examining the representation of the causes of oncological breast disease

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Background: Having to deal with an oncological disease developing in organs that belong to the sexual sphere, such as breasts, can be an extremely painful experience for a woman. Besides representing a major traumatic event in a woman's life and in those of her family members, breast cancer may upset the balances of her psychic, emotional, cognitive and relational life. Women find themselves living an experience that leads to a change in the perception of their body-self. Indeed, this organ represents femininity, sexuality and motherhood. Cancer might therefore trigger past experiences linked to one's own feminine identity anew. The woman might feel her body changing and experience a sense of loss of control and humiliation resulting from the transformation of what she holds most dear. She might also fear to lose her own body integrity, to deny herself because of feeling mutilated, and to feel abandoned by all those who don't accept her in a different body. The disease necessarily leads to an inevitable confrontation with the some of the deepest themes of human existence, such as the body integrity, the image of the body and the grieving process. The current scientific literature identifies the body image of the woman who underwent surgery and her representations of the causes of the disease among the most important psychological factors in the clinical pathway. The present study aims at investigating the two factors in more detail and to relate them to the treatment pathway.

Material (patients) and methods: Key issues such as the different dimensions of the body image of the woman, the impact of the disease on the body image and the attribution of cause of the disease have been analysed through the administration of the *Body Image Interview Questionnaire* (Maggioni C., 1992) to 25 women with breast cancer.

Results: The data that have been collected show that most of the women who were interviewed have a very personal and vague idea of the likely causes of their disease. Furthermore, they don't seem to live their own body and appear to have a destructured body image. Such gathered information suggests the idea that the distorted or missing representation of cause of the disease may give rise to a sense of void responsible for destructuring the body-self.

Conclusions: The reconstruction of a new body image cannot develop without a full awareness about the causes of the disease.

P14 Cross-cultural adaptation, evaluation and validation of the Patient-Reported Outcomes of the Common Terminology Criteria for Adverse Events (PRO-CTCAE): a study protocol

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Introduction and purpose: The US National Cancer Institute's PRO-CTCAE is a tool designed to monitor symptomatic adverse events in cancer clinical trials through patient self-reporting. This work presents the results of the cross-cultural adaptation into Italian of the PRO-CTCAE.

Methods: The study has two stages: a) cross-cultural adaptation through 5 steps: translation, back-translation, approval of pre-final version, cognitive debriefing (through semi-structured interviews, conducted by trained psychologists with 96 patients, to evaluate comprehension of terminology, phrasing, response options, and format), and approval of final version; b) validation, where the final version will be tested prospectively with 300 patients undergoing anticancer treatment. Maximum variation sampling is used to select subjects, with at least 25% of participants with low education level.The study is sponsored by the Italian PRO-CTCAE Study Group (multidisciplinary investigators, voluntary associations and a foundation involved in health education), and approved by Ethics Committees at 17 participating centres.

Results: The comparison of two independent forward translations revealed literal ('same words') and semantic ('same meaning') equivalence for 29 of the 80

PRO-CTCAE symptom terms. The translation of the expression "at its worst" in the questions on severity proved particularly challenging. Merging of translation and discussion between translators produced a single translation which was back translated by two separate translators. Thirty symptom terms exhibited complete literal and semantic equivalence to the original for both back translations, while 76 showed semantic equivalence. For one symptom in particular, the meaning between the original and the back translations greatly differed "Pain in the abdomen (belly)" vs "stomach ache". The Expert Committee reviewed all items, agreed improvements, and produced the pre-final version of the Italian tool. The US NCI approved the pre-final version. The pre-final version is now being examined through cognitive debriefing, the results of which will be presented at the 2015 AIOM conference.

Conclusion: The study will produce a validated Italian version of the PRO-CTCAE to be used in cancer clinical trials to improve reporting of side-effects of anticancer treatments. Supported by an "unconditional grant" from GSK.

P15 Evaluation of distress in the patient and in caregivers, in the communication of the diagnosis during the first oncology visit. Studio SA15

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Objective: The SA15 study is an observational study performed at the Oncology Day Hospital in the Hospital "G. Procida "of Salerno. The aim of the study was to see how and what affect the distress in cancer patients and caregivers during the oncology first visit. During the first visit e was notified of the patient the diagnosis and prognosis.

Materials and methods: Between January 2014 and January 2015, 240 first visits were carried out at the Oncology Ambulatory. Of the 240 patients seen, 180 patients were evaluated because they received medical treatment (chemotherapy, hormone therapy, immunological and biological therapies). Of the 180 patients, 120 patients had a caregivers, and other 60 did not want to identify a caregivers. After the communication of the diagnosis and prognosis was administered to the patient and the caregivers of the Distress Thermometer, only in the visual evaluation, without requiring the compilation of five list of problematic area. The first visits were made by two medical oncologists, one with certified skills in communication.

Results: The results of this evaluation showed a fundamental datum, the patients have high levels of distress after the communication of the diagnosis and prognosis. Median values of patients were of 7 (range 2-10). Median values of caregivers were 8 (range 3-10). Caregivers were level of distress even higher than those of patients. For the 60 patients who had not identified a caregiver, the median values of the Distress Thermometer was 6 (range 1-10). The evaluation of the distress was also influenced by the doctor which disclosed the diagnosis and prognosis. In patients who had received the communication from the doctor who had experience in the of communication, the levels of distress was significantly lower.

Conclusions: From this observation it is clear how important communication to the patient and the caregivers, but even more it shows how importrant training staff who work with the fragility of the cancer patient. Not a good communication leads to higher levels of distress.

P16 Loneliness during protective isolation in patients with haematological malignancies: a three-dimensional conceptual model

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Background: Patients with haematological malignancies are often nursed in protective isolation for hematopoietic stem cell transplantation, in order to prevent hospital-acquired infections. During protective isolation, patients may experience stress, anxiety, anger, depression, insomnia and loneliness. Loneliness, although a relevant determinant of poor health and quality of life, is under-conceptualized and measured. From a meta-synthesis of qualitative research on the lived experience of patients in protective isolation a conceptual model of loneliness was generated including 3 dimensions: suffering (+), relationship with oneself (-), problems in the relationship with others (+). The purpose of this study is to use these findings to develop a tool able to assess loneliness in haematological isolated patients.

Material and methods: Following the European Guidelines of the Statistical System the conceptual model of loneliness, as a consequence of isolation, was used to develop the items for the questionnaire., Two focus-groups were conducted with 10 experts who systematically evaluated the indicators of patients' loneliness with a structured form in order to verify face validity. The experts included nurses, haematologists, psychologists, and a former patient.

Results: Items for "suffering" refer to boredom, burden of loneliness, powerlessness, amplification of fears, feeling imprisoned, restriction in movement, distress, suffering orders, lack of privacy, helplessness. Items for "relationship with oneself" refer to being focused on oneself, cognitive reappraisal, attribution of meaning to isolation, inner growth, self-esteem. Items for "problems in the relationship with others" refer to loss of touch and closeness, fear of abandonment, lack of comprehension, lack of someone to talk to, danger in the contact with others, feeling cut off from the world.

Conclusions: Patients in protective isolation suffer because of loneliness, lack of freedom and total distress. They need to relate with themselves to cope with being isolated. This happens when patients regulate their emotion and their own attitude to adapt to hospitalization. This adaptation is necessary for fostering hope and implies a search for meaning, associated with what patients perceive as protective. Patients try to remain open to the outside world thanks to the relationships with others, and to maintain reciprocal support.

P17 "Yoga project in Oncology: observational study of the Yoga effects in cancer patient. The Poliambulanza experience"

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Background: In recent years, literature has reported an increase in the use of Complementary Alternative Medicine (CAM) by cancer patients to manage symptoms related to the disease or side effects of the treatments. Yoga is one of the most widely used complementary and alternative medicine therapies to cope with the most common symptoms of cancer as anxiety, depression, fatigue and sleep disorders. Recent studies conducted with cancer patients indicate that Yoga is associated with improvement in overall QOL, emotional well-being, physical symptoms and distress. In April 2013 we started the "Yoga project in Oncology " which involved the use of specific exercises of this discipline as a complement of cancer treatments. The aim of this study was to evaluate the impact of Yoga training on mood, fatigue and sleep quality in metastatic cancer patients.

Material and methods: The Yoga intervention used the Yoga Ratna approach, consisting of pranayama (breathing exercises), gentle yoga asanas (postures) and meditation. The program includes 8 weekly group meetings lasting 1.5 hours, trained by a Yoga professional teacher with a psychologist. At the beginning (T0) and at the end (T1) of the training we administered the following tests: Hospital Anxiety and Depression Scale (HADS) to evaluate anxiety and depression; Fatigue Symptom Inventory (FSI) to assess fatigue symptoms; Pittsburgh Sleep Quality Index (PSQI) to assess sleep quality.

Results: Sample consisted of 35 patients with metastatic cancer receiving chemotherapy. The majority of the patients were women (65.7%), the mean age was 55 years, 62.8% of patients were married and 45.7% were employed with a medium-high level of education (57.1%). All patients had advanced disease: 54.3% breast cancer, 31.4% colorectal cancer; 8.6% others gastrointestinal tumors and 5.7% pancreatic cancer. The preliminary results showed a not statistically significant trend concerning anxiety and depression improvement and a better sleep quality. In addition, we found an increase of fatigue symptoms.

Conclusions: These results don't show statistically significant correlations probably because the still small sample treated so far. Moreover patients continued to receive medical treatment (chemotherapy) during Yoga training and this condition could have influenced their fatigue perception. Nevertheless, every participant expressed a very positive evaluation of this experience concerning a better body awareness and anxiety control.

P18 Skin parameters evaluation in breast cancer patients during adjuvant chemotherapy

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Background: Since 2007 the Oncological Unit at Carrara hospital has implemented an Aestethic Medicine Practice, where patients are professionally monitored and adviced on the most appropriate interventions to prevent or limit blemishes following cancer therapies.

Matherials and methods: Forty breast cancer patients undergoing adjuvant chemotherapy with epirubicin cyclophosphamide (EC) were randomly assigned to receive appropriate dermocosmetic tratment protocol and to maintain routine skin care approach. The dermocosmetic protocol consists of a liquid cleanser and an emulsion with specific INCI and specified characteristics as nichel and flavour free; moreover these products were indicated for reactive skin. We measured skin

parameters: corneometry and sebometry for body and face before starting each cycle of EC. Dermotest SIT 3 ME.DI.TER is used for measurements.

Results: Body and face sebometry is statistically significant (p < 0,001) between the two groups; body corneometry doesn't reach statistically significance (p < 0,021), face corneometry is statistically significant(p < 0,011). The randomised group receiving skin-care protocol shows better cosmetic outcomes.

Conclusions: Prophilaxis with appropriate dermocosmetic skin care products is able to contain, almost eradicate, skin damage (reduction of sebum and corneometry) caused by chemotherapy (EC). Moreover inappropriate use of generic skin care products without professional guidance can aggravate skin damage caused by chemotherapy.

P19 Psychosocial distress in project HuCARE - a preliminary study

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Background: Psychological distress could be considered one of the most severe mental health issues – specifically at the time of diagnosis – in oncological treatments. The attention in helping the patient to cope with the diagnosis, treatment and its side effects becomes the primary focus. To face this problem, project HuCARE promote the humanization of cares offered to cancer patients based on the evidence of an immediate detection of psychological distress. The present research aimed to realize a portrait of severity of psychological distress of HuCARE patients. In particular, we aimed to test the distance between the HuCARE fixed cut-off for distress for the most frequents type of tumor both in inpatients and outpatients.

Methods: Using an observational research design, oncological patients ($N = 211$) were consecutively enrolled at the "Presidio Ospedaliero" of Saronno, Saronno (VA) and "Ospedale di Busto Arsizio", Busto Arsizio (VA); in particular, participants were hospitalized either at the Department of Medical Oncology nor at DH. According to HuCARE guidelines patients were tested with PDI (Cronbach's alpha = .78) in order to understand the severity of their psychological distress.

Findings: In order to determine oncological localization frequency and to measure their distance from a HuCare-based cut-off (= 35) descriptive analysis and One-sample t-test ware performed. After stratifying patients for tumor localization, One-sample t-test showed that all DH groups have obtained a distance significantly lower than the cut-off. Contrariwise, hospitalized patients showed a non-significant distance from the cut-off; specifically, for individuals affected by colon cancer ($t = -1.971$; $p = .106$); pancreatic cancer ($t = -2.054$; $p = .064$) and lung cancer ($t = -1.453$; $p = .177$).

Conclusion: These results showed an interesting portrait of oncological patients in two different medical settings but – at the same time – in two different hospitals. These findings permit to evaluate clinical psychological resources that could be available for patients with a different localization of cancer. These results also allow to improve the development of the means and to create psychosocial intervention based on the specific location of the oncological pathology.

P20 "The long survival in oncology: which QoL? Finding study in more than five years after the end of treatment"

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Background: The introduction of effective therapies and screening programs has improved the neoplastic pathology resulted in a gradual reduction of mortality with a gradual increased number of people with past oncological healed. Today cancer is partly comparable to other chronic disease with whom our society has learned to live with a good level of quality of life. The increase number of people who after exceeded with the tumor and overcoming the acute phase, they fit the social environment, require the deepening scientific and clinical. the conditions of long-term survival and healing

Methods: In the year 2014 the prospective study involves 22 women, patients with a previous diagnosis of gynecological cancer apparatus that least five years, have concluded the treatments and they are free from disease, The patients are subjected to psychological interview and compile two questionnaires: The Psychological General Well Being Index, which is able to provide an index that measures the state of wellbeing or discomfort linked to the emotional sphere and affective, the Female Sexual Function Index, which investigates the perception of their sexual satisfaction.

Results: From the questionnaire showed that the sample responds with values of wellness in the subscales of anxiety,depression, health, positivity while shows a decrease of the total score in the subscales self-control and vitality.The results obtained so far show a psychological profile of long-term survivors, comparable to that of the general population, with specific subjective experiences,especially in reference to certain areas of the patient's life such as for example of sexual satisfaction. We observe that 67% did not try sexual desire, with: 61%, emerges considerable difficulty in reaching the excitement, with:72% have difficulty in lubrication during sexual activity, 76% feels pain during sexual activity and pain hinders the sexual relationship.

Conclusions: The data, seems to want that connotation of "base", attributed to sexuality by OMS, given that describe areas problematic that seem unite, much of the sample, the clinical terms, this translates in the utility to facilitate communication with the patient on sexuality themes. Legitimizing the research of the best possible quality, even in this domain of quality of life.

P21 First visit is never forgotten

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Background: The first oncological visit is a central moment in the treatment and in the establishment of the therapeutic relationship; the meeting with the oncologist involves psychological aspects and has a strong emotional impact on patients (pts). First visit is the time of diagnosis communication and therapeuthic condivision. Pts arrive at the first visit with expectations, fears, fantasies, ideas not only about their health conditions, but also about the doctor and the relationship with him.

Materials and methods: In our Oncology Unit we give an important value to the first visit. We recognize that disease has both an organic and a psychological component. That is the reason why we choose to plan the majority of first visits both with doctor and psychologist. This is an important legitimation of emotional impact of cancer and the possibility that the experiences related to that event can then find spaces of expression, listening and processing. Cohoperation between psychologist and oncologist can improve a positive exchange between two visions to face pts that are often different. Steps of the first visit are: - Preliminary view of the medical oncologist and psychologist - Presentation to the patient and the caregivers of the Psycho-Oncology Service - Drafting of brief psychological report that will be included in the medical record - Possible first date for a psychological support if necessary The aims: - Increase the therapeutic alliance and adherence to treatment path - Focus on patients and family members considered 'at risk' for an early taking care, to decrease the risk of psychopathological manifestations - Facilitate the comparison between different professionals.

Results: In 2014 we made 210 joint visits (65% of total), 52 pts with breast cancer, 47 colon, 35 with gastric cancer, 21 with gynecological cancer, 25 lung, 15 melanoma and 15 more. 28 pts and eight caregivers were taken into care after the first visit, while in other situations it is active a surveillance in cohoperation with the team of care.

Conclusions: The presence of the psychologist in the Unit, the cohoperation and the communication with health staff has improved early detection of psychological suffering situations. Psychoncological service integrated with oncological treatment is a valuable resource for patients and caregiver that are facing a state of vulnerability.

P22 Early assessment of distress in cancer patients treated in DH setting

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According to NCCN vers. 1.2014, distress is a multifactorial unpleasant emotional experience of a psychological (cognitive, behavioral, emotional) social and spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms and treatment. Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness and fears to problems that can become disabling such as depression, anxiety, panic, social isolation, and existential and spiritual crisis. Although largely under-recognized, distress is the sixth vital sign and is reported in 30-40% of newly diagnosed cancer patients. To assess the level of distress in newly diagnosed cancer pts receiving chemotherapy in our DH, between 1st and 2nd course, patients were screened by mean of self administered tools (Hospital Anxiety and Depression Scale (HADS) and Distress Thermometer and Problem List (DT-PL))

followed by a clinical interview. HADS is a 14 items measure of anxiety (7 items) and depression (7 items). DT is a visual analogue tool evaluating the level of distress in the last week on a scale from 0 to 10. PL is a 36 problems list grouped into 5 categories. The clinical interview is aimed to express any potential needs and to plan interventions including home assistance, volunteer support, mental health and to encourage more structured psychological support. Between October 2014 and April 2015, 94 pts were evaluated, 3 pts declined to partecipate. Characteristics of evaluated pts were: median age 64yrs (range 38-89), 55 females and 39 males; 27 pts have ≤5 yrs of education, 32 8 yrs, 30 ≤13 yrs, 5 >13 yrs of education; professional status: 56 were retired, 29 employed, 9 unemployed or housewives; tumor type 28 colorectal, 17 breast, 9 lung, 10 gynecologic, 30 other solid tumors. We observed sign of anxiety and depression in 43.62% and 29.79% respectively. Probable levels of anxiety and depression were present in 20.21% and 11.70% and possible levels in 23.41% and 18.09% respectively. 13.8% were administered more structured psychological intervention. Our findings suggest that evaluation of anxiety and depression is feasible and may be included in routine oncological work up of newly diagnosed pts, health care providers should be aware and receive training to better address distress complains in cancer pts.

P23 Integrated support in neoplastic patient and family: experience of molise in ccm 2012 project

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Background: The cancers are chronic diseases in which the medical approach alone is not sufficient. The CCM 2012 project promoted by the Emilia Romagna involves the activation, for small groups, of paths aimed at assessing the changes induced by the disease and set a goal of health. Involved patients aged between 40 and 60 years, with colon and breast cancer, with adjuvant therapy ended not more than 1 year.

Materials and methods: 1 interview to explain the purpose of the meetings and evaluate the motives, 4 weekly meetings, follow-up at 1 and 6 months. 1° wk: material delivery and constitution group; brainstorming on the words health/disease; expressive workshop (card images of places, emotions/analogies); relaxation activities (hero's journey). 2° wk: expressive lab (pairs opposite and activities cards); analysis of relational needs; training for self-regulation of behavior. 3° wk: discussion and choice of health objective; choice of individual transformation process. 4° wk: bargaining goal of health; programming the remote controls. Aim of the course: rework the disease lived, change lifestyles (alcohol and smoking), promote physical activity, education on proper nutrition through specific workshops.

Results: Informed consent was obtained from 18 people (2 men, 16 women; 3 colon and 15 breast cancer). The disease is described with precise images (tortuous and tiring) generating anxiety, restlessness, anger and fear, but in a positive family environment and care. Compared to lifestyle while recognizing as risk factors alcohol and smoking some persist in habits; as for physical activity and nutrition.

Conclusions: In the group showed the importance of sharing emotions related to the disease. A correct lifestyle allows recovery of psychological wellfare and the choice of target health conscious the possibility of change. For smoking, patients believe that it is an important goal, but hardly actionable for this would be desirable to increase smoking cessation workshops, already active with LILT and other prevention interventions.

P24 The importance of network intervention for cancer patient welfare. the ccm 2012 project: the molise experience

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Background: CCM 2012 Project "*Integrated support to sick relatives and cancer patients*" promoted by the Emilia Romagna region, preventive measures are not limited only to primary prevention but can also in secondary/tertiary prevention. The project aims is to test a cancer patient assistance that goes beyond diagnosis and care but takes supports it with a networking model that involves multiple agencies (LILT, ASReM, SIAN, two schools, ARSIAM). It will stress the importance of prevention interventions and changes of life style for a recovery of mental and physical welfare.

Materials and methods: In the context to prevention and promotion of welfare were implemented: cancer prevention training with sensory education workshops to taste (extra-virgin olive oil); educational activities for students Larino's Agrario future operators in the agri-food sector; cooking workshops in collaboration with the hotel of Vinchiaturo. The path took place in 3 stages: 1-network training, education on the themes of foods; 2-preparation cooking workshop with products supplied by Agrario; 3-taste education by students of the hotel sector. The final day of the course saw the participation of patients and students, by creating a menu adapted to the purpose of the project.

Results: Were involved: 4 ASREM operators, 3 volunteers LILT, 1 MMG, 3 teachers, 80 students. From the questionnaire rating 90% of students is satisfied with his school's participation in the project, 88% consider appropriate the project at his school, 100% of patients are satisfied and want to participate in other meetings in theme. The search path of nutritionally suitable to prevention made it possible to select food for preventive properties, easy to prepare and pleasing to the taste.

