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XV NATIONAL CONGRESS OF MEDICAL ONCOLOGY

October 11-13, 2013: Milan, Italy

Guest Editor

Stefano Cascinu
Medical Oncology, Università Politecnica delle Marche, Ancona
President, Italian Association of Medical Oncology (AIOM)

Il Pensiero Scientifico Editore

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.

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(indexed in Current Contents/Life Sciences, EMBASE/Excerpta Medica, Elsevier BIOBASE/Current Awareness in Biological Sciences)

XV NATIONAL CONGRESS OF MEDICAL ONCOLOGY

October 11-13, 2013: Milan, Italy

Abstracts

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

15th National Congress of Medical Oncology
October 11-13, 2013: Milan, Italy

Guest Editor
Stefano Cascinu
Medical Oncology
Università Politecnica delle Marche, Ancona

Dear Colleagues,

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 XV National Congress of our Association.

As usually, the abstracts have been published in a special issue of "Tumori", the official Journal of AIOM. By reading them, there are at least two aspects of satisfaction.

The first one is the increasing number of abstracts. It seems to suggest not only the interest for the Congress but also a diffuse research activity in Italy. This is not limited to a specific geographic area but it involves all the country.

The second aspect is the role of young oncologists. Many and many young oncologists are coauthors of the abstracts and several are first authors. This is probably the most relevant indication at least in my mind: there is a present for AIOM but there will be also a future.

As you can realize by reading this issue, all topics of medical oncology has been covered. These topics, including prevention, screening, translational research, simultaneous care, ethics and multidisciplinary approaches, will be debated in several educational and scientific sessions. We would like to highlight as simultaneous care and multidisciplinary approach are relevant parts 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 mean to forget the daily activity in the ward as well as the ability to answer the patients' daily needs. Nevertheless, at the same way, we must remember that a research activity improves the care of cancer patients in our Units. The ability to conjugate 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 invaluable 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 2011-2013 includes:

- Stefano Cascinu (President)
- Carmine Pinto (*Secretary*)
- Stefania Gori (*Treasurer)*
- Massimo Aglietta
- Giuseppe Altavilla
- Editta Baldini
- Giovanni Bernardo
- Saverio Cinieri
- Fabio Puglisi
- Pierosandro Tagliaferri
- Giuseppe Tonini

We are looking forward to seeing you in Milan.

Prof. Stefano Cascinu
(President of the Congress)

This abstracts book will be available on-line and will also be freely available to all visitors to the following website from October 14th, 2013 (http://www.aiom.it)

Plenary session

1* FOLFOXIRI/BEVACIZUMAB (BEV) VERSUS FOLFIRI/BEV AS FIRST-LINE TREATMENT IN UNRESECTABLE METASTATIC COLORECTAL CANCER (MCRC) PATIENTS: RESULTS OF THE PHASE III TRIBE TRIAL BY GONO GROUP

Cremolini C.[1], Loupakis F.[1], Masi G.[1], Lonardi S.[2], Zagonel V.[2], Salvatore L.[1], Trenta P.[3], Tomasello G.[4], Ronzoni M.[5], Ciuffreda L.[6], Zaniboni A.[7], Tonini G.[8], Buonadonna A.[9], Valsuani C.[10], Chiara S.[11], Carlomagno C.[12], Boni C.[13], Marcucci L.[14], Boni L.[15], Falcone A.[1]

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Background. Doublets plus bev are a standard option for the first-line treatment of mCRC. First-line FOLFOXIRI demonstrated superior RR, PFS and OS compared to FOLFIRI. A phase II study of FOLFOXIRI/bev showed promising activity and manageable toxicities. The objective of the TRIBE trial was to confirm the superiority of FOLFOXIRI vs FOLFIRI when bev is added to chemotherapy (CT).

Patients and methods. Eligibility criteria included: measurable and unresectable mCRC, age 18-75 years, no prior CT for advanced disease. Patients were randomized to either FOLFIRI/bev (arm A) or FOLFOXIRI/bev (arm B). Both treatments were administered for a maximum of 12 cycles followed by 5FU/bev until progression. Primary endpoint was PFS.

Results. Between July 2008 and May 2011, 508 pts were randomized. Patients characteristics were (arm A/arm B): median age 60/61, ECOG PS 1-2 11%/10%, synchronous metastases 81%/79%, multiple sites of disease 74%/70%, liver-only disease 18%/23%, prior adjuvant (adj) 13%/13%. At a median follow-up of 32.3 mos 439 pts progressed and 286 died. FOLFOXIRI/bev significantly increased PFS (median 9.7 vs 12.1 mos, HR 0.77 [0.64-0.93] p = 0.006). A more consistent effect of FOLFOXIRI/bev was reported in no prior adj (HR 0.70 [0.58-0.86]) compared to prior adj group (HR 1.30 [0.75-2.25]), with a significant p for interaction (p = 0.039). Subgroup analyses based on baseline characteristics (PS, site of primary, liver only disease, resection of primary, Kohne score) did not evidence significant interactions between treatment and analyzed factors. Response rate (RECIST) was also significantly improved (53% vs 65%, p = 0.006). FOLFOXIRI/bev did not increase the R0 secondary resection rate in the ITT population (12% vs 15%, p = 0.327), or in the liver-only subgroup (28% vs 32%, p = 0.823). OS results will be presented.

Conclusions. FOLFOXIRI/bev, compared to FOLFIRI/bev, significantly increases PFS and response rate. Subgroup analysis suggests a possible interaction between prior adj CT and PFS benefit. Secondary resection rate does not differ between treatment arms.

2* A RANDOMIZED MULTICENTRE PHASE III STUDY COMPARING WEEKLY VS EVERY 3 WEEKS CARBOPLATIN (C) PLUS PACLITAXEL (P) IN PATIENTS WITH ADVANCED OVARIAN CANCER (AOC): MITO-7 (MULTICENTRE ITALIAN TRIALS IN OVARIAN CANCER) - ENGOT-OV-10 (EUROPEAN NETWORK OF GYNAECOLOGICAL ONCOLOGICAL TRIAL GROUPS) - GCIG (GYNECOLOGIC CANCER INTERGROUP) TRIAL

Pignata S.[1], Scambia G.[2], Lauria R.[3], Raspagliesi F.[4], Benedetti Panici P.[5], Cormio G.[6], Katsaros D.[7], Sorio R.[8], Cavazzini G.[9], Ferrandina G.[10], Breda E.[11], Murgia V.[12], Sacco C.[13], Asensio Sierra N.M.[14], Cinieri S.[15], Pisano C.[1], Salutari V.[2], Lorusso D.[4], Di Maio M.[1], Gallo C.[16], Perrone F.[1]

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Background. CP administered every 3 weeks (3w) is standard 1st line chemotherapy for AOC patients. In a JGOG phase 3 trial, weekly (w) P combined with 3w C prolonged PFS and OS. MITO-7 is an academic phase 3 study, comparing 3w vs w CP (ClinicalTrials.gov NCT00660842).

Methods. AOC chemonaïve pts, stage IC-IV, aged 75, ECOG PS = 2, were randomized to 3wCP (C AUC6 + P 175 mg/m^2, d1q21) for 6 cycles or to wCP (C AUC2 + P 60 mg/m^2) for 18 administrations. Coprimary endpoints were PFS and quality of life (QoL), measured by FACT-O and FACT/GOG-Ntx. With 80% power in detecting HR of 0.75, 2-sided a = 0.05, 383 events were needed for PFS analysis. The arms were compared with a log-rank test and in a Cox model adjusted by stage, PS, residual disease, age and size of institution, following intention-to-treat (ITT). QoL was measured at baseline and weekly for 9 wks: primary measure of QoL was FACT-O Trial Outcome Index (TOI). Interaction between arm and QoL time was tested in a linear mixed model. Toxicity was coded by NCI-CTCAE v3.0.

Results. Between 2008 and 2012, 822 pts were enrolled by MITO, MANGO and GINECO, and 808 pts were eligible for ITT analysis. Median age was 60; stage III (66%) and IV (18%) were prevalent. As of March 18, 2013, with median follow-up 20 months, 410 events were recorded for PFS analysis. Median PFS was 18.8 months with wCP and 16.5 months with 3wCP (HR 0.88, 95%CI 0.72-1.06, p = 0.18). Lack of significant difference was confirmed (HR 0.86, 95% CI 0.71-1.05) in Cox model. For FACT-O TOI, FACT-O and FACT/GOG-Ntx, QoL course in the first 9 weeks was significantly different between arms (p <0.0001). With 3wCP, QoL scores clearly worsened after each chemotherapy course (weeks 1, 4, 7), whilst with wCP, after a small and transient worsening at week 1, scores remained stable.

A significant treatment : time interaction favouring wCP (p <0.0001) was observed also for neurotoxicity subscale. Weekly CP produced significantly less G ≥3 neutropenia (50% vs 39%), febrile neutropenia (3% vs <1%), G ≥3 thrombocytopenia (7% vs 1%), G ≥3 renal toxicity (2% vs 0%), G2 hair loss (58% vs 28%) and G ≥2 neuropathy (16% vs 6%).

Conclusions. Compared to CP every 3 weeks, weekly CP did not significantly prolong PFS, but was associated with better QoL and lower toxicity. Given the observed confidence interval of PFS, MITO7 QoL and toxicity data further support a weekly schedule as 1st line treatment of AOC in clinical practice.

3* A LARGE PROSPECTIVE ITALIAN POPULATION STUDY (PROJECT OF EMILIA-ROMAGNA REGION IN NEURO-ONCOLOGY; PERNO) IN NEWLY DIAGNOSED GBM PATIENTS: OUTCOME ANALYSIS AND CORRELATIONS WITH MGMT METHYLATION STATUS IN THE ELDERLY POPULATION

Franceschi E.[1], Tosoni A.[1], Poggi R.[1], Depenni R.[2], Mucciarini C.[3], Faedi M.[4], Dazzi C.[5], Urbini B.[6], Cavanna L.[7], Marcello N.[8], Crisi G.[9], Michiara M.[10], Pasini G.[11], Bartolotti M.[1], Palleschi D.[1], Albani F.[12], Ermani M.[13], Baruzzi A.[12], Brandes A.[1]

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Background. The role of temozolomide concurrent with and adjuvant to radiotherapy (RT/TMZ) in elderly pts with GBM remains unclear. We therefore evaluated the efficacy of this approach in pts >70 years in the context of the Project of Emilia-Romagna Region in Neuro-Oncology (PERNO), the first Italian prospective observational population-based study in neuro-oncology.

Methods. The criteria for selecting pts enrolled in the PERNO study were: age >70 years; PS 0-3; histologically confirmed GBM; post-operative radiotherapy after surgery; residence in the Emilia Romagna region. Data were collected prospectively.

Results. Patients accrual, started on January 1, 2009, was closed, as planned, on December 31, 2010. In the pts enrolled (N = 53), median overall survival (mOS) was 11.1 months (95% CI 8.8-13.5); survival rates at 1-, 2- and 3-year were 41.5% (95% CI 28.2- 54.8%), 15.2% (95% CI 4.8-25.6%) and 6.1% (95% CI 0-15.9%), respectively. Twenty-eight pts received RT/TMZ, and 25 pts RT alone. mOS was 11.6 months (95% CI 8.6-14.6) following RT/TMZ and 9.3 months (95% CI 8.1-10.6) following RT alone. mOS for pts with MGMT methylated status (N = 17) was 13.5 months (95% CI 7.7-19.2), being 17.2 months (95% CI 11.5-22.9) in those treated with RT/TMZ (N = 6) and 8.8 months (95% CI 2-15.6) in those treated with RT alone (N = 11, p = 0.09). Elderly pts with MGMT unmethylated status (N = 25) had a mOS of 8.5 months (95% CI 6-11, p = 0.014), being 8.5 months (95% CI 2.3-14.7) in pts treated with RT/TMZ (N =10), and 8 months (95% CI 3-12.9) in those treated with RT (N = 15, p = 0.55).

Conclusions. RT/TMZ appears to be more effective in prolonging the mOS of elderly pts in those with MGMT methylation status (17.2 vs 8.5 months), and seem to perform better than TMZ alone, for which mOS was 9.7 months in the Nordic phase III trial. These findings underline the value of the ongoing randomized EORTC 26062-22061/NCIC CE.6 phase III comparing RT/TMZ with short course RT alone.

4* A PHASE II-III STUDY COMPARING CONCOMITANT CHEMORADIOTHERAPY (CRT) VS CETUXIMAB/RT (CET/RT) WITH OR WITHOUT INDUCTION TPF IN LOCALLY ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA (LASCCHN). TOXICITY AND EFFICACY RESULTS (NCT01086826)

Ghi M.G.[1], Paccagnella A.[2], Ferrari D.[3], Foa P.[3], Cossu Rocca M.[4], Verri E.[4], Maiello E.[5], Azzarello G.[6], D'Ambrosio C.[7], Casanova C.[8], Guaraldi M.[9], Mantovani G.[10], Rossetto C.[11], Bonetti A.[12], Cipani T.[13], Crinò L.[14], Koussis H.[15], Pieri G.[16], Gava A.[17], Floriani I.[18]

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Background. This is the first phase III study directly comparing CRT vs CET/RT in LASCCHN. Primary endpoints of this study were to compare: 1) overall survival (OS) of induction vs no induction arms; 2) grade 3-4 in-field toxicity of CRT vs CET/RT. Here we present toxicity results (one of the primary endpoints) and efficacy results (secondary endpoint) for the two concomitant treatments (CRT vs CET/RT), irrespective of induction chemotherapy.

Methods. Untreated patients with LASCCHN of the oral cavity, oropharynx, hypopharynx, stage III-IV, ECOG PS 0, were randomized to a 2x2 factorial design. Patients were randomized from the beginning to one of the four treatment options: *Arm A1:* CRT (2 cycles of cisplatin/5fluorouracil concomitant to standard RT fractionation); *Arm A2:* CET/RT; *Arm B1*: 3 cycles of TPF followed by the same CRT; *Arm B2:* 3 cycles of TPF followed by CET/RT.

Results. A total of 421 patients were randomized: 261 received CRT (131 *Arm A1*+ 130 *Arm B1*) and 160 received CET/RT (80 *Arm A2*+ 80 *Arm B2*). No significant differences were observed in patients' characteristics distribution. At a median follow-up of 35 months, a total of 186 deaths occurred (204 required for final OS analysis). Median PSF was 20.9 mos in CRT arm and 20.7 in CET/RT arm (p = NS). Median OS was 39.5 mos in CRT arm vs 38.2 mos in CET/RT arm (p = NS). In field-toxicities are shown in Table 1.

Conclusions. No significant differences in grade 3-4 in-field toxicities and efficacy were observed between CRT and CET/RT. The number of required events has not yet been reached for the OS evaluation of induction vs no induction arms.

4* - Table 1

	CRT N = 233 (%)	**CET/RT N = 158 (%)**	**p value**
Mucositis + skin in-field, per pts			
Any grade	192 (82)	125 (79)	0.415
Grade 3-4	102 (44)	74 (47)	0.551
Mucositis			
Any grade	182 (78)	114 (72)	0.177
Grade 3-4	89 (38)	57 (36)	0.670
Skin in-field			
Any grade	134 (58)	105 (66)	0.075
Grade 3-4	32 (14)	31 (19.6)	0.120

Session A • Colorectal cancer

A1* BEVACIZUMAB BEYOND PROGRESSION IN METASTATIC COLORECTAL CANCER PATIENTS RECEIVING A FIRST-LINE TREATMENT CONTAINING BEVACIZUMAB: UPDATE OF BEBYP TRIAL BY GONO

Salvatore L.[1], Masi G.[1], Loupakis F.[1], Cremolini C.[1], Schirripa M.[1], Fornaro L.[2], Miraglio E.[3], Granetto C.[3], Antonuzzo L.[4], Giommoni E.[4], Lucchesi S.[5], Barbara C.[6], Boni C.[7], Banzi M.[7], Sonaglio C.[8], Garbarino D.[8], Valsuani C.[9], Bonetti A.[10], Boni L.[1], Falcone A.[1]

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Background. The continuation of bevacizumab (BV) with second-line chemotherapy (CT) beyond progression in patients (pts) who received the anti-VEGF monoclonal antibody (moAb) as part of first-line treatment can improve the outcome. Recently, results of the AIO/AMG ML18147 study demonstrated an improved overall survival (OS) by continuing BV beyond progression.

Patients and method. This phase III study randomized pts with unresectable metastatic colorectal cancer (mCRC) and measurable disease according to RECIST criteria, treated in first-line with BV plus fluoropyrimidine, FOLFIRI, FOLFOX or FOLFOXIRI, to receive a second-line CT with mFOLFOX6 or FOLFIRI (depending on first-line CT) with or without BV. The primary endpoint was progression-free survival (PFS). To detect a HR for PFS of 0.70 with an a and b error of 0.05 and 0.20 respectively, assuming an accrual time of 24 months and a follow-up of 12 months, we planned to randomize 262 pts.

Results. Considering the results of the AIO/AMG ML18147 trial that showed an improved OS with the prosecution of BV beyond progression, the study accrual was stopped prematurely. A total of 185 pts were randomized and 184 pts were included in the ITT analysis (1 pt randomized in error). Patients characteristics for arm A (CT alone) and arm B (CT plus BV) were the following: number 92/92, gender M75%-F25%/M57%-F43%, median age 66 (38-75)/62 (38-75) years, PS = 0 82%/82%, multiple site of disease 76%/77%, liver-only disease 15%/13%. At the first analysis (median follow-up of 18 months) the study met its primary endpoint by demonstrating an improvement in PFS in the BV containing arm. We updated results and at a median follow-up of 30.4 months the improvement in PFS for the experimental arm was confirmed with a median PFS of 5.0 months for arm A and 6.7 months for arm B (HR = 0.66; 95% CI 0.49-0.89; unstratified p = 0.0065). Subgroup analyses showed a consistent benefit in all the subgroups including gender and first-line PFS. Response rates (RECIST) were 18% and 21% (p = 0.71) in arm A and B, respectively. Toxicity profile was consistent with previously reported data. The OS data are still immature, with 70 events in arm A and 66 in arm B and the HR is 0.75 (95% CI 0.54-1.06) in favour of experimental arm (unstratified p = 0.11).

Conclusions. This study demonstrates an improvement in PFS by continuing BV in second-line in pts who had received CT+BV in first-line. Updated survival results will be presented at the congress.

A2* CONFIRMATORY ANALYSIS OF NRAS MUTATION AS POOR PROGNOSTIC INDICATOR AND PREDICTOR OF RESISTANCE TO ANTI-EGFR MONOCLONAL ANTIBODIES (ANTI-EGFRS) IN METASTATIC COLORECTAL CANCER (MCRC) PATIENTS

Schirripa M.[1], Loupakis F.[2], Cremolini C.[2], Morvillo M.[2], Bergamo F.[3], Zoratto F.[4], Salvatore L.[2], Antoniotti C.[2], Marmorino F.[2], Sensi E.[5], Lupi C.[5], Fontanini G.[5], De Gregorio V.[2], Giannini R.[5], Basolo F.[5], Masi G.[2], Falcone A.[2]

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Background. NRAS belongs to RAS family. NRAS mutations are mutually exclusive with KRAS and BRAF mutations and contribute to the activation of Ras/Raf/MAPK pathway. Previous experiences evaluated the prognostic/predictive role of NRAS mutations suggesting a poorer prognosis and resistance to anti-EGFRs for NRAS mutant (mut) mCRC patients. The aim of the present study was to confirm such preliminary findings in a large cohort of mCRC patients.

Material and methods. Data on KRAS (codons 12, 13 and 61) and BRAF-V600E mutational status of mCRC pts referred to our pathology from '09 to '12 were collected. NRAS mutational status (codons 12, 13 and 61) was evaluated in KRAS and BRAF wt patients. OS was calculated from date of diagnosis of metastatic disease. Data on response and PFS according to RECIST were collected for NRASmut irinotecan-refractory pts treated with anti-EGFRs ± irinotecan.

Results. 774 mCRC pts were included. KRAS/BRAF mutations were found in 384 (50%)/69 (9%) cases. NRAS was mut in 47 (15%) out of 318 KRAS and BRAF wt patients. NRAS mut pts had significantly shorter OS in comparison to KRAS-BRAF-NRAS wt pts (HR = 0.60 [0.29-0.99] p = 0.045). BRAF mut pts had significantly worse OS in comparison to NRAS mut pts (HR = 1.75 [1.073-2.87] p = 0.03). No difference was observed between NRAS mut and KRAS mut pts (HR = 0.86 [0.51-1.43] p = 0.61). Eighteen pts out of 47 NRAS mut pts received anti-EGFRs in advanced lines. Eight pts (7 cetuximab-based, 1 panitumumab monotherapy) were evaluable according to RECIST criteria and therefore eligible for the present analysis. None of them responded and only 1 SD was observed. Pooling our results with available data on anti-EGFRs' activity in NRASmut pts in advanced lines of treatment (De Roock, 2010; Peeters, 2013; Andrè, 2012), only 1 response is described out of 35 treated pts (2.9%).

Conclusions. Our data demonstrate that NRAS mutations have a relevant incidence in KRAS and BRAF wt mCRC patients. Present results are consistent with previous experiences and confirm that NRAS mutations affect prognosis of mCRC patients and predict lack of response to anti-EGFRs. Further insights into NRAS mut mCRC biology and prospective validation are warranted.