Conclusions: The project has led to the activation of a network of integrated care to cancer patients, functionally adequate and motivated, which resulted in the achievement of the best results in terms of efficiency.

P25 If you are well ... you work well!

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Background: The National Health Plan 2006-2008 recognizes the growth of diseases linked to psychosocial factors associated with stress (burnout, bullying, etc.), they are identified as occupational diseases, psychic and psychosomatic diseases that originate from an inadequate work organization . Employees are commonly faced with greater demands and less job security, both of which are likely to be stressful, thus psychological disorders especially depression may increasingly be caused by work-related stressors. So this kind of stressors may be the cause of "professional misconduct", "difficulties in the relationship with the patient based on less empathy and sensitivity", but most seriously they interfere with the quality of life of the operator.

Material and methods: The SSD of Psychology of the National Cancer Institute "Fondazione G. Pascale" of Naples has organized a prevention and support intervention, at short, medium and long term, that is addressed to all the healthcare workers of the Institute (doctors, psychologists, nurses etc), aiming at their professional training and at a better and more qualified human resources management. The intervention is characterized by three steps:

- First step: training courses adressed to all the health workers ofthe Institute in order to acquire a better knowledge and awareness of stress diseases
- Second step: support programmes in order to prevent and reduce work diseases
- Third step: follow-up intervention in order to monitor the results over time and to evaluate the organization welfare.

Results: Thanks to this complex intervention we expect to maintain the welfare of the hospital, prevent the main work related stress disorders and reduce conflicts in the working groups.

Conclusions: Working in an oncology department requires enough energy to confront all problems and self-devotion (Lederberg, 1998). Offering care to cancer patients may give rise to stress, dissatisfaction, alienation from work and exhaustion in health professionals. For these reasons it is essential for us to create guidelines in order to guarantee a continuous psychological support for all the healthcare workers.

P26 Find yourself with a smile

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Background: Cancer permanently marks body, leaving scars, mutilations and creating functional alterations. These wounds can persist a long time and leave signs both from physical and psychological . Body changes consequent to surgery and cancer treatments require a process of adaptation and, after many years they condition the sense of general health, personal care, social contacts and sexuality. These changes make patients loose self-esteem and reduce quality of life. Patients feel a sense of loss of physical integrity, they feel strangers in their body.

Materials and methods: Since May 2013 our Department has joined the project "La Forza e il Sorriso" (Strenght and Smile), organizing workshops of beauty for women in cancer treatments.The aim is to give psychological support to patients in cancer treatment and in follow up. During project, we teach techniques to manage the effects of treatments. Through this project we want to help patients to rediscover important rituals such as cohoperation, confidences and alliance between "friends", rediscovering

the pleasure of embrace, makeup or simply meet and go out from home, home where often patients stay closed because of fear and shame. 5/6 women to each laboratory; they are followed by three beauty consultants volunteers, specially trained; during two and half hour session they help the participants to take care of their image and to cope with the secondary effects of cancer therapies. Psychologist is always present during these sessions. Women know about beauty laboratory through information materials and website. At the end of each session, every woman receives a beauty-bag donated by the association, to practice at home. At the end of each session we ask patients to complete an anonymous satisfaction questionnaire.

Results: 18 workshops were conducted, involving 72 women. Average age 55 years (range 24-69). 73% breast cancer. 81% in treatment, 19% in follow-up, 26.5% metastatic. Women have expressed great enthusiasm for taking part to the initiative. Questionnaires showed that: 70% felt valued and beautiful, 55% more cheerful and serene, 45% inspirating and positive, 30% renewed; no woman reported to feel herself like before.

Conclusion: Chemotherapy and its consequences will never stop to create fear, but certainly the women who were accompanied to the care of their appearance, are outputs from the meetings with a look and a new posture, different, more aware of their own femininity and with a positive attitude.

P27 End of life in cancer patients: something more?

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End of life in cancer patients brings us to an ethical evaluation not only concerning the patient but also regarding society since prolonging therapies which are sometimes very expensive, means an improper use of resources which could be used to help patients who could gain a real advantage from them. Many studies suggest that optimal palliative care can effectively manage the symptoms of most cancer patients during most of the course of the disease. A particularly difficult problem is palliative sedation; in fact apart from the most common symptoms such as pain, dyspnoea and anxiety, palliative sedation is the last resort used at the end of life to relieve severe and refractory symptoms. The objective of this treatment is to relieve the burden of unacceptable and unnecessary suffering for terminal cancer patients and to do so in such a manner to preserve the moral sensibilities of the patient, the medical professionals involved in his or her care and concerned family and friends. Before teaching techniques to control the most common symptoms in terminal cancer patients such as pain, dyspnoea, anxiety and palliative sedation it is important to empathize a culture focused on the doctor-patient relationship The current lack of definition of best practices could explain the difficulties facing the attending oncologist and consequently, at least in part, the high number of patients who request further therapy in the final stage of the illness even though the advantages in terms of survival will most probably be minimal or totally absent**:** they continue to cling to this illusion. However, inevitably we must ask ourselves who has the absolute right to deprive someone of an irrational hope. Patients have the right to accept or reject therapy and more often than not continue to hope even though the situation may be hopeless. The role of the doctor is not to offer hope which is only an illusion but, and this is probably the most crucial point in the doctor/patient relationship, the doctor must help patients reduce their expectations while, at the same time, heighten the patient's trust in the doctor and to comfort patients in the knowledge that they are not alone, and that their physical and psychological suffering will be the doctor's only concern. At the beginning of the twentieth century Franz Kafka frequently said: "It's easy to write a prescription for medicine but talking to people who are suffering or dying is more, much more difficult".

P28 Evaluation of distress in women to be a breast mri. the mri is a exam level ii, after mammography. bc14 study, performed at the oncology day hospital in the hospital "g. da procida", of salerno

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Background: The BC14 is an observational study.The aim of the study was to see how and what affects the distress in patients (pz) carry out a brest MRI, after a clinical examination, an ultrasound and a mammography.

Materials and methods: Between January and July 14, 50 women were enrolled in this study. After signing the informed consent, women filled out a card with personal data, the Distress Thermometer and the Psychological Distress Inventory.

Results: The personal data point out: Median age 55 years;Good instruction; Employment stable 46%; 64% of pz is married; Previous diagnostic tests:44% the Mammography and 36% the Ultrasound; A family history of breast cancer by 42%. The analysis of distress evaluated with TD showed:22% of the subjects showed emotional distress as a value of 1,14% of the subjects showed emotional distress as a value of 7. The analysis concerning the list of five problem areas point out: 35/50 pz had no practical problems.12% has practical problems in the care of the children and on the economic management; The relationship distress in the affinity with the children is 11%, with partners is 8% and the other is 15%; For emotional problems, there was a high percentage with the worry (37%), less for the fear (19%), the nervousness (19%) and sadness (14%); With regard to physical problems, respondents report a high percentage for the sense of fatigue and tiredness (26%), memory/concentration (12%), sleep (10%), and how to appear (6%). An analysis of the PDI emerges: The desire to talk to others decreased in 30 pz,even if in a not very high; 31 pz have lost little tranquility of everyday life I had before; In 34 of the respondents occurred a moment of anxiety and inner tension; The Fatigue has recorded in 28 pz,13 refers instead to feel better; The sense of loneliness was described by 10 pz, while 25/50 reported moments of discouragement or depression; Only 8 pz think their illness or suspected illness can create problems of physical image that were not there before; 42 do not think they feel worthless and will; Only 11 pz report a decrease of interest in the world that surrounds it; In 10 interviewees occurred a decrease in their sex drive and only in 8 pz occurred that the disease has negatively affected their relationships with others.

Conclusions: The result of the BC14 study showed high levels of distress in pz about to perform an MRI of the breast, and raise the need to assess the support of a psychoncologist to provide adaptive coping strategies to stress.

P29 Psycho-social assistence for oncological patients, to reveal and answer to the patient and caregiver's psychological discomfort

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Background: Many evidences and numerous studies show that the oncological disease a part from effecting patient's physical wellness and health, often provide several forms of psychological discomfort charachterised by symptoms of anxiety and depression which could be in many cases very significant in a clinic situation (Greer, Park et al., 2010). Moreover, diagnosis of a cancer has a huge phycal, sensitive and practical impact on patients' life and on their family life. In the majority of the cases caregivers and patients' relatives are generally the first and fundamental resource, and so the quality of the cares received and the achievement of positive therapeutic results depends above all on the caregivers' ability to offer a proper support (Lutgendorf & Laudenslager, 2009). The general objective is the definition of a "global take in charge" model for the patient and his family. Ø Verifying, monitoring and recording the distress, anxiety and depression prevalence in a sample of oncological patients in any clinic oncological situation, (department, ambulatory, day-hospital, ecc.) and the specific caregivers; Ø Noticing the risk factors where to act in advance and limiting the pathological effects of emotional disease in the patient and in their caregiver; Ø Distinguishing psychological needs during the first examination for the patient-caregiver, in appropriate intervals and when clinic conditions are modified involving social services and the net of local voluntary associations; Ø Improving assistence for patients and for their families.

Material (patients) and methods: The sample consists of patients belonging to the Operative Unit of Oncology of the Azienda Ospedaliera dei Colli.Measures and instruments for noticing what is established in the intervention model: To evaluate anxiety and depression: Hospital Anxiety Depression Scale; To evaluate the distress will be used the "Distress gauge" an *ad hoc* questionnaire to measure the satisfaction degree of the assistance and of the received information.

Results end conclusions: In this work are described the ways of the multidisciplinary intervention and the measures of the projectual objectives.

P30 "The group's waiting room: groups of self- help in oncology"

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Background: Cancer patient try emotions like fear, disorientation and discomfort, especially in poorly "protected" area as the waiting room of the hospital. The loneliness, isolation, and the inability to share their history of disease makes it difficult to continue to "live". The self-help groups, represent a time of sharing for patients, with the aim of supporting the woman in such a difficult time. In the group, the participants find comfort and mutual support.

Methods: Our prospective study involving 3 groups of mutual help each one formed by 5 women patients, meetings take place on a weekly basis for a total of 6 days in 2015. Fifteen women, median age 50 (range 42-72) affected by breast or ovarian cancer. The group were lead by an medical oncologist, a gynecologist, and a psychotherapist. The

patients undergo psychological interview to evaluate the adhesion and fill by anonymous questionnaire, purpose-built at the end of the group.

Results: The questionnaires administered to groups (15 patients) showed that: 60% of the patients increase in the desire to quit, 85% of the patients tried comfort in comparison with the other, 75% of the patiens found answers to questions that concerned her self, 90% of women say that meeting other women with the same experience helps you feel less alone in the fight against cancer. The sharing continues even after the closure of the groups; Women continue to meet and exchange ideas, breaking the wall of solitude, in which they felt imprisoned.

Conclusions: The sharing of problems and fears strengthens the ability to look at the present and the future in a positive and constructive way. Patients maintain relationships and undergo to therapies with more compliance and with an hope.

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Session R. Miscellanea

R01 Phase II study of everolimus in combination with octreotide LAR as first line setting for patients with neuroendocrine tumors (I.T.M.O. study): a 5-years update

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Background: We previously presented data of this phase II study showing that the combination of Everolimus and Octreotide LAR for advanced neuroendocrine tumors (NETs), as first line setting, is an active and safe treatment (ASCO 2013,Abs. 4136). This abstract is an update after 5 years.

Methods: We performed a phase II, multicenter trial using a Simon two-stage minmax design. Patients withadvanced well differentiated, previously untreated neuroendocrine tumorsof the gastroenteropancreatic (GEP) tract and of the lung, continuously received Octreotide LAR 30 mg every 28 days in combination with Everolimus 10 mg per day. The primary endpoint was Objective Response Rate (ORR).

Results: A total of 50 patients (58% males) were enrolled; 36 (72%) of these patients have been treated for more than 1 year. The median exposure to study drugs is 118 weeks (range 47-242). Currently 4 patients are still taking advantage from the above mentioned treatment. The primary tumor site was: liver 2 pts, pancreas 11 pts, small intestine 8 pts, lung 7 ptsand unknown in 8 pts. Approximately 70% of these patients had no carcinoid syndrome and 50% have been surgically treated at the primary tumor site. The ORR was: CR 1 pt, PR 8 (22%) pts, SD 27 (75%) pts. The median TTP is 38 months (95% CI 19–n.d.) and the median OS has not been reached. The updated data up to 06/2015 will be presented during the next meeting.

Conclusion: Everolimus in combination with octreotide LAR has shown to be active in advanced NETs. The current study showed a further prolongation of TTP, as well a long exposure to the study drug without unexpected long term side effects. The treatment with two drugs has induced objective responses, but also long duration SD.
Acknowledgements:Italian Trials in Medical Oncology (I.T.M.O.) group, Giacinto Facchetti Foundation and Novartis.

R02 Time to response (TTR) and early tumor shrinkage (ETS) in recurrent glioblastoma patients treated with bevacizumab: an exploratory analysis of the prospective randomized AVAREG (ML25739) phase II study

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Background: The treatment of recurrent glioblastoma (GBM) remains an open issue, and the role of bevacizumab (BEV) has been widely debated since a few studies compared this agent with the standard treatments.

Methods: a multicenter, randomized (2:1), phase II study (EudraCT: 201100136346) with BEV 10 mg/kg iv every 2 weeks or fotemustine (FTM) 75 mg/m2 iv day 1815 followed, after a 35 days interval, by fotemustine 100 mg/m2 every 3 weeks, was conducted. The primary endpoint was overall survival at 6 months (OS6). ETS was assessed with central review exploratory analysis. T1contrast enhancing area and T2/FLAIR were evaluated as predictors for OS rates with ROC analysis and the test for AUC. The best cutoff values were found with the maximization of Youden's Index. The groups obtained were analyzed with KaplanMeier procedure and compared with univariate and multivariate Cox proportional hazards model.

Results: 91 patients with recurrent GBM were enrolled in 10 Italian centers between 11/2011 and 9/2012. The median age was 57 years (range: 2878). Fiftynine patients were enrolled in the BEV arm and 32 patients in the FTM arm. OS6 was 62.1% (95% CI: 48.474.5) and 73.3% (95%CI: 54.187.7), OS9 was 37.9% (95%CI: 25.5–51.6) and 46.7% (95%CI: 28.3–65.7) in the BEV and FTM arms, respectively. Median OS was 7.3 months (95%CI: 5.89.2) in the BEV arm and 8.7 months (95%CI: 6.315.4) in the FTM arm. The response rate was 29% (95%CI: 1842) and 9% (95%CI: 225) for patients treated with BEV and FTM, respectively. TTR ($p = 0.05$, HR = 0.46, 95%CI:0.211.00) and ETS > 15% in T1 contrast enhancing area at first disease assessment ($p = 0.040$, HR = 0.511,95%CI:0.2690.971) could predict OS in patients treated with BEV but not with FTM (TTR and ETS with FTM: $p = 0.19$ and $p = 0.4$, respectively). Patients achieving an ETS = 15% had significantly longer OS than those achieving an ETS < 15% (8.4 vs 5.2 months).

Conclusions: BEV and FTM are both active drugs in recurrent GBM. TTR and ETS might be helpful predictors of GBM outcome in patients treated with BEV

R03 Prognostic factors in glioblastoma patients treated with the nitrosourea fotemustine at first relapse after the Stupp regimen: results from the GLIOSTRY (GLIOblastoma regiSTRY) of the AINO (Italian Association of Neuro-Oncology)

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Background: Nitrosourea-based regimens are commonly used in Europe for patients with glioblastoma (GBM) failing radiotherapy plus temozolomide. However, predictive and prognostic factors need to be further investigated in this population. The aim of this study was to analyze the presence of predictive and prognostic factors in a large cohort of Italian GBM patients treated with nitrosourea fotemustine (FTM) or in combination with bevacizumab (BEV) at first relapse following the Stupp regimen.

Patients and methods: Clinical, molecular, radiological and survival data were collected from 34 Italian centers involved in the treatment ofGBM. Progression free survival (PFS) and overall survival (OS) were estimated using Kaplan-Meier method. A Cox regression model was carried outfor univariate and multivariate analyses.

Results: a total of 921 patients (587 males, 64%) were screened and 670 were included in this analysis. The median age was 56 yrs. The median PFS of FTM was 103 days. At univariate analysis, MGMT methylation (129 d methylated vs 90 d unmethylated tumors, $p < 0.001$) and the association with BEV (148 d FTM plus BEV vs 97 d FTM alone, $p < 0.0001$) were significantly associated with longer PFS. Both MGMT status (HR 0.64, 95% CI 0.52-0.79; $p < 0,001$) and association with BEV (HR 0.71, 95% CI 0.56-0.92, $p < 0,008$), maintained their prognostic significance at multivariate analysis. The median OS with FTM was 197 days. Age (200 d < 65 yrs vs 182 d > 65 yrs, $p = 0.010$), Karnofsky Performance Score (213 d KPS 90-100 vs 182 d KPS < 80), extent of initial surgery (213 d gross total vs 184 d partial removal, $p = 0.002$), MGMT status (246 d methylated vs 176 unmethylated, $p < 0.001$) and association of FTM and BEV (238 d FTM plus BEV vs 187 d FTM alone, $p = 0.030$) resulted significant at univariate analysis, whilst only MGMT status (HR 0.60, 95% CI 0.48-0.76, $p < 0.001$) and the association FTM plus BEV (HR 0.73, 95% CI 0.56-0.95, $p = 0.022$) were confirmed at multivariate analysis.

Conclusions: Our results underline the predictive and prognostic role of MGMT in GBM patients treated with FTM at recurrence and support that the use of FTM in combination with BEV in this population.

R04 Pharmacokinetic analysis of irinotecan administered in FOLFIRI regimen in combination with bevacizumab from patients enrolled in a genotype-driven phase I study

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Background: Genotype-driven phase I studies could represent an innovative strategy for defining the relationship between genotype and maximally-tolerated dose (MTD), in order to redefine dose or treatment modalities of cytotoxic drugs for therapy personalization. For instance, *UGT1A1*28* polymorphism represents an important pharmacogenetic determinant for irinotecan based chemotherapy and, based on this background, we planned a dose-escalation phase Ib study to assess the recommended dose of irinotecan in FOLFIRI regimen in combination with bevacizumab (BV) in metastatic colorectal cancer patients (pts) according to *UGT1A1*28* polymorphism.

Methods: Eligible pts were stratified in 2 groups based on the *UGT1A1 *1/*1* or **1/*28* genotype. The starting dose was 260 mg/m^2, and was escalated to 310 and 370 mg/m^2 if 0/3 or <2/6 pts had a dose limiting toxicity (DLT). The MTD was defined as the dose at which <4/10 pts had DLT (grade 3-4 non hematologic or grade 4 hematologic toxicity during the first cycle). In order to define the potential effect of BV, irinotecan pharmacokinetics was evaluated in absence and presence of BV in each patient. The pharmacokinetics of irinotecan and its main metabolites was evaluated twice during the first chemotherapy cycle.

Results: 48 pts were enrolled (47 were evaluable for DLTs during cycle 1: 24 **1/*1* pts and 23 **1/*28* pts). The MTD resulted 260 mg/m^2 in the **1/*28* cohort (irinotecan AUC_{last} (area under the curve) 13.65 ± 6.44 h·μg/mL) and 310 mg/m^2 (irinotecan AUC_{last} 14.50 ± 6.36 hμg/mL) in the **1/*1* cohort. Furthermore, a preliminary analysis of plasma concentration-time profiles of irinotecan and its main metabolites highlighted that BV decreases AUC_{last} of SN-38, irinotecan active metabolite, ($p = 0.026$).

Conclusions: This phase I study showed that a dose of irinotecan higher than the standard dose (180 mg/m^2) can be safely administered according to the *UGT1A1*28* polymorphism. Moreover, it seems that not only the genetic makeup, but also BV affects the MTD of irinotecan. This study has become part of a new European Project (HORIZON2020), aimed at creating point-of-care devices for quantification of chemotherapeutic drugs in small body fluid for real-time therapeutic drug monitoring. Data obtained will be used for the analytical and clinical validation of the new devices.

R05 Febuxostat a new weapon in armamentarium of tumor lysis syndrome management: results of Florence pivotal study

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Background: Tumor lysis syndrome (TLS) is an oncologic emergency characterized especially by elevated serum uric acid (sUA). Febuxostat (FEB) is an orally administerd selective xanthine oxidase inhibitor to reduce sUA.

Methods: This was a randomized, double blind phase III trial of FEB vs Allopurinol (ALL) in terms of control of sUA level and preservation of renal function in patients undergoing chemotherapy (CT) for hematologic malignancies at intermediate to high risk of TLS. Patients were stratified according to TLS risk and sUA level to FEB or ALL starting from 2 days prior CT and continued for 7-9 days. Assigned treatment was blinded, while daily dose level (low/standard/high containing ALL 200/300/600 mg or fixed FEB 120) was upon investigator's choice. Primary endpoints were sUA area under the curve (AUC sUA1-8) and change in serum creatinine (sC) level both from baseline to Day 8, analyzed through ANCOVA including treatment and stratification factors as covariates. Secondary endpoints were response rate (sUA ≤ 7.5 mg/dL from CT start to Day 8), incidence of laboratory and clinical TLS and safety. The study was run in 79 sites in Europe and Brazil (NCT01724528).