A3* PHARMACOGENETIC PROFILING FOR TOXICITY OF OXALIPLATIN AND FLUOROPYRIMIDINES. FINAL REPORT FROM AN ANCILLARY PROTOCOL TO THE TOSCA TRIAL

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Background. In the TOSCA trial, an ancillary pharmacogenetic study was conducted for a prospective association analysis of known genetic variants with toxicity, useful for optimizing the management of patients during adjuvant chemotherapy. Current evidence is often limited to retrospective and not powered studies.

Methods. TOSCA is a multicentre, randomized, phase III study conducted in radically resected high risk stage II and III colon cancer patients treated with 6 or 3 months of either FOLFOX-4 or XELOX. We analyzed 17 polymorphisms in 11 genes related to 5-fluorouracil/oxaliplatin pathways, detoxification, transport and DNA repair (*TS*, *MTHFR*, *ERCC1*, *XRCC1*, *XRCC3*, *XPD*, *GSTT1*, *GSTP1*, *GSTM1*, *ABCC1*, *ABCC2*) and investigated their association with the maximum grade of toxicity (MGT) and the time to toxicity (TTT) as recorded for its maximum grade. Sample size calculation was based on an expected prevalence of an unfavourable genotype profiling of at least 30%. 105 grade 3-4 (also 2 for neurotoxicity) selected toxicity events (approximately 440 patients) allowed to detect an odds ratio (OR) of at least 2.0 associated to the group with unfavourable genotypes with a power of 90% and a I -type error of 5%, for a bilateral test.

Results. 534 patients were enrolled (195 in the 6-month FOLFOX-4 arm, 194 in the 3-month FOLFOX-4 arm, 69 in the 6-month XELOX arm, 76 in the 3-month XELOX arm). Regarding the proportion of stage II-III patients, the study sample is representative of main study sample, according to the two options of adjuvant chemotherapy and treatment duration (3 versus 6 months). 517 patients were analyzed. For neurotoxicity and neutropenia we have observed the required events. The *XRCC3 TT* (rs# 861539) genotype was protective for neurotoxicity (TTT) with a 0.58 HR (95% CI = 0.35-0.96; p = .03), the *GST-T1/M1 null*/+ genotype was associated with risk of neurotoxicity (TTT) with a 2.46 HR (95% CI = 1.07-5.65; p = .03). The *GST-T1/M1* +/+ genotype was associated with protection risk of netropenia (MGT) with a 0.51 HR (95% CI = 0.27-0.95; p = .03).

Conclusions. The results of this study are useful for improving the monitoring of potentially cured colon cancer patients undergoing adjuvant chemotherapy. It will be evaluated whether the genetic profiles, for which a statistically significant association in terms of MGT/TTT was observed, will determine different dose intensity and then possible different clinical outcomes.

A4* RESULTS OF OBSERVER STUDY ON SKIN TOXICITY AND CETUXIMAB BASED REGIMEN COMPLIANCE IN FIRST-LINE CHEMOTHERAPY OF METASTATIC COLORECTAL CANCER (MCRC)

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Background. Cetuximab significantly improves efficacy when added to chemotherapy in patients (pts) with KRAS *wild-type* metastatic colorectal cancer (mCRC). The ObservEr Study evaluated the quality of life, skin toxicity management and treatment compliance of cetuximab based regimens in first-line chemotherapy of mCRC patients.

Methods. ObservEr is a non-interventional, multicenter, prospective study. Primary endpoint is change in QoL during first-line treatment, with focus on the impact of dermatological toxicity. QoL (Dermatology Life Quality Index/DLQI and EORTC QLQ C30) is assessed at baseline and weekly for the first 8 weeks of treatment, then at every evaluation visit until PD or withdrawal. Secondary endpoints are efficacy, rate of liver metastases resection, incidence of serious adverse events.

Results. Between April 2011 and November 2012, 29 Italian centers enrolled 233 pts, with 229 evaluable patients. Patients characteristics were: 154 (67.2%) males, 75 (32.8%) females; median age 65 (39-81) years; PS ECOG 0-1 100%; potentially resectable liver metastases 64 (27.9%); irinotecan regimens 150 (63.4%), oxaliplatin regimens 69 (30.2%), other regimens 10 (4.3%). Median interval between request and result of KRAS test was 10 days. Prophylactic skin treatment with vitamin K1 cream was used in 164 (71.6%) pts, reactive treatment included vitamin K1 in 60 (26.0%). Grade 1-2 skin toxicity was observed in 147 (64.2%) pts, and grade 3 in 30 (13.1%); no grade 4 was detected. No significant difference in grade 3 skin toxicity was observed between males vs females (14.9 vs 9.3%; p = 0.238), age <60 vs ≥60 years (19.2 vs 10.3%; p = 0.062), irinotecan vs oxaliplatin regimens (11.3 vs 17.4; p = 0.563), 5-fluouracil vs capecitabine (14.8 vs 9.6; p = 0.697); prophylactic vs reactive treatment (14.6 vs 10.0%; p = 0.626). Cetuximab compliance ≥70% of dose was reached in 212 (92.6%) pts, with permanent discontinuation of the drug related to toxicity in 12 (5.2%) pts. Median duration of

cetuximab treatment in the 153/229 pts who already stopped was 15 weeks (range 1-60.1 weeks).

Conclusions. These results show that the introduction of the Italian skin toxicity management recommendations and K1 cream in the prophylactic or reactive treatment reduce the incidence of grade 3 skin toxicity with improvement of cetuximab compliance.

A5* IS IT USEFUL TO WAIT LONGER THAN CONVENTIONAL 6-8 WEEKS BETWEEN PRE-OPERATIVE CHEMORADIOTHERAPY AND SURGERY IN LOCALLY ADVANCED RECTAL CANCER? A SYSTEMATIC REVIEW WITH META-ANALYSIS

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Objective. This review considers the influence of the time lapse between the end of pre-operative chemoradiotherapy (CTRT) and surgery on the pathologic complete response (pCR) in locally advanced rectal cancer, in order to evaluate possible benefits of a time-interval longer than conventional 6-8 weeks.

Summary Background Data. The standard of care of locally advanced rectal cancer is pre-operative, long course (5-fluorouracil-based) CTRT. A period of 6-8 weeks from CTRT is currently considered the most effective timing to perform surgery.

Methods. A systematic research, concerning prospective or retrospective studies reporting oncological results of pre-operative CTRT in locally advanced rectal cancer, was carried out on PubMed, Embase, ISI Web of Science and The Cochrane library (CENTRAL). The primary endpoint, reported as relative risk (RR), was the rate of pCR. Secondary endpoints were overall survival (OS), disease-free survival (DFS), R0 resection rates, sphincter preservations and wound/anastomotic complications. A meta-analysis was performed, using the fixed- or random-effects model, with Review Manager 5.1.

Results. We have found thirteen trials including 3,584 patients. An interval longer than 6-8 weeks from the end of pre-operative CTRT and surgery significantly improved pCR (RR 1.42, 95% CI 1.2-1.69; p <0.0001) that increased from 13.9 to 19.5% in longer interval group. No significant differences for OS, DFS, R0 resection rates, sphincter preservation and complication rates were observed.

Conclusions. A time-interval from the end of pre-operative CTRT and surgery, longer than the 6-8 weeks period, increases by 6% the rate of pCR in rectal cancer, with a similar outcome and complication rates. These results have to be validated prospectively in a randomized trial.

A6 PROGNOSTIC VALUE OF INCIDENTAL BETABLOCKERS USE IN METASTATIC COLORECTAL CANCER PATIENTS RECEIVING FIRST-LINE TREATMENT. AN UPDATE

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Background. Preclinical and retrospective studies suggested an antitumor activity for the incidental use of anti-hypertensive betablockers in various tumour types, reducing metastasis, tumor recurrence and increasing survival. Data regarding colorectal cancer are lacking. We tried to assess the correlation between the incidental use of betablockers and clinical outcome in colorectal cancer patients receiving first-line therapy.

Material and methods. 250 colorectal cancer patients, treated with first-line chemotherapy alone (135 patients) and with chemotherapy plus bevacizumab (115 patients), were analysed for progression-free survival and overall survival, using the Kaplan-Meier method. A p value <0.05 was considered for statistical significance. Patients were stratified for betablockers use, age, sex, site of metastases, previous adjuvant chemotherapy and ECOG performance status.

Results. Thirty-one patients (12%) were on treatment with betablockers at the time of first-line therapy: 22 (16%) in the chemotherapy alone group and 9 in the bevacizumab group (8%). In both groups patients receiving or not betablockers were similar for all main clinical characteristics. In the chemotherapy alone group, patients receiving betablockers showed an improved RR (60% vs 33%, p = 0.044) and overall survival (mOS 41.3 vs 25.7 months, p = 0.03, HR: 2.26, 95% CI 1.05-3.24). Only a trend for improved progression-free survival was noticed. In the 115 patients receiving chemotherapy with bevacizumab a trend towards a worse overall survival was seen for patients receiving betablockers, although this was not statistically significant (mOS 16 vs 23.7 months, p = 0.26, HR: 0.64, 95% CI 0.22-1.49). No significant differences were seen in regards of progression-free survival or different response rate patterns between the two groups.

Conclusions. Our analysis confirms a potential prognostic role for the use of betablockers in colorectal cancer patients treated with chemotherapy. Our findings are in line with preclinical studies suggesting that beta-adrenergic signalling may regulate cancerogenesis and tumor invasiveness. Our analysis suggests a potential worse outcome for patients on betablockers receiving bevacizumab-based treatment, although the small number of patients precludes any definitive conclusion. We suggest that in future prospective trials the incidental use of betablockers will be considered a stratification factor for clinical outcome.

A7 MYC AMPLIFICATION IMPAIRS SENSITIVITY TO ANTI-EGFR MONOCLONAL ANTIBODIES IN KRAS WILD-TYPE METASTATIC COLORECTAL CANCER (MCRC) PATIENTS

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Background. Monoclonal antibodies against Epidermal Growth Factor Receptor (EGFR) demonstrated efficacy in metastatic colorectal cancer (mCRC) patients without mutations in the *KRAS* gene. Previous data in breast and lung cancer suggested that *MYC* gene copy number (GCN) affects sensitivity to anti-EGFR agents. Aim of the present study was to investigate whether *MYC* GCN influences sensitivity to anti-EGFR strategies in *KRAS* wild-type (wt) patients who have no benefit from cetuximab or panitumumab therapy.

Material and methods. This retrospective study was conducted in a cohort of 206 *KRAS* wt mCRC patients treated with cetuximab/panitumumab, either alone (N = 19) or in combination with chemotherapy (N = 187). *MYC* amplification was assessed by fluorescence *in situ* hybridization (FISH) in primary colorectal cancer tissue samples.

Results. In the study population response rate (RR) was 32.6%, median progression-free survival (PFS) 5.9 months and median overall survival (OS) 12.6 months. *MYC* was successfully evaluated in 202 cases and resulted amplified (*MYC*+) in 13 patients (6.3%). Among the 11 patients evaluable for response, *MYC*+ patients showed a significantly higher progression rate (63.6% versus 27.2%, p = 0.016), shorter PFS (3.0 months versus 6.2 months, p = 0.168) and significantly shorter OS (11.3 months versus 13.0 months, p = 0.038) than individuals lacking *MYC* amplification (*MYC*-).

Conclusions. Our results suggest *MYC* amplification as a biomarker potentially useful for refining selection of *KRAS* wt mCRC candidate for anti-EGFR treatment.

A8 COI-B (CAPECITABINE, OXALIPLATIN, IRINOTECAN AND BEVACIZUMAB, AS FIRST-LINE TREATMENT FOR METASTATIC COLORECTAL CANCER. A PHASE II ITMO STUDY

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Background. A dose-finding phase I/II trial that evaluated the maximum tolerated doses of a combination of three drugs with irinotecan, oxaliplatin and capecitabine (COI regimen) has been conducted (Bajetta, Ann Oncol 2007). We therefore assessed the safety and activity of the combination of COI regimen plus bevacizumab in patients with colorectal cancer.

Material and methods. Patients with colorectal cancer, wich was judged to be unresectable for metastatic disease, were treated with the combination of bevacizumab (5 mg/kg on day 1) and COI regimen (irinotecan 180 mg/m^2 on day 1, oxaliplatin 85 mg/m^2 on day 1, capecitabine 2000 mg d2-6; q14), as first-line treatment in six centres in Italy. Induction treatment (COI and bevacizumab) was administered for a maximum of 8 cycles, followed by maintenance treatment with bevacizumab (7.5 mg/kg iv on d1, q21) until progression.

Results. From June 2009 to March 2011, 51 patients were enrolled; all patients were assessed for safety and efficacy. Median age was 56 yrs (41-69); M/F: 59%-41%; ECOG PS 0-1/2:90-6%/4%; metastatic sites: 1/>1: 22%-78%; only liver metastasis 9%; primary tumor on site: 51%, peritoneal carcinosis: 14%; LDH(>UNL):46%. ORR: 58% (CR: 4%); SD: 37%; PD: 5%; median PFS: 10 mos (95% CI: 7.3-11.6). Median OS: 22 mos. The most common adverse event (G1-4) was diarrhoea (86%), vomiting (33%), neutropenia (21%) and peripheral neuropathy (14%). Main adverse events (G3-4): diarrhoea (31%), hypertension (10%), neutropenia (6%), gastrointestinal perforation (2%). No treatment-related deaths occurred.

Conclusions. Results confirm the feasibility of the COI regimen when combined with bevacizumab. The activity of the regimen is documented and it appears interesting if we consider the clinical poor prognostic factors of the study population. An analysis on biological parameters is ongoing and it will be available.

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A9 PROGNOSTIC ROLE OF KRAS IN CRC PATIENTS TREATED WITH BEVACIZUMAB: A META-ANALYSIS OF 12 TRIALS

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Background. The predictive significance of KRAS in advanced colorectal cancer (CRC) treated with anti-epidermal growth factor receptors (EGFR) monoclonal antibodies is well known. However the prognostic and predictive value of KRAS in patients treated with bevacizumab (B) + chemotherapy is not clear. We conducted a systematic review and meta-analysis of published trials, reporting response and survival with first-line, B-based chemotherapy in both wild type (wt) and mutated (mut) metastatic CRC, with the aim to evaluate its predictive and prognostic significance.

Material and methods. A literature search of PubMed, EMBASE, Web of Science, and Cochrane Register of Controlled Trials was performed. The primary endpoints included objective response rate (RR), progression-free survival (PFS), and overall survival (OS). The pooled odds ratios (ORs) and hazard ratios (HRs) were extracted or calculated from published data either using fixed effect model or random effect model according to heterogeneity between studies.

Results. Twelve studies were retrieved (6 phase III trials, 1 randomized phase II and 3 single arm phase II studies and 2 prospective series). A total of 2266 patients were analysed (54%

were KRAS wt). The overall RR was 54.8% for KRAS wt patients and 48.3 for KRAS mut groups (OR 1.42, p = 0.02). Median PFS was better in KRAS wt patients compared with that in KRAS mut patients (11.8 versus 9.42 months; HR = 0.85; 95% CI: 0.74-0.98; p = 0.02). Similarly, median OS was significantly longer in wt KRAS patients compared with that in mut counterpart (24.5 versus 19.3 months; HR = 0.65; 95% CI: 0.46-0.92; p = 0.01).

Conclusions. This meta-analysis shows that KRAS wt status is a good predictive factor for anti-VEGF-based therapies. Wild type patients present also a better survival, and so KRAS status seems to be a prognostic factor in CRC patients treated with B.

A10 INTERIM ANALYSIS RESULTS OF ABOVE PHASE II STUDY WITH BEVACIZUMAB IN PATIENTS WITH INITIALLY NOT RESECTABLE/BORDERLINE RESECTABLE COLORECTAL LIVER-LIMITED METASTASES

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Background. Bevacizumab (bev)-based therapy has demonstrated clinical efficacy for the neoadjuvant treatment of patients with CLLM. There are no data concerning the benefit of bev maintenance therapy after induction with bev-based therapy for patients who underwent R0 liver resection.

Methods. Untreated metastatic pts with histologically confirmed colorectal cancer with liver-limited mets were treated before surgery with the combination therapy mFOLFOX-6/bev for 5 cycles followed by one cycle of mFOLFOX6 alone (without bev). Post-operative chemotherapy + bev was restarted 5 weeks after surgery: patients were treated with the combination therapy mFOLFOX-6 + bevacizumab for additional 6 cycles. Immediately at the end of the post-operative phase, patients were treated with bev alone for 52 weeks (1 year). We report here an IA for the first 26 out of pre-planned 77 patients. Patients received oxaliplatin 85 mg/m^2 by intravenous infusion (i.v.) on day 1, i.v. LV 200 mg/m^2 on day 1, followed by 5-FU 2.400 mg/m^2, by continuous infusion over 46 hours + bev 5 mg/kg i.v. on day 1 q2w. Eligibility criteria included adequate organ function and ECOG PS 0-1. All pts were candidates for neoadjuvant therapy and categorized according to the following surgical criteria: i) unresectable CLLM, ii) borderline resectable CLLM, where R0 surgery cannot be guaranteed, iii) "high risk" resectable CLLM based on number and mets size. Primary endpoint was ORR.

Results. According to ITT analysis, 26 out of 27 enrolled pts were assessable for ORR. Patients characteristics were: sex 18M/8F, median age 64.5 years [37-77], PS 0/1: 23/3. Site of primary tumor: rectum 2, colon 24. Syncronous/metachronous metastases: 24/2. Unresectable 14, borderline resectable 6, "high risk" resectable 6. ORR was 16 responders (61.5%, all PR) and 10 non-responders [38.5%: 7 SD (26.9%) and 3 withdrawals], respectively. Fourteen (53.8%) underwent R0 liver resection. Grade 3 related AEs (%) were: neutropenia 1 (3.8%) [and 2 G4 (7.6%)], myocardial infarction 1 (3.8%), fatigue 2 (7.6%), proteinuria 1 (3.8%), hypertransaminasemia 1 (3.8%).

Conclusions. IA results show high RR of mFOLFOX6/bev in CLLM treatment, resulting in high rate of R0 liver resection with good safety profile. Data should be confirmed and the role of bev maintenance elucidated with trial final results.

A11 QUALITY OF LIFE ANALYSIS IN PATIENTS WITH METASTATIC COLORECTAL CANCER (MCRC) TREATED IN FIRST-LINE CHEMOTHERAPY WITH CETUXIMAB BASED REGIMEN. THE RESULTS OF THE OBSERVER STUDY

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Background. Quality of life (QoL) is paramount to patients (pts) during palliative treatment of mCRC. The ObservEr Study evaluated QoL and treatment compliance of cetuximab based regimens in first-line chemotherapy of mCRC patients.

Methods. ObservEr is a non-interventional, observational, prospective study. The primary endpoint is the evaluation of changes in QoL during the period in which a first-line treatment chemotherapy is given, with specific focus on the impact of the dermatological toxicity of this treatment. Data on QoL (Dermatology Life Quality Index/DLQI and EORTC QLQ-C30) is assessed at baseline and weekly for the first 8 weeks of treatment and then at every evaluation visit until PD or withdrawal for any cause.

Results. Between April 2011 and November 2012, 233 pts were enrolled in 29 Italian centers, with 229 evaluable patients. Patients characteristics were: 154 (67.2%) M, 75 (32.8%) F; median age 65 years (39-81); PS ECOG 0-1 100%; symptomatics 23 (10.0%); IRI regimens 150 (63.4%), OXA regimens 69 (30.2%). QoL assessed by DLQI questionnaire was evaluable in 221/229 (96.5%) at baseline and in 175/229 (76.4%) at week 8 (W8). EORTC QLQ-C30 questionnaire compliance was 221/229 (96.5%) pts at baseline and 164/229 (71.6%) at W8. No deterioration of QoL was observed from baseline to W8 both by DLQI (from median score 0 at baseline to 1 at W8) and EORTC QLQ-C30 for Global Health Status (from median score 67 at baseline to 58 at W8). The functional scales did not record changes for emotional aspects, fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties (median changes = 0). Slight changes were observed in physical functioning (score from 86 to 80), and role/cognitive/social functioning (score from 100 to 83).The changes of all QoL assessment from baseline to W8, according to skin toxicity management protocol, revealed no significant differences between prophylactic and reactive skin toxicity management both by DLQI ($p = 0.389$) and by EORTC QLQ-C30 ($p = 0.449$). In this same interval time, the analyses for single-item scales of DLQI in prophylactic vs reactive skin toxicity treatment showed an improvement of skin symptoms (itchy, sore, painful or stinging) ($p = 0.015$) and emotional/social functions ($p = 0.004$) in the prophylactic group.

Conclusions. In the ObservEr study, evaluations of QoL based on DLQI and EORTC QLQ-C30 show that QoL was maintained when cetuximab was added to first-line chemotherapy.

A12 FDG-PET/CT (PET) IN THE EARLY PREDICTION OF BENEFIT FROM FIRST-LINE CHEMOTHERAPY PLUS BEVACIZUMAB (BEV) IN METASTATIC COLORECTAL CANCER (MCRC)

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Background. The conventional assessment of response according to RECIST seems not optimal to estimate the actual benefit from antiangiogenic agents. A recent experience suggests the potential role of PET in the early prediction of benefit from first-line chemotherapy in mCRC. The aim of the present study was to evaluate the metabolic PET response to one single cycle of chemotherapy plus bev in mCRC patients (pts).

Patients and methods. PET was carried out at baseline and on day 13 in 51 unresectable mCRC pts, treated with biweekly bev-containing regimens; computed tomography (CT) scan was performed at baseline and every 2 months. PET response was defined by >15% decrease in FDG uptake in the dominant proportion of lesions, in the absence of metabolically progressive lesions. CT response was defined according to RECIST 1.0.

Results. PET response rate was 73%. PET responders achieved longer PFS compared to PET non-responders (median PFS: 11.0 vs 8.3 months; HR = 0.45 ([95% CI 0.14-0.93] $p = 0.035$). RECIST CT response rate was 62% and 57%, in PET responders and non-responders, respectively ($p = 0.76$). At an exploratory analysis, among pts (N = 15) reporting a RECIST-defined stable disease (SD), those with a percentage decrease in FDG uptake higher than the median value (>33%) had significantly longer PFS in comparison to those with a lower PET response (median PFS: 9.4 vs 7.4 months; HR = 0.2 ([95% CI 0.005-0.24] $p = 0.0006$).

Conclusions. Early PET response, assessed after one single cycle of chemotherapy plus bev, predicts PFS, while it does not correlate with traditional RECIST response. In the subgroup of pts reporting a RECIST SD, the early reduction in FDG uptake correlates with PFS. On the basis of our results, early PET response on day 13th could represent an early predictor of benefit from bev plus chemotherapy in mCRC.

A13 CAPECITABINE, OXALIPLATIN, IRINOTECAN AND CETUXIMAB (COI-E REGIMEN) AS PERIOPERATIVE TREATMENT OF BORDERLINE RESECTABLE OR HIGH-RISK COLORECTAL CANCER (CRC) LIVER METASTASES: A PHASE I/II STUDY

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Background. A phase I/II study was performed to determine the safety and activity of capecitabine, oxaliplatin, irinotecan and cetuximab as perioperative treatment in pts with liver-limited CRC and contraindication for upfront surgery due to borderline resectable or high-risk disease.

Patients and methods. Six pts received as first dose level: irinotecan (180 mg/m^2) and cetuximab (500 mg/m^2) day 1, oxaliplatin (85 mg/m^2) day 2 and capecitabine (1000 mg/m^2 orally b.i.d.) on days 2-6; four biweekly cycles were administered both pre- and post-operatively. Since this was the recommended phase II dose (RP2D), 32 additional pts were enrolled from November 2008. After June 2009, the protocol was amended to enrol KRAS exons 2-4 wild type. Main inclusion criteria: primary tumor resected; no extraepatic disease; borderline liver resectability (involvement of >1 hepatic vein or >4 liver segments, or portal vein embolization, *in situ* splitting and two-stage hepatectomy, or intraoperative radiofrequency ablation) or at least one adverse prognostic factor: >4 metastases; CEA >200; synchronous metastases. Primary endpoint: response rate (RR); secondary endpoints: R0 resection; safety; pathological response; relapse-free survival (RFS) and overall survival (OS).

Results. The RP2D was identified at the first level, due to occurring of G3 diarrhoea in 1/6 pts. Overall, 38 pts enrolled and 36 evaluable for response (2 still on preoperative treatment). RR was 84% (all 30 PR), with 4 (11%) SD and 2 (5%) PD. Potentially curative surgery was performed in 34 pts (2 inoperable) and R0 resection was achieved in 26 (76%), in addition with radiofrequency ablation in 2. Patients characteristics: M/F: 25/13; median age 58 years (35-72); synchronous disease: 30/38 (79%); N+ at primary tumour: 26 (68%), single metastasis: 15 (40%), 2-4 metastases: 16 (42%) and >4 metastases: 7 (18%), CEA >200: 2 (5%), KRAS mutation: 8 (21%) and BRAF mutation: 2 (5%), N+ hilar nodes: 2/34 (6%), extrahepatic disease: 5/34 (15%, with 2 extrahilar nodes, 2 peritoneal carcinosis, 1 second primary CRC). Regarding the 36 pts evaluable for safety, grade 3-4 AEs oc-

curred in 15/36 (42%), mainly diarrhoea. At a median follow-up of 40 months, median RFS was 12.3 months. OS survival data are not mature and may be presented at the Meeting.

Conclusions. Biweekly COI-E is feasible and active. The regimen is well suited for liver downstaging in KRAS wild type CRC before curative surgery.

A14 LONG-SURVIVORS WITH LUNG METASTASES AND KRAS MUTATIONS HAVE AN INCREASED RISK TO DEVELOP BRAIN METASTASES FROM COLORECTAL CANCER

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Background. Brain metastases (BM) occur in 1-4% of metastatic colorectal cancer (mCRC) patients (pts). Retrospective series evidence that pts with a long survival (>1 year) from the diagnosis of mCRC are more frequently affected. Moreover, BM seem to be associated with lung metastases and KRAS activating mutations. The identification of clinical and molecular features correlated with BM may allow to define a specific subpopulation more likely to develop BM, thus to benefit from neuroimaging follow-up and early treatment.

Material and methods. We prospectively tested the hypothesis that a higher incidence of BM occurs in a population of mCRC pts with a survival time from the diagnosis of mCRC ≥10 months, lung metastases and KRAS exons 2 and 3 mutations. Given a reported incidence of BM in unselected mCRC of around 3% (H0) and expecting an incidence in an "at risk" population selected on the basis of the 3 above reported features of 10% (H1), setting α and β errors to 0.05 and 0.10 respectively, we adopted the Fleming single-stage design for calculating the sample size of our analysis. The null hypothesis would have been rejected if at least 7 out of 104 "at risk" pts developed BM.

Results. 623 pts, enrolled in clinical trials treated with first-line chemotherapy and bevacizumab, were included in the overall study population in order to identify 105 (16.9%) pts who simultaneously had a survival time from the diagnosis of mCRC ≥10 months, lung metastases and KRAS exons 2 and 3 mutations. Twenty-six (4.2%) out of 623 pts developed BM. Fourteen out of 518 (2.7%) not "at risk" pts presented BM, while 12 out of 105 (11.4%) "at risk" pts did. The incidence of BM in the two groups differed significantly (Fisher's exact test, p = 0.0004). The null hypothesis was rejected according to the original design.

Conclusions. This analysis confirms the hypothesis that the concomitant presence of the 3 analyzed risk factors increases the probability of developing BM in mCRC patients. Based on these data, the opportunity to consider a neuroimaging exam, such as brain CT scan or MRI, in this specific population might be taken into account in order to provide an early diagnosis of BM and therefore the most appropriate therapy in an asymptomatic phase.

A15 EFFECTS OF PRIMARY TUMOR RESECTION ON LONG TERM SURVIVAL IN METASTATIC COLORECTAL CANCER PATIENTS

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Background. Primary tumor and metastases from colorectal cancer can undergo surgical treatment in a small percentage of AJCC stage IV patients. Chemotherapy (CT) can often allow conversion from unresectable to resectable disease. Literature shows improved outcomes after resection of liver metastases.

Material and methods. We performed a retrospective analysis on 54 patients, 41 male and 13 female, with metastatic colorectal cancer followed at our Oncology Unit from 2005 to 2012, to compare survival in patients with lung or liver or other metastatic site and unresected primary tumor versus patients with resected primary tumor in presence of multiple metastases. We also compared patients with evident metastatic disease versus patients resected on primary and metastatic sites.

Results. Median age was 63 years. Twelve patients had unresected primary tumor besides metastatic involvement. Twenty-one of 54 patients underwent first-line CT with bevacizumab, 33 without bevacizumab (1 with cetuximab). Fourteen of them underwent surgery for primary site and liver or lung metastases or for peritoneal involvement before, during or after first-line CT. Median PFS was 8.0 months (mean 7.1 months; 95% CI 5.8-8.5) for patients with metastatic disease and unresected primary tumor versus 10.0 months (mean 11.3 months; 95% CI 9.2-13.5) for metastatic patients with resected primary tumor (p = 0.002; HR 0.40; 95% CI 0.07-0.56). Median OS was 15.5 months (mean 20.1 months; 95% CI 12.6-27.5) versus 34.0 months (mean 37.6 months; 95% CI 30.7-44.5), respectively (p = 0.0005; HR 0.29; 95% CI 0.03-0.39). In patients with or without primary tumor resection who did not undergo metastasectomy median PFS reached 9 months (mean 9.1 months; 95% CI 7.6-10.7) versus 15 months (mean 14.9 months; 95% CI 9.2-20.5) for patients who underwent primary tumor resection and metastasectomy without macroscopic residue (p = 0.01; HR 0.50; 95% CI 0.22-0.84). Median OS was 22.5 months (mean 26.3 months; 95% CI 20.9-31.7) versus 50.5 months (mean 55 months; 95% CI 44.7-65.2), respectively (p <0.0001; HR 0.16; 95% CI 0.10-0.45). The multivariate COX analysis confirmed resection of primary tumor and metastases resections as independent variables for PFS while only primary tumor resection predicts for OS.

Conclusions. These results suggest that primary tumor resection, despite delay of first-line CT, provides survival benefit. The removal of primary tumor microenvironment can affect prognosis and natural history of the disease.

A16 MANAGEMENT OF LIVER METASTASES FROM COLORECTAL CANCER: IMPACT OF LOCOREGIONAL TREATMENTS IN CLINICAL PRACTICE

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Background. Despite of lack of randomized clinical trials, metastasectomy and/or other locoregional treatments (radiofrequency ablation (RF) or transcatheter arterial chemoembolization (TACE) of liver metastases for colorectal cancer are commonly used in clinical practice.

Material and methods. We retrospectivly collected cases of patients with colorectal cancer liver metastases treated at our institution from 2006 to 2012.

Results. We collected 114 patients, median age 68 years (range 43-87), with synchronous liver metastases in 72 of them (63.2%), metachronous in 42 (36.68%). The great part of them underwent chemotherapy (93%), alone (52 patients, 45.6%) or in combination with locoregional treatments (61 patients 53.5). According to locoregional treatments, 29 pts underwent surgery (25.4%), 20 pts RF (17.5%), 10 pts surgery and RF (8.8%), 2 pts surgery, RF and TACE (1.8%). Median PFS was 11 m (95% CI 8-13) and median OS was 28 m (95% CI 20-36). Survival analyses pointed out following variables as prognostic factor in term of median PFS and OS: oxaliplatin-based first-line chemotherapy vs irinotecan- or 5FU/capecitabine alone-based chemotherapy (mPFS 14m vs 10m vs 7m respectively, p = 0.02; mOS 35m vs 24m vs 19m, p = 0.04); surgery vs no-surgery (mPSF 14m vs 8m, p = 0.0002); RF (mOS 40m vs 21m, p = 0.009) with better survival for patients who underwent surgery or RF first-line treatment than which ones who firstly underwent chemotherapy (mPFS 13m vs 10m, p = 0.008; mOS 39m vs 41m vs 20m, p = 0.0001); response to first treatment (RC 62m vs RP 34m SQ 38m vs PD 16m, p <0.0001). Among patients undergoing surgery, the percentage of RC was significantly higher than other groups (surgery 40.0% vs RF 35.7% vs CT 10.1% (square chi = 0.003); mOS was similar both in patients firstly operated and in patients forstly treated with conversion chemotherapy with at least a partial response (39m vs 33m, p = 0.318). Locoregional treatments were associated with a significant longer partial hospitalization (day hospital) (268.9+- 223.6 days vs 189+- 153.9 days, t test = 0.009).

Conclusions. Locoregional treatments of liver metastases, chosen according to clinical and patients characteristics but also to patients preferences, seems to contribute to better survival and to a longer day-hospital management of cancer patients instead of ordinary hospitalization.

A17 MANAGEMENT OF COLORECTAL CANCER (CRC) PATIENTS WITH LIVER METASTASES (LM) IN THE MONO-INSTITUTIONAL BOLOGNA EXPERIENCE

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Background. In metastatic (m) CRC pts it is necessary to define the therapeutic strategy from the outset, choosing from the different therapeutic options available.

Methods. Data of pts with mCRC, treated between 2004 and December 2013 at the Bologna S. Orsola-Malpighi Hospital Medical Oncology Unit, were collected in a specific registry for the purposes of this analysis.

Results. Three hundred and twenty-three pts with mCRC were evaluated. The pts characteristics: 199 (61.6%) M and 124 (38.4%) F; median age 64 years (range 25-85); primary tumor 253 (78.3%) colon, 70 (21.7%) rectum; 200 (61.9%) pts diagnosed at IV stage, 123 (38.1%) pts relapsed; 152 (47.1%) pts with only LM, 116 (35.9%) synchronous and 36 (11.1%) metachronous; 171 (52.9%) pts with other metastatic sites. In 152 (47.1%) pts with only LM, 23 (15.1%) had 1 lesion and 129 (84.9%) had 2 or more. Twenty-seven (17.8%)/152 pts underwent surgery directly: 23 (85.2%) R0 resection, 2 (7.4%) R1 and 2 (7.4%) R2. In 14 (51.9%)/27 pts primary tumor and LM were simultaneously resected, in 13 (48.2%) LM were resected after the primary tumor. Twenty-two (81.5%) pts/27 received postoperative chemotherapy (CHT), 5 (18.5%) pts underwent intensive follow-up. The disease-free survival (DFS) in directly resected LM pts was 27 months (95% CI 3-33), the overall survival (OS) was 60 months (95% CI 36-84). One hundred and twenty-three out of 152 LM pts (80.9%) underwent first-line (1st-L) CHT: 89 CHT (67 oxaliplatin based, 11 irinotecan based, 11 fluoropyrimidine), and 34 CHT plus monoclonal antibodies (17 bevacizumab, 7 cetuximab/panitumumab). Forty-three out of 123 pts (35.0%) underwent liver surgery after 1st-L: 30 (69.8%) R0, 4 (9.3%) R1 and 9 (20.9%) R2. The DFS in pts with LM resected after 1st-L vs non-resected was 14 (95% CI 11-17) vs 6 months (95% CI 5-7), p <0.001; the OS was 36 (95% CI 28-44) vs 15 months (95% CI 12-18), p <0.001. Two pts with multiple LM did not receive any treatment because of rapid disease progression. One pt was resected R0 after 3rd line chemotherapy. In the 70 (46.1%) pts with LM resected (upfront or after CHT) vs 82 (54%) non-resected pts the DFS was 14 (95% CI 11-17) vs 6 months (95% CI 5-7), p <0.001; the OS was 44 (95% CI 35-53) vs 15 months (95% CI 12-18) p <0.001.

Conclusions. Adequate management of mCRC with LM results in a significant improvement of "cure" rates. In our series 46.1% of pts underwent resection of LM, achieving a median OS of 3.8 years and 10% survival at 5 years in resected patients.

A18 PRELIMINARY SAFETY ANALYSIS OF A PHASE II TRIAL WITH FOLFOXIRI AND BEVACIZUMAB (BV) FOLLOWED BY CHEMO-RADIOTHERAPY (CRT) AND BV IN LOCALLY ADVANCED RECTAL CANCER (LARC) (TRUST TRIAL)

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Background. Induction chemotherapy (CT) before CRT is an interesting option in LARC. BV improves the results of fluoropyrimidine-based CT and FOLFOXIRI plus BV is an effective treatment option in metastatic colorectal cancer.

Material and methods. Patients (pts) with rectal adenocarcinoma at <12 cm from the anal verge, stage N+ or cT4 or high

risk cT3 (MRI criteria) were treated with 6 cycles of biweekly FOLFOXIRI (irinotecan 165 mg/m^2 day 1; oxaliplatin 85 mg/m^2 day 1; folinate 200 mg/m^2 day 1; 5FU 3200 mg/m^2 48 h c.i. starting on day 1) and BV (5 mg/kg day 1) followed by concomitant CRT (50.4 Gy in 28 fractions over 5.5 weeks + 5FU 225 mg/m^2/day c.i. or capecitabine 825 mg/m^2/bid continuously + BV 5 mg/kg on days 1, 15, 28). Surgery is planned 7-9 weeks after the end of CRT. Primary endpoint is 2-year disease-free survival.

Results. From April 2012 to May 2013 14 pts were enrolled, 13 completed CRT and 8 underwent surgery (5 pts ongoing). Patients characteristics were: M/F, 78%/22%; median age 55 years (range 33-67); cT3/cT4, 78%/22%; cN0/N+, 22%/78%. Main grade (G) 3/4 toxicities during induction treatment were neutropenia (43%), febrile neutropenia (7%), diarrhea (7%), stomatitis (7%) and hypertension (7%). Only 1 patient did not complete induction CT, as he died due to bowel perforation and febrile neutropenia with sepsis after the first cycle. During CRT no G4 toxicities were observed while main G3 toxicities were hand-foot syndrome (HFS) (31%), proctalgia (23%), proctitis (23%) and diarrhea (15%). All patients received 50.4 Gy and median CRT duration was 7.1 weeks (range 5.9-10.2). Surgery was low anterior resection in 88% of pts and abdomino-perineal resection in 12%. None of the patients had early post-surgical complications. Pathological staging was: T0/1/2/3 (38%/12%/12%/38%), N0/1 (75%/25%). Tumor downsizing was achieved in 63% of pts and nodal downstaging in 50%. Pathologic complete response (pCR) was reached in 38% of pts (3/8).

Conclusions. These preliminary results show that induction CT with FOLFOXIRI + BV is feasible with manageable toxicities (mainly neutropenia). During CRT we observed an excessive incidence of HFS and mucosal toxicity probably due to the intracellular accumulation of folinate administered during induction CT. For that reason, considering the promising results in terms of pCR we decided to proceed by amending the protocol, slightly modifying the schedule of capecitabine during CRT (800 mg/m^2/bid for 5 days per week).

A19 EARLY PET/CT SCAN IS MORE EFFECTIVE THAN RECIST IN PREDICTING OUTCOME OF PATIENTS WITH LIVER METASTASES FROM COLORECTAL CANCER TREATED WITH PREOPERATIVE CHEMOTHERAPY PLUS BEVACIZUMAB

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Background. Markers predictive of treatment effect might be useful to improve the treatment of patients with metastatic solid tumors. Particularly, early changes in tumor metabolism measured by PET/CT with FDG could predict the efficacy of treatment better than standard dimensional RECIST response.

Methods. We performed PET/CT evaluation before and after 1 cycle of treatment in patients with resectable liver metastases from colorectal cancer, within a phase 2 trial of preoperative FOLFIRI plus bevacizumab. For each lesion, the maximum SUV (SUVmax) and the total lesion glycolisis (TLG) were determined. Based on previous studies, a = 50% reduction from baseline was used as a threshold for significant metabolic response. We used six measures to assess metabolic response: highest SUVmax and highest TLG (the largest observed SUVmax or TLG value within each patient), total SUVmax and total TLG (the sum of all SUVmax or TLG values within each patient), SUVmax-by-lesion and TLG-by-lesion (defining a patient as responder only if all lesions were responding). Standard RECIST response was assessed with CT after 3 months of treatment. Pathologic response was assessed in patients undergoing resection according to Mandard's classification. The agreement between metabolic and RECIST and pathologic response was tested with the Mc Nemar's test; the ability to predict progression-free (PFS) and overall survival (OS) was tested with Log-rank test and a multivariable Cox model.

Results. Thirty-three patients were analyzed. After treatment there was a notable decrease of all the PET/CT measures. A strong asymmetry between PET/CT and RECIST responses was observed with SUV-based measures, while no significant asymmetry was found between PET/CT and pathologic responses. Early metabolic PET/CT response (either SUV- or TLG-based) had a stronger, independent and statistically significant predictive value for PFS and OS than both RECIST and pathologic response at multivariate analysis, although with different degrees of statistical significance. Predictive value of RECIST response was not significant at multivariate analysis.

Conclusions. Early PET/CT response during preoperative treatment of patients with liver metastases from colorectal cancer was significantly predictive of long-term outcomes and its predictive ability was higher than that of RECIST response after 3 months of treatment. Such findings need to be confirmed by larger prospective trials.

A20 EVALUATION OF PERIOD 2 GENE (PER-2) BIOLOGIC PROFILE IN ADVANCED COLORECTAL CANCER (ACC) PATIENTS TREATED WITH CHRONOMODULATED CHEMOTHERAPY

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Background. Circadian rhythms, modulated by clock genes expression as the *Period* genes (PER-1, PER-2, PER-3), are involved in cancer growth. PER-2 loss in colorectal cancer cell lines and in animal models increases tumorigenesis by b-catenin and cyclin D activation (Wood P, Cancer Res 2008). PER-2 loss in ACC patients (pts) was linked to a worse prognosis (Iacobelli S, ASCO 2008). The aim of this study was to identify a PER-2 biological profile related to proliferative indexes and treatment activity. Moreover miRNA related to clock genes were studies as miR-219 (target of CLOCK and B-MAL1), miR-206 (which affect mammalian circadian clock), and miR-132 acting at the CNS level.

Methods. We retrospectively evaluated 59 ACC pts, treated with first-line chronomodulated triplet combination (irinotecan + oxaliplatin + folinic acid + 5-fluorouracil) ± cetuximab. Immunostaining for PER-2, EGFR, ERb1, ERb2, Cyclin D1, b-catenin, K-RAS and B-RAF mutations was performed. MirRNAs -206, -132, -192, -194 and -219 were evaluated on FFPE tumor tissues and their expression levels were examined.