Results: 346 patients were included with similar baseline demographics in both groups. 82.1% of patients were at intermediate risk of TLS, 87.6% had a baseline sUA ≤ 7.5 mg/dl and 82.7% received standard dose level. Intention to treat (ITT) analysis: mean AUC sUA1-8 (mgxh/dl) was significantly lower in FEB arm (514.0 +/- 225.71 vs 708.0 +/- 234.42; $p < 0.0001$). No significant difference in mean sC change(%) occurred between FEB and ALL arms (-0.83 +/- 26.98 vs -4.92 +/- 16.70 respectively, $p = 0.0903$). No significant difference was detected among secondary efficacy endpoints. Incidence of all adverse events (AEs) and related AEs was 67.6% vs 64.7% and 6.4% vs 6.4% in FEB and ALL arm, respectively.

Conclusions: In this largest TLS prevention trial FEB proved to be significantly superior over ALL with a 28% lower exposure to sUA during CT, moreover without requirement for any dose adjustment in patients with preexisting mild or moderate renal impairment. FLORENCE study results were the basis for the FEB European approval for the TLS prevention and treatment granted in May 2015.

R06 Disthyroidism during immune checkpoints inhibitors treatment: toxicity or something more?

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Background: Immune checkpoints inhibitors (ICI) are characterized by a high therapeutic index; among toxicities, immune-related thyroiditis has been reported. The aim of this study is to report the grade and severity of thyroiditis and to evaluate whether clinical antitumor responses are correlated with the onset of thyroiditis.

Material and methods: We retrospectively evaluated 104 metastatic solid tumor patients treated at our Institute with ICI from 2010. We defined thyroid toxicity according to CTCAE version 4.0 and the disease control rate (DCR: CR, PR, SD) as efficacy endpoint. Correlation between disthyroidism and DCR was assessed by Fisher's exact test.

Results: Of 104 patients, 32 (30.8%) were treated by anti PD-1, 32 (30.8%) by anti PDL-1, 34 (32.7%) by anti CTLA-4 and 6 (5.7%) by combo (anti PD-1 + anti CTLA-4). Population was heterogeneous, ranging from the first to the 8th line of therapy, and affected by the following cancers: 42 (40.4%) lung (38 NSCLC, 4 SCLC), 40 (38.5%) melanoma, 9 (8.6%) RCC, 7 (6.7%) gastric, 2 (1.9%) bladder and one each for colon, salivary glands, thyroid and uterine leiomiosarcoma. Best responses were: 3 CR, 14 PR, 33 SD and 54 PD; 50 (48%) of patients achieved DCR. Considering the two largest groups, in melanoma DCR was 6/9 (66.7%) for anti PD-1, 11/31 (35.4%) for anti CTLA-4 and 2/4 (50%) for combo group; in NSCLC it was 4/6 (66.7%) for anti PD-1 and 18/32 (56%) for anti PDL-1 group. Twenty-nine patients developed disthyroidism (subclinic, G1, G2 hypo/hyperthyroidism): 2/34 (6%) in anti CTLA-4, 10/32 (31%) in anti PD-1, 14/32 (44%) in anti PDL-1, 4/6 (67%) in combo group respectively. DCR statistically significant correlated with the onset of disthyroidism (68.9% vs 40.0%, p: 0.009); no correlation was detected between toxicity grade (subclinic and G1 from one side, G2 from the other side) and DCR (p: 1.0).

Conclusions: We found a significant correlation between clinical responses and onset of thyroiditis in solid tumor metastatic patients during the treatment with ICI, in particular with anti PD-1 and anti PDL-1. For this reason, the evaluation of thyroid function should be performed routinely during anti PD-1 and anti PDL-1 treatment. Finally, if this evidence will be confirmed on a large and homogeneous series of patients, the onset of thyroiditis could become predictive of response to ICI.

R07 Role of D-dimer (DD) Assays in the Diagnostic Evaluation of Pulmonary Embolism (PE) in patient with cancer: a new "tailored" cut-off value for D-D, preliminary results of a mono-institutional study

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Background: Cancer patients show an increased susceptibility to develop thromboembolic diseases. PE is a common cause of morbidity and mortality in patients with cancer. Having cancer is included also as a variable in the prognostic scale of acute symptomatic PE. The diagnosis of pulmonary embolism remains challenging despite the development of well-validated clinical algorithms, largely because of nonspecific clinical features and lab tests that confuse clinician suspicion. D-dimer test is an essential part of the PE diagnostic algorithm but it is an inefficient value in patients who are elderly or have other comorbidities,it has to be associated to other investigations. A high value of DD,even lower than expected,suggests which patients can develop thromboembolic disease especially PE.

Objective: In our study we reviewed the correlation between the magnitude of DD value and the diagnosis of PE in cancer patients and we suggest a cut-off value to identify more specifically patients at risk for PE.

Methods: We retrospectively evaluated 422 patients(years 2012-2013),193 women, 229 men, median age 67 yrs. We had DD values, chest CT scan and cardiology evaluation of all patients. All of them had a DD value higher than normal and >500 ngr/mL.We have related this DD value with radiological and cardiological evidence of PE. All patients hadmetastatic disease and were inchemotherapy treatment in our department. DD value was quantified through latex enhanced turbidimetric immunoassay(n. v. < 250 ngr/ml).

Results: Among all patients with a chest CT scan and with a DD value >500,we observed 33/422 (7.8%) PE events.We found a DD value greater than 800 ngr/ml(range 816-3501)in every patient who showed radiological evidence of PE.Patients with PE showed a high Pulmonary Artery Pressure Value(n.v. < 35 mmHg)derived from Echocardiographic Doppler study in 73% of cases (range 37-100 mmHg), echocardiographic evaluation showed a Right Ventricular Dilatation in 53% of cases.

Conclusions: This retrospective analysis points out that,to have high suspicion of PE, we should consider a DD value greater than 800 ngr/ml.Therefore this value can be considered as a new "tailored" cut-off to suspected PE in cancer patients.In case this high DD value is found,an accurate cardiological evaluation and a chest CT scan is suggested even in case of nonspecific symptoms for PE.In this patients,however,is appropriate to consider starting a continuous prophylaxis with low- molecular-weight heparin, immediately.

R08 The "Elderly Project" by the Fondazione Italiana Linfomi (FIL): a prospective multidimensional assessment of elderly patients with diffuse large B-cell lymphoma

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Background: The initial approach to elderly patients with Diffuse Large B Cell Lymphoma (DLBCL) is mostly based on a subjective judgment of the physician. Comprehensive Geriatric Assessment (CGA) is based on the use of the ADL (Activity of Daily Living), IADL (Instrumental ADL) and CIRS-G (Comorbidity Index Rating Scale for Geriatrics) and represents a tool to standardize initial patients fitness status and for planning systemic therapy.

Material and methods: FIL designed a prospective study with the aim of providing clinicians with a standardized tool to assess CGA in elderly patients with DLBCL before treatment start and to validate CGA results on a large series of patients. This study was conducted using a web based tool to perform CGA evaluation of all patients ≥65 yrs with DLBCL at diagnosis. Patients <80 yrs, without impairment of ADL and IADL and without severe comorbidities were considered FIT; those with intermediate fragility or those ≥80 years with FIT profile were classified as UNFIT (UN); those with severe impairment of ADL, IADL and CIRS and those ≥80 yrs with an UN profile as FRAIL (FR). Planned sample size was 600 patients.

Results: At time of current analysis 307 patients have been registered: 44%, 22%, and 34% were classified as FIT, UN and FR, respectively. By univariate analysis, the three categories differed in terms of median age (p < 0.001), B-symptoms (p = 0.008) and ECOG PS > 1 (p < 0.001). Eigthy-one (26%) didn't have any comorbidity at CIRS scale and 11% had at least one of grade 3; the most frequent grade 3 events were those referred to heart (4.2%) and vascular system (3.3%). Data on planned treatment were available in 254 patients (82%, 80% and 90% FIT, UN and FR respectively). Chemotherapy with rituximab was scheduled in 96% of FIT and UN patients; R-CHOP-like regimen was planned in 100%, 96% and 60% of FIT, UN and FR patients, respectively. Only 10% of FR patients were referred to a palliative treatment. Dose reduction was scheduled in 10% and 14% of UN and FR respectively.

Conclusions: The initial data show that currently many italian centres treat elderly DLBCL with CHOP-like regimens independently from fitness status. CGA represents an objective assessment of elderly subjects with DLBCL that can be used to assist physicians in the initial approach to the patient. This project has the aim of extending and simplifying the use of CGA, to further validate it and to identify possible new criteria to improve our ability to select patients.

R09 Emergencies in cancer patients: data on 15,623 cases from a large volume single centre from 2001 to 2013

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Background: Cancer patients (pts) present often with acute syndromes requiring an urgent management. This scenario has dramatically changed during the last years due to the higher prevalence of cancer pts on active treatment, and specific drug–related safety issues. The aim of this study was to determine the main clinical characteristics, relevant needs and possible outcomes in the population of cancer pts admitted to our Emergency Department (ED).

Methods: We performed a retrospective cohort study on 15,623 pts out of 1,101,259 adult pts (1.42%) admitted to our ED between January 2001 and December 2013 for cancer-related problems. Demographics, clinical findings and hospitalization rate were gathered from the administrative sources of the local database.

Results: Mean age was 65.1± 14.8, women prevalence slightly higher. The majority of visits occurred during normal hours (77.6%) and working days (74.4%). Pts not requiring a urgent treatment, according to triage assessment, were 60.4%. Only 14.7% of pts were referred to ED by another physician (GPs, surgeon, medical oncologist). For 63.2% it was a self-decision and was not specified for the remaining group. The chief complaints were fever 21.5%, pain 27.7%, asthenia 13.6%, dyspnea 13.1%, gastrointestinal (vomiting 15.3%, diarrhea 2.7%), hematologic (anemia 4.3%, neutropenia 1.9%, thrombocytopenia 0.5%). Complaints related, or possibly related, to an active antitumor treatment, i.e. chemotherapy and/or radiation therapy, are under evaluation and will be outlined at the meeting. Pts receiving an active treatment were 21.9%. The most common cancer sites were gastrointestinal (30.5%), lung (20.1%), ovarian (8.53%), breast (8.17%). Pts with metastatic disease were 21.2%. Hospitalization rate was 73.7%. Pts discharge due to symptoms improvement was 19.3%. Mortality at the ED was 0.9%. Hospitalization was refused by 3.7% of pts.

Conclusions: A better understanding of emergency care needs for cancer pts is crucial for implementing the quality of care and optimizing the resources of the healthcare system. Further analyses and prospective studies are warranted to define possible outcomes and algorithms for the most appropriate treatments of cancer-related problems.

R10 Disease prevalence, tumour stage, and results of testing in the pilot phase of a service for cervical cancer screening and diagnosis in northern Tanzania

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Background: We carried out a pilot phase for cervical cancer screening in the Mwanza and Mara Regions (Tanzania), reporting on the diagnostic performance of procedure and on the association between demographic, socioeconomic and health-related characteristics of attending women and their probability of being diagnosed with high-grade cervical disease and invasive cervical carcinoma.

Methods: The pilot targeted 7 districts and was launched in 2012 after a community-level information campaign.Women aged 15-64 years were invited to take part. Women were interviewed using a structured questionnaire and were offered the visual inspection of the cervix with acetic acid (VIA) and Pap smear. Patients resulting positive with VIA who were ineligible for immediate cryotherapy were invited to the Bugando Medical Centre (BMC) of Mwanza for colposcopy. Pap smears were evaluated by pathologists of BMC.

Results: We evaluated data from the first consecutive 2,500 women. Those women presenting with a clinically overt cervical cancer and those with missing data were excluded. 2,342 women (median age 38 yrs) were eligible. We reported 572 (24.4%) subjects with previous diagnosis of sexually transmitted diseases and 192 (6.6%) HIV-positive subjects. Women with VIA findings suggestive of high-grade cervical disease and carcinoma were 7.3%, with positive predictive value of 64.7% and detection rate of 47.0‰.The corresponding figures of the Pap smear were 6.1%, 59.2%, and 35.9‰. In multivariate analysis, the factors independently associated with the prevalence of disease included district of residence, history of untreated sexually transmitted diseases, parity and negative HIV test (inverse association). The probability for affected patients to have an invasive versus a pre-invasive disease varied significantly between districts, and was lower in HIV-positive women and in women practicing breast self-examination – the latter being the strongest determinant.

Conclusions: The performance of VIA compared well with Pap smear. Factors associated with the prevalence of disease were used to target the promotion of attendance. The inverse association between breast self-examination and the probability to have an invasive versus a pre-invasive disease is probably due to a previous spontaneous cervical screening practice and confirms the potential value of cancer awareness and education for sub-Saharan women.

R11 Survival and prognostic factors in very elderly patients (pts) with diffuse large B-cell lymphoma (DLBCL): a retrospective analysis of 281 patients over 80 years

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Background: The outcome of pts with DLBCL has substantially improved over the last decades. However lymphoma-related mortality in very elderly pts (>80 yrs) has not declined, mainly due to the administration of less aggressive treatments. Currently in this population there are no validated methods to properly identify pts fit enough to receive standard immunochemotherapy, primarily because they are not included in clinical trials.

Methods: In this retrospective analysis we selected pts with 80 or more yrs with newly diagnosed DLBCL between 1981 and 2013 from 4 Institutions in Northern Italy and Switzerland. All data were retrieved from local databases. Pts were treated with a variety of regimens chosen by referring physicians. Primary endpoints were overall survival (OS), progression free survival (PFS), cause specific survival (CSS).

Results: We included 281 pts. Median age was 84 yrs (range 80-97); 144 pts (51%) had advanced disease (stage III-IV) and 42 pts (37%) bulky disease >7cm. Most of them had ECOG PS 0-1 (58%) and few comorbidities (Charlson Comorbidity Index 1-2 in 41%pts). Pts were treated as follows: 14 (5%) no active treatment or steroids, 28 (10%) radiation therapy or surgery alone, 73 (26%) chemotherapy without anthracycline, 166 (59%) chemotherapy with anthracycline, 119 (50%) anthracycline and rituximab. At a median follow-up of 5.7 yrs (range 3.2-9.8) for the entire cohort 5-year PFS, OS and CSS were respectively 26% (95% CI, 20-32), 31% (95% CI, 25-37%), and 42 % (95% CI, 35-49%). Lymphoma was the main cause of death (42.7%). Age (80-85 vs >85 yrs), ECOG-PS, LDH, Ann Arbor stage, haemoglobin (<10 g/dl) and renal failure appeared to be prognostic for OS at multivariate analysis. Interestingly, Charlson Comorbidity Index did not influence survival. Five-year CSS and OS were significantly improved in pts who received rituximab (respectively 58% vs 29%, p <0.001 and 45% vs 20%, p < 0.001) or anthracyclines (respectively 45% vs 37%, p = 0.046 and 37% vs 21%, p = 0.012).

Conclusions: The accurate selection of very elderly pts able to tolerate standard immunochemotherapy is crucial in order to predict treatment related toxicity. As in younger population, pts >80 yrs without significant comorbidities treated with anthracycline and rituximab have an excellent outcome. Geriatric assessment scores and specific prognostic factors still need to be prospectively validated in this population.

R12 Risk for developing hyponatraemia in cancer patients treated with targeted therapies: a meta-analysis

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Background: Although targeted therapy lacks of typical adverse events of cytotoxic chemotherapy, several drug-related toxicities have been reporting in cancer patients. Hyponatraemia has been reported with targeted therapies in cancer patients. Literature data suggest that hyponatraemia can be considered an unfavourable prognostic factor in cancer patients and it has been also hypothesized to adversely affect the response to anticancer treatment. Aim of the study was to perform an up-to-date meta-analysis in order to determine the incidence and relative risk (RR) in patients with solid tumors treated with these agents.

Materials and methods: The published scientific literature regarding hyponatremia in peer-review journals was extensively reviewed using the MEDLINE and Pubmed databases. Eligible studies were selected according to PRISMA statement. Summary

incidence, RR, and 95% Confidence Intervals were calculated using random-effects or fixed-effects models based on the heterogeneity of selected studies.

Results: A total of 4803 potentially relevant trials were identified: of them, 13 randomized phase III studies were included in this meta-analysis. 6670 patients treated with 8 targeted agents were available for this analysis: 2574 patients had hepatocellular carcinoma, whilst 4096 had other malignancies. The highest incidences of all-grade hyponatraemia were observed with the combination of brivanib and cetuximab (63.4) and pazopanib (31.7), while the lowest incidence was reported by afatinib (1.7). The highest incidence of high-grade hyponatraemia was reported by cetuximab (34.8), while the lowest incidences were reported by gefitinib (1.0). Summary RR of developing all-grade and high-grade hyponatraemia with targeted agents was 1.36 and 1.52, respectively. The highest RRs of all-grade and high-grade hyponatraemia were associated with brivanib (6.5 and 5.2, respectively). Grouping by drug category, the RR of high-grade hyponatraemia with angiogenesis inhibitors was 2.69 compared to anti-Epidermal Growth Factor Receptors Tirosine Kinase Inhibitors or monoclonal Antibodies (1.12).

Conclusions: Treatment with biological therapy in cancer patients is associated with a significant increased risk of hyponatraemia, therefore frequent clinical monitoring should be emphasized when managing these and newer targeted agents.

R13 Clinical and molecular predictors of survival in elderly glioblastoma patients treated with radiotherapy and concomitant temozolomide: a multicenter study of aino (Italian Association of Neuro-Oncology)

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Background: The efficacy of Temozolomide(TMZ) plus radiation therapy(RT) in elderly patients with glioblastoma is unclear. We performed a large multicenter retrospective study to analyze prognostic factors and clinical outcome in these patients.

Patients and methods: inclusion criteria for this multicenter retrospective study were age ≥65 years, newly histologically confirmed glioblastoma, ECOG PS 0-2, adjuvant treatment with RT plus TMZ. Generally, brain MRI was performed every 2 or 3 months. Survival curves were performed by Kaplan-Meier methods.

Results: we enrolled 237 patients; the average age was 71 and ECOG PS was 0-1 in 196 patients; radical/subtotal surgery was performed in 174 cases. MGMT was analyzed in 151 patients and was methylated in 56%. IDH1 was assessed in 100 patients and was mutated in 6%. Seventy-one patients were treated with RT 40Gy and 166 with RT 60Gy. Progression-free survival (PFS) and overall survival (OS) were 11.3 and 17.3 months, respectively. Overall Survival was 19.4 vs 13.8 months for patients treated with RT 60Gy and 40Gy ($p = 0.02$); OS was 17.7 vs 16.1 months for patients treated with radical/subtotal surgery vs partial/biopsy surgery ($p = 0.02$); OS was 21.2 vs 13.6 months for methylated and unmethylated MGMG ($p < 0.001$). On multivariate analysis, radical/subtotal surgery, RT 60Gy, methylated MGMT and ECOG PS 0-1 were independent predictors of longer survival. Twenty-five patients (10%) had grade 3-4 haematological toxicity during the concomitant treatment.

Conclusions: Concomitant treatment is effective and safe in GBM elderly patients, especially in patients with an optimal performance status. In these patients, an aggressive approach with an extensive surgery and standard therapy may be useful. Mutant IDH1 patients showed a trend for better outcome while MGMT methylation status was the most important prognostic factor.

R14 Prognostic value of MGMT gene promoter methylation evaluated on ten CpG sites in patients with glioblastoma multiforme: a single-institution experience

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Background: O6-methylguanine-methyltransferase (MGMT) gene promoter methylation status is associated with improved survival in newly diagnosed glioblastomas (GBM) and is recognized as a predictive biomarker for Temozolomide. MGMT CpG island includes 98 CpG sites (CpGs) and patterns of methylation are rather heterogeneous. We aimed to investigate which CpGs are critical and how many of them should be analyzed to define the methylation status in a real-life cohort.

Materials and methods: we analyzed 121 GBM patients treated at the University Hospital of Udine (Italy) between January 2008 and June 2014. Clinical and molecular data were recorded at diagnosis. Methylation level of 10 single CpGs (74-83) was analyzed by means of pyrosequencing. Instead of average methylation, as usually reported in literature, we classified each CpGs methylation level as low (< 9%), intermediate (IM; 9-29%) and high (HM; >29%) and prognostic impact of each CpG was explored through uni and multivariate Cox regression, adjusted for significant clinical features.

Results: in univariate analysis, a statistically significant association was observed between the methylation of all CpGs, except the 78, and outcome [progression free survival (PFS) and overall survival (OS)]. The prognostic value, adjusted for clinical features, varies according to methylation level (See table). ECOG performance status (0-1 vs 2-3) and age (≤70 vs >70) retain their statistical significance in multivariate model.

Conclusions: our analysis shows that the impact of CpGs methylation on PFS and OS varies according with CpGs analyzed. Therefore, a second step of our study will be a multivariate analysis to test the association between outcome, methylation level and treatment. Methylation quantification of single CpGs, or a specific combination of them, might improve outcome prediction.