Results. Clinical data: M/F: 32/27; median age: 57 yrs; median liver involvement 53%; cetuximab used in 38% of pts; liver resection: 42%. Response to chemotherapy: PR 61%; SD 25.4%; PD 10.2% (2.4% not evaluable). Biological data: pts with PER-2 loss (-)expressed more frequently EGFR (73%) ($p < 0.0001$); ERb1 (77%) ($p = 0.07$); ERb2 (88.5%) ($p < 0.0001$), cyclinD1 (69.2%) ($p = 0.06$) and b-catenin (84.6%) ($p = 0.02$). PER-2 (-) was also associated to high miR-206 and miR-219 expression. Explorative multiple correspondence analysis showed that response to chemotherapy was observed in pts with a biological profile characterized by PER-2 expression (+), EGFR (-), ERb1 (-), b-catenin (-) and low miR-206 expression.

Conclusions. Our data confirmed that: 1) PER-2 loss (-) was associated to cell proliferation activation, confirming *in vitro* data; 2) PER-2 expression (+) was linked to cell proliferation inhibition, low miR-206 expression and response to chemotherapy.

A21 AFLIBERCEPT (AFL) IN COMBINATION WITH FOLFIRI FOR THE 2ND-LINE TREATMENT OF PATIENTS WITH METASTATIC COLORECTAL CANCER (MCRC): INTERIM SAFETY AND QUALITY OF LIFE (QOL) DATA FROM THE ITALIAN SUBGROUP OF THE AFLIBERCEPT SAFETY AND QUALITY OF LIFE PROGRAM (ASQOP)

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Background. In the phase 3 VELOUR trial, afl + FOLFIRI (irinotecan, 5-FU, leucovorin) demonstrated a statistically significant overall survival benefit compared with FOLFIRI alone in mCRC pts previously treated with an oxaliplatin-containing regimen. The VELOUR trial supported the initiation of the multinational Aflibercept Safety and Quality-of-Life Program (ASQoP) to collect additional safety and QoL data from mCRC patients. Interim data collected by Italian investigators are reported.

Methods. At the cut-off date, 48 pts (safety population) from 17 Italian sites had completed >1 cycle of afl + FOLFIRI. Treatment cycles were repeated q2wks up to disease progression, unacceptable toxicity, death, or investigator/pt decision. FOLFIRI starting dose and dose modifications were at the investigator's discretion. Safety was assessed at each cycle and up to 30 days after last drug administration. The EuroQol EQ-5D™ , selected as a utility measure instrument, was self-administered within 3 days prior to first treatment and at the beginning of every odd treatment cycle. The EQ-5D population consists of pts completing the questionnaire at baseline and at least once postbaseline, and who received at least part of 1 treatment dose. The percentage of pts with grade 3/4 AEs in the safety population of the Italian subset of ASQoP was compared with that in VELOUR.

Results. Baseline demographic characteristics of the Italian ASQoP subset were similar to VELOUR. EQ-5D data from 26 pts were analyzed; 54% were male; median age 60 years; 88.5% had ECOG score of 0. Mean ± SD utility index at baseline was 0.77 ± 0.20 and remained unchanged at cycle 3 (0.78 ± 0.26) in 24 evaluable patients. 50% of pts of the Italian ASQoP subset experienced >1 G3/4 AE vs 83.5% in VELOUR. G3/4 hypertension and diarrhea were 14.6% and 6.3%, respectively, vs 19.1% and 19.3% in VELOUR. G3 infections (SOC) occurred in 8.3% vs 12.3% in VELOUR. No fatal events were reported.

Conclusions. Enrollment in ASQoP has enabled collection of additional safety and QoL data for afl in mCRC pts. Preliminary health-related QoL data from the Italian subset suggest that treatment with afl does not result in decrements in QoL for patients treated with afl + FOLFIRI. These interim results support the favorable safety profile of afl + FOLFIRI and have identified no new safety signals. The incidence of AEs with the afl + FOLFIRI combination in the Italian subset of ASQoP is lower than in VELOUR and clinically manageable in practice.

A22 MGMT (O6-METHYLGUANINE-DNA-METHILTRANSFERASE) PROMOTER METHYLATION IN BRAIN METASTASES (BM) FROM COLORECTAL CANCER (CRC) AND CORRESPONDING PRIMARY TUMORS

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Background. A comprehensive molecular and biological characterization of BM from CRC is currently lacking, although their occurrence is progressively increasing. MGMT deficiency due to promoter methylation is reported to exist in 30 to 40% of intestinal carcinomas. Moreover, ongoing phase II clinical trials are testing the activity of alkylating agents (such as dacarbazine or temozolomide), suggesting that their usefulness is limited to CRC patients harboring this specific epigenetic modification. Aim of this retrospective cohort study was to evaluate MGMT promoter methylation in BM form CRC and their corresponding primary tumors.

Methods. We identified a cohort of 52 consecutive CRC patients who underwent neurosurgical resection of BM in the last 15 years in our Hospital, and retrieved from archive their formalin-fixed, paraffin-embedded samples. Corresponding primary tumors for concordance analysis were available for 40 patients. After DNA extraction, conversion of unmethylated cytosines to uracils was carried out. MGMT promoter methylation status was

analysed by pyrosequencing technology using a commercially available kit (MGMT plus®, Diatech Pharmacogenetics) according to manufacturer's instructions on a PyroMarkTMQ96 ID system (Qiagen) with PyroMark CpG (Qiagen) software. The test is designed to detect and quantify methylation level in ten CpG sites in exon 1 of MGMT gene. Survival curves were calculated with Kaplan-Meier method.

Results. In the cohort series, median age at the time of BM resection was 65 years (35-82), median survival after brain surgery was 170 days. MGMT promoter methylation was found in 33 out of 52 cases (63.4%). Discordant results were found in 5 out of 41 matched cases (12.2%): 2 cases were MGMT methylated on the primary site but had unmethylated brain lesions, while 3 cases acquired the epigenetic modification. Survival post brain surgery was not influenced by MGMT promoter methylation (median survival 163 vs 193 days).

Conclusions. MGMT promoter methylation is common in BM from CRC, occurring in approximately 60% of the cases. In order to better use all available treatment resources, there is the need to further characterize the biologic profile of BM from gastrointestinal tumors.

A23 NOTCH AND DLL4 EXPRESSION AND CLINICAL OUTCOME IN BEVACIZUMAB TREATED PATIENTS WITH METASTATIC COLORECTAL CANCER

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Background. Delta-like 4 ligand (DLL4)-mediated Notch signalling has been implicated in tumour-resistance to anti-vascular endothelial growth factor (VEGF) therapy by inducing the formation of large vessels and by triggering multiple pathways in preclinical models. In order to investigate mechanisms of resistance to angiogenesis inhibitors, Notch and DLL4 expression was correlated with response and survival in a series of bevacizumab-treated metastatic colorectal cancer (mCRC) patients.

Material and methods. Notch and DLL4 expression was evaluated by immunohistochemistry (IHC) on 67 primary CRC enrolled within randomized clinical trials assessing first-line bevacizumab plus chemotherapy. A control series of advanced CRC treated with chemotherapy alone was also examined.

Results. Notch positivity was localized to the cytoplasm or nucleus of malignant epithelial cells. In all, 12/63 (19%) evaluable primary tumours had a high Notch expression (IHC 3+). A cytoplasmic DLL4 immunoreactivity of large and small tumour vessels was observed in 21/46 (46%) and in 10/58 (17%) evaluable CRC, respectively. Seven of the 12 cases (58%) with high Notch expression experienced progressive disease compared with 5/51 (10%) Notch negative cases ($p < 0.01$). Median progression-free survival was 2.4 months for Notch positive cases compared with 12.2 months for Notch negative cases ($p < 0.01$). Median overall survival was 17.7 months for Notch positive cases compared with 30.8 months for Notch negative cases ($p < 0.01$). No correlation was found between Notch expression and clinical response in a smaller series of patients treated with chemotherapy without bevacizumab. No correlation was found between DLL4 expression and outcome.

Conclusions. Clinical trials investigating the therapeutic efficacy of bevacizumab in CRC did not explore the impact of DLL4-Notch pathway on response and clinical outcome. Our results may suggest the involvement of Notch pathway in mediating tumour resistance to bevacizumab in CRC patients.

A24 MTHFR C677T GENE POLYMORPHISMS AND SUSCEPTIBILITY TO CARDIOVASCULAR ADVERSE EVENTS IN METASTATIC COLORECTAL CANCER TREATED WITH CHEMOTHERAPY PLUS BEVACIZUMAB

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Introduction. Methylentetrahydrofolate reductase (MTHFR) is a key enzyme regulating intracellular folate levels, which affect DNA synthesis and methylation. It has been hypothesized that tumors exhibiting deficient MTHFR variants such as 677T may be more sensitive to FU cytotoxicity than tumors bearing the common MTHFR variants 677C. Moreover this gene polymorphism has also been considered as potential factor for 5-fluorouracil toxicity. The present study investigated MTHFR C677T gene polymorphism in patients affected with metastatic colorectal cancer (mCRC) treated with chemotherapy and bevacizumab.

Patients and methods. Fifty-four patients with mCRC receiving first-line chemotherapy with folfiri-bevacizumab were included in the study. Clinical responses were evaluated according to RECIST criteria while toxicity according to CTCAE v3.0. Peripheral blood samples were collected from each patient and genomic DNA was extracted from WBC for testing C677T polymorphisms.

Results. Overall response rate (ORR) was 41%: 1 (2%) complete response (CR), 21 (39%) partial response (PR), 18 (33%) stable disease (SD) and 14 (26%) disease progression (PD). Ten (18%) patients experienced G3-4 cardiovascular toxicity (hypertension, arterial and venous thrombotic events). MTHFR 677C/C: 677C/T: 677T/T = 13: 30: 11 patients respectively. Patients with 677C/T and 677T/T mutations showed an ORR = 46% compared with 23% in 677C/C genotype ($p = 0.13$). G3-4 cardio-vascular adverse events resulted more frequent in mutated MTHFR 677T/T with regard to both 677C/T and 677C/c genotypes (Table).

A24 - Cardiovascular toxicity

MTHFR	G3-4		p value
	Yes	No	
677C/C	1	12	<0.01
677C/T	3	27	
677T/T	6	5	

Conclusions. These data showed an association between MTHFR C677T polymorphism and cardio-vascular adverse events in patients with mCRC treated with chemotherapy and be-

vacizumab. Further evaluations are required to better define the role of such polymorphism in clinical practice.

A25 CLINICAL OUTCOMES IN PATIENTS WITH COLORECTAL CANCER AND LIVER METASTASES: "THE TIMES THEY ARE A-CHANGING"

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Background. Hepatic resection is the recommended treatment for resectable colorectal liver metastases (CLM). If surgical resection is not achievable chemotherapy remains the main therapeutic choice. Recent data by Kopetz et al. showed a really high median survival time both in resected CLM (65.3 months, 95% CI, 51.6 to 70.6 months) and in patients only treated with chemotherapy (26.7 months, 95% CI, 24.9 to 28.6 months). Innovative surgical and medical treatments, including targeted therapies, subtend these results. Aim of our study was the retrospective analysis of clinical outcome in CLM patients.

Materials and methods. 108 CLM patients, observed at our Institution from 2005 to 2012, were included in the study. Clinical outcomes in resected and non-resected patients were compared.

Results. Demographic and clinico-pathological features are reported in the Table. The median follow-up period was 21months.

A25 - Table

	Resected N = 54 N (%)	Non-resected N = 54 N (%)	p value
Age, years			
Median	67	67	ns
Range	47-81	31-83	
Sex			
M	28 (52)	35 (65)	ns
F	26 (48)	19 (35)	
Rectum	20 (37)	6 (11)	
Colon	34 (63)	48 (89)	<0.05
Primary tumour-resection	54 (100)	46 (85)	<0.01
Extrahepatic metastases	5 (9)	20 (37)	<0.01
N liver metastases			
1	27 (50)	6 (11)	
2	5 (9)	10 (18)	< 0.001
3	8 (15)	6 (11)	
4	3 (5)	2 (4)	
>4	9 (17)	30 (56)	
Liver metastases size			
≤30 mm	37 (68)	27(50)	<0.01
>30 mm	12 (22)	27(50)	
Bilateral liver metastases	22 (40)	35 (65)	< 0.05
Synchronous liver metastases	30 (56)	30 (55)	ns
≥2 lines of CHT			
0	10 (18)	0	< 0.05
1	23 (43)	24 (44)	
≥2	20 (37)	28 (52)	
Median OS	55	47	
Range (months)	38-72	34-60	0.07

Conclusions. Our results showed a satisfying trend in survival time both in resected and in non-resected patients, it is agreeable with the "changing times" for CLM patients.

A26 MICRORNA PROFILING IN METASTATIC COLORECTAL PRIMARY TUMOR AND STROMA

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Background. Bevacizumab (bev) is routinely used in the treatment of metastatic colorectal cancer (mCRC). Nowadays, no definite predictive factor for its clinical benefit is known. MicroRNAs (miRNAs) are small, non-coding, RNA molecules involved in regulation of several cellular mechanisms. Specific miRNAs have been found down- or up-regulated in colorectal cancer and associated with prognosis or response to treatments. We used microarray technology to profile miRNA expression both in primary tumour and stromal tissue of patients (pts) affected by mCRC cancer.

Methods. Fifty-seven mCRC pts were treated in first-line with chemotherapy (47 FOLFIRI, 7 FOLFOX/XELOX, 3 FOLFOXIRI) plus bev. For each case, a representative haematoxylin and eosin-stained section from primary tumour was reviewed, and neoplastic and stromal areas were selected and separately scraped, from corresponding unstained slides. MiRNA expression profile was analysed by microarray analysis. MiRNA expression in the tumour or in the stroma was correlated with some characteristics of the disease: stage at diagnosis (coded as TNM II-III vs TNM IV), and site of metastases (codes as liver vs other). miRNA were considered differentially expressed in the categories only if the confidence level from the analysis was greater than 95%. miRNA levels were also correlated with the progression-free (PFS) and the overall survival (OS).

Results. 134 miRNAs were found as significantly differentially expressed in stroma versus tumor: 47 down-regulated and 87 up-regulated (all p <0.0001). Nine miRNAs resulted to be significantly differentially expressed in the tumour of patients with stage IV versus stage II-III at diagnosis. Seven miRNAs were differentially expressed in pts with metastases only in the liver as opposed to pts with metastases only in the lung. All the miRNA found to be differently expressed by microarray will be validated by RT-PCR. High expression of hsa-miR-26b-5p, hsa-miR-361-5p, and hsa-miR-3651 was found to be significantly correlated with better PFS and OS at univariate analysis.

Conclusions. miRNA expression in the primary tumour may regulate the aggressiveness of the disease, the preferential site of distant metastases, and affect prognosis of mCRC pts treated with first-line chemotherapy plus bevacizumab.

A27 PYROSEQUENCING DETECTION OF LOW FREQUENCY KRAS MUTANT ALLELES PREDICTS THE RESPONSE TO EGFR THERAPY IN METASTATIC COLORECTAL CANCER

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Background. KRAS mutational status is the only biomarker routinely used to select EGFR therapy in metastatic colorectal cancer (mCRC), with direct sequencing being the gold standard for the detection of KRAS mutations. However, other high sensitive technologies have been proposed, and, among others, pyrosequencing, but, at present, the level of test sensitivity which is required to provide predictive information in clinical practice is still in question.

Patients and methods. A retrospective analysis of KRAS codons 12 and 13 mutations by pyrosequencing and direct sequencing was performed in 192 mCRCs to evaluate whether pyrosequencing may improve the predictive value of KRAS mutational status.

Results. Direct sequencing failed to detect KRAS mutations in 4/31 mCRCs with low frequency of mutated alleles, whereas pyrosequencing allowed the detection of an additional 12 low frequency KRAS mutations in 141 mCRCs KRAS-wild type at direct sequencing. After analyzing the cohort of 97 KRAS-wild type tumors treated with anti-EGFR antibodies, 9 additional mutations were revealed in the non-responders, whereas none of the responders exhibited a KRAS-mutated genotype upon pyrosequencing re-evaluation. Of note, KRAS-mutated tumors upon pyrosequencing re-evaluation showed a worst progression-free survival after EGFR therapy. Finally, KRAS-wild type mCRCs with both technologies, but primarily resistant to EGFR therapy, exhibited 3 BRAF and 5 exon 20 PIK3CA mutations which were absent in the responder subgroup.

Conclusions. The capacity of pyrosequencing to detect low frequency of mutant alleles suggests that it may improve the KRAS predictive value for the selection of anti-EGFR agents.

A28 THE INTERACTION BETWEEN METASTATIC DISEASE EXTENSION AND MOLECULAR PROFILE INFLUENCES METASTATIC COLORECTAL CANCER (MCRC) PATIENTS OUTCOMES

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Background. Molecular markers are required to refine prediction of mCRC outcomes. KRAS mutation is associated to specific metastatic sites. No association was evident for BRAF mutation but its negative prognostic role is confirmed. We analyzed, for differences KRAS and BRAF mutation profiles, outcomes obtained in a cohort of mCRC pts, according to number of metastatic sites.

Material and methods. 106 pts treated with 1st-line Folfiri or Folfox plus bevacizumab chemotherapy were assessed for response to treatment and survival. Their primary tumor samples were retrospectively screened for conventional KRAS and BRAF mutations by DNA amplification and direct sequencing. Chi-square Fisher's exact test was used to compare objective response rate (ORR) between groups. PFS and OS curves were calculated and compared through Kaplan-Meier methods and long-rank test respectively.

Results. In overall population, 73 pts had a single metastatic site while 33 pts presented multiple disease sites. KRAS status was assessed in whole population whereas BRAF in 88 out of 106 pts; their mutations were detected in 39 and 12 pts respectively. In single and multiple metastatic sites groups, there was no statistically significance difference in terms of ORR, progression-free survival (PFS) and overall survival (OS) regardless KRAS status. With regard to BRAF profile, a benefit in PFS and OS has been revealed in multiple metastatic sites pts with wild-type (wt) BRAF tumor (PFS: 11 months (mos) wtBRAF vs 6 mos mutant (mt) BRAF tumor, $p = 0.02$; OS: 26 mos vs 19 mos respectively, $p = 0.04$). Multiple metastatic sites group obtained a statistically significance advantage in ORR and PFS in pts with wtKRA/wtBRAF tumor (ORR: wtKRAS/wtBRAF 61.5% vs 26.6% pts with at least one mutation, $p = 0.03$; PFS 12 mos vs 9 mos respectively; $p = 0.01$). Inferior ORR and PFS in pts with at least one mutation were influenced by BRAF mutation ($p = 0.02$). Finally, there was no outcomes difference in single metastatic site group compared to BRAF expression and the two markers association.

Conclusions. Our data highlight that pts outcomes are not influenced by KRAS or BRAF status when mCRC affecting single organ. Contrary, in extensive mCRC the BRAF negative prognostic role induces lower ORR, PFS and OS values in pts with mtBRAF tumor. The knowledge of metastatic disease extension and molecular profile can help to guide management of mCRC patients.

A29 IDENTIFICATION OF A TPM3-TRKA REARRANGEMENT IN HUMAN COLON CARCINOMA, AND DEVELOPMENT OF A METHODOLOGY TO IDENTIFY PATIENTS FOR TREATMENT WITH TRK INHIBITORS

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Background. The NTRK1 gene encodes the tyrosine kinase TRKA (Tropomyosin related kinase A), a high-affinity Nerve Growth Factor receptor which plays an important role in the development and maturation of the central and peripheral nervous systems. Physiological expression of TRKA is restricted to subsets of neuronal crest-derived cells and it is not generally expressed in other normal tissues. TRKA was originally identified from a human colorectal carcinoma (CRC) sample as a component of a transforming oncogene generated by somatic rearrangement of the 5' region of the tropomyosin 3 gene (TPM3) and the 3' of NTRK1, including TRKA kinase domain (Barbacid et al., 1986). Recurring chromosomal rearrangements of NTRK1 with different 5' fusion partners (TPM3, TPR, TFG) were subsequent-

ly described in ~5-12% of papillary thyroid carcinomas, but no extension of the original observation has been reported for CRC.

Material and methods. Formalin Fixed Paraffin Embedded (FFPE) CRC samples were analysed by RT-qPCR, using primers designed for detection of TRKA extracellular or kinase domain expression and in parallel by immunohistochemical analysis (IHC) with anti-TRKA c-terminus specific antibody.

Results. We recently identified a TPM3-NTRK1 rearrangement in the KM-12 CRC cell line, and demonstrated that the resulting activated TRKA oncogene is the driving force for proliferation and survival in these cells, which we found to be highly sensitive to NMS-P626, a potent and selective TRKA kinase inhibitor (Ardini et al., EJC, S8: 39-40, 2010). Here we describe detailed genomic characterization of this lesion in KM-12 cells, and the set-up of an RT-qPCR method for assessing selective expression of intracellular vs extracellular TRKA domains to detect potentially oncogenic NTRK1 rearrangements in clinical samples. Using this method, we analysed 50 FFPE CRC samples and identified one case harbouring a TPM3-NTRK1 rearrangement. In parallel, IHC analysis of TRKA intracellular domain expression performed in blind on the same sample set led to independent identification of the same case as being highly positive for TRKA protein expression.

Conclusions. These data confirm the presence at low frequency of NTRK1 gene rearrangement in CRC, and validate IHC with an anti-TRKA antibody as a readily applicable method for screening CRC FFPE samples. This method is currently being applied for recruitment of patients who are potentially suitable for treatment with TRKA kinase inhibitors.

A30 NEUTROPHIL/LYMPHOCYTE RATIO (N/L) AS AN INDEX OF INFLAMMATORY RESPONSE IN METASTATIC COLORECTAL CANCER (CRC) PATIENTS TREATED WITH FLUOROURACIL, IRINOTECAN AND BEVACIZUMAB (FOLFIRI-BEV)

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Background. High N/L, as a measure of enhanced inflammatory response, has been demonstrated to be a negative prognostic factor for pts with localized CRC. Inflammation, in fact, increases vascular permeability thus favouring cancer cell invasion through blood vessels and metastatic spread. In the present study, we aimed at evaluating the prognostic value of N/L in metastatic CRC (mCRC) pts treated with standard first-line chemotherapy.

Methods. Consecutive mCRC pts (N = 106, male:female = 58:48) treated with first-line FOLFIRI-Bev between June 2008 and October 2011 at our institution were included. Exclusion criteria were treatment with steroids and active infection. Leukocyte, neutrophil and lymphocyte counts and their ratio were routinely assessed before each treatment cycle and correlated with outcome together with platelet count (PLT), monocyte count, haemoglobin concentration (Hb), CEA, CA19.9, Karnofsky Performance Status (KPS), number of metastatic sites (NMS), body mass index.

Results. At univariate Cox regression analysis, high baseline leukocytes, neutrophils, N/L, PLT, NMS, CEA and CA19.9 and low Hb and KPS were all significantly associated with poor prognosis. At multivariate Cox regression analysis only N/L, CEA and KPS were confirmed to be independent prognostic factors, with N/L being the most powerful prognosticator (65% increased risk of death for 1-unit increase in N/L = exp (b) 1.65, 95% CI 1.30-2.09, p <0.0001; median Overall Survival (mOS) for pts with N/L <2.5 as compared to N/L >2.5 = 46 vs 24 months, respectively, p 0.007). Surprisingly, FOLFIRI-Bev-induced inflammatory response was of a different nature, as pts in whom N/L increased after four cycles of chemotherapy had a prolonged mOS, and this was independent of objective response. Among pts with stable disease (N = 40), those in whom N/L increased or was maintained had a 64% reduction in the risk of death as compared to patients with significant N/L decrease (i.e. >50% decrease over baseline value): mOS 60 vs 22 months, respectively, HR 0.36, p 0.02.

Conclusions. We were able to confirm the prognostic value of baseline N/L for mCRC pts approaching first-line FOLFIRI-Bev. However, FOLFIRI-Bev-induced inflammatory response seems to be of different nature and may contribute to the efficacy of this regimen. The specific molecular pathways involved in FOLFIRI-Bev-induced inflammation warrant further research.

A31 5-FU MONITORING IN COLORECTAL CANCER CLINICAL PRACTICE: IS IT PRACTICAL, IS IT USEFUL?

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Background. Current dosing of 5-Fluorouracil (5-FU) is based on body surface area (BSA) but has been associated with significant pharmacokinetic (PK) variability, with low exposure and loss of efficacy or high exposure and severe toxicity. In this study, we evaluated the Saladax My5-FU immunoassay on our CRC patients receiving 5-FU continuous infusion (CI) regimens.

Methods. Blood samples across different cycles were obtained from 24 patients receiving CI 5-FU: the mean dose of 5-FU administered was1151 mg/m^2 (range 440-1270mg/m^2). In total 57 EDTA samples were drawn typically a minimum of 1hr before the end of the 5-FU CI at 5-FU steady state concentration. The 5-FU concentrations were subsequently quantified on a Roche Cobas® 6000 using a homogeneous immunoassay (My5-FU™ , Saladax Biomedical, Inc.).The 5-FU AUC was calculated from the reported plasma concentrations and one result was discarded as it was clearly an outlier.

Results. The 24 patients analyzed demonstrated a wide range of AUCs: ranging from 2.7 to 37mg.h.l-1with a mean of 12.2 mg.h.l-1and a standard deviation (SD) of 6.19 mg.h.l-1. There was no significant correlation observed between 5-FU dose and AUC for any of the regimens - overall R2 = 0.0312; p = 0.576. Additionally analyzing samples taken across different cycles showed a Mean AUC in earlier cycles slightly lower than that seen in later cycles (11.4 vs 12.8 mg.h/l) and the occurrence of anomalous values decrease significantly in later cycles.

A31 - Table

Regimen	Patients/ Samples	Mean AUC mg.h.l-1	SD AUC mg.h.l-1	Number of patients below range
Folfox 4	9/24	13.7	7.0	8 (89%)
Folfiri	7/18	8.4	2.7	7 (100%)
De Gramont	7/13	14.4	6.2	6 (86%)
5-FU/LV	1/1	15.3	-	1 (100%)

Conclusions. This study has shown that the measurement of 5-FU is now a practical proposition, the stabilizer allows for simple sample collection and the pre-analytical aspects are easy to handle. These data also support the previous reports that standard BSA dosing of 5-FU leads to a high PK variability. Using the optimal AUC range of 20-30 mg.h.l-1, out of the 24 patients, 22 (92%) were under the target level with only 2 out of the 24 receiving an initial dose resulting in an AUC within the target range. Exposure appeared independent of regimen. Based on the results of this small study it appears that sampling and measuring concentrations of 5-FU during CI to adjust the dose to reach optimal exposure is practical and may be a rational approach to delivering effective treatment.

A32 MOLECULAR BIOMARKERS FOR A PROGNOSTIC STRATIFICATION OF K-RAS WILD TYPE COLORECTAL CANCER PATIENTS RECEIVING IRINOTECAN-CETUXIMAB: A PROSPECTIVE STUDY

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Background. Translational research identified numerous putative markers for a "beyond-k-ras" selection of colorectal cancer patients receiving cetuximab, but none of these entered clinical practice mainly because prospective validation is lacking. The aim of our study was to evaluate whether a panel of biomarkers, prospectively analysed may be able to predict patients' clinical outcome more accurately than K-RAS status alone.

Patients and methods. Metastatic, K-RAS wild type colorectal cancer patients, candidate to receive second/third-line cetuximab with chemotherapy have been prospectively allocated, after informed consent, into 2 groups on the basis of their genetic profile: favourable (BRAF and PIK3CA exon 20 wild type, EGFR GCN ≥2.6, HER-3 Rajkumar score ≥8, IGF-1 immunostaining <2) and unfavourable (any of the previous markers altered or mutated). All patients received cetuximab treatment as planned by treating physician who was unaware of biomarkers results. To detect a difference in terms of response rate (RR) among patients with an unfavourable profile (estimated around 25%) and patients with a favourable profile (estimated around 60%), assuming a probability alpha of 0.05 and beta of 0.05, required sample size will be 46 patients.

Results. Thirty-one patients have been enrolled, most patients (27, 86%) received cetuximab as third-line. Eleven patients (35%) were allocated to the favourable profile and 20 patients (75%) to the unfavourable profile. Patients with the unfavourable profile showed 1 BRAF mutation, 2 PIK3CA exon 20 mutations, 12 cases of EGFR GCN <2.6, 13 cases of HER-3 and 11 cases of IGF-1 overexpression respectively. RR in the favourable and unfavourable group was 7/11 (64%) and 1/20 (5%) (p = 0.008) respectively. The favourable group also showed an improved median TTP (8 months vs 2.6 months, p = 0.0007) and OS (16 months vs 6 months, p = 0.0002).

Conclusions. Our results suggest that prospective selection of candidates for cetuximab may be able to improve clinical outcome in patients with a favourable profile. This approach, if confirmed, may also allow an early switch to alternative treatment in patients with an unfavourable profile.

A33 PROSPECTIVE ANALYSIS OF THE EARLY MODULATION OF PLASMA AMPHIREGULIN DURING TREATMENT WITH CETUXIMAB AND IRINOTECAN IN METASTATIC COLORECTAL CANCER PATIENTS

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Background. The potential role of amphiregulin (AR) tissue levels in the prediction of benefit from anti-EGFRs in metastatic colorectal cancer (mCRC) patients (pts) was suggested by retrospective series. Preclinical and preliminary clinical experiences showed a modulation of plasma EGFR ligands during the treatment with cetuximab. Previous data by our group evidenced that a significant increase of plasma AR occurred one hour after the administration of cetuximab and higher increases were associated with worse clinical outcome in KRAS and BRAF wt irinotecan-refractory mCRC pts receiving cetuximab and irinotecan.

Patients and methods. We designed a prospective confirmatory study in the same setting of mCRC patients. To detect a HR for PFS of 2.3 for pts with high AR levels one hour after the administration of cetuximab (1hr-AR) compared to those with low levels, with two-sided a = 0.05 and b = 0.2, 45 events were required. The median value was adopted as cut-off. Plasma AR levels were assessed by means of validated ELISA kits.

Results. Forty-nine KRAS and BRAF wt pts were included. A significant early increase of AR levels was observed (median increase +24.7%; median levels of baseline AR and 1hr-AR: 18.06 and 24.06 pg/mL, respectively; Wilcoxon signed rank test, p <0.0001). At a median follow-up of 20.4 mos, median PFS and OS were 4.6 and 12.1 mos, respectively. No differences in PFS or OS were observed according to 1hr-AR levels (median PFS 5.5 vs 4.6 mos, HR: 0.76 [95% CI: 0.40-1.32], p = 0.322; median OS: 15.6 vs 13.4 mos, HR: 0.77 [95% CI: 0.36-1.62], p = 0.485).

Conclusions. This prospective experience confirms that AR early increases one hour after the administration of cetuximab. Underlying biological mechanisms should be investigated. Never-

theless, this modulation of AR does not predict clinical outcome. Our work underlines the need to prospectively validate retrospective findings in independent series, to assess their reliability.

A34 OXALIPLATIN-BASED ADJUVANT CHEMOTHERAPY IN ELDERLY PATIENTS WITH STAGE III COLON CANCER: RETROSPECTIVE ANALYSIS FROM A SINGLE CENTRE

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Introduction. Fluoropyrimidines (FP) are a well established adjuvant therapy in elderly patients (pts) with stage III colon cancer, due to the improvement in relapse-free and overall survival reported by clinical trials and retrospective analyses. However, the role of oxaliplatin in the treatment of this subgroup remains controversial.

Methods. We retrospectively evaluated 97 consecutive ≥65 yrs pts who received radical surgery for stage III colon cancer between 2008 and 2010 at our hospital. We assessed pts characteristics and comorbidities, administration of adjuvant treatments, toxicities of therapies and outcome, with a minimum follow-up period of 3 years.

Results. Median age was 74 (range 65-96): 21 pts were 65-69 yrs old (younger-old), 46 pts were 70-79 yrs old (old-old) and 30 pts were 80 yrs or older (oldest-old). G1-G2 adenocarcinomas were found in 87 pts while G3 tumors were diagnosed in 10 patients. Tumor stages were T1, T2, T3, T4 in 4, 8, 62, 23 pts respectively. Median number of examined nodes was 16 (range 9-57) and median number of positive nodes was 2 (range 1-12). Thirty-four of 97 pts didn't receive any adjuvant therapy due to frailty (25 pts had cardiovascular comorbidities): 14 of them developed metastases (12 pts died due to cancer), 10 pts died for other causes and 10 pts are alive and free-disease. Sixty-three of 97 pts with PS ≤2 and limited comorbidities received adjuvant chemotherapy: 28 pts with FP plus oxaliplatin and 35 pts with FP alone. Among pts performing oxaliplatin-based regimens, G2-3 peripheral neuropathy occurred in 66% of old-old pts and in 46% of younger-old pts leading to dose reduction or discontinuation. Other G2 or 3 side effects were fatigue, nausea and diarrhea: they were more common in old-old than in younger-old pts (86% and 69% respectively). Among pts receiving FP-based therapy, dose reductions were necessary in 15 pts (42%) due to fatigue, nausea and diarrhea: 6 pts were oldest-old and 9 pts were old-old. None of 7 younger-old pts reduced or discontinued chemotherapy. Seven of 28 pts (25%) treated with oxaliplatin + FP and 17/35 pts (48%) receiving monochemotherapy developed metastases with a median DFS of 13 (range 6-35) and 18 months (range 6-52) respectively.

Conclusions. Our observation confirms that in elderly pts adjuvant chemotherapy containing oxaliplatin and FP is feasible and is associated with fewer relapses. However the neurologic toxicity is frequent, particularly in pts older than 70.

A35 CAN CARDIO-VASCULAR TOXICITY AND BMI EVALUATIONS PREDICT OUTCOMES IN PATIENTS TREATED WITH CHEMOTHERAPY PLUS BEVACIZUMAB FOR METASTATIC COLORECTAL CANCER?

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Background. The combination of bevacizumab with FOLFIRI or FOLFOX is recognised as a standard therapeutic regimen for metastatic colorectal cancer (mCRC). The occurrence of hypertension is currently being discussed as a surrogate marker for efficacy in patients treated with antiangiogenic agents. A high Body Mass Index (BMI) has been associated with an increased risk of recurrence and death in CRC patients. In the present study, the relationship between clinical outcomes and cardiovascular toxicity of such regimens as first-line therapy in mCRC patients was analyzed. Moreover tumour response was regarded according to BMI.

Patients and methods. Patients included in the study had an ECOG PS ≤2 and underwent at least three chemotherapy cycles. ECG was performed every 3 months. Clinical responses were evaluated according to RECIST criteria while toxicity according to CTCAE v3.0. BMI was categorized as follows: ≤25 and >25 kg/m^2.

Results. Eighty-seven patients were enrolled: 54 males and 30 female; median age: 61.6 years, range 31-76; 73% colon, 27% rectum; 68% liver metastases, 37% lung metastases; 87% bevacizumab plus FOLFIRI, 13% bevacizumab plus FOLFOX; 54% BMI = 25. Overall 77% of the cases obtained a clinical benefit: CR: 3%, PR: 38%, SD: 36%. Twelve patients experienced G3-4 cardiovascular adverse events: 4.6% hypertension; 5.7% venous thrombosis; 3.4% arterial thrombosis. There was a significant association between the occurrence of G3-4 hypertension and clinical response ($p < 0.05$). Moreover clinical responses were more frequent in patients with a BMI = 25 with respect to the others (Table).

A35 - Table

	G3-4 Hypertension			BMI		
	yes	not		≤25	>25	
Responders (CR+PR)	4	31	<0.05	26	9	<0.01
Non-Responders	0	52		21	31	
Total	4	83		47	40	

Conclusions. Both the occurrence of high grade hypertension and a BMI ≤25 appeared associated with positive clinical outcomes in patients with mCRC treated with chemotherapy and bevacizumab.

A36 SECOND-LINE TREATMENT WITH INTRA-ARTERIAL INFUSION OF IRINOTECAN-LOADED DRUG-ELUTING BEADS (DEBIRI) VERSUS INTRAVENOUS THERAPY (FOLFIRI) FOR HEPATIC METASTASES FROM COLORECTAL CANCER: A PHASE III STUDY

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Background. Metastases to the liver receive most of their blood supply from the arterial route, therefore for patients with hepatic metastases from large bowel cancer, hepatic arterial infusion adopting drug-eluting beads preloaded with irinotecan (DEBIRI) may offer a chance of cure.

Patients and methods. In a multi-institutional study, 74 patients were randomly assigned to receive DEBIRI (36) versus systemic irinotecan, fluorouracil and leucovorin (FOLFIRI, 38). The primary endpoint was survival; secondary endpoints were response, recurrence, toxicity, quality of life, cost and influence of molecular markers.

Results. At 50 months, overall survival was significantly longer for patients treated with DEBIRI than those treated with FOLFIRI (p = 0.031, log-rank). Median survival was 22 (95% CI 21-23) months, for DEBIRI and 15 (95% CI 12-18) months for FOLFIRI. Progression-free survival was 7 (95% CI 3-11) months in the DEBIRI group compared to 4 (95% CI 3-5) months in the FOLFIRI group and the difference between groups was statistically significant (p = 0.006, log-rank). Extrahepatic progression had occurred in all patients by the end of the study, at a median time of 13 (95% CI 10-16) months in the DEBIRI group compared to 9 (95% CI 5-13) months in the FOLFIRI group. A statistically significant difference between groups was not observed (p = 0.064, log-rank). The median time for duration of improvement to quality of life was 8 (95% CI 3-13) months in the DEBIRI group and 3 (95% CI 2-4) months in the FOLFIRI group. The difference in duration of improvement was statistically significant (p = 0.00002, log-rank).

Conclusions. This study showed a statistically significant difference between DEBIRI and FOLFIRI for overall survival (7 months), progression-free survival (3 months) and quality of life (5 months). In addition, a clinically significant improvement in time to extrahepatic progression (4 months) was observed for DEBIRI, a reversal of the expectation for a regional treatment. This suggests a benefit of DEBIRI treatment over standard chemotherapy and serves to establish the expected difference between these two treatment options for planning future large randomized studies.

A37 NEGATIVE INFLUENCE OF SMOKING CONTINUATION ON THE THERAPY COMBINED WITH BEVACIZUMAB IN PATIENTS WITH ADVANCED COLON CANCER

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Background. It is well known that cigarette smoking is the most important cause of lung cancer and other types of tumor. We set out to analyze the role of cigarette smoking in patients undergoing chemotherapy combined with bevacizumab at the Veneto Oncology Institute IRCCS in Padua (Italy) in order to see if the smoking continuation during chemotherapy treatments affects positive results.

Material and methods. It is an observational monoistitutional analysis that covers 187 patients (59% male) undergoing chemotherapy in combination with bevacizumab for the treatment of colon and rectum cancer and included in the Onco-AIFA national register for monitoring of innovative anticancer drugs. The observation period begins in June 2006 and finishes in February 2012. From the Onco-AIFA register we obtained the personal data as well as the pathology and treatment details, while from hospital discharge records and medical records we were able to acquire socio-demographic information and the number of health benefits. The Kaplan-Meier method was used to analyze the overall survival (OS) and progression-free survival (PFS) data.

Results. Among the information collected we concentrated on the data related to smoking and we found out that 55% of patients were non-smokers, 26% smokers and the remaining 19% ex-smokers. We observed responses to treatment for 183 patients (98%): 5 complete response (3%), 51 partial response (27%), 93 stable disease (50%), 34 progressive disease (18%). The study revealed that being a smoker is a determinant of the OS of patients: in particular non-smokers showed a median survival of 25 months, ex-smokers of 20 and smokers of 17 (p = 0.021). The median PFS was calculated for 166 patients and it was 12 months for non-smokers, 10 ex-smokers and 7 smokers (p = 0.036).

Conclusions. It should be noted that in the whole sample of patients the smoking continuation reduces survival. Therefore, in addition to an increased risk, there is a reduced benefit in terms of clinical conditions and response since cigarette smoking reduces the effects of anticancer chemotherapy.

A38 PROGNOSTIC VALUE OF CIRCULATING TUMOR CELLS IN PATIENTS WITH METASTATIC COLORECTAL CANCER

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Introduction. Despite the important progress in the treatment, metastatic colorectal cancer (MCRC) remains a poor prognosis neoplasm. We investigated whether the presence of circulating tumor cells (CTCs) predicts treatment efficacy and progression-free survival (PFS) in patients with newly diagnosed MCRC who were about to start first-line therapy.

Patients and methods. Between January 2011 and September 2012, 43 patients with MCRC were evaluated for the presence of CTCs. In this study a cut-off different from the most widely employed in the literature (≥1 vs ≥3 CTCs) was used. The patients (21 male and 22 female) had a median age of 63.25 years (range 40-81yrs). Enumeration of CTCs in 7.5 mL of blood was carried out with the FDA-cleared Cell Search system. CTCs count was performed before the start of first-line therapy.

Results. CTCs were detected in 20 patients (46.5%, median age 65.25 yrs, range 46-80 yrs); 23 patients (53.5%, median age 61.35 yrs, range 40-81 yrs) had a value of CTCs = 0. At a median follow-up of 13 months the median PFS was 5.2 months for patients with a value of CTCs ≥1 and 9.6 months for patients with a value of CTCs = 0 (p <0.0001). To date there is not yet a sufficient number of events in order to calculate the median overall survival (OS) of patients.

No significant correlation was found among the presence of CTCs and other clinico-pathological parameters such as: site of metastasis, histological type and performance status.

Conclusions. Our data confirm the literature knowledge. The detection of CTCs before initiation of first-line therapy is highly predictive of poor prognosis in patients with MCRC. The value of CTCs ≥1 could be a valid alternative cut-off to use in further studies.

A39 PANITUMUMAB AFTER PROGRESSION ON CETUXIMAB IN PATIENTS WITH KRAS WILD-TYPE (WT) METASTATIC COLORECTAL CANCER (MCRC). A SINGLE INSTITUTE EXPERIENCE

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Background. Cetuximab and panitumumab are monoclonal antibodies (moAbs) that target EGFR, approved for the treatment of KRAS WT MCRC. Few data describe the activity of panitumumab after cetuximab-irinotecan based regimen failure.