Table: R14

		PFS		OS	
CpG site		HR	P value	HR	P value
74	HM	0.614	0.0674	0.582	0.0618
	IM	0.456	0.0106	0.291	0.0007
75	HM	0.723	0.1955	0.652	0.1188
	IM	0.477	0.0091	0.365	0.0016
76	HM	0.560	0.0432	0.637	0.1488
	IM	0.728	0.1715	0.545	0.0158
77	HM	0.634	0.1338	0.587	0.1161
	IM	0.627	0.0462	0.600	0.0362
78	HM-IM			Na	
79	HM	0.596	0.0479	0.485	0.0143
	IM	0.528	0.0076	0.467	0.0027
80	HM	0.659	0.0971	0.522	0.0207
	IM	0.453	0.0026	0.335	0.0002
81	HM	0.602	0.0450	0.508	0.0161
	IM	0.402	0.0009	0.352	0.0004
82	HM	0.533	0.0093	0.476	0.0042
	IM	0.671	0.1210	0.532	0.0212
83	HM	0.581	0.0306	0.499	0.0106
	IM	0.544	0.0128	0.452	0.0025

HM = high-methylation; IM = intermediate methylation; na = not applicable.

R15 Fighting cancer in developing countries: a cooperative model of oncology service in uganda

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Background and aim: in Subsaharian Countries cancer detection and therapy still represents a challenge. The most relevant issues are:1) Inadequate cancer facilities 2) Inadequate funds for cancer 3) Cost of Cancer treatment is too high 4) Many patients being misled by distinguished hospital staffs and community members 5) Few centers of cancer diagnosis and treatment in the countries. Since march 2012 to February 2015 a cooperative project implemented by italian non-profit organization(AISPO, AFRON, POF) and funded by Italian Ministry of Foreign Affairs was held in order to provide opportunities for female cancer prevention and treatment. Aim of the Project was to improve prevention and clinical services for diagnosis and treatment of Cervix (CC) and Breast Cancer (BC) at St. Francis Hospital Nsambya in Kampala (Uganda).

Methods: a staff of oncologists, nurses and laboratory technicians provide integrated and consecutive missions in order 1) to improve screening procedures for CC and BC; 2) to provide logistics, procedures and treatment knowledge in oncologic care, applying international standards and procedures.

Results: during the project more than 900 days of training and technical assistance were provided. 3 nurses with advanced training and skills on chemotherapy preparation and administration and 10 nurses with practical training have been procured and a Day Hospital facility has been set up. CC and BC campaign reached more than 250.000 women, with 5800 women screened and 471 cervix cancer/pre cancer lesion and 87 breast cancer detected. Improvement in cancer therapy was also reached, with increasing number of patients admitted for chemotherapy (CT) since 2012 (8 new pts, 25 CT cycles delivered) to 2014 (43 new pts, 150 CT cycles delivered). During the 3 years of the project the surgical activity also raised, with an enhancement of 60% . The biomedical department performances improved from 275 in 2012 to 555 in 2014 instruments in use . Moreover, oncologic medical record, informed consent, CT delivering chart, surgical procedures and multidisciplinary management team have been shared and assessed.

Conclusions: to build strong partnership for better cancer services in developing countries is crucial and cooperative modalities of intervention could really provide definitive tools of improvement.

R16 Procalcitonin as diagnostic marker in febrile cancer patients

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Background: In oncologic patients (pts) fever is a non-specific clinical marker and could represent a sign of different clinical settings. Today, procalcitonin (PCT) seems to be the most promising infection marker. Our study aimed to define the potential role of PCT used as an earlier diagnostic marker in a cohort of pts with fever (>38.3°C or 2 consecutive >38°C readings) and solid tumor diagnosis followed in our center.

Patients and methods: This retrospective observational study enrolled 431 consecutive pts. All of them performed hemoculture (HE) and basal PCT assessment before starting antibiotic therapy. We used the normal PCT reference laboratory cut-off of ≤0.5 or >0.5 ng/dL. Gram positive (G+), negative (G-) or Fungi infection were detected.

Results: Among the whole population 37.1% of pts showed a PCT value ≤0.5 ng/dL, while 62.9% >0.5 ng/dL. 80% of pts with PCT ≤0.5 ng/dL presented a negative HE and the remaining 20% a positive HE, while among pts with PCT >0.5 ng/dL, 45% showed negative HE and 55% a positive one. In the HE positive population the PCT median value was 16.81 vs. 4.72 for the HE negative pts. A statistically significant difference in PCT levels between the two pts' subgroups was observed ($P < 0.0001$). Moreover comparing PCT values in pts with positive and negative HE through the ROC analysis, we obtain in the positive HE subpopulation an AUC of 0.7 and a cut-off of 1.52 ng/dL reached high sensitivity (61.6%) and specificity (70.1%). Using this last cut-off, instead of the normal reference value, we achieve a risk reduction to overestimate an infection status of 23.4%. Additionally we observed that among pts with positive HE, 72% presented a G- colonization, 24.6% a G+ infection and 3.4% a funginemia. With a further ROC analysis we showed that the PCT cut-off of 1.52 ng/dL for the G- isolations was associated to a sensitivity of 72.1% and specificity of 70.1% (AUC 0.77; $P< 0.001$). Finally we demonstrated that our new PCT cut-off of 1.52 ng/dL seems to be more reliable to identify the negativity of a HE in this oncologic pts reaching statistical significance ($P = 0.0247$).

Conclusions: We support the clinic usefulness of serum PCT dosage in febrile advanced solid tumor pts. A PCT cut-off of 1.52 ng/dL could be helpful to identify a G- bacteremia in this specific population and could help clinicians in the management of the antibiotic therapy and consequently to prevent undue delays of specific oncologic treatments.

R17 Neuroendocrine differentiation in breast carcinoma: clinicopathological features and outcome

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Background: Primary neuroendocrine (NE) breast carcinoma (BC) is an entity lacking definite diagnostic criteria with a wide range of prevalence and poorly defined clinical behavior. We evaluated the prevalence, clinicopathological features and the clinical outcome of NEBC.

Patients and methods: Immunoistochemical staining for synaptophysin and chromogranin A was carried out on whole section from archival specimens of 1232 consecutive cases of invasive BC. We divided NEBC in focal (10-49% positive cells) and diffuse (≥50% positive cells). We compared outcome of patients with NEBC with strictly matched patients with non-NEBC, using 12 clinicopathological parameters.

Results: One hundred twenty-eight BC showed NE differentiation: 84 were diffuse and 44 focal. NE differentiation showed a significant association with T4 stage ($P = 0.001$), solid papillary and mucinous histological type ($P < 0.0001$), G2 grading ($P = 0.002$), positive ER ($P = 0.003$) and PR ($P = 0.002$). Kaplan-Meier analysis revealed that patients with NEBC had a trend towards a statistical significance for worse clinical outcome for DFS ($P = 0.04$) but not for cancer specific survival ($P = 0.20$). We did not find significant differences for clinicopathological features, DFS and cancer specific survival between diffuse and focal NEBC.

Conclusions: We showed that NEBC represent 7-10% of invasive BC; 74% of NEBC are no special type invasive BC, however the more frequent histotypes with NE differentiation are solid-papillary (70%) and mucinous carcinoma (20%). Almost 90% of NEBC are ER + /HER2- and more than half ER + /HER2-/Ki-67 > 15%. NE differentiation shows a trend towards a statistical significance for a worse prognosis for DFS but not for cancer specific survival and the extent of NE marker expression doesn't seem to correlate with clinical behavior.

R18 Association between patient reported outcomes and vibratory perception threshold test for measuring neurotoxicity in patients with chemotherapy induced peripheral neuropathy

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Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a dose-limiting complication of cancer treatment and sometime a long lasting toxicity that affects quality of life of cancer patients (pts). The assessment and perception of CIPN sensory impairment between clinicians and pts has not yet been fully addressed, and an objective tool for its evaluation is still lacking. Biothesiometry is a simple, non-invasive, fast and cheap tool to evaluate sensory impairment in neuropathic pts. We evaluated the vibration perception threshold (VPT) by biothesiometry in patients affected by CIPN.

Patients and methods: Patients who received taxanes and/or platinum (Pt)-based chemotherapy and with symptomatic peripheral neuropathy were eligible for the study. Peripheral neuropathy was graduated by two validated patient-based questionnaires: the Patient Neurotoxicity Questionnaire (PNQ) and the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (Fact/GOG-Ntx) questionnaire. VPT was calculated as sum of values measured on both the big toes (VPTbt) and on both the external malleoli (VPTem). Single measure VPT range was 0.1-60.0 Volts (V). VPTs by groups were reported as median (Inter-quartile range, IQR). Statistical analysis was performed by Mann-Whitney test.

Results: 37 pts (9 males 28 females) with symptomatic CIPN were enrolled. Median (range) age was 62 (32-80) years. According to the PNQ and FACT/GOG-Ntx questionnaire scores, 21 and 16 pts had Grade (pG) 1 and pG2 neuropathy, respectively. Age was not statistically different between the two groups ($p = 0.14$). Median (IQR) big toes VPTbt was 12.4V (5.4-29.5) and 42.4V (18.3-120) in pG1 and pG2 neuropathic pts, respectively ($p = 0.003$). Median (IQR) external malleoli VPTem was 4.0V (2.7-6.9) and 11.5V (4.0-91.5) in pG1 and pG2 neuropathic pts, respectively ($p = 0.023$).

Conclusions: VPT measured on big toes and external malleoli was lower in pG1 compared to pG2 CIPN pts and the difference was statistically significant. Biothesiometry, combined with clinician assessment and patient reported outcome, might be a useful tool to achieve a more comprehensive knowledge of CIPN and a reliable assessment of both the severity and the quality of CIPN-related sensory impairment.

R19 Temozolomide dose-dense regimen in high grade gliomas: dose-finding/phase II study

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Purpose: Temozolomide (TMZ) is standard therapy, increasing efficacy in newly diagnosed or recurrent primary central nervous system (CNS) tumors. A dose-dense schedule was designed to better define the proper efficacy/safety balance and discriminate sensitive/resistant subgroups according to O6-methylguanine-DNA methyltransferase (MGMT) expression. A dose-finding/phase II study was designed to evaluate recommended dose, safety, activity and efficacy of TMZ dose-dense, according to 5 days on/9 days off (5/14 d) regimen.

Patients and methods: Upfront or recurrent CNS patients were enrolled. Dose-finding was designed according to intra- and inter-patient approach in 5 dose levels to evaluate TMZ recommended dose: 150, 180 mg/m^2 d1-5 every 21 days; 150, 180, 200, mg/m^2 d1-5 every 14 days. Safety was evaluated according to limiting toxicity syndromes (LTS), defined as LTS single site, consisting of LT alone (LTS-ss), and LTS multiple sites (LTS-ms), double LT or LT associated to other G2-3 not LT. Efficacy was evaluated and compared by log-rank test.

Results: Thirty-four CNS patients were enrolled (19 glioblastoma, 13 grade III glioma, 1 grade II multiple relapses, 1 misunderstood diagnosis). First 13 patients were enrolled in the dose-finding. First patient was treated at I-II dose level, without LT. At III level, the first patient and 2 new patients were treated, without LT. At IV level, 7 patients were treated with 1 LTS-ms (G3 thrombocytopenia and G3 neutropenia for 4 weeks). At V level 3 patients were treated, 2 LT (G3 thrombocytopenia, G2 hepatic toxicity for >4 weeks). Thus, recommended dose was 180 mg/m^2 d1-5 every 14 days. More, 21 patients were treated in the phase II trial. Objective response rate was 14.7%, disease control rate 55.8%. At 33 weeks median follow-up, progression free survival (PFS) and overall survival (OS) were 20 and 47 weeks, respectively; PFS-6 months 35%. PFS and OS were not significantly different in low (0-10%) and high (>10%) MGMT protein expression patients, while OS was significantly different in relapse and sub-total disease (72 and 40 weeks, p 0.029), respectively. Cumulative G3-4 toxicities were: leucopenia 11.7%, neutropenia 11.7%, thrombocytopenia 14.6%, anemia 2.9%, asthenia 2.9%. LTS were 5 (14.7%), LTS-ss 1, LTS-ms 4.

Discussion: The present dose-finding study proposed TMZ dose-dense regimen as safely administered at 180 mg/m^2 d1-5 every 14 days, recommended dose. Preliminary efficacy data showed promising PFS and OS.

R20 Carboplatin and etoposide chemotherapy in extrapulmonary poorly differentiated neuroendocrine carcinomas

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Background: Extrapulmonary poorly differentiated neuroendocrine carcinomas (NECs) clinically resemble a small cell lung cancer (SCLC), where carboplatin has been reported as active as cisplatin, combined with etoposide. We studied carboplatin/etoposide combination in patients with extrapulmonary NEC.

Patients and methods: Consecutive patients with histological diagnosis of extrapulmonary unresectable locally advanced or metastatic NEC were enrolled. Overall response rate (ORR) was primary endpoint, whereas disease control rate (DCR), toxicity, progression free survival (PFS) and overall survival (OS) were secondary endpoints.

Results: Forty-six patients were treated with Etoposide 100 mg/m2/day over three days and Carboplatin AUC 4-6 on day 1, every three weeks. Median age was 58 years (range 23-75). Thirty-nine patients were untreated and 7 pre-treated. Overall response rate was 54% (6% complete responses and 48% partial responses). Disease control rate was 78% (ORR + stable disease). Neutropenia was the most frequent grade 3-4 toxicity (22%), with 4 episodes of febrile neutropenia (9%). All type grade 3-4 toxicities occurred in the 33% of patients, leading to chemotherapy discontinuation in 2 cases (4%). Globally, PFS was 5 months (95% CI: 4.2 - 6.9) and OS 14 months (95% CI: 11.5 - 21.1).

Conclusions: Carboplatin/etoposide combination is active and manageable in patients with extrapulmonary NEC. In a cross-study comparison, it is worth noting that our activity data are similar to, or even higher than, those reported for cisplatin/etoposide. Based on different toxicity profile, carboplatin could be considered as a possible alternative to cisplatin in this clinical setting.

R21 IRST WL: a tool to measure the workload of clinical research coordinators in oncology

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Background: Cancer clinical trials (CT) have become more complex and require dedicated personnel (Clinical Research Coordinators [CRC]) involved in activities including regulatory and administrative aspects and protocol- and patient-related procedures.Few experiences on how to measure the workload (WL) of a CT have been published.We measured the specific WL of CRCs using a simple, objective tool developed at our institute.

Methods: The WL measurement tool considers 3 aspects of trial complexity: protocol management-related WL and patient (pt) management-related WL, subdivided into pt treatment management-related WL and pt follow-up management-related WL. A partial score is calculated for each section based on the specific score for: a) study promoter (profit, no profit); b) frequency of monitoring site visits; c) disease setting (advanced, adjuvant, neoadjuvant); d) number of centralized procedures; e) frequency of hospital visits to receive treatment; f) type of follow-up.The WL score pertaining to the study protocol (a-b) is trial-specific and not related to pt numbers. Scores for the treatment and follow-up sections are multiplied by the number of pts still undergoing treatment (c-d-e) and the number undergoing follow-up (f). The total WL for each trial is the sum of protocol-related partial scores and pt-related partial scores. IRST WLs were measured each month by 19 full-time CRCs in 7 sites of the Romagna Oncology Network to evaluate the reproducibility (when the study was active in two or more network sites) and accuracy of the measurement tool.

Results: From 1.04.15 to 31.03.15, 215 CRC WLs were calculated. Each CRC was involved in a median of 22 trials (range 5-52). More than 50% of studies were active in two or more Network sites and score reproducibility was very high (> 90%), with little difference in the number of centralized procedures and frequency of site monitoring visits.Variations in total WL scores among CRCs (from 270 to 950) and differences over time (up to 15% from month to month) were observed, reflecting the subjective perceived workload, regardless of the involved number of ongoing trials and recruited pts. A monthly score of between 450 and 600 was hypothesized as an appropriate WL value for a full-time CRC.

Conclusions: The IRST WL measurement tool could be a valuable aid to evaluating clinical trial complexity, estimating appropriate workloads for full-time CRCs, and planning personnel resource requirements.

R22 Immunotherapy (ImT), what Lung Cancer and Melanoma patients (pts) ... and physicians, know

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Background: The centrality of the Immune System (IS) in tumoral immune-surveillance has led to the development of new drugs rapidly affirmed as paradigm of treatment for certain cancers, like advanced melanoma. The re-evaluation of the immunogenicity of Non-small Cell Lung Cancer (NSCLC) has opened a new field of research, with an attempt to apply ImT also to this disease.

Material and methods: AIOM (Associazione Italiana di Oncologia Medica) together with WALCE (Women Against Lung Cancer in Europe) supported a multicenter survey to investigate pts' knowledge about the ImT, their expectations in terms of toxicity and efficacy, and to evaluate physicians' attitude with ImT. The survey has been distributed (10th of November 2014-19th of March 2015) to 77 NSCLC pts (prevalently men, over 60s) and 89 melanoma pts (equally distributed for gender and age). A similar electronic survey has been filled out by 128 and 68 physicians dealing with NSCLC and Melanoma, respectively, who reported to employ ImT in their clinical practice in 55% and 74% of cases.

Results: Table 1 shows main data on pts' expectations about ImT. Only 19% of NSCLC pts, compared to 73% of melanoma pts, declared to have been already treated with ImT. NSCLC and melanoma physicians globally reported a positive attitude for ImT, expecting to improve their clinical practice in the next future (88% and 99% of cases, respectively). They have speculated a non-limiting toxicity profile in 77% and 76% of cases.

Table: R22 Pts' perception about ImT

	NSCLC pts (%)	Melanoma pts (%)
Nature of the ImT*		
Vaccine	5	4
Biological agent	10	12
Antibiotic	1	1
Drug involving the IS to fight cancer	64	80
Not known	25	2
Source of informations*		
General Practitioner	6	4
Referring Physician	40	88
Referring Nurse	1	1
Patients	3	0
Internet	0	3
Newspaper/social networks	10	1
Other	30	3
Not known	10	1
Pts' knowledge about toxicity*		
None	51	18
Lower toxicity than chemotherapy	18	30
Equal toxicity than chemotherapy	5	3
Different toxicity from chemotherapy	22	52
Other	6	1
Not known	3	0
Pts' expectation*		
Not know	44	6
Believing in the informations received from physician	19	37
Efficacy and better tolerability than chemotherapy	22	29
Same efficacy of chemotherapy	0	4
Good efficacy	10	22
Other	3	4
No answer	4	0

* Possibility of multiple choices.

Conclusion: Although the role of ImT for NSCLC treatment, as just happened for melanoma, still needs a confirmation by the ongoing clinical trials, pts and physicians widely express great expectation, waiting for a large anti-cancer efficacy together with a low toxicity.

R23 The role of the activation of mTOR pathway in patients with advanced neuroendocrine tumors treated with everolimus

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Background: Everolimus (Eve), an inhibitor of mammalian target of Rapamicin (mTOR), is part of the therapeutic armamentarium for patients with advanced, progressive, well- or moderately-differentiated pancreatic neuroendocrine tumors (pNETs). To date, there are no validated biomarkers predicting Eve efficacy in NETs. The aim of our study is to explore whether the expression of phosphorilated (p)-mTOR and p-70S6K (a downstream effector of mTOR) correlates with the outcome of patients with NETs treated with Eve.

Patients and methods: paraffin-embedded tumor tissue specimens derived from NETs of various origins, treated with Eve at our Institution within different clinical trials or expanded access program, were examined for the expression levels of p-mTOR (clone 49F9, Cell Signaling Technology/CST) and p-70S6K (clone 1A5,CST) by immunohistochemistry. Positivity was quoted when at least 5% of tumor cells reacted with at least a moderate (2+) intensity staining. Response rate (RR), progression-free survival (PFS) and overall survival (OS) were analyzed in the group of p-mTOR positive (p-mTOR pos) and p-mTOR negative (p-mTOR neg). Univariate and multivariate Cox regression analysis (adjusted for age, site of origin and grading) were performed.

Results: 24 patients with advanced NETs treated with Eve were included in the analysis. 8/24 (33,3%) patients were p-mTOR pos and p70S6K pos (the concordance rate was 100%). 14/24 (58,3%) patients had a NET of pancreatic origin, 6/24 (25%) an ileal NET and 4/24 (16,7%) had a NET of other origin. 9/24 (37,5%) patients had a G1 NET, 14/24 had a G2 NET, while only 1 patient had a neuroendocrine carcinoma (NEC). 6/24 patients had a functioning NET. All p-mTOR pos tumors were G1; 5/8 were ileal NETs, while the other three were respectively NET of lung, thymic and unknown origin. We observed a trend towards a better median PFS and OS in the p-mTOR pos group than in the p-mTOR neg group (18,2 and 39,9 months versus 13 and 32,4 months, respectively) without any statistical significant difference both in univariate and multivariate analysis. Similar RR were observed in the two groups and the toxicity profile was comparable with the literature data.

Conclusions: despite the limited and heterogeneous case series and the retrospective design, the study suggests that the activation of mTOR pathway can predict better outcomes in patients with NETs treated with Eve. These results warrant further confirmation in a prospective setting.