Material and methods. The aim of this study is to assess if panitumumab has some activity in pts with KRAS WT MCRC that has progressed on prior cetuximab.

Results. We retrospectively analysed 25 pts with KRAS WT MCRC who received from 07/2009 to 01/2013 panitumumab after progression on cetuximab. Median age was 63 yrs (40-78), primary site tumor: colon 64%, rectum 36%; synchronous metastases 36%, metachronous 64%. The sites of metastases were only liver 44%, liver and lung 8%, other sites 48%. All pts had previously received cetuximab associated with irinotecan (20 pts) or oxaliplatin (5 pts) and subsequently received panitumumab. We withdrew cetuximab because of intolerance in 4 pts (16%), while 21 pts (84%) with ECOG PS 0-1 who had previously responded to cetuximab (ORR plus SD lasting more than 5 months) received panitumumab "off-label" after progression on cetuximab because strongly motivated to continue treatment without chemotherapy. Median cycles of panitumumab were 7 (1-54). Twenty pts were evaluable for ORR (5 pts received 1-2 cycles and then died). We observed one PR (5%); five pts (25%) had SD with a median duration of 9 months. Median PFS was 5 months (3-28) and median OS 8 months (5-41). All pts were evaluable for toxicity. No patient developed anemia, nor neutropenia. One patient (4%) developed grade 2 CTCAE version 4.03 thrombocytopenia. Eight pts (32%) developed grade 2-3 CTCAE version 4.03 dry skin or rash, 2 pts (8%) grade 2 CTCAE version 4.03 nausea-vomiting.

Conclusions. Panitumumab has minimal benefit in pts with KRAS WT MCRC who have progressed on prior cetuximab and this approach up to date should not be adopted in the clinical practice. Our data anyway, with all the limits of a retrospective analysis, show a longer PFS and OS as compared to other few series in the same setting. Further confirmatory prospective studies with larger series of pts would be necessary.

A40 BEVACIZUMAB RELATED TOXICITY IN METASTATIC COLORECTAL CANCER (MCRC). A SINGLE INSTITUTION EXPERIENCE

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Background. Bevacizumab (Bev) is the first antiangiogenic agent proven to extend survival in association with 5-fluorouracil-based chemotherapy regimens in mCRC. It has been approved in first- and second-line treatment for mCRC; it is well tolerated, its side effects are predictable and it does not modify toxicity profile in the treatment of mCRC. This study evaluated the safety of Bev combined with first-line chemotherapy in patients (pts) with previously untreated mCRC.

Patients and methods. Between October 2010 and March 2013, 55 consecutive patients with mCRC were treated with Bev based chemotherapy. The median age was 62 yrs (63% under 65 yrs and 37% over 65 yrs), 33 pts male (60%), 22 female (40%), 39 (70%) resected and 16 (30%) unresected primary tumors; 20 (36 %) showed only liver metastases, 5 (9 %) only lung metastases, 10 (18%) combined liver and lung metastases, 6 (10%) liver, lung and limph nodes metastases, 4 (7%) peritoneal carcinosis, 3 (5%) bone metastases. They received chemotherapy plus Bev 5 mg/kg every 2 weeks (B-Folfiri) or 7.5 mg/kg every 3 weeks (B-capecitabine) both followed by maintenance with Bev 7.5 mg/kg q21. Patients were evaluated for adverse events (AEs) and serious adverse events (SAEs), graded according to National Cancer Institute Common Terminology Criteria for AEs (version 3).

Results. Eligible pts received Bev combined with chemotherapy for a median of 20 weeks and Bev alone as maintenance for a median of 15 weeks. No reported cases of wound healing, congestive heart failure and reversible posterior leukoencephalopathy syndrome. We also reported a head femoral osteonecrosis (1 pt). Mortality for AEs was 1.8 % for gastrointestinal (GI) perforation (1 pt). Bev was temporarily suspended in 2 pts (3%) cause of proteinuria G1-2 and it was permanently suspended in 7 pts (13%) 1 (1.8%) for venous thromboembolism, 3 (5%) for GI perforation, 1 (1.8%) for arterial thromboembolism, 1 (1.8%) for bowel obstruction, 1 (1.8%) for medical treatment required.

Conclusions. Bev was generally well tolerated and its safety profile in routine clinical practice is consistent with results observed in prospective randomized clinical trials and large observational study (BEAT and BRiTE).

A40 - Table

Main toxicities	Grade 1-2 (%)	Grade 3-4 (%)
Arterial hypertension	13 (24%)	-
Proteinuria	2 (3%)	-
Bleeding	4 (7%)	-
Gastrointestinal perforation	-	3 (5%)
Arterial thromboembolism	-	1 (1.8%)
Venous thromboembolism	1 (1.8%)	1 (1.8%)

A41 MAINTENANCE THERAPY WITH BEVACIZUMAB ALONE AFTER INDUCTION CHEMOTHERAPY (CHT) + BEVACIZUMAB (BEV) IN METASTATIC COLORECTAL CANCER (MCRC) PATIENTS: IS IT ALWAYS OF BENEFIT?

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Background. Standard options for mCRC treatment include FOLFOX/XELOX/FOLFIRI/XELIRI CHT regimens together with BEV in mutated KRAS patients. Different studies have consistently demonstrated that the addition of BEV to CHT improves ORR, PFS and OS in comparison to CHT alone. On the contrary, few data are available at the moment about the real benefit of maintaining BEV beyond CHT, in particular in those pts who did not achieve ORR (CR+PR).

Patients and methods. We retrospectively reviewed the data of 37 mCRC pts treated at our Institution from 01/2008 to 01/2011 with FOLFIRI (N = 21), FOLFOX (N = 13) or FOLFOXIRI (N = 3) as 1st- or 2nd-line CHT in combination with BEV at standard doses. Median age was 66 years (26-81), Male/Female ratio was 22/15; 26 pts received 1st-line CHT and 11 2nd-line therapy. Median DFI was 13 months (6-44 months). All pts had visceral site involvement. Median number of cycles received as 1st-line CHT was 12 (10-12) and 12 (10-12) as 2nd-line CHT. Disease restaging was planned after 6 and 12 cycles. In the case of PD, BEV with 2nd-line CHT was allowed. Median number of BEV maintenance cycles was 11 (3-48). Objective responses at the end of the 6th cycle were: CR + PR = 26/37 (70.2%), SD 11/37 (29.8%). Among those pts who showed OR during induction therapy, 35% of them progressed during maintenance therapy, in comparison to 18.2% of those with SD. Among these latter pts, 27.3% of them reported a better response during maintenance BEV (3/11, 27.3%) (Table 1).

Table 1 - OR during induction and maintenance therapy according to previous response

	Induction phase (6th cycle)	Maintenance therapy (6th cycle)		
		OR	SD	PD
CR + PR	26/37 (70.2%)	17/26 (65%)	0/26 (0%)	9/26 (35%)
SD	11/37 (29.8%)	3/11 (27.3%)	6/11 (54.5%)	2/11 (18.2%)

Conclusions. Maintenance therapy with BEV seems to be of benefit independently of response to previous induction therapy with CHT and BEV. Further data are warranted to confirm these results.

A42 EFFECTIVENESS AND SAFETY OF INTENSIVE TRIPLET CHEMOTHERAPY PLUS BEVACIZUMAB, FIR-B/FOX, IN YOUNG-ELDERLY METASTATIC COLORECTAL CANCER (MCRC) PATIENTS

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Background. Triplet chemotherapy plus bevacizumab (FIr-B/FOx) can increase efficacy in first-line metastatic colorectal cancer. Effectiveness was evaluated in fit young-elderly patients.

Patients and methods. FIr-B/FOx schedule weekly 2 days/12h-timed-flat-infusion/5-fluorouracil 900 mg/m^2, weekly alternating irinotecan 160 mg/m^2/bevacizumab 5 mg/kg, or oxaliplatin 80 mg/m^2. KRAS codon 12/13 and BRAF c.1799 T >A mutations were screened by SNaPshot and/or sequencing. MCRC were classified as liver-limited and other multiple metastatic. Activity, efficacy were evaluated and compared, using log-rank test; individual limiting toxicity syndromes, using chi-square test.

Results. Enrolled young-elderly, 28; median follow-up, 17 months; objective response rate 79%, median progression-free survival 11 months, liver metastasectomies 18%, 37.5% in liver-limited, median overall survival 21 months. According to KRAS genotype, objective response rate, progression-free survival and overall survival: wild-type 92%, 14 months, 38 months; mutant 77%, 7 months, 19 months. Clinical outcome was significantly different in liver-limited compared to other multiple metastatic, while not according to KRAS genotype. G3-4 toxicities: diarrhea 21%, mucositis 11%, neutropenia 11%. Limiting toxicity syndromes were 46%, significantly more multiple than single site (39% versus 7%, chi square 3.832).

Conclusions. FIr-B/FOx is highly effective and tolerable, with significantly increased limiting toxicity syndromes multiple sites, in fit young-elderly metastatic colorectal cancer patients. Clinical outcome may be significantly prolonged in liver-limited, compared to other multiple metastatic.

A43 EVALUATION OF COLORECTAL CANCER (CRC) PATIENTS ENROLLED IN CLINICAL TRIALS BETWEEN 2002-2013 AT MEDICAL ONCOLOGY UNIT OF BOLOGNA ST ORSOLA MALPIGHI HOSPITAL

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Background. The systematic information of rates and characteristics of CRC patients (pts) enrolled in clinical trials in oncology centers are lacking. The aim of this analysis is to evaluate the enrollment in a single oncology unit according to different settings of CRC patients.

Methods. The pts referred to the Medical Oncology of S. Orsola-Malpighi Hospital are recorded in a specific data base (Fyle MakerPro-6). From January 2002 to March 2013 2,412 CRC pts were registered. We evaluated individual clinical data records for all registered CRC pts, including pts put on a treatment program and those enrolled in clinical trials.

Results. 1,420/2,412 (58.8%) started a therapeutic program: 1,010 (71.1%) with colon cancer, and 410 (28.9%) rectal cancer. 422/1,420 (30%) pts were enrolled in clinical trials. Patients characteristics: 257 (61%) male, 165 (39%) female; median age 65 years (25-87); median ECOG-PS 0 (0-1). Distribution of pts by type of clinical trial was: 84 (20%) pts in profit studies, 313 (74%) pts in no-profit studies, 25(6%) pts in observational studies. The distribution of CRC pts enrolled in clinical trials by site, age and treatment setting is reported in Table 1.
The distribution of pts in two different time periods by age is reported in Table 2.

Conclusions. This analysis shows a satisfactory percentage (30%) of pt enrollment in clinical trials, with a predominance of studies on first-line chemotherapy for metastatic disease and ade-

A43 - Table 1

Treatment setting	All patients	Age ≤65 colon	Age ≤65 rectum	Age >65-75 colon	Age >65-75 rectum	Age >75 colon	Age >75 rectum
Neoadjuvant	58 (13.7%)	0	22 (32.3%)	0	22 (41.5%)	0	14 (61%)
Adjuvant	13 (3.1%)	7 (5%)	4 (5.9%)	2 (2.1%)	0	0	0
Metastatic 1st line	195 (46.2%)	79 (57.2%)	28 (41%)	58 (60.4%)	11 (20.7%)	17 (38.6%)	2 (8.7%)
Metastatic 2nd line	24 (5.7%)	5 (3.6%)	6 (8.8%)	4 (4.2%)	6 (11.3%)	2 (4.5%)	1 (4.3%)
Observational	132 (31.3%)	47 (34%)	8 (11.7%)	32 (33.3%)	14 (26.4%)	25 (56.8%)	6 (26%)
Total	422 (100%)	138 (100%)	68 (100%)	96 (100%)	53 (100%)	44 (100%)	23 (100%)

A43 - Table 2

Period	Age≤65 years	Age >65-75 years	Age >75 years
2002-2006	64 (31%)	74 (49.6%)	23 (34.3%)
2007-2013 (first quarter)	142 (69%)	75 (50.4%)	44 (65.7%)
Total	206 (100%)	149 (100%)	67 (100%)

quate inclusion of elderly patients.The elderly pts rate has progressively increased in recent years.

A44 POSTOPERATIVE DETECTION OF CIRCULATING TUMOR CELLS PREDICTS TUMOR RECURRENCE IN COLORECTAL CANCER PATIENTS

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Introduction. Circulating tumor cells are thought to play a crucial role in the development of distant metastases. Their detection in the blood of colorectal cancer patients may be linked to poor outcome, but current evidence is controversial.

Material and methods. Pre- and postoperative flow cytometric analysis of blood samples was carried out in 76 colorectal cancer patients undergoing surgical resection. The EpCAM/CD326 epithelial surface antigen was used to identify circulating tumor cells.

Results. Fifty-four (71%) patients showed circulating tumor cells preoperatively, and all metastatic patients showed high levels of circulating tumor cells. Surgical resection resulted in a significant decrease in the levels of circulating tumor cells. Among 69 patients undergoing radical surgery, sixteen had high postoperative levels of circulating tumor cells, and twelve (75%) experienced tumor recurrence. Postoperative high level of circulating tumor cells was the only independent variable related to cancer relapse. In patients without circulating tumor cells, the progression-free survival rate increased from 16% to 86%, with a reduction in the risk of tumor relapse greater than 90%.

Conclusions. High postoperative levels of circulating tumor cells accurately predicted tumor recurrence, suggesting that assessment of circulating tumor cells could optimize tailored management of colorectal cancer patients.

A45 CIRCULATING TRYPTASE AND C-KIT EXPRESSING CELLS AS NOVEL BIO-MARKERS OR MOLECULAR PHARMACOLOGICAL TARGETS IN COLORECTAL CANCER PATIENTS: A PILOT STUDY

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Background. Data from tumour models suggest that mast cells (MCs) accumulate near tumour cells before angiogenesis onset and that they are required for primary tumour progression. Tryptase, a serin protease stored in MC granules, plays a fundamental role in angiogenesis. MCs can release tryptase following c-Kit receptor activation. Here, we assess tryptase serum levels in colorectal cancer patients (CRC) before and after radical surgery resection and c-Kit expressing cells in primary tumour tissue to evaluate their possible clinical-biological significance.

Material and methods. Seventy-one patients with stage B and C CRC were selected. Samples of blood were taken from CRC patients 1 day before and after surgical resection. Venous blood was dispensed into a tube for serum (Becton Dickinson Hemogard Vacutainer Systems, Plymouth, UK). Serum blood samples were centrifuged at 1,500g for 10 minutes and then aliquoted and frozen at -80 °C. Tryptase levels were measured using the UniCAP Tryptase Fluoroenzymeimmunoassay (Pharmacia,Uppsala, Sweden). In addition, primary tissue section were immunostained with a primary anti c-Kit antibody (A4502**;** Dako, Glostrup, Denmark) by mean of immunohistochemistry.

Results. Mean ± s.d. tryptase level was 6.57 ± 4.51 μg/L and 4.92 ± 3.71 μg/L pre and post-tumour surgical resection, respectively. A statistically significant difference between pre and post-tumour surgical resection tryptase level concentrations was found ($p = 0.000$) by Student t-test. A strong correlation between pre-tumour surgical tryptase level and c-Kit expressing cells was also found ($r = 0.82$, $p = 0.000$). No correlation among tryptase levels, c-Kit expressing cells and the main clinical-pathological features were found.

Conclusions. Our results demonstrated higher serum tryptase levels in CRC patients before surgical treatment, suggesting the

release of tryptase from c-Kit positive infiltrating cells in primary CRC tissue. On the other hand, tryptase levels decreased after surgery. We suggest that tryptase may play a role as a novel biomarker in CRC patients. In this context, tryptase inhibitors, such as gabexate and nafamostat mesilate, might be evaluated in adjuvant clinical trials as a new anti-angiogenetic approach.

A46 CONSERVATIVE TREATMENTS IN EARLY DISTAL RECTUM AND ANAL ADENOCARCINOMA

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Background. The standard radical treatment for early stage anal adenocarcinoma and very distal rectum is abdomino-perineal amputation. We retrospectively reviewed a small series of three patients with this pathology, who refused radical surgery after local excision. Treatment outcome and functional preservation of anal sphincter were evaluated.

Material and methods. From March 2012 to February 2013 three patients were treated with adjuvant radiotherapy after local excision of ano-rectal adenocarcinoma. Median age was 63 years (range 57-79), 1 was male and 2 female. Two patients had a pT2 cN0M0 anal adenocarcinoma (1 grade 2, 1 grade 3), and the other one pT1 cN0M0 rectal disease (grade 2, free deep margin <1 mm) near anal sphincter. All the patients had been informed on the standard treatment, but refused it. So that, an adjuvant treatment had been proposed: the first patient was treated with pelvic intensity modulated radiotherapy up to 48 Gy, 2 Gy/fraction (fz), followed by endocavitary high dose rate (HDR) brachytherapy, 10 Gy, 5 Gy/fz. The second patient was treated with pelvic external beam 3D radiotherapy, 46.8 Gy, 1.8 Gy/fz, followed by endorectal HDR brachytherapy boost, 8 Gy, 4 Gy/fz, to the surgical bed. The third patient, that had already undergone pelvic irradiation (45 Gy with Cobalto 60) 22 years before, was treated with only endocavitary HDR brachytherapy, 40 Gy (32 Gy to the entire anal canal, 8 Gy on half involved canal), 4 Gy/fz.

Results. After a median follow-up of 12 months (range 3-14) all the patients are disease-free, and sphincterial function is preserved.

Conclusions. According to our data, conservative treatment of adenocarcinoma of distal rectum and anal canal could be feasible, but these interesting results must be confirmed by larger series and longer follow-up.

A47 GENOTYPING ANALYSIS IN A PATIENT WITH SEVERE HYPERTRIGLYCERIDAEMIA INDUCED BY CAPECITABINE

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Background. Capecitabine is known to rarely cause raised serum triglycerides (TG). Today, the exact mechanism of this adverse event remains enigmatic. Herein, we report results of genotyping analysis in a patient who developed severe hypertriglyceridemia, during capecitabine treatment in combination with oxaliplatin.

Patients and methods. A stage III rectal cancer patient, female and 52-year-old, was treated with oral capecitabine 2500 mg/m^2 divided in two daily doses for 14 days on a 21-day cycle for eight cycles**.** Twelve weeks after the start of capecitabine treatment, a lipid profile was performed revealing a marked increase in the serum level of TG (1292 mg/dL) without any modification in total cholesterol. After treatment discontinuation, we studied the patient genetic profile from whole blood sample. DNA was purified with the QIAamp DNA Mini Kit. The 5-FU pharmacogenomic profile was performed with the "fluoropyrimidines response" kit (Diatech, Jesi, AN, Italy) evaluating the presence of the following genetic markers: the methylenetetrahydrofolate reductase (MTHFR) gene C677T and A1298C polymorphisms, the dihydropyrimidine dehydrogenase gene (DPYD) and the thymidylate synthase promoter (TSER) 28bpVNTR. Polymorphisms of MTR (Methionine synthase) gene A2756G were analyzed by Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP). Total plasma homocysteine (tHcy) concentration was measured by high-performance liquid chromatography (HPLC).

Results. Genetic analysis evidences in patient's blood: i) heterozygosis (C/T) at MTHFR C677T gene marker and MTHFR A1298C (A/C), both associated with reduced enzyme activity inducing increased Hcy levels and altered distribution of intracellular folate; ii) mutation (2R/2R) at TSER 28bp VNTR, associated with a significant increase in the incidence of adverse events; iii) DPYD profile (G/G) and MTR profile (A/A) were wild type. After treatment discontinuation, serum TG rapidly returned to baseline level.

Conclusions. Heterozygosis C/T at MTHFR gene is associated with high concentration of both TG and tHcy. Genotype MTR A/A is correlated with a normal serum level of total cholesterol. These results strongly suggest to check dyslipidemia and particularly hypertriglyceridemia during capecitabine chemotherapy.

A48 BONE METASTASIS IN RECTAL ADENOCARCINOMA WITH HIGH LEVEL OF ALPHA-FETOPROTEIN, SUCCESSFULLY TREATED WITH CHEMOTHERAPY: A CASE REPORT AND REVIEW OF LITERATURE

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Introduction. High levels of alpha-fetoprotein (AFP) have been described in a marginal percentage of gastro-intestinal neoplasms. This anecdotic literature data was reported for the first time in a Mayo Clinic retrospective study in 1975, and subsequently in one similar Asiatic case report but occurring with liver involvement. We describe a case of rectal adenocarcinoma with increase of AFP successfully treated with chemotherapy.

Methods. A medline search was conducted to review the literature for cases of increase of AFP in colorectal cancer. We report a case of a 62-year-old caucasian man with history of rectal adenocarcinoma (AJCC 2002 stage II) diagnosed on December 2008, treated with concomitant radiochemotherapy, obtaining a complete response. In 2010 back pain was related to occurrence of bone metastases, subsequently confirmed with 99mTc methylene diphosphonate (MDP). Bone biopsy revealed poorly differentiated adenocarcinoma with immunohistochemical profile: Cytocheratine 7-, Cytocheratine 20+, CDX2+, PSA-, TTF1-, Cytocheratine LMWCK+, Cytocheratine HMWCK-, EGFR+ (score 3+) as intestinal primary. Laboratory tests showed high levels of carcinoembryonic antigen (CEA) 449.27 ng/dL and AFP 13,741 ng/mL. No germinal component was revealed on histopathology and the occurrence of a second tumor was excluded. Infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX-4) was given from December 2010 to July 2011 (for a total of 12 chemotherapy cycles). CT scan, 18F-fluoro-D-glucose Positron Emission Tomography (18F-FDG-PET) and CEA evaluation were performed at baseline and repeated every 9 weeks. AFP evaluation was examined on every course.