R24 Efficacy and safety of the VEGF inhibitor bevacizumab in combination with fotemustine for high-grade gliomas

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Background: High-grade gliomas are the most common and aggressive group of primary central nervous system tumours and are characterized by diffuse infiltration of brain parenchyma and prominent angiogenesis. Glioblastoma is associated with a median overall survival (OS) of 6 months after recurrence and anaplastic astrocytomas 11 months after recurrence. A therapeutic target, highly expressed in glioma tumours, is vascular endothelial growth factor (VEGF), a key protein regulator of new blood vessel formation and tumour angiogenesis. Bevacizumab is a therapeutic humanized recombinant monoclonal antibody that binds to and inhibits the activity of VEGF.

Material and methods: We have investigated the efficacy and safety of bevacizumab in combination with chemotherapy (fotemustine-FTM-) for recurrent high-grade glioma (anaplastic astrocytomas, anaplastic oligoastrocytomas, anaplastic oligodendrogliomas –non-GBM- and glioblastoma-GBM-) at first recurrence after prior therapy. From January 2011 to March 2015 data of 35 patients were collected. From recurrence, we estimated 6-month progression-free survival (PFS-6), OS and toxicities therapy-related. The treatment consisted of an induction phase with FTM at 75 mg/m^2 intravenously on day 1, 8 and 15 and bevacizumab at 10 mg/kg intravenously on day 1 and 15, followed after an interval of 4 weeks by a maintenance phase with bevacizumab at 10 mg/kg every 2 weeks and FTM at 75 mg/m^2 every 3 weeks until tumour progression or unacceptable toxicity. Patients who required progressive FTM dose reductions received bevacizumab alone. Response to therapy was evaluated using the RANO Criteria and adverse events were graded according to the NCI-CTCAE v4.0.

Results: The median time from original diagnosis to recurrence was 13 months for GBM and 35 months for non-GBM gliomas. PFS-6 rate was 45% for GBM and 67% for non-GBM; median OS was 14 months for GBM and 21 months for non-GBM patients. Most patients experienced grade 1 or 2 toxicities; grade 1 toxicities includes hypertension and proteinuria (n = 5), fatigue (n = 10), epistaxis (n = 4) and deep vein thrombosis (n = 1); grade 2 toxicities were predominantly hematologic including anemia (n = 1), neutropenia (n = 4) and thrombocitopenia (n = 5).

Conclusions: Our findings support previously reported data that FTM/bevacizumab-based regimens are active in the treatment of patients with relapsed high-grade gliomas, and was also very well tolerated by patients showing no G3 or G4 adverse events.

R25 "Green oncology": a new paradigm for medical oncology

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For many years medicine has followed a biomedical model based on linear thinking and a disease-oriented doctor-patient relationship. Today this framework

must be replaced by a biopsychosocial model based on complexity theory and a person-oriented medical team-patient relationship. However, the new model is already proving no longer adequate or appropriate, and current events are urging us to develop an ecological model in which the medical team takes into account both individual illness and population health as a whole, since all of us are part of the biosphere. In recent years, the rising costs of cancer treatment have raised a serious issue of economic sustainability and Medical Oncology is without doubt the medical specialty that today has pressing economic problems, as does the population of our planet. We now need to rapidly address this issue, and everyone of us must try to reduce his ecological footprint, measured as CO2 production. Medical oncologists need to reduce the ecological footprint of their professional activity by lowering the consumption of economic resources and avoiding environmental damage as much as possible. This new paradigm is endorsed by the Italian College of Hospital Medical Oncology Directors (CIPOMO). A working group of this organisation has drafted the "Green Oncology Position Paper": a proposal (in accordance with International Guidelines) to all Italian oncologists, aiming for the same end results; for a more appropriate management of health care and the careful use of resources in order to protect the environment and the ecosystem during the daily exercise of their professional activities, the 11 items can be found at www.cipomo.it. The economic crisis must oblige us to make urgent choices regarding appropriateness and spending. We need a new paradigm, where Medical Humanities play the same role as high technology medicine and where it is accepted that the medical oncologist is the expert of neoplastic disease and the patient is "the expert" of his own "life". We must be aware that "A new approach to medicine is possible": in this approach the central point is the patient, but even more important is the medical-patient relationship, avoiding any risk of over diagnosis and over treatment. In our opinion the key word of future Medical Oncology will be" Resilience". In summary Green Oncology is the new paradigm that can give us not only economic but also environmental sustainability.

R26 Phospho-mTOR expression levels, proliferative acitivity (Ki67) and pancreatic primary tumor may influence the response to everolimus in neuroendocrine tumor patients: results from an Italian preliminary study

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Background: MTOR inhibitors are approved for the treatment of advanced neuroendocrine tumors. However, scarce data are available on clinical or pathological predictors of response to these agents. The aim of the study is to test in a pilot series the presence of clinical and pathological predictors of response to mTOR inhibitors.

Patients and methods: Clinical and pathological characteristics (sex, age, location of the primary tumor, tumor grade and Ki-67 index) and the expression of phosphorylated forms of mTOR and p70S6K were correlated with response to therapy in 20 neuroendocrine tumor patients treated with everolimus.

Results: Seven patients had partial response (PR), 10 were stable (SD) and three progressed (PD) under everolimus treatment. Pancreatic location and higher mean Ki-67 index were significantly associated with a better response ($p = 0.03$ and $p = 0.04$, respectively). Phospho-mTOR and p-S6K levels were significantly correlated each other ($p < 0.0001$). No differences in p-mTOR and p-p70S6K expression levels were observed in tumors segregated according to tumor site. In paired matched samples, the expression of p-mTOR was increased in 5 out of 9 metastatic tissues, compared to the corresponding primary tumors. p-mTOR and p-p70S6K were not significantly correlated with response to treatment. However, all PD and a minority of PR/SD cases had high expression levels of p-mTOR.

Conclusions: Some specific tumor characteristics seem to be associated with response to mTOR inhibitors and should be validated in larger series.

R27 Low toxicity profile of the combination of bendamustine plus rituximab in elderly frail patients with newly Diagnosed Diffuse Large B-Cell Lymphoma (DLBCL)

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Introduction: R-CHOP is the gold standard for the treatment of elderly patients with DLBCL. However, unfit and frail patients frequently do not qualify for CHOP-based chemotherapy. Alternatives are an urgent medical need. Bendamustine plus rituximab (BR) has been established as a standard treatment of indolent lymphomas and preliminary data have shown a promising activity in DLBCL, both in the relapsing and upfront setting.

Material and methods: Within the Fondazione Italiana Linfomi (FIL), we started a phase II study (R-BENDA frail study, EUDRACT2011-001421-24) in elderly patients (>70 years) with a newly diagnosed DLBCL not suitable for R-CHOP-based chemotherapy. All patients were evaluated according to ADL, IADL and CIRS-G and were considered FRAIL if the following criteria were meet: in patients aged 70-80 ADL < 4 or IADL<5 or one grade 3 comorbidity or >8 grade 2 comorbidities; in patients older than 80 years ADL > 5 or IADL > 6 or 5-8 grade 2 comorbidities. Patients received bendamustine at a dose of 90 mg/m^2 daily on days 1 and 2 of each 28-day cycle along with rituximab on day 1 for up to 6 cycles.

Results: From February 2012 to February 2014, 49 patients were enrolled in 24 Italian centers. The majority (57%) were male and 57% had stage III-IV with 41% elevated LDH. The median age was 82. Overall, 83% of the planned cycles were delivered without dose reduction or delay; grade 3/4 neutropenia was reported in 25% of cycles followed by anemia 21%, and thrombocytopenia 20%. One case of febrile neutropenia was observed. Grade 3-4 non-hematological toxicity was mild and reported in 6% of cycles including 3 episodes of cardiovascular events and 7 other cases of different toxicities (one creatinine increase, one fatigue, one bleeding, one peripheral neurotoxicity, one hyponatriemia, one hyperglycemia and one liver toxicity). Two deaths during treatment have been observed (cardiac failure and sudden death). At the interim analysis (23 patients) the overall response rate was 56% with a complete response rate of 39%.

Conclusions: Combination therapy with BR demonstrates low toxicity profile in this high risk population. The promising results on activity can encourage clinicians to considered BR for the treatment of FRAIL elderly patients with DLBCL not eligible for R-CHOP.

R28 Pre-emptive pharmacogenetic testing implementation for chemotherapy dosage optimization: the translational experience at CRO of Aviano

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Background: Pharmacogenomics (PGx) is one of the first clinical applications of the postgenomic era and allows personalized medicine rather than the established 'one size

fits all' approach. A pre-emptive PGx testing shouldreduce 'trial and error' prescribing and lead to more efficacious, safer and cost-effective drug therapy.Its application in routine patient care is still limited, despite national and international guidelines. We have recently completed a retrospective genotyping of 603 cancer patients, treated with fluoropyrimidines (FL), demonstrating that the test specificity for the prediction of early G ≥ 3 toxicity based on the analysis of DPYD-rs3918290, -rs55886062, and -rs67376798 was 99%. rs3918290 and rs67376798 were associated to G ≥ 3 toxicity after bootstrap and Bonferroni correction (P = 0.003,P = 0.048). rs55886062 was not significant likely due to its low allelic frequency, but one out of two heterozygous patients (compound heterozygous with rs3918290) died from toxicity after one cycle. Our data on the role of UGT1A1*28 in predicting the occurrence of early severe (G ≥ 3) toxicity after an irinotecan (IRI) based treatment have been published.

Methods: Based on these data, current literature, and SIF-AIOM guidelines, the Experimental and Clinical Pharmacology Unit of CRO (Aviano) has set up during 2014, a clinical PGx service accessible to Medical and Radiotherapic Oncology Units.

Results: Up to date 233 cancer patients candidate to a therapy with either FL or IRI were referred to the Pgx service prior to treatment. Based on the genotype data for DPYD (rs3918290, rs55886062, rs67376798), or UGT1A1*28 a starting dose adjustment was suggested for 18 patients, possibly preventing an early and potentially life-threatening toxicity in 7 cases (3%), roughly estimated on our previous data. A PGx electronic report is embedded in the patient clinical record. A further result of this experimental service was a progressive sensitization of the oncologists on PGx, demonstrated by the increasing rate by time of patients referred for pre-treatment genotyping. Cost-effectiveness and HTA studies are ongoing to assess the clinical utility of a pre-emptive PGx approach in oncology.

Conclusion: Based on this successful experience and according to the international CPIC and DPWG guidelines we have planned to increase the drugs to be tested in our Institute for PGx based dose adjustment and move another step toward a safer and more efficacious personalized medicine.

R29 ONCO-T-PROFIL: treatment of patients with refractory metastatic solid tumors according to a molecular characterization of potential predictive biomarkers

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Introduction: Patients with refractory metastatic cancer have been shown to benefit from molecular profiling of tumor tissue. The "ONCO-T-PROFIL" project was launched in March 2014 at the Department for Haematology and Oncology of Innsbruck Medical University. Within 2 years our project aims to recruit 100 patients with stage IV cancer. Our data presented here is based on an interims-analysis.

Methods: Formalin-fixed tumor tissue specimens are submitted for molecular profiling to a certified laboratory in the USA (CARIS Life Intelligence©). Profiling methods used to identify and characterize potential predictive biomarkers include IHC, NGS and CISH/FISH. Druggable tumor targets and corresponding drug candidates were selected based on an evidence-based information system that associates the biomarker status to agents with potential clinical benefit or potential lack of benefit. Clinical benefit was defined as a PFS ratio (=PFS upon the last therapy/PFS upon treatment according to the molecular profile) ≥ 1.3.

Results: Until April 2015, tumors from 50 patients have been molecularly profiled and in 48 (94%) one or more druggable target structures were detectable. So far, 19 (38%) patients have been treated or are currently undergoing treatment according to their molecular tumor profile. To date, 7 of 19 (36%) patients have benefitted by reaching a PFS ratio of ≥ 1.3.

Conclusions: Up to now a subset of our patients showed a clinical benefit from a therapeutic regimen based on molecular typing. Our data demonstrate that a subgroup of patients can benefit from an individualized treatment approach based on molecular profiling.

R30 New european clinical trials regulation: perception and expectations in Italy

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Background: In July 2012 the European Commission formalized the proposal for a European Clinical Trials Regulation (ECTR), which would repeal the EU Clinical Trials Directive 2001/20/EC. The new regulation, which entered into force in June 2014, is expected to be applied in the European Union (EU) no earlier than May 2016. The ECTR aims at creating a productive environment that should favour the management of clinical trials (CT), highlighting on the highest standards of patient safety, increased transparency and swift application procedures.

Methods: An anonymous online survey was distributed among italian Clinical Research Coordinators (CRC) and professionals in the field of clinical research. The survey, composed by 19 questions, was levelled at obtaining a picture of the insiders' knowledge of regulations and an understanding of which aspects will have a major impact on their work.

Results: 112 professionals, mostly CRC (87.5%), answered the questionnaire. Of these, 80.4% were aware of the new ECTR through courses/congress (48.2%), internet research (33%), personal reading (33%), network (15.2%) and other sources (15.2%). All respondents feel the need to transmit ECTR information to their Principal Investigators and 65.2% believes site staff is not yet fully aware of the novelty. Indeed, 92% deems that, so far, the Institutional conduits have not provided adequate training and 88.4% believes that Hospital Mangements have failed to engage in or plan out for the changes needed to adapt to ECTR. According to the respondents the most innovative aspects of ECTR are the centralization of procedures (74.2%), the European Portal (71%) and new timing (44.1%). ECTR will have important consequences both on Investigator Initiated CT and Commercial ones and will facilitate their conduct for 51.6% of respondents. The responses show that some topics have not been adequately addressed, as the minor involvement of Ethics Committees in the procedures (41.4%). Most respondents (71.4%) admit lacking in a clear stance about ECTR despite almost all (85.7%) are sure that it will have direct and immediate impact on their work.

Conclusion: The ECTR will definitely be a great challenge therefore adjustment and adaptation to new procedures are urgently solicited to reinforce competitiveness and attraction of italian investigational sites.

R31 Concordance of PET/CT and bone marrow biopsy in lymphoma staging

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Background: Bone marrow (BM) involvement in lymphomas is of outmost relevance as it defines stage IV disease. BM biopsy is the standard procedure to assess lymphoma cell infiltration. Although usually safe, it can be inconvenient and sometimes painful for the patient. Some studies demonstrated that 18- fluoro-deoxyglucose Positrone Emission Tomography/Computed Tomography (PET/CT) can adequately replace BM biopsy when focal radionuclide captation is found in bones . The purpose of this study was to evaluate the role of PET/CT in the assessment of bone marrow involvement in patients affected by Hodgkin Lymphoma (HL) and Non-Hodgkin Follicular (FL), Diffuse Large B cell Lymphomas (DLBCL) or high-grade lymphomas.

Patients and methods: The study population consisted of 89 consecutive patients enrolled from january 2013 to march 2015: median age was 61 years, 12 patients (13.5%) were affected by HL, 21 by FL (23.6%), 47 (52.8%) by DLBCL and 9 (10.1%) by different high-grade lymphomas . All patients underwent routine staging procedures and, excluding stage I disease and the patients who refused, 61 patients were evaluated with both PET/CT and BM biopsy.

Results: In the group of patients with HL and a PET/CT positive for bone marrow involvement, a positive BM biopsy was found only in 2 of 4 patients (50%); on the other hand 4 of 5 patients (80%) without BM involvement at biopsy had negative PET/CT. In the group of patients with FL 4 out of 4 (100%) had a positive PET and bone marrow involvement, while 6 of 7 (85%) patients without BM involvement had also negative PET/CT. In the group of patients affected by DLBCL and high-grade lymphomas (considered togheter) the correlation between positive PET/CT and biopsy was demonstrated only in 2 of 9 patinets (22%); when PET/CT was negative 26 of 32 patients (81.5%) had negative BM biopsies. The accuracy of PET/CT in assessing BM infiltration was 67%, 91% and 68% in HL, FL, and DLBCL + high-grade group, respectively.

Conclusions: PET/CT plays a central role in the diagnosis, staging and response assessment of patients with HL, FL and high-grade lymphomas, but in our experience PET/CT did not demonstrate to accurately replace BM biopsy in the evaluation of BM involvement in case of HL and high-grade lymphomas. In the latter group the discordant result was mostly disappointing. On the contrary a significant concordance was found in case of FL where, according to our data, a positive PET/CT can overcome the need for BM biopsy.

R32 Druggable aberrations in solid tumors: an overview on ALK and ROS-1 status

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Background: Anaplastic Lymphoma Kinase(ALK) and C-Ros Oncogene-1(ROS-1) are receptors with tyrosine kinase activity, found activated as result of rearrangement in several tumors; those targets are druggable, successfully used in NSCLC and potentially useful to treat other solid tumors harboring ALK and ROS-1 aberrations.

Material and methods: We retrospectively collected data about ALK (584 cases) and ROS-1 (403 cases) status in patients with solid tumors, analyzedin 2014 at our Pathology Department. ALK and ROS-1 status (rearrangements and copy number change) were evaluated byfluorescence in situ hybridization(FISH). Gene copy number (GCN) gain was defined as a mean of 3 to 5 fusion signals in ≥10% of cells; amplification as presence of clusters or 10-15 fusion signals in ≥10% of cells.

Results: ALK status assessment was possible in 570/585 (97%) cases, while ROS-1 status was evaluated in 388/403 (96%). We identified 5/388 (1.3%) ROS-1 rearrangements: 4 were lung adenocarcinomas and 1 colon cancer. Frequency of ROS-1 rearrangements was 2.7% (4/147 cases) for lung cancer and 0.9% GI cancer (1/114 cases). GCN abnormalities were more frequent in melanoma (77%), neuroendocrine (39%) and NSCLC (32%, 3/4 cases of ROS-1 amplification were squamous carcinoma). We found 14/570 (2.5%) cases positive for ALK rearrangements: 12 lung adenocarcinomas, 1 colon cancer and1 myoepithelioma. Frequency was 3.9% in lung (12/310) and 0.8% gastro-intestinal cancer (1/126). Several GCN abnormalities were documented in lung adenocarcinoma (53%), pancreatic (50%) and colon (40%) cancer.Seven out of the 19 rearranged cases (5 ALK and 2 ROS-1) were tested for both genes: aberrations appear to be mutually exclusive while 3/5 (60%) ALK rearranged had a ROS-1 deletion associated. ALK and ROS-1 were not rearranged in pancreatic (n = 14), H&N (n = 22), biliary tract (n = 18), renal (n = 14), breast (n = 12) cancer, melanoma (n = 13) and a miscellanea of other solid tumors (n = 30).

Conclusions: We confirm the rate of ALK and ROS-1 rearrangements reported in literature for NSCLC (3.9% and 2.7% respectively). In other solid tumors the percentage of rearrangements is very low but among melanoma, neuroendocrine, pancreatic and colon cancer there is a significant rate of GCN changes.It remains of crucial importance to better define the role of such aberrations as hypothetical biological targets, possibly with evaluation of ALK and ROS-1 status with both immunohistochemistry and mutational profile.

R33 Early rehabilitation after surgery for glioblastoma multiforme: report from a monocentric experience

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Background: Neuro-oncological patients often present neurological deficits related to tumor itself and/or to the administered treatments. Although previous studies have demonstrated the effectiveness of rehabilitation treatment for neuro-oncological patients, few data still exist about the role of rehabilitation in patients who underwent surgery for gliomas.The aim of this experience was the evaluation of functional outcomes when rehabilitation is administered early after neurosurgery for glioblastoma multiforme (GB).

Methods: From January 2010 to January 2014 we consecutively enrolled 39 pts who underwent surgery for GB. Main characteristics of pts were as follows: M:F = 23:16, median age: 62 yrs (36-73), median ECOG PS 1 (1-3), complete surgery 24 pts – partial surgery 15 pts. All pts were admitted to our Rehabilitation Unit within two weeks of surgery. No patient was treated with chemo and/or radiotherapy during the rehabilitation period. All pts were evaluated using a core set of scales: Functional Indipendence Measure (FIM), Sitting Balance Score, Standing Balance Score, Hauser Index, MGH Functional Ambulation Classification (MGHFAC). Pts were evaluated before the beginning (T0) and at the completion of rehabilitation treatment (T1).

Results: At T0 median FIM, Sitting Balance score, Standing Balance score, Hauser Index and MGHFAC scores were 44 (28-57), 1.2 (0.6-2), 0.4 (0.3-0.9), 8.5 (7.9-9.5), 1.1 (0.3-2.2), respectively. After the planned four weeks of rehabilitation programme we observed a substantial improvement in all the evaluated scales: total FIM 80,1 (45-105), Sitting Balance score 3,1 (2,7-4,4), Standing Balance score 2,1 (0,6-3,7), Hauser Index 6,0 (3,1-0,9), MGHFAC 2,7 (1,1-4,5).

Conclusions: Based on these findings, early rehabilitation for pts who underwent surgery for GM clearly improves functional outcome.

R34 Metastatic well or moderately differentiated Neuroendocrine tumors (WDNET) treated with sequences of different Somatostatin Analogs (SSA) - Lanreotide LAR (La), Octreotide LAR (Oc): a single center experience

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Background: PROMID and CLARINET trials demonstrate an improvement in PFS of SSA versus placebo in WDNET. Octreotide LAR and Lanreotide Autogel shows little difference in mechanism of action, with different affinity to Somatostatine receptor. A possible resistance to first line treatment with SSA could be up and down regulation of somatostatin receptor and a second line treatment with a different SSA could be a therapeutic strategy. We evaluate retrospectively the efficacy, safety, and tolerability of the sequences of these two different SSA in WDNET observed in our Institute between 2000 and 2015. We compare retrospectively the use of different SSA in second line with Everolimus + SSA used in second line in our institution in order to compare the experimental strategy with standard treatment.

Methods: Patients (pt) affected by WD NET were given Oc 30 mg/month or La 120 mg/month by intramuscular injection as first line treatment. At disease progression, pt were given a second line treatment with the other SSA. Efficacy was evaluated by response rate according to RECIST criteria and in terms of time to tumor progression (TTP). Safety and tolerability were evaluated by assessing the onset of adverse events and treatment feasibility.

Results: 24 pts were evaluated: primary tumor was pancreas (p), midgut (mi), colon, and unknown (u) respectively in 7,11,1 and 5 pts. In first line treatment, considering all 22 pt, median TTP was 17,52 months (range 1,93–105,13), with 16 SD, 4 PR and 2 PD. In second line treatment, median TTP was 14,9 months (range 1,60–160,43) with 20 SD e 2 PD. 4 pt are still in treatment. No pt complained from any severe adverse reaction.

Conclusions: The results of our study suggest that a second SSA is effective in tumor progression control of WD NET even after first line treatment with other SSA.

R35 The follow-up and lifestyle (FUCSAM project). Oncology Network of Piemonte and Valle d'Aosta (ROPVdA): preliminary data

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Background and rationale: Recent results have strenghtened the evidence that lifestyle factors can benefit not only the quality of life of cancer survivors,but also overall survival, and decrease the risk of recurrence from cancer.Integrating life-style support into standardised models of aftercare for cancer survivors is a challanging purpuse.The osservazional FUCSAM study aims to assess the impact of an intervention designed to

change the lifestyle of patients in follow-up after treatment of colorectal and breast cancer followed by different Interdisciplinary Groups and Care.

Material and methods: Eligible patients: breast or colorectal cancer (histologically confirmed), at first follow-up after surgery and adjuvant medical therapy (if indicated), free of disease, able to walk and with informed consent.Data detected: personal, therapies, comorbility, stage at diagnosis, anthropometric, clinical and bioumoral parameters (height, weight, weistline, PAO, glucose, cholesterol profile), adherence to programs on lifestyle, changes carried out by local Patients Associations (activities evaluated by the project scientific committee). All patients were handed information brochures and recommended adherence to specific programs, if any.

Results: Until now13/22 local hospitals have joined the FUCSAM project after of the ethics committee approval.Patients enrolled are 513 (98 colorectal cancer, 415 breast cancer) and 75% are <70 years old. 167/382 women with breast cancer (40%) had the diagnosis through mammography screening (55% in age group target), while 25/90 of patients with colorectal cancer have being diagnosed within the local screening program (12.5% ??women-31.3% men, 38.5% in the age group target).The waist measurement was >80 cm in respectively 73.7% and 59% of women with previous breast and colorectal cancer, >90 cm in 66% of men.Metabolic syndrome was detected in 25% of women (17% with prior breast cancer) and in 24% of men.The analyss of the impact of the adherence to a healthier lifestyle on anthropometric and clinical parameters is underway.

Conclusions: First study results show that the introduction of lifestyle recommendations within the follow-up protocols is feasible.After diagnosis of cancer, people are more inclined to consider the relationship between their behavior and the effects on health.To encourage the adoption and maintenance over time of new habits, the ROPVdA will plan to provide practical guidance for the realization of the desired changes.

R36 First Prospective Bone Metastases (BM) Data Base: One-Year experience

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Introduction: BM are the main cause of morbidity and morbility in cancer patients, overall because of complications defined as SRE (skeletal-related event). At now, data concerning BM are obtained retrospectively from monocentric experiences. BM Data Base 's primary aim is to collect clinical and epidemiological prospective data in order to better understand the natural history of BM and to obtain information about SREs. The secondary objectives are to evaluate clinical factors related both to the primary tumors and to BM, their biological behaviors and the effectiveness of specific treatments on SRE.

Materials and methods: BM Data Base is a multicenter prospective observational study, which has as Coordinating Center (CC),IRCCS IRST of Meldola. It will allow to gather information on patient's medical history of using an online software tailored for these data . Database's platform consists of 4 files containing information regarding patient demographics, BM and primary tumor's characteristics, as well as their evolution, in particular the onset and the types of SREs. Data are updated every 6 months by the participating centers and reviewed by CC.

Results: Approved by the Ethics Committee (EC) of the CC on February 2014,the BM Data Base is active from October 2014. To date, 9 centers have been activated and have access to the platform,7 are waiting for the final approval, 6 have submitted the application form to the EC of CC and 9 is taking steps into submission . At present, 181 patients (110 Female and 71 Male) have been included in the data base from 6 centers with at least 2 months of enrollment as we can see in table 1. From the second archive we obtain informations concerning the medical history of the primary tumor. The number and percentage of cases collected are shown in table 2.

Table 1 : R36

Center	Frequency	Percentage %
IRST - Meldola	118	65
Lugo (Ravenna)	4	2
Rimini	36	20
Lecce	17	10
Bari	4	2
Carpi	2	1
Total	181	100

Table 2 : R36

Primary tumor site	Frequency	Percentage %
Stomach	5	3
Colon-Rectum	4	2
Small cell lung cancer	11	7
Not-small cell lung cancer	24	14
Breast	84	49
Prostate	31	18
Others	12	7
Total	171	100

Conclusions: BM Data Base is the first Italian prospective multicentric experience to study the natural history of BM from different neoplasia. The data analysis will not only provide epidemiological information that will help to better understand the frequency and clinical impact of BM, but also on the patients' quality of life and prognosis as well as indirectly on health care system costs related to them.

R37 Predictive factors of efficacy of Somatostatine Analogs (SSA) in Gastroenteropancreatic Neuroendocrine Tumors (GEP-NET)

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Background: PROMID and CLARINET studies showed antitumor activity of SSA, respectively Octreotide LAR (Oc) and Lanreotide LAR (La), in well and moderately differencieted GEP-NET. Both studies enrolled populations that differed in ki67 level, liver metastatic involvement, octreoscan baseline status. Data on predictive factors of efficacy of SSA in NET are lacking. In this retrospective study, we analyze our experience with SSA in metastatic GEP-NET, to evaluate possible predictive factors that can guide physician's choice.

Methods: A retrospective analysis was conducted on 121 patients (pts) with advanced GEP-NETs treated upfront with Oc (30 mg 1 fl every 28 days) or La (120 mg 1 fl every 28 days) until disease progression: 56 gastrointestinal (GI) NET pts, 46 pancreatic (P) NET pts, primary tumor was unknown in 19 pts. Grading was G1 in 42pts, G2 in 51, not identifiable in 28 pts. Baseline Octreoscan was performed in 74 pts and positive in 56 pts, negatve in 18 pts.

Results: Median time from NET diagnosis and SSA treatment was 5 months (0,5 -1300 months). Response was obtained in 16 pts (13%), stable disease in 94 pts (78%) and progressive disease in 11 pts (9%). In GI NET pts, P NET pts and unkown primary, median PFS was respectively 41, 24 and 19 months (p value 0,079) with a trend in favor of GI NET. In pts with hepatic tumor volume <25% PFS was 27 months, In pts with hepatic tumor volume >25% PFS was 15 months (p value 0,009; HR 0,45 95% CI of ratio 0,252 to 0,818) In pts with baseline Chromogranin A (CgA) lower then 250 U/L or higher then 250 U/L PFS was respectively 33,1 months and 12 months (p value <0,001; HR 0,45 95% CI of ratio 2,131 to 3,356) In pts with ki67 index <2% and Ki67>2%, median PFS was respectively 34 and 24 months and not significantly different (p value 0,205; HR 0,73 95% CI of ratio 0,457 to 1,813). In pts with Baseline Octreoscan Positive and negative, median PFS was respectively 21 and 33 months and not significantly different (p value 0,27; HR 1,34 95% CI of ratio 0,7725 to 2,516).

Conclusions: Low level of CgA, low hepatic tumor volume are favourable predictive factor of SSA efficacy . SSA showed comparable efficacy in all ki 67 index groups, in all baseline Octreoscan status suggesting that Octreoscan doesn'I identify responsive pts . SSA showed comparable efficacy in terms of PFS in both PNET and GI NET with a trend in favor of GI NET.

R38 Alternative schedule of Fotemustine in elderly patients with recurrent glioblastoma: a phase II prospective study

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Background: Elderly patients (EP) represent a large portion of population affected by glioblastoma (GBM). It is unclear the role of chemotherapy as second line. We performed a prospective single-arm phase II study analyzing the efficacy and tolerability of an alternative schedule of Fotemustine (FTM) in EP with recurrent GBM.

Patients and methods: We enrolled patients (PTS) => 65 years with recurrent GBM after standard adjuvant treatment, histologically confirmed at diagnosis, with a ECOG PS <= 2. PTS with a second surgery were excluded. Brain MRI was performed 2 weeks

before starting chemotherapy and subsequently, each 2 months or when clinically indicated and evaluated according RANO criteria. PTS received FTM 80mg/m2 every 2 weeks for five consecutive administrations, and then every 4 weeks until progression or important toxicity. Primary endpoint was overall survival (OS). Toxicity was recorded according to CTCAE v. 4.0.

Results: From January 2012 we analyzed 34 PTS: mean age was 70 (range 65-82); 25 PTS (74%) were M and 9 (27%) were F. ECOG PS was 0-1 in 28 PTS (82%), and 2 in 6 PTS (18%). MGMT methyaltion was assessed in 25 PTS and was methylated in 15 PTS (44%). Median progression free survival (PFS) and median OS from beginning of FTM therapy was 4.5 months and 7.6 months, respectively. OS from GBM diagnosis was 17.9 months. Patients with methylated MGMT had a trend for longer survival from starting FTM therapy: 9.2 months vs 5.6 months for patients with unmethylated MGMT ($p = 0.1$). The most important grade 3-4 toxicity was haematological toxicity (27% of PTS): neutropenia (12%), thrombocytopenia (9%), e lymphopenia (6%). No other significant toxicities were registered. No PTS discontinued therapy due to toxicity. Analysis of quality of life (QoL) is ongoing.

Conclusion: This alternative schedule of FTM is effective and safe in EP with recurrent GBM . PTS with methylated MGMT showed a trend for longer survival.

R39 Diffusion-MRI and angiogenic profiling in patients with advanced well-differentiated pancreatic neuroendocrine tumors treated with everolimus

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Background: Everolimus and sunitinib were approved for progressive pancreatic neuroendocrine tumors (pNETs), based on progression free survival (PFS) benefit. Tumor response assessment was based on RECIST criteria, known to be inadequate for molecular target agents; furthermore predictive factors of efficacy are unknown. Diffusion-weighted imaging (DWI) – magnetic resonance imaging (MRI) exploits differences in the motion of water molecules in vivo at a biologically meaningful scale, calculating the variability of tumor apparent diffusion coefficient (ADC). Endothelial circulating cells have been validated as potential prognostic and predictive factors in breast cancer. Therefore we decided to evaluate the effect of everolimus with a number of circulating angiogenic factors and the DWI-MRI in patients with pNETs.

Material and methods: This is a biological prospective trial (clinicaltrials.gov: NCT02305810). All patients received everolimus according to routine clinical practice. At baseline, after one month and three months of therapy, and at disease progression, a biological evaluation was performed including: circulating endothelial cells (CECs), circulating endothelial precursor (CEPs), vascular endothelial growth factor (VEGF) and its receptor (VEGFR), basic fibroblast growth factor (bFGF) and thrombospondin-1 (TSP-1), and DWI-MRI when possible.

Results: thirty-eight patients have been enrolled so far; this is a preliminary analysis regarding 22 patients who have the complete three-month biological evaluation. Median values of circulating biomarkers above the derived cut-off, correlated with a reduced risk in terms of PFS. CECs-140+ and VEGFR values were inversely related to a worse PFS. Inconsitent data were available for OS, maybe due to the limited number of patients. ADC median values tend to increase in the first 3-6 months, anticipating the clinical and imaging response. However, the trend of ADC is less reliable in the first 3 months, because of greater heterogeneity. Median PFS and mOS were 11.8 and 35.1 months, respectively.

Conclusion: no clear correlation was observed between the angiogenic profiling evaluation and the clinical outcomes in this preliminary analysis of our ongoing biological study. DWI-MRI seems improve the stratification of early responder patients. These data, however, need to be verified when the accrual will be completed.

R40 Evaluation of diagnostic investigations used in breast cancer patients resident in Latina province during three years follow up after diagnosis

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Background: Strict adherence to published guidelines for follow up investigations in breast cancer (BC) is still debated.

Objective: Evaluate diagnostic investigations BC follow up during three years after diagnosis using Cancer Registry and administrative data.

Materials and methods: Population based study.Patients with BC diagnosis in the years 2009/2010 were identified from Latina Cancer Registry(RTPLT)data base. Record linkage with hospital admissions and outpatient services in the three years following diagnosis was performed. Mammography (MAM), liver ultrasound (LU), bone scan (BS), chest xray(CXR), PET,markers(MRK) and oncologic visits(OV) were stratified by stage (I,II,III) molecular classe(MC), nodal status(pN) and age(<46, 46-65, >65) only in patients alive,without metastasis and at least 36 months follow up For statistical evaluation were used the chi-square test and the Cochran Q test.

Results: 761 patients with BC (43 is and 319 invasive) were identified from RTPLT :614 patients were considered for analysis by age, 535 for stage, 513 for pN, 418 for MC.

Table: R40

Investigations	1 Year N. (%)	2 year N. (%)	3 year N. (%)
LU	361 (58%)	347 (56%)	326 (53%)
CXR	355 (58%)	335 (54%)	302 (49%)
BS	416 (68%)	179 (29%)	128 (21%)
PET	185 (30%)	114 (19%)	87 (14%)
MRK	480 (78%)	511 (83%)	492 (80%)
OV	399 (65%)	397 (65%)	397 (65%)
MAM	319 (52%)	337 (55%)	298 (49%)

LU:No association with stage, pN, MC; association with middle age after first year ($p = 0.05$, $p = 0.01$).
CXR:No association with stage, pN, MC; association with older patients in the first year ($p = 0.01$).
BS:Association with stage II/III in the three years ($p = 0.05$, $p < 0.0001$, $p = 0.002$), with pN+ in second year ($p < 0.0001$), and with younger age in the third year ($p = 0.001$).
PET:Association with stage II/III in second ($p = 0.001$) and third year ($p = 0.03$)with MC (triple negative) in the third year ($p = 0.02$), and with younger age in the third year ($p = 0.02$).
MRK: Association in the first year with early stage ($p = 0.02$), with pN- ($p = 0.01$) and Luminal A ($p = 0.03$).
MAM:Association with early stage.($p = 0.02$) in the first year and with older than 45y in the third year ($p = 0.01$). All exams were reduced during the three years particularly PET in early stage, BS for all stage. OV were reduced for older patients but increased for younger.

Conclusions: Only BS and PET are relate to stage. Delayed MAM in II/III stage is due probably to adjuvant chemotherapy.Cancer Registry data could be used for assessing the follow-up strategies performed in a specific area directing further investigation.

R41 Physical exercise and eating habits in cancer survivors

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Background: Healthy eating habits and active lifestyle have been shown to reduce mortality in chronic disease as in secondary prevention. The purpose was to assess a correct eating habits and physical exercise in overweight cancer survivors, for helping them in integrating back into normal life and in order to improve their life quality and potentially their long-term survival chances.

Patients and methods: 26 overweight cancer survivors (from 41 to 75 years old) were enrolled on a physical exercise program. On the first visit (T0), weight, body mass index (BMI), waist and hip circumferences, skin fold for estimation of fat mass and Bio Impedance Analysis (BIA) for hydration status were assessed. To each subject was given a food diary, to assess his eating habits. This approach were to correct wrong eating habits. After a week, they received personal advice on nutritional issues on the basis of the American Cancer Society Guidelines. Statistical analysis was performed with ANOVA test.

Results: A total of 22 breast cancer patients and 4 colon cancer patients (1 patient metastatic from enrollment) were recruited. During a follow up period of median 37 months, 24 patients were still alive and 21 were free of relapse disease: 1 death for a second metastatic lung cancer, 1 death for colon cancer progression and 3 breast cancer relapse. From the analysis of food diaries, it emerges that fat and sodium consumption was high with low intake of fruits and vegetables. After having changed their eating habits, the following results were observed: after 6 months (T6) the anthropometrics and hydration parameters showed a variation (weight T0: 73.28 ± 16.11 kg, T6: 72.10 ± 15.00 kg; $p < 0.01$; total water T0: 50.94 ± 6.51%, T6:51.78 ± 7.51%; $p < 0.05$; extra-cellular water T0: 47.78± 4.70%, T6: 47.98 ± 4.90%; $p < 0.01$); after 12 months (T12) the program had a significant effect (weight T12: 71.85 ± 14.78 kg; $p < 0.02$, BMI T0: 27.38 ± 6.51 kg/m2 T12: 26.86 ± 6.10 kg/m2; $p < 0.05$; waist circumference T0: 87.96 ± 15.21 cm, T12: 86.38 ± 13.16 cm; $p < 0.05$).

Conclusions: The findings suggest the importance of nutritional advice along with physical exercise, to improve nutritional status and body composition in overweight cancer survivors. Variation in weight, BMI, waist circumference, total water and extra-cellular water, are been useful for reducing risk factors in chronic disease, including cancer.

R42 Circulating microRNAs (miRNAs): Biomarkers for Lung Cancer

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Smoking is the most important risk factor in developing lung cancer but also air pollution plays a significant role in increasing the risk. Data obtained from ESCAPE (European Study of Cohorts for Air Pollution effects) take into consideration people being observed for 13 years. During this period 2.095 people were affected with lung cancer and, for each of them, it was studied the exposition of the so-called particulate (PM 10 e PM 2,5) linked principally to traffic pollution, but also to other substances caused by heating or manufacture. No doubt about the result: for each increase of 5 µg/m3 of PM 2,5, the RR of lung cancer increases by 18%, while it rises by 22% for each increase of 10 µg/m3 of PM10. It is, therefore, the particulate the main responsible factor of the cancer effect. The International Agency for Cancer Research has included air pollution and particulate among human carcinogens of type 1. Prevention from disease still remains a problem: the medical diagnosis is made, in 80% cases, when the cancer is already in its advanced phase. The miRNA are small not codifying molecules of RNA with the capacity of modulating the genic expression and are expressed in an aberrant manner in cancers. The miRNA are tissue molecules and disease-specific actively released by cancer cells and by their microenvironment in the system. Circulating miRNA are stable and quantifiable in the plasma, too. The miRNA deregulate directly the expression of mRNA. Their amplification is in correlation with tobacco habit and air pollution. Circulating miRNA are expression of lung tumour progression and can be considered specific biomarkers. Blood samples gathered during a large retrospective study on 939 strong smokers, enrolled in the randomized study Multicentric Italian Lung Detection were used to determine the predictive, diagnostic and prognostic utility of the molecular test of miRNA circulating in the blood. The molecular test estimates the levels of twenty-four miRNAs in the blood plasma. The miRNA test showed a sensitivity of 87% in detecting the lung cancer. In consideration of all the analyzed individuals, the miRNA test reported a negative predictive value of the 99% for disease identification and 99.86% for prediction of lung cancer deaths, underlying the high specificity of the test in the correct identification of the individuals not affected with cancer. The high specificity of miRNA test reduced by 80% the number of false positives detected by spiral Tac.

R43 How a Clinical Trial Office can improve the independent Clinical Research: the Italian Sarcoma Group experience

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Background: The Italian Sarcoma Group (ISG) is a no profit group of professionals established on 1997 with the aim to increase the quality of sarcoma treatment and to promote independent Clinical Research (CR). From 2010 ISG adopted a complete management of research, by implementing a Clinical Trial Office (CTO). CTO was asked to guarantee the compliance with the regulatory requirements of CR and to provide a central support for participating sites in conducting Clinical Trials (CTs), fostering a collaboration between them.

Methods and results: When CTO was created 4 CTs were ongoing, mainly managed by investigators. The increasing strictness imposed by CR regulations, the possibility to increase the numbers of CTs in collaboration with other cooperative groups and a greater interest from pharmaceutical companies in supporting independent research, arose the need of an internal unity for CR. This need led to the creation of a CTO that fully manages all Clinical Operation Activities: feasibility, regulatory submissions, startup, monitoring, site's training and support, pharmacovigilance, data management. A recent activities analysis demonstrated how this model of organization has led to a greater competitiveness of the group. On 2015 ISG promotes 20 CTs in more than 130 centers, with an increase of 5 times in the last 5 years. Between ongoing CTs 80% (n = 16) are interventional and 20% (n = 4) observational and the 50% (n = 8) of the interventional studies are supported by pharmaceutical companies.