Results. After first chemotherapy course the AFP value reduced from 13,741 ng/mL to 4,499 ng/mL. After third cycle AFP was 61 ng/mL. We reported a complete response according to RECIST and confirmed to 18F-FDG-PET after twelve courses of chemotherapy. Patient did not receive any additional treatment, and to date there is no evidence of disease recurrence. Subsequent AFP dosage was always in normal range. No severe toxicity was described.

Conclusions. An unusual condition, single bone metastasis with increased AFP value, from rectal cancer was successfully treated with standard chemotherapy achieving a complete disease control 53 months after diagnosis. To date the prognostic role of AFP in colorectal cancer is uncertain.

A49 CORRELATION BETWEEN BIOLOGICAL AGENT BASED REGIMENS AS FIRST-LINE TREATMENT AND OUTCOMES IN PATIENTS WITH KRAS WILD TYPE METASTATIC COLORECTAL CANCER (mCRC)

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Background. In the last few years, the treatment of mCRC has been changed by the introduction of biological agents in our clinical practice. Among patients (pts) with mCRC the presence of KRAS wild type (wt) status defines a clinical subset that benefits not only from the use of cetuximab but also of bevacizumab. Nowadays there is not a standard treatment as first-line in this subgroup.

Methods. In this observational, single-institution, retrospective study we analyzed, from April 2008 to April 2013, 33 pts with a histological confirmed diagnosis of mCRC and KRAS wt status. The aim of the study is to evaluate the correlation between the use of one biological agent (cetuximab, bevacizumab) and another one, used in combination with chemotherapy regimens in first-line therapy and the impact on PFS and OS.

Results. Median age was 61.8 years (range 38-79), 19 male (57.5%). Twenty-five pts (75.7%) had a performance status (PS) ECOG 0; 1 pt (3%) PS 1, 2 pts (6%) PS 2. All pts had a metastatic disease, the liver was the most common site of localization in 22 pts (66.6%). Treatment: 17 pts (51.5%) received cetuximab based regimens (C-R); 16 pts (48.4%) were treated with bevacizumab based regimens (B-R). The median progression-free survival (PFS) was 12.87 mos (range 2-36) in C-R and 12.25 mos (range 3-25) in B-R, the relationship between mPFS wasn't statistically significant. The mOS was 30.17 mos (range 2-65) in C-R and 25.25 mos (range 4-64) in B-R; this data was analyzed by standard statistical test but it wasn't significant (p values 0.45). In the C-R we reported the following toxicity: skin 1 pt (3%) G1, 2 pts (6%) G2, 1 pt (3%) G3, gastrointestinal 2 pts (6%) G1, 2 pts (6%) G2, 2 pts (6%) G3, asthenia 1 pt (3%) G2, and neutropenia 1 pt (3%) G2. In the B-R we highlighted asthenia 1 pt (3%) G3, thrombocytopenia 1 pt (3%) G2, hypertension 1 pt (3%) G2, and proteinuria 1 pt (3%).

Conclusions. Our data are limited by the small sample size and didn't detect any difference in PFS and OS that could guide clinicians to choose a treatment rather than another, but in the C-R group was reported a trend in favor of OS. Probably a randomized prospective study with cetuximab based regimen followed by bevacizumab based regimen or reverse sequence treatment therapy could highlight the best strategy.

A50 WHEN PET IS MISLEADING IN COLON CANCER: A CASE REPORT AND REVIEW OF LITERATURE

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Background. PET is gaining growing importance in preoperative staging of many cancers but false positive results could lead to a wrong diagnosis and both overtreatment or undertreatment.

Materials and methods. The patient was a 66 years old female, referred to our hospital in 2010 with a diagnosis of sigmoid colon adenocarcinoma (pT2 pN2 G1). She underwent adjuvant chemotherapy with FOLFOX4 schedule for 10 cycles and the last two cycles with the only De Gramont schedule for systemic reaction to oxaliplatin. In 06/2012 at CT and PET scan evidence of mediastinal and lumbar nodes and hepatic neoformation (S VII) CT-scan negative, but PET-scan positive. Hepatic biopsy confirmed a metastasis from colon cancer. Notwithstanding a bronchial needle-aspiration (06/2012) negative for tumor cells with rare lymphoid and metaplastic epithelial ciliar cells, surgeons, considering the patient as affected by systemic metastatic disease, were reluctant to perform hepatic surgery. For this reason a long discussion went on for weeks. The patient, on the other hand, didn't want to undergo chemotherapy at all. Finally a mediastinoscopy (11/2012) was performed and in PET positive nodes granulomatous lymphadenitis epithelioid sarcoid-like with signs of hyalinosis was detected.

Results. At last in January 2013 hepatic subsegmentation was performed with diagnosis of colon metastasis while granulomatous chronic process sarcoid-like was evidenced at histological typing of lumbar nodes. At 6 months follow-up the patient is disease-free.

Conclusions. In literature few data refer to sarcoid reactions in malignant tumors: 1 case in hepatocellular carcinoma, 2 in early gastric carcinoma; 13 cases in breast cancer; some in melanoma, testicular neoplasia and Hodgkin's and non-Hodgkin's disease; few cases in lung cancer. Some of the authors assume that sarcoid reaction may be a marker of an immunologically mediated antitumor response of macrophages activated by T-lymphocytes and this to be related with a better prognosis. It is known that in granulomatosis PET scan may result positive. Our case confirms the common view that PET cannot ever avoid histology if the positivity may change definitively a surgical approach. Our patient could have been treated with useless systemic chemotherapy instead of curative surgery. This evaluation may have a relevant impact from a clinical but also ethical and economic point of view.

A51 SUCCESSFUL TREATMENT WITH MAINTENANCE CETUXIMAB AFTER FOLFIRI/CETUXIMAB AS FIRST-LINE THERAPY IN A PATIENT AFFECTED WITH PRIMARY COLON CANCER (CRC) AND SYNCHRONOUS UNRESECTABLE LIVER METASTASES. A CASE REPORT

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Introduction. For most patients with metastatic CRC, treatment is palliative rather than curative. The improved understanding of the underlying pathology and molecular biology has successfully merged with advances in diagnostic techniques and local/systemic therapies. However, only a small proportion of patients with inoperable liver metastases can be converted to a potentially curable state through surgical resection after systemic therapy.

Case report. We report the case of a 58-years-old man who came to our observation in February 2011 with a stenosing G3 adenocarcinoma of the sigmoid colon and multiple liver metastases. No K-ras mutations in codons 12 and 13 were detected. As the patient was defined inoperable an endoprothesis was placed in the sigma and a first-line treatment according to the FOLFIRI/cetuximab regimen was started. The treatment was well tolerated, just a G2 face and chest skin rash and a G1 diarrhea were recorded, and after six courses a CT scan showed a reduction in the number and size of liver lesions and of wall thickening of the sigmoid colon. Chemotherapy was continued up to 12 cycles and the subsequent evaluation showed a further reduction at both sites but the liver disease was not resectable yet. Maintenance cetuximab was given for six months. So nearly at one year from diagnosis the patient was re-evaluated by the surgeon and considered operable. On March 2012 the patient underwent a left hemicolectomy, resection of two liver lesions (S4) and regional nodes dissection (adenocarcinoma G2-G3, pT3 pN1a pM1). Two months later, after selective portal vein embolization, a right hepatectomy was performed and the histology confirmed multiple metastases from intestinal adenocarcinoma. No further treatment was given and after one year of follow-up the patient is still disease-free.

Conclusions. This case is an example of how the target-therapies such as cetuximab, associated with standard chemotherapy can further increase the number of patients with initially unresectable liver disease to be surgically operable. Our patient is still alive and free from recurrent disease after 27 months. The role of cetuximab as a "conversion or downstaging agent" able to increase resection rates, response rates, PFS and OS in the K-ras wild type population when added to irinotecan-based regimen without increasing the hepatotoxicity, is confirmed in this case report.

A52 CEA AND CA19.9 IN THE EARLY PREDICTION OF RESPONSE FROM FIRST-LINE CHEMOTHERAPY (CT) PLUS BEVACIZUMAB (BEV) IN METASTATIC COLORECTAL CANCER (MCRC)

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Background. In mCRC setting, translational research studies are increasingly aimed at discovery and validation of predictive factors for response to biological drugs. CEA and CA19.9 are biochemical mks routinely measured for monitoring treatment response in mCRC patients. Their predictive value during CT based on targeted agents has not been properly investigated. The objective of the present study was to evaluate the correlation between biochemical mks trend and corresponding pathologic response after four cycles of CT plus bev in mCRC patients.

Material and methods. Blood sampling was performed to evaluate mks values at baseline and on day 60 in 74 unresectable mCRC pts, treated in first-line with biweekly bev-containing regimens; computed tomography (CT) scan was performed at baseline and every 3 months. Normal CEA and CA19.9 serum levels were considered if less than 5 ng/mL and 37 U/mL respectively. CT response was defined according to RECIST 1.1.

Results. At baseline sample, 48 out of 74 pts had abnormal mks values; other 26 pts presented normal levels. At the fourth bev doses, 40 out of 48 pts had mks decrease, 8 pts a further mks increase while other 26 pts still had normal values. Response rate (RR) was 42.5% in pts with mks decrease while 7 out of 8 pts with further mks increase showed a progression disease. Correlation between serum mks variations and CT responses amounted to 50% and proved to be statistically significant ($p = 0.04$; relative-risk 0.10; 95% CI: 0.01-0.94). Retrospectively was observed that pts with reduction of mks were 67.5% wild-type KRAS tumor, 45% wild-type BRAF tumor and 82.5% presented a single metastatic site. The mks reduction was on average of 55%. We compared in terms of RR and progression-free survival (PFS) pts with mks decrease ≤55% vs pts with mks decrease >55%. There were no statistically significant differences between two groups, in particular RRs were 53.3% mks decrease <55% pts vs 36% mks decrease >55% pts, $p = 0.3$; and PFS was 11 months in both groups, $p = 0.8$.

Conclusions. On the basis of our results, early CEA and

CA19.9 variation assessed after four cycles of CT plus bev predicts response to treatment in mCRC pts, but unfortunately the reduction level does not correlate with PFS.

A53 ACTIVITY OF ELECTROCHEMOTHERAPY (ECT) IN THE TREATMENT OF CUTANEOUS AND SUBCUTANEOUS METASTASES OF ADENOCARCINOMA OF THE RECTUM. A CASE REPORT

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Background. The incidence of cutaneous metastases from colorectal adenocarcinoma is rare (about 4-5%) and associated with a poor prognosis (median OS 3-18 months). Usually these lesions appear within 24 months after surgery and are partially sensitive to chemotherapy. Their management is often difficult and compromises the quality of life, with complications such as pain, bleeding, ulceration, and infectious processes. ECT has been tested successfully on unresectable or recurrent skin nodules of breast cancer, melanoma, basal cell carcinoma, Kaposi's sarcoma and head and neck cancer.

Materials and methods. We report the case of a 71-year-old woman with cutaneous and subcutaneous metastases from adenocarcinoma of the rectum submitted to one course of ECT. The skin metastases occurred three years after the abdominoperineal resection and progressed after various chemotherapy regimens. ECT course consisted in the infusion of bleomycin 27,000 IU and the subsequent insertion of the needle electrodes, with a hexagonal centered configuration on all the macroscopic lesions. After that the electroporation began by the application of a single electric pulse of 1 mAm. The treatment lasted 25 minutes.

Results. The patient obtained a complete response and an analgesic and hemostatic effect in all the nodules one month after the conclusion of ECT.

Conclusions. In our experience ECT has shown to be safe and well tolerated with an improvement in the quality of life. In the future we should investigate further how to increase the activity of ECT in combination with other interventions, such as radiation and target therapy.

Session B • Head and neck tumours

B1* SORAFENIB IN RECURRENT AND/OR METASTATIC SALIVARY GLAND CARCINOMAS (RMSGCS): A PHASE II TRIAL (NCT01703455)

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Background. Palliative chemotherapy is the standard treatment for RMSGCs, although clinical results are dismal and limited in the time. Anti-angiogenetic agents have demonstrated some activity in adenoid cystic carcinoma (ACC), suggesting a rationale to test these agents such as sorafenib, also in relapsed and/or metastatic histotypes other than ACC.

Materials and methods. Subjects with proven RMSGC were enrolled to receive sorafenib at 400 mg BID q28 days until disease progression, unacceptable toxicity or consent withdrawal. Primary endpoint was response rate (RR) according to RECIST; secondary objectives included RR according to CHOI criteria, disease control rate (DCR) and toxicity. Thirty-seven subjects were required to test the null hypothesis that RR will be ≤5% versus the alternative that RR ≥20% within a two stage Simon design. Four responders were necessary to reject the null hypothesis. Immunoistochemical analyses were performed on pretreatment FFPE samples to test PDGFRB, PDGFRA, VEGFR2, KIT and Myb expression; BRAF mutation was investigated by sequencing; MYB-NFIB and MECT1-MALM2 gene fusions were analyzed by FISH. Results 19 ACC and 18 non ACC subjects were accrued. Six PRs according to RECIST were assessed resulting in a RR of 16% (95% CI 6.2-32.0) (11% in ACC and 22% in non ACC). DCR was 76%; PR according to CHOI was observed in 10 cases. The AE profile was generally consistent with previous sorafenib studies; AEs >G3 were 24%. Median PFS was 9 months for ACC versus 4 months for non ACC (p = 0.0367). At a median follow-up of 12 months (range 7-28+ months): 3 patients are still receiving sorafenib, 14 are no longer being treated and 20 have died. Thirty-four out of 37 tissue samples were analyzed: all samples (100%) showed PDGFRB immunostaining restricted to stromal component, as well as VEGFR2 immunostaining in the endothelial cells. PDGFRA expression was observed in the stromal component of 25% of cases, whereas KIT expression was restricted to ACC (100%). Among ACC, IHC revealed Myb protein expression in 15/17 (88%) cases and the MYB-NFIB fusion oncogene was observed in 9/13 (69%). No MECT1-MAML2 fusion oncogene was identified in HG-MECs. No BRAF gene mutation was found in 32 samples. RET analysis is ongoing.

Conclusions. Sorafenib is active in RMSGCs. Molecular analyses failed to identify a correlation between the activity of sorafenib and its tailored targets; the anti-angiogenetic activity seems to be the main mechanism of action.

B2* BIOLOGICAL MARKERS IN TONGUE CANCER TREATED WITH RADICAL SURGERY

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Background. Squamocellular carcinoma of the tongue accounts for approximately 20% of head and neck cancers (HNC). It mainly affects men in the sixth decade of life. Known risk factors are smoking and alcohol consumption, but cases not supported by these risk factors are increasing worldwide. Radical surgery is the milestone of treatment for early local disease and can be a valid option, together with radiotherapy and chemoradiation (CRT) for locoregionally advanced forms.

Material and methods. Patients with local or locoregional squamocellular tongue cancer discussed in a multidisciplinary team and judged suitable for radical surgery between 2004 and 2011 were prospectively followed at San Paolo Hospital, Milan. Median age was 58 (range 37-82), males/females rate was 2:1. All pts underwent marginal tongue resection or hemiglossectomy. A selective neck dissection was performed in 57 cases (76%). Lymphonodal involvement was present in 24 cases while in 33 cases there was no evidence of nodal spread. Surgery was radical in all cases. An immunoistochemical evaluation of various biological markers was performed, namely EGFR, PDGFR, Bax, Bcl-2, VEGF-R and p53. Furthermore the presence of Human Papilloma Virus (HPV) infection in tumor specimens was analyzed by polymerase chain reaction with HPV L1 and HPV-11,16,18-specific E6-E7consensus primers.

Results. Seventy-five patients were operated and followed for a median period of 60 months. Among all patients PFS and OS were 73.4% and 86.2% respectively. Only 9 out of 75 (12%) expressed HPV and in this subgroup PFS and OS were 62.2% and 85.7% while PFS and OS in HPV negative pts were 74.7% and 86.1%. Median PFS and OS were not reached. No statistically significant correlation was found between these subgroups in terms of PFS and OS as no difference was found among the biomarkers analyzed and the same outcomes.

Conclusions. An accurate selection of candidates to radical surgery can improve PFS and OS. Our data indicate that HPV expression does not confer a better prognosis, confirming the different behavior of tongue cancer compared to oropharyngeal cancer. This preliminary observation needs to be further exploited in a larger trial. The expression of biological markers of apoptosis, angiogenesis and cell replication does not correlate with clinical outcomes, in line with current knowledge. New biological factors should be evaluated in order to find predictive and prognostic correlations.

B3* HPV16 DETECTION IN HNSCC AND CORRELATION WITH P16 EXPRESSION AND OVERALL SURVIVAL

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Background. We sought to determine the presence of Human papillomavirus type 16 (HPV16) in tumor samples from patients (pts) with locally advanced HNSCC through E1, E6 and L1 viral fragments detection. Our aim was to establish their prognostic role in oropharynx tumors (OT) and in non-OT, then to correlate positive (pos) or negative (neg) samples for each fragment with p16 expression.

Materials and methods. We analyzed 206 samples (OT/non-OT: 66/140) from pts treated with CRT between 1997 and 2011 (175M/31F; median age 59.6, range 20.6-85.6). E1, E6 and L1 fragments were detected by PCR on DNA extracted from PFFE tissues using specific primer pairs; DNA of pos and neg control cell lines was added. Amplicons were visualized on 2% agarose gel. p16 expression was analysed by IHC.

Results. Although we found a different % of pos samples for each fragment studied, OT showed, overall, a significantly higher % of pos samples vs non-OT: E1 pos was 19.7% in OT and 4.3% in non-OT ($p < 0.001$), while E6 pos was 68.2% in OT and 50.7% in non-OT ($p = 0.02$) and L1 was pos 45.5% in OT and 20.7% in non-OT ($p < 0.001$). When PCR positivity was correlated to OS, we observed a significant correlation in the OT population with E1 ($p = 0.016$; median OS = 161.8 in pos vs 15 months in neg). Neither E1 in non-OT ($p = 0.145$) nor E6 nor L1 in OT and non-OT ($p = 0.189$ in OT and $p = 0.242$ in non-OT for E6; $p = 0.426$ in OT and $p = 0.97$ in non-OT for L1) reached any difference in overall survival (OS). p16 pos was 68% in OT and 50% in non-OT ($p < 0.007$). We have previously demonstrated that p16 high positivity (>50%) confers a survival advantage in patients with OT, while in the non-OT the same pos values correlate with a non-significant negative prognostic effect. A significant correlation between E1 pos samples and p16 high expression was found in OT ($p < 0.001$). This correlation was not seen in non-OT with E1 neither with E6 nor L1 in the whole population. We identified 3 OT pts E1 pos but p16 neg and 35 ptsE1 neg but p16 pos. Analysis of OS suggested E1 pos to be a stronger prognostic marker in OT then p16 pos ($p = 0.005$).

Conclusions. E1 positivity by PCR may be of clinical relevance in OT. Discrepancies seen with E6 and L1 should be further investigated considering the biological cycle of HPV16. E1 positivity has an even stronger effect as p16 high pos (>50%) in OT. Moreover, where both determinations were not consistent, E1 positivity seems to correlate with OS better than p16.

B4 P16 EXPRESSION IN HNSCC: IDENTIFICATION OF THE CUT-OFF AND PROGNOSTIC VALUE IN OROPHARYNX TUMORS (OT) VS NON OT

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Background. We analyzed tumour samples from patients with locally advanced HNSCC to establish a predictive cut-off of p16 expression and to compare its role in OT vs non OT.

Materials and methods. We analyzed 206 samples from patients treated with CRT between 1997 and 2011. Patients characteristics were: M/F 175/31; median age 59.6 (range 20.6-85.6); primary site OT/non OT 66/140. 93% pts were heavy smokers (>10 pack/year). p16 was calculated by IHC. Positivity (pos) was defined as ≥1% pos cells. On the basis of the clinical literature, we considered two cut-off in pos cells (10% and 70%). Therefore, we initially compared four groups: negative (0 pos cells), low pos (1-9%), median pos (10-69%) and high pos (70-100%). Based on early results, we later considered only one cut-off (50%) and 3 groups: negative, low pos (1-50%) and high pos (51-100%).

Results. p16 pos was 68% in OT and 50% in non OT ($p < 0.007$). Taken together, the pos status confers a survival (OS) advantage (36.8 months vs 19.5 months, $p = 0.06$). Considering the 3 positivity levels (low, median and high), only high pos tumours show a better OS in the OT group (median 22.5, 15 and 97.9 months respectively, $p = 0.098$) while no difference emerges in the non OT. If we include also the p16 negative tumours, the latter behaves as the low pos and the median pos in OT, and as all the three pos groups in non OT. The cumulative analysis showed that the pos values place around two focus points at a median value of 2% (lower focus, median value of all the pos values between 0 and 50%, range 1-45) and 96% (higher focus, median value of all pos values between 51 and 100%, range 55-99). On these findings, we than divided p16 pos tumours in two groups < and >50% pos. OT showed a larger number of cases in the >50% group (31%) compared to non OT (17%) ($p = 0.08$). p16 high pos (>50%) confers a survival advantage in patients with OT, while in the non OT the same pos values correlate with a non-significant negative prognostic effect.