Conclusion: Contribution of ISG researchers to the international community was very attractive from the earliest years of the ISG creation. Recent changes in the international CR scenario, which requires hard-and-fast methodology and in depth knowledge and expertise, has highlighted the need to identify expert professionals who manage and run the multifaceted aspects of CTs. The productive collaboration between clinicians and CTO has enabled to support the increasing CR activity with high scientific and ethical standards.Next to an increase in the number of CTs, participating sites and overall enrolled patients, this new ISG organization has reached an important trend about the speeding up of CR. Reduced time for regulatory approvals, immediate and continuous support to sites, a speed in data collecting and analyzing are making the ISG CR increasingly attractive to pharmaceutical industries, despite of the problems that have characterized the independent CR in the last years.

R44 Cancer Registries Underestimate both the Type of Disease and also Number of Cases due to Pollution

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Background and target: Inhabitants in polluted areas often request that Cancer Registries (CR) be established in order to check the alleged increased health risk in their areas. This request is understandable, but it is also misleading, because environmental pollution can also be caused by many non-carcinogenic substances. The exclusive use of CR does not represent the overall amount of diseases attributable to all non-carcinogenic pollutants which can only be achieved by taking into account other sources of data (such as mortality, morbidity, etc.) which are already available in the local health agencies (ASL) and regional health departments.

Methods: Some studies conducted on populations living in industrial areas (such as steelplants, SENTIERI study) were reviewed. Both pollution and health Indicators (cancer and non-cancer) were available. The excess of non-cancer cases attributable to pollution were estimated.

Results: The analysis concerning tumors underestimated 40-97% of cases attributable to environmental pollutant factors. The SENTIERI study considered as non-cancerous 57% of total deaths attributable to pollution (707 cases per year). This underestimation can be explained as: tumors are relatively rare in the population and are often competing with other diseases; tumors have a long latency period and they are prevalently limited to the effect of carcinogenic agents only. CR, by definition, exclude the large number of all non-neoplastic diseases; CR are very expensive tools usually aimed at clinical trials rather than environmental issues; CR provide reliable results only after 3 to 5 years from their establishment; updates are not always timely; CR in Italy only cover 51% of the population; moreover, a large number of people living in polluted areas are not covered by CR.

Conclusions: CR are extremely sophisticated and useful tools in public health, but their *exclusive* use in polluted areas can cause two miscalculations: both underestimation and under evaluation of the overall risks related to type of diseases and to the total number of patients attributable to environmental contamination at local and national level. These errors may also block both primary prevention and law applications. Finally, in order to estimate the exact number of non-neoplastic cases attributable to environmental pollution, we suggested adopting the scientific approach normally used in CR and we recommend that CR be avoided as an exclusive tool in polluted areas.

R45 Tumor incidence analysis in contaminated site Trento North. The data of Sentieri Project

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Objectives: Sentieri Project, coordinated by National Institute of Health with involvement of the Italian Association of Cancer Registries regards the analysis of mortality, cancer incidence and hospital admissions in populations living near centers/areas with significant environmental contamination as to be recognized as "sites of national interest "(SIN). The only one SIN in Trentino province is Trento North, site until the early 80s, of three chemical plants, and with evidence of contamination of soil and groundwater by organic lead and polycyclic aromatic hydrocarbons. Cancer incidence data in residents of municipality of Trento in the period 1996-2005 are presented and discussed.

Material and methods: For SIN Trento north, cancer incidence in municipality of Trento was calculated in reference to the center-north of Italy, considering the cases registered by the cancer registry of the province of Trento 1996-2005. Standardized incidence rate (SIR) with 90% CI for all cancers and specified sites, was computed distinguishing between men and women

Results: For all cancers, excluding non-melanoma skin, residents in Trento, men and women, have a SIR lower than the expected with a statistically significant difference. Men have statistically significant excess for Esophagus (219, 181-262), Larynx (119, 100-142), Gallbladder (137, 102-180) and Melanoma (136, 113 to 162); women have statistically significant excess for Hodgkin Lymphoma. We collaterally have an excess although not statistically significant, in men and women, with respect to mortality and hospitalization for chronic degenerative neurological diseases.

Conclusions: Cancer excess found in residents in the town of Trento can find explanations other than a causal environmental hypothesis that can not directly emerge considering the study design of the Sentieri project whereas the incidence data for all cancers lower than expected, could depend on the fact that the analysis was conducted at the whole Municipality and not at suburban level (the polluted site), probably causing the effect to dilute and reduce the percentage of incidence and consequently leading to a misjudgement in data interpretation. An in-depth analysis about Hodgkin Lymphomas is in each case to be considered appropriate. A study on the resident population around the SIN Trento North in the 70s has to be evaluated for the feasibility, also as regard other available data (e.g. chronic neurological diseases, Parkinson's Disease).

R46 Patients with Neuroendocrine Neoplasms: prevalence of Ectopic Cushing's Syndrome (ECS) in our experience

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Introduction: Ectopic Cushing syndrome (ECS) has been described as a rare syndrome in patients (pts) with neuroendocrine neoplasms (NENs)

Aim(s): The effective prevalence of ECS in NENs has not been extensively studied.

Materials and methods: We evaluated 198 pts (112 females, mean age 46 ± 19 yrs) with NENs, referred at our Department from 2000 and 2015: 12 gastric, 7 duodenal, 50 pancreatic (1 glucagonoma, 2 insulinoma), 23 small intestinal, 26 appendiceal, 14 colonal, 24 lung, 7 unknown primary origin (UPO), 2 nasal, 28 Merkel, 2 ovarian, 1 uterus, 2 laryngeal.

Results: 20 (10%) pts had sporadic functioning NEN (7 carcinoid syndrome, 5 gastrinoma, 3 insulinoma, 3 ECS, 2 5HIAA secretion) and 178 non-functioning NENs. 3 pts (44 + /-17 yrs, 2 females, 1,5% of total and 15% among functioning NENs) had ECS: 1 atypical lung carcinoid (stage 4), 2 UPO (stage 4). In first case, patient developed acute ipokaliemia and hypertension, before diagnosis of carcinoid, and was treated with somatostatin analogues, mitotane and metirapone; pt is still alive with good control of hypercortisolermia 22 months after diagnosis. Pts with UPO, treated with chemotherapy, died both rapidly, 2 and 5 months after ECS diagnosis.

Conclusion: 10% of NENs pts in our experience had functioning NEN, whereas only 1,5% develop an ECS. Pts with ECS had often bad prognosis, but our findings suggest that, if suspected and rapidly treated, it could be compatible with long survival.

R47 Secondary breast cancer prevention: it's time to get moving!

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Background: Physical activity is an important determinant of beneficial health conditions among cancer survivors, including breast cancer. Many literature data showed the deleterious associations between overweight, low levels of physical activity and poor prognosis of breast cancer. Physical activity (PA) is not contraindicated in breast cancer (BC) patients, on the contrary, there are growing evidences of PA positive effects on prognosis and quality of life, supporting more and more the claim to implement it in the daily care.

Methods: Since January 2014 we have prospectively enrolled all high risk patients between 18 and 70 years treated to our department for invasive early-stage breast cancer (stage I-III). High risk has been defined by one or more of the following inclusion criteria: body mass index (BMI) > 25, diagnosis of metabolic syndrome, increased level of blood testosterone and/or insulin. All high risk patients receive a periodical personalized educational intervention by a physiatrist for physical activity and by a nutritionist for a mediterranean diet (low in animals fat and enriched of fibers, fruits and vegetables).

Results: From 300 BC patients, we have identified 47 high risk BC patients; all of them have been accepted the educational interventions. At the time of analysis the median age was 57 years (range 30-70). 41/47 women (87%) had a BMI over 25 and specifically 40% were roundly obese (BMI > 30). 21% of women had a previous diagnosis of metabolic syndrome, while 15% of them had a normal weight but were enrolled for increased level of insulin and testosterone (11% and 4%, respectively). Most of tumors have positive hormonal receptors (luminal phenotype, 84.8%) and high proliferative index (Mib-1 > 20%, 66% of cases). Lymph nodes were disease-positive in 54.3% of cases. Despite the higher incidence of luminal BC, 66% of patients underwent to chemotherapy while only 32% of subjects received endocrine therapy alone. To date all patients are alive and free of disease.

Conclusion: Our preliminary analysis suggest that tumors of obese women have usually negative prognostic features as higher incidence of positive nodes and markers of biological aggressiveness. Nowadays, weight management with diet and lifestyle should be an integral part of the treatment of women with BC, using a multidisciplinary and personalized approach.

R48 The role of CEUS in the differential diagnosis of superficial lymphadenopathy: preliminary results of a prospective study

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Aim: The aim of the study is to evaluate the role and the sensitivity of contrast enhanced ultrasound (CEUS)in comparison with conventional ultrasound (US-grayscale and Doppler methods) to differentiate benign and malignant superficial lymphadenopathy.

Methods: In a prospective study,up to now 25 consecutive patients with superficial lymphadenopathy (lateral-cervical, axillary and inguinal) were enrolled and examined with US (grayscale, color-Doppler-Power and E-flow) and CEUS. The suspect of malignancy was based on various gray scale - US diagnostic criteria, such as shape, border, echogenicity, calcification, necrosis, or vascularization pattern by Doppler US examination. CEUS was performed with 2.4 ml intravenous bolus of contrast agent SonoVue. Final diagnosis was confirmed by histology (FNAB or surgical speciemens examination).

Results: Of the 25 histologically examined lymph nodes, 11 were benign (reactive and inflammatory, 3 of them due to tuberculosis), 14 were malignant (8 metastases and 6 lymphomas). Sensitivity, specificity and accuracy of US conventional was 51-57-55% respectively. CEUS showed intense homogeneous enhancement in 7 of the 11 benign lymph nodes; an intense but inhomogeneous pattern ("rotten wood pattern") in 3 tuberculous lymph nodes; an attenuated and homogeneous enhancement in a single

lymph node. CEUS showed four different contrast patterns in malignant lymph nodes: a) inhomogeneous enhancement with multiple small non-perfused areas in 7 of 7 metastases; b) intense and homogeneous enhancement (similar to reactive lymph nodes) in 2 of 5 lymphomas; c) inhomogeneous and dotted enhancement ("snowstorm pattern") in 2 of 5 lymphomas; d) absence of perfusion in 1 of 5 lymphomas. Specificity, sensitivity and accuracy of CEUS were the 84-79-80% respectively.

Conclusions: These preliminary results of a trials in progress indicate that the use of CEUS can increases the degree of diagnostic accuracy of conventional characterization of superficial lymphadenopathy.

R49 Integrating mobile Health (mHealth) Information Technology for the safe administration of chemotherapy (CT)

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Background: The process of prescribing, preparing, and administering current chemotherapy treatments is complex, and prescription and administration errors are still common. Numerous organizations (FDA, IOM,etc) have highlighted that the potential benefits of the introduction of electronic and mHealth information technologies, to support the safe delivery of intravenous chemotherapy, could be exponential in the context of a highly integrated computerized system.

Materials and methods: A Safe Therapy Mobile (STM) System, fully integrated with the electronic oncological patient record (eOPR), has been developed for the safe delivery of intravenous CT. eOPR includes a library of all the CT regimens used and supports the computerized prescriber order entry (CPOE). This details dose, dilution volume, sequence, and infusion rate of every single CT and ancillary drug, which is automatically associated with a specific barcode. The other components of the system are: a barcode-assisted medication administration (BCMA) system (which includes barcoded drug labels, disposable RFID bracelets for patients, RFID tags for nurses), a radio frequency identification (RFID)/barcode reader and a tablet. The tablet communicates via Bluetooth with the RFID/barcode reader and via Wi-Fi with the eOPR, in order to import the CPOE and export the electronic medication administration records (eMARs), which contains the tracking data. The usability and acceptability of the system was investigated by means of a modified questionnaire administered to nurses.

Results: STM System The system never failed to match the patient/nurse/drug sequence association correctly, and proved to be accurate and reliable in tracing and recording the entire administration process. Nurses had a positive perception of all of the dimensions considered in the questionnaire (the quality of their working life, and the usefulness and ease of use of the system), except for the fact that the system appeared to slow down bedside operations, although no significant objective differences in the duration of chemotherapy administration were found after the system was introduced.

Conclusions: The STM system which is fully integrated with our complex and composite information system, guarantees privacy, security, interoperability and real-time communications, and is successfully used from the last 12 months at a busy day hospital for adult oncological patients.

R50 "Share & Meet" project: an innovative telemedicine solution for remotization of pathology and e-oncology

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Background: The incidence of tumors in developing countries is dramatically increasing;the ability to provide early diagnosis, treatments, follow-up care and the availability of reliable epidemiological data has a strong impact on the cancer survival. Although telemedicine implementation largely remains a privilege of developed countries,it could be of great utility and efficacy in developing countries lacking appropriate health care facilities by allowing for the performance of good level health care practices. There is currently a longstanding partnership between IRST and the Bugando Medical Centre - Mwanza, Tanzania (BMC)."Share & Meet" project includes a novel telematics platform oriented to oncology and its related branches. We are developing the project between BMC departments and Italian stakeholders with cooperative programs including training of medical staff through e-learning programs, remote pathology diagnosis and other e-oncology applications

Material and methods: After some years of on-field work,in synergy with the BMC pathology lab we are launching the telepathology facility. We carried out several experimental sessions to investigate the compatibility of Menarini D-Sight+ and Aperio eSlide Manager telepathology web applications with our telematics platform, together with other concurrent telemedicine applications such as Virtual Private Networking, conference calling, LOG80 digital medical record, webconference for e-learning, Internet browsing.

Results: The statistical analysis on the detected data confirmed the expected behavior of the platform in terms of transmission parameters optimization, with a strong action of transmission defects compensation and bandwidth enhancement tools. The subjective feedback from medical pathologist performing remote diagnostic activity is very good in standard operating conditions and remains acceptable introducing strong shortage of transmission resources. The goodness of real-time audio/video streaming depends on the application used and the transmission regimen. The operational efficiency of LOG80 is quite impacted in a very low quality transmission regimen

Conclusions: We validated the system in a wide range of conditions.The pathology images remotely viewed are compliant with the diagnostic requirements in terms of definition and magnification. Share&Meet is characterized by a high level of innovation which increases efficiency and efficacy of health practices and can boost the use of telemedicine in low income countries.

R51 Thoracentesis in cancer patients with severe thrombocytopenia: ultrasound guide improves safety

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Background: Patients with severe thrombocytopenia are considered at risk for bleeding during invasive procedure like thoracentesis. In such patients, ultrasound (US) – guided thoracentesis may be a valid approach, however there is lack of data on the safety and efficacy of US-guided thoracentesis performed in cancer patients with severe thrombocytopenia.

Materials and methods: We retrospectively analyzed the efficacy and safety of thoracentesis in cancer patients including those with severe thrombocytopenia, defined as platelet count ≤30 109/L From January 2005 to December 2011, 441 patients with cancer underwent thoracentesis. Procedures were divided into two groups: Group A: thoracentesis performed without US-guidance and Group B: thoracentesis performed with US –guidance. All procedures were evaluated for hemorrhagic complications as defined by the National Institutes of Health Common Terminology Criteria for Adverse Events.

Results: A total of 441 consecutive evaluable patients that underwent thoracentesis were included in the present study, in 310 cases thoracentesis (70.29%) was performed with US-guidance, while in 131 (29.71%) without it. Forty-one of 441 patients (9.30%), had severe trombocytopenia, of these, 9 patients were in Group A and 32 in Group B. There were three hemorrhagic complications out of 41 procedures performed in patients with severe thrombocytopenia: all these 3 complications were in group A (1 grade, 1 and 2 grade 2), zero hemorrhagic complications were registered in group B.

Discussion: US-guided thoracecntesis is a safe and effective approach in cancer patients with severe thrombocytopenia, and our data indicate that US-guidance is associated with decreased risk of bleeding complication with thoracentesis in patients with severe thrombocytopenia.

R52 Dysgeusia in oncological patients: issues and solutions in evaluation

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As part of a study protocol of National Cancer Institute (INT) about creation of a personalized nutrition program for Hospice patients to respond to taste alterations, the Pharmacy Department has been asked to provide support in evaluating the extent of dysgeusia, characteristic of many patients undergoing chemo / radiotherapy. Consultation of literature, Guidelines on Somatologic Diagnosis of the Italian Society of Hospital Otolaryngologists; evaluation of the most suitable detection procedure to be used. Subjective gustometria is the only technique used in clinical practice to diagnose dysgeusia. Two types of gustometria can be recognised: based on chemical tests and electrical tests. The evaluation of taste with chemical tests consists of putting solutions of the 4 tastes (sweetness, saltiness, bitterness, sourness) into contact with the taste receptors located on the tongue. This kind of test is challenging and interpreting

the results is not always easy. Much more used is elettrogustometria, with more reliable results. However, considering INT patients, chemical testing seems to be the most suitable procedure. Usually, the substances used are: sucrose for sweet, sodium chloride for salty, quinine hydrochloride for bitter (not available, replaced with magnesium sulphate) and citric acid for acid. The Pharmacy prepared solutions containing increasing concentrations of those standards, starting from the maximum solubility of the substances. The solutions were blind-tested on 10 non-ill volunteers in order to choose the 4 final concentrations that will be used on INT patients. 50 patients from Hospice and Palliative Care Department will be evaluated, with 3 dedicated nurses. After placing at least 10 drops of the solution on the tongue, the patient will be asked which kind of taste he/she perceived. Every taste will be followed by rinsing with water and a 1-hour break. Before starting the test, the patient's oral/perioral region will be checked, as well as the mouth pH: if the pH is not basic, the alkalinization will be obtained with rinsing the mouth with bicarbonate solutions. Even if the number of pharmacovigilance signaling is increasing (167 reports between 2005-2014), dysgeusia is often neglected. However, its evaluation is important in order to improve patients' quality of life and this will be the aim of the next observational study that will take place in the Hospice of INT.

R53 The role of pharmacists in prevention and management of extravasation

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Extravasation is a phenomenon characterized by drug leakage from vascular bed. Factors that may contribute are: size and condition of vessels, site, sequence and rate of infusions, drugs characteristics, patient's pre-existing conditions. Epidemiological data consider extravasation as a rare event (prevalence 1%-6.5%), suggesting that this condition is often not reported or recognized. In addition to this, the information available in literature is miscellaneous and lacks consistent evidence. Therefore, Pharmacy Department of National Cancer Institute (INT) decided it was necessary to define standard methods to manage extravasation and to provide specific guidelines. Consultation of SIFO and ESMO Guidelines, relevant scientific literature, drugs technical sheets, website extravasation.org.uk, and (for contrast media) ESUR Guidelines. All experiences collected in INT. The best way to treat extravasation is prevention: staff should be trained on drug administration and extravasation management and patients encouraged to report any discomfort. The general treatment of extravasation includes: early detection, stopping infusion, aspirating as much drug as possible, defining affected area with a dermographic pencil, placing the limb in elevated position, calling the doctor and the pharmacist for a shared assessment of the situation and prescribing a treatment if needed. The extravasation should then be recorded on a dedicated form, a copy of which goes to Pharmacy, which is involved in all the aspects of the process. The recommended antidotes in case of extravasation are: Hyaluronidase, DMSO, Sodium Thiosulfate and Dexrazoxane. Each of these is specific for some drugs and not all of them entail administering an antidote. Regarding this, the INT Pharmacy provided specific Guidelines and a first aid kit. At present, considering 135.000 chemotherapies/year, the cases of extravasation reported in INT are 51: 21 in 2013, 20 in 2014 and 12 in 2015. Of these, 33 were treated with an antidote, two of which required physical therapy as well. Extravasation is seen as an example of "nursing malpractice" and for this reason is often not reported. Instead of being blamed, the nurse should appear as a "detector" and motivated to report the problem early, so as to reduce the risk of serious problems for the patient. The support provided by the INT Pharmacy aims at this: ensuring greater security for healthcare workers, patients and the facility itself, especially in legal terms.

R54 Privileges in medical oncology: the model of the Sicilian Region

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Background: The privileges, within the meaning of Anglo-Saxon, define the degree of complexity of the procedures that each operator relating to a health care facility is authorized to do and / or coordinate; they reflect the levels of competence achieved and the ability to mantain and / or implement them. The achievement of a privilege, representing an accreditation of the operator in respect of the health facility in which he works.The conferment of privileges can ensure that the benefit to the patient will always play by the doctor who has the expertise to carry it out, to promote the professional development of each individual physician and to motivate individual professionals to grow over time clarifying the starting point and the future expectations.

Methods: A joint working group AGENAS / Sicilian Department of Health / Oncology Group of the Province of Catania has developed, implemented and validated a model of clinical governance of privileges

Results: The Working Group has defined that the "privileges" in medical oncology are classifiable in three distinct functional areas, mutually interrelated, in the to ensure the highest quality of service rendered to the patients. These functional areas are the following: a) clinical care; b) management; c) ??training and research: activities of organizing and conducting training courses, seminars and conferences; In each area the privilege are divided into: a) Class I or "basal, b) Class II or "special".Only for the areas "Management" and "education and research" have been provided privileges of Category III or "emergency". The working Group also identified the three levels of autonomy Autonomy to be allocated to the oncologists: 1st) Full autonomy: This level provides that the activities or the procedure can be performed by the physician in full autonomy; 2nd) Authorized with superivision;3rd) Unauthorized: This level requires that the physician is not authorized to conduct firsthand activity or procedure, but that it can assist the performance of the same in the presence of a doctor who has been given the level autonomy. The Department of Health of the Sicilian Region has determined the adoption by law of the model by all the oncology institutions in the Region.

Conclusion: To our knownledge our model is the first example of a law-based adoption of a clinical governance system of Privileges in Medical Oncology in a regional context.

R55 Style modification in breast and Colorectal Cancer Patients: results of a pilot study Long-Survivors

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Observational evidence suggests that patients with breast and colon cancer who engage in moderate levels of physical activity after diagnosis have up to a 50% lower risk of recurrence compared with inactive individuals. Furthermore, excess body weight continues to be associated with an increased risk of breast cancer recurrence, and preliminary data suggest that weight gain after breast cancer diagnosis may be associated also with a worse prognosis. Since March 2012, 35 early stage breast and 3 colorectal cancer patients (pts) have been enrolled in a nutritional and physical activity intervention observational study, as previously described. Briefly, a personalized nutritional intervention and regular leisure-time exercises or walking groups have been established. Pts have been followed monthly by a dietitian and the psychologist in order to verify compliance, strengthen motivation and monitor the weight trend. After six months of treatment all the parameters (and measurements at the start of treatment) are reassessed in order to evaluate the efficacy of the intervention. Median age is 53 years, 35 female and 3 male, median BMI 28. Nineteen out of 31 Breast cancer pts had been treated with chemotherapy followed by hormonotherapy and 7 had only hormonotherapy and 5 only chemotherapy. Up to now 21 pts have been fully evaluated. Adherence to the program was 65%. Non adherence was caused by the non motivated psychological attitude in 9 and by job and family problems in 4. In the patients who completed the program the median weight loss was 6,2 Kg (1,7-9,5). Twenty-three of the 25 compliant pts referred a satisfaction not only in their body image and self confidence but also a better quality of life throughout the 6 months' intervention.. Most of them is continuing the physical activity of the study by themselves proving this project has changed in part their life-style. Supported by Fondazione Peretti.

R56 X-Rays absorption evaluation in cancer patients submitted to cosmeceutical prophylaxis with smoothing emulsion and sun protecion factor cream during radiotherapy

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Background: Many oncological departments take care not only of cancer but of skin damage due to radiotherapy. During radiotherapic treatments cosmeceuticals treatments are used with smoothing emulsion and high sun protection factor (SPF) in prophylaxis of radiodermatitis. This study evaluates if these products can reduce x-rays absorption.

Matherials and methods: The study evaluates x-rays absorption before on plexigas and then on pig's skin. Varian mod Clinac 600-CD with acceleration's power 6MV is used;

Farmer IBA mod.FC65-P 0,65cm^3 as ionization chamber and Scanditronix-Wellhofer mod. Dose 1 as electromer were used to measure the dose. T trasmission as ratio between dose measured on plexigas and plexigas with smoothing emulsion and SPF cream and on pig's skin and pig's skin with the cosmeceutical products is evaluated.

Results: T trasmission is not statistically significant in plexigas with smoothing emulsion and SPF cream or without these cosmeceutical products. T trasmission is statistically significant in pig's skin with smoothing emulsion and SPF cream; it is more than in pig's skin without SPF cream

Conclusions: Cosmeceuticals products used for prophylaxis of radiodermatitis don't block radiations useful for treatment.

R57 Molecular diagnosis in metastatic cancer. molise experience

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Background: The Molecular Oncogenetic Laboratory's arises to support medical therapy for metastatic cancer and to benefit cancer patients, come from the Oncology Units of Molise Hospitals, of "target therapy" for the treatment of colorectal, lung, breast and gastric cancers, melanoma and CML.

Materials/methods: The laboratory has two sections: FISH and molecular. By FISH we assess the status of *HER2* in breast and gastric cancer with Leica BOND system HER2 FISH probes LSI® HER2/CEP17® FISH PathVysion®. The processing of samples is standardized in a semi-automatic system and the interpretation of fluorescent signals is done according to the reccomendations Asco/Cap 2013. By FISH, in manual mode, we evaluate the translocation BCR/ABL in CML. Real Time-PCR, by kits EntroGene®, is used to assess the status of all-*RAS*, *EGFR* and *BRAF* genes respectively in colorectal carcinoma, lung adenocarcinoma and melanoma. RT-PCR involve the use of mutation-specific probes, that due to cancer genetics heterogeneity, are not always able to detect less frequent mutations. The cyto-histological samples used are evaluated for cellularity and suitability analysis. The protocols used comply with the recommendations AIOM/SIAPEC-IAP.

Results: From 2014 to date we have been analyzed 116 samples. 46 subjected to FISH (41 breast and 5 stomach). In 32 cases FISH resulted negative, in 9 positive and 5 samples were unsuitable for analysis. 6 samples were tested for diagnosis or follow-up of LMC. In 3 was present t (9; 22). In molecular biology, we evaluated 64 samples (12 *EGFR*, 13 *BRAF*, 39 *RAS*). 43 samples came from primary cancer and 21 from metastases. The results were: 2 mutated (ex19del) and 10 wt for *EGFR*; 6 mutated (V600E) and 7 wt for *BRAF*; 22 mutated (9 for G12D, 3 for G12V and G13D, 2 for G12a and A146X, 1 for Q61R, G13C and G13V) and 16 wt for *KRAS;* 1 *NRAS* mutated (Q61R).

Conclusion: As soon as possible we will expand the panel of oncogenes with FISH probes (MM, LLA, LLC, *ALK* rearrangements). It is hoped that the Laboratory will become a reference center for the entire region Molise. The laboratory adheres to programs of National Quality Control for the certification of scientific procedures and diagnostic data products.

R58 Feasibility of bendamustine in elderly patients with b-cell non hodgkin lymphomas

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Background: Bendamustine, an old powerful alkylating agent with potential antimetabolite properties, has demonstrated efficacy in patients (pts) with indolent and aggressive B cell non-Hodgkin lymphomas (NHLs), including chronic lymphocytic leukemia (CLL). Bendamustine alone or in combination with rituximab, is associated with haematologic toxicity and risk of infections: this is particularly important in the elderly pts, more susceptible than the younger population. We want evaluate the feasibility of bendamustine in 1st line and at relapse in NHL in pts over 65 years, in which incidence increases markedly with age.

Material and methods: Between January 2012 and December 2014, 13 outpatients, 7 F (54%) and 6 M (46%) with NHLs, aged 66-88 years (median 77) were admitted to SOC Oncologia in Santo Spirito Hospital of Casale Monferrato. There were not frail pts at evaluation with G8 test performed at the first interview. Charlston Comorbidity Index (CCI) score was 3-7 (median 4) determined more advanced age than for the concomitant illness. 2 women were chemotreated in adiuvant setting with CMF for breast cancer some years before. ECOG PS was 0 (38%) or 1 (62%). 6 pts (46%) had large cell, 3 (23%) follicular NHLs and 4 (31%) LLC. Stage: IIE 1 pt (8%), III 9 (69%), IV 3 (23%). 4 pts (31%) were pretreated and in relapse. All were treated with bendamustine 60-90 mg/m^2 (in relation to CCI, G8 score and physician's expertise), 60-minutes intravenous infusion, days 1 and 2 every 4 weeks for 4-6 courses, 11 (85%) in association with rituximab. We want evaluate safety and tolerability of bendamustine in NHLs in 1st and 2nd line in elderly pts. Antiemetic and opportunistic infections prophylaxis was performed.

Results: Complete and partial remission was observed respectively in 7 (54%) and 2 (15%) pts, progression in 3 (23%). The treatment was well tolerated and it did not affected the quality of life. Neutropenia was the most frequently reported toxicity with grade 3 in 31% of all treatment cycles. Other grade 3-4 toxic effects were rather low, with anemia in 7% and thrombocytopenia in 2% of the total treatment cycle. 1 pt developed herpes zoster.

Conclusions: Bendamustine treatment is associated with a good therapeutic performance and are increasing use alone or in combination with rituximab for its activities in lymphoid malignancies with high response rate. In elderly setting this drug can be considered safety and well tolerated both in 1st line and in retreatment.

R59 ONC-2014-001: An open-label phase II study of regorafenib in patients with metastatic solid tumors who have progressed after standard therapy - RESOUND

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Background: Tumor-associated angiogenesis is one of the essential hallmarks in cancer development and metastasis. With the advancement in understanding of tumor angiogenesis and VEGF, a number of agents have been developed to target VEGF for treatment of cancer. These targeted agents can affect downstream VEGF signal transduction by unique mechanisms at different cellular and extracellular levels. Regorafenib is an orally administered multikinase inhibitor showing non-specific binding to several intracellular kinases, with potent inhibitory activity against VEGF receptors 1–3 (VEGFR1, VEGFR2, and VEGFR3), PDGFRB, FGFR1, RAF, TIE2, and the mutant oncogenic kinases KIT, RET, and BRAF. The Italian medicines agency (AIFA) has approved regorafenib for the treatment of colorectal cancer and GIST, but clinical activity was observed also in other cancer types. Our aim is to investigate the potential role of this multikinase inhibitor in different types of cancer after failure of standard therapies.

Methods: Enrollment into this single arm, single-stage, phase II trial (ONC-2014-001) has begun. Eligible patients must have surgically unresectable locally advanced or metastatic melanoma, sarcoma (angio-, leiomyo- and sinovial sarcoma) pancreatic or ovarian cancer refractory to available standard treatment. A planned amendment will include shortly also a court of B2-B3 thimoma and thimic carcinomas. Other inclusion criteria include: ECOG performance score <2; adequate bone marrow, liver and kidney functions and at least one measurable lesion according to RECIST 1.1. Patients will be excluded if they experienced arterial or venous thrombo-embolic events within the 6 months before start of study medication. Each cohort of tumors will be assessed by itself. As of May 1st, 2015, 6 of the planned 80 pts have been enrolled to receive regorafenib 160 mg orally once a day, 3 weeks on/1 week off. Pts are evaluated by CT or MRI scan at 8-week intervals. The primary endpoint is to evaluate efficacy of regorafenib in each tumor cohort in terms of 2-month progression-free survival. Secondary endpoints include overall survival and safety. Treatment continues until confirmed disease progression or unacceptable toxicity. Patients discontinued from study treatment will be followed for survival. This trial is expected to complete enrollment by October 2017, and no interim analyses are planned before.
Clinical trial information: NCT01892527.

R60 AIFA anti-tumor drugs platform break: a good clinical management

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Background: When the AIFA (Agenzia Italiana del Farmaco) online drugs prescription program was broken in December 2013, every Italian oncology ward didn't have the means to record the new prescriptions of monitored anti-tumor drugs on the program itself, as required by the national guidelines. This system damage also prevented the access to the old data of patients still in treatment. At the Oncology Day Hospital of Guastalla, after this event a new inner database was created in order to record all the new prescriptions. For patients who began anti-tumor treatments before the break, old data prescriptions were needed to continue the chemotherapy. These

were taken from the paper medical records and inserted in the database. AIFA did not give any guideline or direction to follow after the program break. April 2014, AIFA created a completely new platform for recording drug prescriptions. From that moment, every Oncology Unit had to insert in the new program both all the drugs prescribed during previous 16 months and the new prescriptions not later than December 2014.

Materials and methods: In our Oncology DayHospitalin Guastalla, a target working group was created in order to perform this job. The group was composed by an oncologist and a pharmacist, both supervised by their respective chiefs. They met twice a week to record all the pending data, working from 8.30 to 14.The work was very hard because of the inadequate AIFA guidelines and the delayed answers to team queries. Both oncology and pharmaceutical Department suffered from the absence of a single professional referent . For each patient and for each drug, the working group had to collect the natural history of the disease, the time of progression and the number of chemotherapy cycles. This analysis was necessary for every drug in order to obtain the pay back of the costs of the treatment itself. In fact, there are different types of pay back in relation to the cancer diagnosis, the kind of drug and the results of the treatment.

Results: The working team succeeded in completing the AIFA new drug prescription program before the deadline. The local Health Trust received the expected pay back for the prescribed treatments.

Conclusions: This experience is an example of an integrative work between professionals from different areas. Successful results could be obtained thanks to the good management skills of the professionals involved, despite the lack of guidelines and support from AIFA.

R61 The liquid biopsy as a new ally to fight cancer?

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Background: The new methods for molecular diagnosis let us to detect circulating tumor cells(CTCs)in peripheral blood. The so called "liquid biopsy" is a modern uninvasive approach really promising: it offers the great potential to better understand the biology of metastasis and resistance to targeted therapies. Thanks to the analysis of these cells we could follow our patients over time and, for example, identify them in an early-stage of reccurence. The main problem is that CTCs are very hard to find because they are rare, and the amount of available sample is limited (mainly due to extraction and conservation process). The aim of our work is to dose levels of mutatedCTCs in circulating plasma of patients suffering from cancer of different site. The primary objective is evaluate the agreement between mutational status of the primary tumor (or metastatic lesion) and the blood mutatedCTCs levels; the second endpoint is the correlation with clinical response parameters such as TTPorRFS.

Patients and methods: This is an open, multicenter study.From1st May 2015 we enrolled patients (accrual is 50) suffering from metastatic melanoma, colorectal cancer and lung. Each patient was analysed for BRAF, KRAS, EGFR mutational status respectively, performed on primary or metastatic lesion according to international guidelines for GPC.We took a whole blood sample (5ml) from each patient at baseline, after each administration of chemotherapy and every month of follow up. Each blood sample was used for the collection of plasma, obtained by two following centrifugations (2500g×10min, at 4°C). The recovered plasma was then divided into1m Lvials and stored at-80° Cup to the subsequent extraction of CTCs. The extraction of circulating DNA was carried out manually using a commercial kit, whilst the assessment of the DNA obtained was carried out by the technique of RealTime PCR.

Results: the study has just started, but we expect to obtain promising data, according to the results already reported in the literature from several preclinical studies. The main goal is to correlate the data obtained to clinical outcome of our patients, in order to allow the early diagnosis of relapses due to the mechanisms of resistance to molecular targeted therapies.

Conclusions: We expect to find a statistically significant data, and even if the number of patient is limited (only 50) we think it should be enough to see if there's some clinical correlation between CTCs levels and clinical outcome and, eventually, confirm them in larger clinical trials.

R62 Multicenter, randomized, phase II, double-blind trial of a combination of anthocyanins and curcumin for colon cancer prevention in subjects with colorectal adenoma. The MIRACOL study

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Background: Evidence from epidemiological studies and clinical trials indicates that removal of AP decreases the incidence of CRC. Nearly 70% incidence of CRC, has been linked to diet. Among dietary agents, anthocyanins and curcumin represent reliable chemopreventive candidates due to their capacity of modulating key steps of inflammatory processes, cell proliferation and tumor progression. In recent studies in CRC patients, anthocyanins administered for 7 days were dose-dependently effective in reducing the proliferation index Ki-67 (Thomasset S et al, CaPR 2009) and a group of subjects treated with curcumin at the dose of 4gr for 4 weeks, demonstrated a significant reduction of ACF numbers (Carroll RE et al, CaPR 2011). Here we propose to test a combination Mirtoselect® (*Vaccinium myrtillus L.* extract =36% of anthocyanins, Indena Spa) with a bioavailable form of curcumin, Meriva® (curcumin phospholipids =18% =22% of curcuminoids, Indena Spa).

Methods: Based on a previous window of opportunity trial of allopurinol (Puntoni M et al, CaPR 2013), we designed a presurgical, double-blind, placebo-controlled, randomized, phase II trial in patients with colorectal AP. After baseline colonoscopy and biopsies of the target polyp and adjacent normal mucosa, 100 subjects with histological confirmation of AP >1 cm will be assigned (50 per arm) to either placebo or Mirtoselect® 2 tablets/die (500mg each) + Meriva® 2 tablets/die (500mg each) treatment for 4 weeks before polipectomy. The primary endpoint is the IHC nuclear expression of β-catenin as a surrogate for colon carcinogenesis. The study is 85% powered to detect an absolute difference of 10% between arms in the change (pre-post treatment) of β-catenin levels in adenoma tissue. Secondary endpoints are Ki-67, p53, NFkβ, and evaluation of treatment tolerability. The study is ongoing in 3 Italian sites, while a centralized laboratory in Germany will assess the plasma concentrations of compounds in a subgroup of subjects.

Trial status: This trial is registered with ClinicalTrials.gov NCT01948661. Enrollment started in March 2014: 18 subjects has been screened, 15 subjects were eligible and have been randomized. So far no AE have been reported. Patients' accrual is expected to be completed in March 2016.

Conclusion: This study could better elucidate molecular mechanisms and provide a strong rationale for the use of curcuminoids and anthocyanins in a phase III trial to reduce the incidence of CRC in individuals at increased risk.

R63 Follow up to 10 years and pathologic complete response (pCR) after neoadjuvant chemotherapy in locally advanced breast cancer patients treated from 2005 to 2010: a monocentric experience

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Aim: There is no doubt about the role of neoadjuvant chemotherapy with a combination of anthracyclines and taxanes to obtain a pathological response; but has the pathological response a real valour on overall survival (OS)? In literature a meta-regression-analisys of Amoroso (2014) did not support the use of pCR as surrogate endopoint for DFS and OS in unselected BC patients. We show our little experience of clinical practice with a median follow up of 10 years.

Methods: From 2005 to 2010 in our day hospital we treated 32 patients with locally advanced breast cancer (stage III) documented histologically by tru-cut, pre- and post-menopausal women (range age 72-23 years) with carcinomatous mastitis(6 patients) or nodule clinically superior to 5 cm and clinically positive axillary nodes. This group includes 4 patients triple negative,18 patients ER positive and HER2 negative,4 patients ER and HER2 positive,4 patients ER negative and HER2 positive,2 patients ER and HER2 negative but PgR positive. After chemotherapy neoadjuvant only 1 of 32 patients did not perform surgery for personal reasons; the others were all subjected to surgery.

Results: Currently at a median follow up of 10 years 19 of the 32 patients are alive and 13 are dead; 3 of the 19 alive had relapse disease and are still ongoing chemotherapy treatments. We stratified them according to value of Ki67, grading nodal status and comorbidities. 3 of the 13 patients who died were triple negative; eight ER positive and HER2 negative; one ER and HER2 positive; none was ER negative and HER2 positive, one ER and HER2 negative but PgR positive. 6 of the 13 patients died had the partial response pathological, 3 complete response. 5 of the 19 patients alive had complete response and 8 partial response. One of the three patients alive is in recurrent disease and is in the group ER + /HER2-; one in ER + / HER2+ and one in ER-/HER2+.

Conclusions: our little data reveal that, in our setting of patients, there is not a significant correlation between pCR and survival; so the pCR can not be considered the only surrogate of OS especially for the disease ER positive and HER2 negative. Perhaps it might be due to the lower responsiveness to chemotherapy of these disease. Further studies are needed to assess the impact of pCR and the correlation with OS; further assessment of the patients treated with neoadjuvant chemotherapy in the years 2010-2015 are actually ongoing in our center to increase the number patients and then have more reliable data.

R64 No country for children

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Epigenetic modification, as result of adaptation to the external environment, influences the expression and function of the genetic code and can determine dysfunctions and diseases already present at birth, or that will develop later in childhood or in adult life. The influence of environmental carcinogenesis appears to be becoming increasingly clear on the progressive growth in the incidence of most cancers and also in the increase of cancer in childhood and adolescence. The incidence rate for pediatric tumors in Italy (children: 175.4 cases per million/year, teenagers: 270.3) is one of the highest in the Western world (France 138; Germany 141). In our country, the increase in the incidence from 1998-2002 was 2% per year for all pediatric cancers, while the European average in the same period was 1.1% and 0.6% in the USA. In the subsequent publication AIRTUM of 2012 the same rate appeared steady from 2003-2008, but still remained higher than in other countries. The incidence in teenagers (15-19 years) has remained unchanged but globally in the decade 1998-2008 there was an annual increase of 2% mainly due to Hodgkin lymphoma, thyroid cancer and melanoma in females. The SENTIERI study conducted by the Italian Health Institute (ISS) could respond at least in part to the question posed in the AIRTUM document: "there is no explanation for the fact that Italian rates of incidence of cancer in children aged 0-14 years continues to be among the highest in the world ". In fact in the 44 Italian polluted sites (SIN), studied from 1995 to 2009 there were 3,332 deaths in the first year of life for each cause, versus an expected number of 3,206 (+126). In Taranto mortality data (2003- 2008) reported an increase of 35% in deaths from all causes under one year of age and perinatal mortality increased by 71%, with an overall increase in the incidence of all cancers in the whole population of 30%. There appears to be a continuing sort of reticence in combining data of studies with etiological hypotheses and also in planning epidemiological studies. They continue to verify the number of people affected, instead of trying to remove the possible/probable risks and check, then, the successful reduction of incidence and/or mortality for that cause. A drastic reduction is mandatory in the exposure of the population to carcinogens, to protect our health and especially that of future generations.

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