Conclusions. The cut-off of p16 expression of clinical relevance can be considered 50% of pos cells. Effect of p16 pos is evident only in OT while it disappears in non OT. A negative prognostic impact in non-OT should be investigated. Smoking cannot be considered a confounding factor in our series since most of pts were heavy smokers (>10 pack/year). For the same reason, the prognostic role of p16 expression may result attenuated.

B5 THE DUAL PI3K/MTOR INHIBITOR PKI-587 ENHANCES SENSITIVITY TO THE ANTI-EGFR MONOCLONAL ANTIBODY CETUXIMAB IN HUMAN HEAD AND NECK CANCER MODELS

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Background. EGFR is a transmembrane tyrosine kinase receptor that plays a central role in regulating cell division and death, and it's often overexpressed in head and neck squamous cell carcinomas (HNSCC). The anti-EGFR monoclonal antibody (mAb) cetuximab is the only targeted agent approved for the treatment of HNSCC, but low response rates and disease progression depending on cetuximab resistance are frequently reported. Since the PI3K/mTOR signaling pathway has recently been found to play an important role in the pathogenesis and invasion of HNSCC, we investigated its involvement in the onset of cetuximab resistance.

Methods. We used different human HNSCC cancer cell lines, including A431 and FaDu (sensitive to cetuximab), Detroit562 and Kyse30 (resistant to cetuximab) cells. We tested the effects of the dual PI3K/mTOR inhibitor PF-05212384 (PKI-587), alone and in combination with cetuximab, on cell survival, apoptosis and signal transduction. We also studied the effects of the combination on nude mice xenografted with Kyse30 cells.

Results. The combination treatment of PKI-587 and cetuximab is able to enhance sensitivity to cetuximab in HNSCC cells *in vitro*, even in presence of resistance to the anti-EGFR mAb. The combination inhibits cells survival and activation of several signaling transducers, including Akt, p70S6K, MAPK; moreover, when the two drugs are used together, the treatment induces transducers of apoptosis such as caspase 3 and caspase 9, particu-

larly in sensitive cells. Consistently, although a significantly inhibition of proliferation is observed in all cell lines treated with PKI-587 in combination with cetuximab, the activation of apoptosis is evident in sensitive but not in resistant cell lines. These results prompt us to investigate whether PKI-587 may activate different mechanisms of cell death in cetuximab sensitive and resistant cell lines. In nude mice xenografted with Kyse30 cells, the combined treatment significantly reduces tumor growth and prolongs mice survival.

Conclusions. We demonstrated that the PI3K/mTOR inhibition plays an important role in the rescue of cetuximab resistance. Indeed the combined treatment with PKI-587 and cetuximab significantly reduces the activation of several intracellular transducers involved in cell proliferation and survival. These results suggest the development of a possible new clinical strategy based on the combination of cetuximab and PKI-587 in HNSCC patients resistant to cetuximab.

B6 DYSPHAGIA IN HEAD AND NECK CANCER PATIENTS (HNCPS). A MULTIDISCIPLINARY APPROACH (MA) IS NEEDED. RESULTS OF AIOM-AIRO JOINT COMMITTEE

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Background. Dysphagia is defined as the difficulty or impossibility to swallow liquids, food or medication and can occur during the oropharyngeal or the oesophageal phase of swallowing. Frequent causes of dysphagia, in HNC patients, include neurological, neuromuscular structural and iatrogenic causes. It is an underestimated symptom. Patients who cannot swallow adequately before treatment are at greater risk for chronic dysfunction.

Materials and methods. A group of AIOM-AIRO experts met on 4th of February to discuss and organize a standard behaviour on supportive care of the patient with head and neck cancer receiving chemo-radiotherapy(CRT). Our group revised guidelines and proposed suggestion on dysphagia. Our conclusions will be voted and discussed in a web conference.

Results. In the Table1 we summarize the most accepted suggestions for HNCPs candidate to curative CRT (high level of consensus).

Conclusions. Sharing these guidelines has been difficult, considering the different speciality and point of view of each expert (ENT, radiation and medical oncologist, speech pathologists), but we considered that MA is fundamental to improve treatment in HNC patients.

B6 - Table 1
Suggestion from AIOM-AIRO Dysphagia supportive care group

Nutrition and swallowing experts evaluation
Clinical evaluation for signs and symptoms that herald dysphagia - inhalation - aspiration (advisable also in asymptomatic HNCPs)
Administration of a pts-rated scale evaluating subjective dysphagia and its impact on QoL pre- during and post-CRT
All patients with dysphagia signs or symptoms should be referred to a swallowing expert
Swallowing abnormalities should be evaluated with instrumental testing such as FEES (Fiberoptic Endoscopic Evaluation of Swallowing) and/or VFS (Swallowing Videofluoroscopy)
Simulation computed tomography (S-CT) based delineation guidelines for DARS (dysphagia aspiration-related structures) and collection of dosimetric parameters are suggested
Acute mucositis can worsen dysphagia and increase the risk of pulmonary complications. When possible the lowest dose to oral mucosa is advisable
Patients may benefit from strategies aimed at the prevention of swallowing dysfunction after curative CRT such as preventive swallowing exercises during treatment
All patients with dysphagia need to be evaluated by a nutrition expert. Institutional guidelines to standardize the criteria for artificial nutrition (patient selection, timing and methods) are advisable

B7 LONG-TERM SURVIVAL IN ADVANCED HEAD AND NECK CANCER PATIENTS TREATED WITH AL-SARRAF CHEMOTHERAPY SCHEME PLUS CETUXIMAB

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Background. Head and neck cancer is the sixth most common cancer worldwide with more than 650,000 new diagnosed cases each year and the management requires a multidisciplinary approach. Anyway combined conventional therapeutic modalities still demonstrate the high incidence of locoregional failure and poor overall five-year survival rate, estimated about 50%. Cetuximab, an anti-EGFR monoclonal antibody, has been approved in combination with radiation therapy for locally or regionally advanced squamous cell carcinoma, and with a platinum-based combination or as a single agent after failure of platinum-based chemotherapy for recurrent or metastatic cancer. The overall survival (OS) was 24.4 months when cetuximab was added to radiotherapy compared with 14.9 months (radiotherapy alone) and 10.1 months when added to a platinum-based combination compared with 7.4 months (chemotherapy alone).

Material and methods. We reviewed clinical records of 31 patients from January 2010 to April 2013. All patients had histological confirmed head and neck squamous cell carcinoma and they were previously treated with surgery or/and radiotherapy. All patients received cisplatin or carboplatin 100 mg/m^2 on day 1 followed by 5-FU 1000 mg/m^2/day for 4 days combined with weekly cetuximab (initial loading dose of 400 mg/m^2 followed by weekly doses of 250 mg/m^2). Al-Sarraf cycles were repeated every 3 weeks for a maximum of 6 cycles. Thereafter cetuximab was continued as a single agent until disease progression or unacceptable toxicity. All patients were evaluated every week by physical examination and every three months by imaging with CT or/and MRI or/and PET.

Results. All patients received the planned treatment. Sites of the primary lesion were larynx (N = 16), tongue (N = 8) and

pharynx (N = 7). The median age was 61 years, 24 patients were male and 7 were female. The median OS was 11 months. There were 7 long-term survivors out of 31 with 24 months of median OS; in detail 4 larynx's carcinomas, 2 cancers of tongue and 1 of the pharynx. Treatment-related toxicities were cetuximab-induced skin rashes (G2 and G3), neutropenia and thrombocytopenia (G1-G3).

Conclusions. Our review confirms median OS in patients treated with combined therapy with Al-Sarraf + cetuximab, but also demonstrates the presence of long-term responsive patients. As we know, in literature there are other cases of long term-survivors; is there a possible molecular implication in different responses?

B8 DIFFUSION MRI WITH INTRAVOXEL INCOHERENT MOTION (IVIM) FOR EARLY PREDICTING RESPONSE IN HEAD AND NECK CANCER PATIENTS UNDERGOING CHEMO-RADIOTHERAPY. PRELIMINARY EXPERIENCE

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Background. The diffusion MRI is a technique that allows to obtain non-invasively information on the cellularity of tissues. With this study we aim to evaluate imaging biomarkers for early predicting response in head and neck (HN) cancer patients undergoing chemo-radiotherapy (CH-RT).

Material and methods. We enrolled 32 patients receiving CH-RT for HN cancer, with tumor location in the nasopharynx (14 pts), oropharynx (12 pts), hypopharynx and larynx (6 pts). Each patient underwent four serial MRI exams, all including T2-weighted and diffusion images: before RT, at week 3 of RT (after 35 Gy), at the end of treatment (after 70 Gy) and a follow-up examination 8 weeks after the end of RT. From the diffusion images the following parameters were obtained: f (perfusion fraction), D (pure diffusion coefficient) and ADC (apparent diffusion coefficient). Changes of tumor size and diffusion parameters in the course of RT were quantified and correlated with the response, based on morphological criteria.

Results. Five patients presented residue of T and N in the MRI 8 weeks after RT. Our data showed that there is a great variability in the tumor shrinkage during treatment. Patients with higher pre-treatment ADC values had worse prognosis. Both ADC and D values increased in all patients during RT (on average 65-75%), with larger changes in patients showing a better response to therapy. While pre-treatment f values and its modifications during RT showed a greater variability.

Conclusions. Our preliminary results suggest that lower pre-treatment ADC values and larger increases in both ADC and D during treatment may help in predicting tumor response to CH-RT.

B9 THE PROGNOSTIC ROLE OF HPV STATUS IN OROPHARINGEAL CANCER: A SINGOL INSTITUTION EXPERIENCE

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Background. The incidence of oropharyngeal cancers has increased and Human Papilloma Virus (HPV) has been recognised as a risk factor in the last decades. The HPV-positive tumours are today recognized as a distinct subset of head and neck cancers with its own clinico-pathological and risk profile and have a significantly improved prognosis regardless of treatment strategy.

Materials and methods. From January 2004 to January 2013 at Oncology Department, Modena University Hospital, 115 patients (pts) with oropharingeal SCC were included in our clinical database (median follow-up 20 months). In May 2013 we retrospectively reviewed our clinical data and identified 29 pts with known HPV status. Detection and subtyping of HPV was performed by polymerase chain reaction (PCR). Aim of the present study is to define the prognostic value of HPV in our series, in particular to correlate HPV status with survival.

Results. Within the 29 pts with known HPV status, 27 had primary tonsil cancer (93%) and 2 primary cancer in the base of tongue (7%). We found 22 HPV positive cancers (82%) and 5 HPV negative (18%). Serotypes were the following: 16 HPV-16 (73%), 2 HPV-33 (9%), 1 HPV-18 (4%), 3 not known (14%). All patients were in stage III or IV. Eight pts (38%) received induction chemotherapy (TPF) followed by concomitant chemoradiotherapy with cisplatin with intention to cure; 14 pts (62%) received chemotherapy and radiotherapy in concomitant schedule without induction chemotherapy (8 pts received cisplatin of 100 mg/m^2, three times throughout the course of radiotherapy, 5 pts received weekly cetuximab and 1 pt received poli-chemotherapy including CDDP and 5-FU). In HPV tested pts we observed an improved median overall survival in the HPV positive group versus HPV negative group (28 months vs 8 months, respectively).

Conclusions. In accordance to literature, our analysis confirmed that HPV+ status is an important prognostic factor associated with a favorable survival among pts with head and neck cancer.

B10 SOMATOSTATIN ANALOGUES IN THE TREATMENT OF ADVANCED DEDIFFERENTIATED THYROID CANCER

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Background. Differentiated thyroid carcinoma is usually a slow growing and curable disease, but recurrence occurs in 20-40%, and dedifferentiation in up to 5% of cases. This situation represents a therapeutic dilemma and a critical area of research. Several new drugs are currently being tested, like small molecule tyrosine kinase inhibitors, and some agents re-inducing tumor io-

dide uptake. Somatostatins have a down-regulatory effect on various physiological process: their use in the management of some endocrine tumors is well recognized. Their use in thyroid cancer is not established, although there is evidence of high somatostatin receptor 2 expression in thyroid tumors.

Materials and methods. From July 2009 until now we treated 5 metastatic thyroid carcinoma pts, 0 M, 5 F, average age 58 (48-69), ECOG PS 1 (0-2), already treated with 131I, on average 4 cycles (2-6), 1 pt had lung metastases, 2 lympho-nodal, 1 bone, 1 nodal and lung. Periodic assessment with TG and iodine whole-body scan was programmed. As the disease progressed with evidence of poor iodine uptake, an octreoscan was performed. In positive test cases, the somatostatin analogue therapy was started.

Results. Average progression-free survival was 36 months. All the patients are still alive, maintaining a good PS, without drug-related symptoms.

Conclusions. Our experience suggests that somatostatin analogue treatment may be a potential therapeutic target in the treatment of advanced dedifferentiated thyroid cancer.

B11 FIRST-LINE CHEMOTHERAPY IN 108 PATIENTS AFFECTED BY RECURRENT OR METASTATIC SALIVARY GLAND MALIGNACIES (RMSGM)

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Background. Recurrent/metastatic salivary gland malignancies (RMSGM) are not manageable by means of surgery and/or radiotherapy; chemotherapy (CT) represents a palliative strategy without any curative purpose. In this abstract we report the results of CT in 108 cases of RMSGM.

Material and methods. We enrolled 108 patients with radiologically documented progression of RMSGM. Five pts received cisplatin (DDP) 100 mg/m^2 d 1, q 3wks; 8 pts doxorubicin (DOX) 75 mg/m^2 d 1, q 3wks; 30 pts vinorelbine (VNB) 30 mg/m^2 d 1 and 8, q 3 wks; 9 pts DDP 60 mg/m^2 + epirubicin (EPI) 60 mg/m^2 + 5-FU 600 mg/m^2 d 1, q 3 wks; 42 pts DDP 80 mg/m^2 d 1 + VNB 25 mg/m^2 d 1, 8, q 3 wks, and 14 pts carboplatin (CBDCA) AUC 5.5 + paclitaxel (Taxol; TAX) 175 mg/m^2 d 1, q 3 wks. The maximum number of CT cycles was 6.

Results. Patients characteristics were as follows: 65 males (60%) and 43 females (40%); median age: 57 yrs (range 20-74); 42 pts (39%) had ECOG PS = 0 and 66 pts (61%) PS 1-2 (0-2); histological evaluation was as follows: adenocarcinoma 28 pts (26%), adenoid cystic carcinoma 63 pts (58%), undifferentiated carcinoma 12 pts (11%) and malignant mixed tumors 5 pts (5%); the disease was local in 40 pts (37%), local + distant metastases in 30 pts (28%) and only metastatic in 38 pts (35%).

Conclusions. DDP is probably the most effective single drug scheme; our data suggest that VNB has superimposable results with a better gastroenteric and renal toxicity profile. Single drug CT seems less effective than multi drug CT with DDP-based schemes. DDP+EPI+5-FU is as effective as DDP+VNB; CBDCA+TAX seems to have worse clinical outcomes than DDP combinations. The impact of CT on symptoms is quite good while on survival needs further investigations, moreover our data confirm the need of new biological target agents to improve clinical outcomes in RMSGM.

Drug	Pts N	ORR %	NC %	mPFS (m)	mOS (m)
DDP	5	20	60	4	6
DOX	8	20	25	3	5
VNB	30	20	30	5	8
DDP + EPI + 5-FU	9	33	22	7	9
DDP + VNB	42	33	33	7.5	10.5
CBDCA + TAX	14	14	45	5	8

B12 PSYCHOPHYSICAL FUNCTIONING AND QUALITY OF LIFE IN OROPHARYNGEAL CANCER TREATED WITH DIFFERENT THERAPEUTIC APPROACHES

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Background. The treatment of oropharyngeal squamous cell carcinomas (OSCC) may heavily affect patient's quality of life (QoL). Aim of our study was the evaluation of the impact of different treatments on physical and psychological functioning and on QoL of patients affected by stage III-IV disease.

Material and methods. The enrolled sample was composed by 94 OSCC patients divided into 3 subgroups based on treatment modalities: surgery + adjuvant radiotherapy (S + RT: 30 patients), exclusive concomitant chemo-radiotherapy (CT + RT: 30 patients) and exclusive chemotherapy (CT) in 34 patients not suitable for surgery and/or radiotherapy. Psycho-oncological assessment included: Hospital Anxiety Depression Scale (HADS), Montgomery-Asberg Depression Scale (MADRS), Mini-Mental Adjustment to Cancer scale (MINI-MAC), EORTC QLQ C-30 questionnaire with the specific module Head and Neck 35 (H&N35).

Results. The 60 patients primarily treated with S + RT or CT + RT presented superimposable clinical and tumour characteristics while those treated with exclusive CT were affected by stage IV disease and in the 90% of cases underwent previous treatment exclusive or combined treatment such as surgery, radiotherapy and chemotherapy. In the following Table, data about physical and psychological functioning and on QoL of the 3 subgroups of patients are summarized.

Conclusions. In stage III-IV OSCC treatments have a strong influence on QoL and coping styles. Patients treated with CT + RT were characterized by a lower percentage of self-reported anxiety and depression and higher EORTC Global QoL score. More than one third of patients treated with S + RT had overt symptoms of anxiety and depression. Stage IV patients treated with palliative CT had elevated level of anxiety, depression and low quality of life. Auto-evaluation is less effective in depression assessment. The role of concomitant psychological supportive care should be evaluated in these patients treated with different approaches.

B12 - Table

	HADS anxiety	HADS depression	MADR depression	EORTC global QoL score
S + RT	33.3%	30.5%	40.1%	71.42
CT + RT	22.2%	13.9%	40.1%	76.05
CT	70.6%	67.5%	76.4%	49.04

B13 DOES REMNANT FROM DIFFERENTIATED THYROID MICROCARCINOMA PATIENTS REALLY NOT BE TREATED WITH IODINE-131 ABLATION?

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Aim. Remnant ablation by radioiodine is generally not recommended in patients presenting uni- or multifocal cancer <1 cm, without other higher risk features. We retrospectively studied low-risk patients (pts) with differentiated thyroid cancer (DTC) less than 1 cm recruited for radioiodine therapy (RAI).

Methods. Ninety-one pts (79 women, age 49.4 ± 10 yrs) with DTC were recruited for RAI. Patients underwent pre-therapy ultrasonography (US), those with suspected/ambiguous lymph-nodes were excluded and proposed for cytology. Treated pts underwent post-therapeutic whole body scan (WBSt) completed by neck/chest SPECT-CT, when necessary (e.g. evidence of uptake outside of thyroid bed). A target lesion on SPECT-CT was defined as an identifiable lymph-nodal site presenting a matched significant iodine uptake. Patients were followed up for 13 ± 2 months thereafter.

Results. All pts/cancers were pT1. Mean histological diameter was 0.66 ± 0.25 cm. Six patients were excluded because of clear nodal involvement at US. Thirty (35%) out of 85 pts had suspicious WBSt as per lymph-nodal involvement which was confirmed at the following SPECT-CT acquisition in most part of pts (25/30; 83 %). Overall detected target lesions was 34, ten (29%) had interim positive fine needle cytology.

Conclusions. A significant part of low risk DTC patients, for whom RAI is not recommended, presents an incidental evidence of lymph-nodal involvement at WBSt confirmed by SPECT-CT, when performed. Such setting would have not been treated by I-131. Indications for RAI in DTC low risk patients could be revised at least considering a different dimensional cut-off for the primary lesion.

B14 SURVEILLANCE OF HEAD AND NECK CANCER (HNC) PATIENTS: CLINICAL AND RADIOLOGICAL EXAMS OR SYMPTOM DRIVEN FOLLOW-UP?

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Background. It is still debated if surveillance compared to symptom driven follow-up is really useful in HNC patients, to detect and manage recurrences at the earliest opportunity.

Material and methods. We considered a series of stage III-IV HNC pts treated between 1998-2010 at our Institution with definitive or postoperative chemo-radiotherapy. We evaluated pts without evidence of disease 6 months after treatment end. Follow-up was performed with clinical exam every 3 months for the first year, then every 4-6 months until the 4th year, then annually until the 5th year; locoregional radiologic evaluation was performed with head and neck MRI or CT scan at least 2 times/year for the first 2 years and yearly in the following 2 years. A total body CT scan or PET was done yearly in the first 5 years. Patients with both locoregional and metastatic recurrence were considered in the distant metastasis group. Pattern of recurrences including second tumors was analyzed distinguishing between clinical or radiological detection and pt self-referral.

Results. We present a series of 430 pts, with a median follow-up of 39 months. 136 pts (32%) were diagnosed with a recurrence or a second tumor. In particular, 45 (33%) were locoregional recurrences, 52 (38%) distant metastases and 39 (29%) second tumors (13 NSCLC, 11 HNC, 2 SCLC, 5 oesophageal cancer, 3 CRC, 3 others). Median time to locoregional recurrence was 13 months (range 7-51), while to second tumor detection was 31 months (range 7-110). Pattern of recurrence and second tumor discovery according to curability is shown in the Table.

B14 - Table

	Potentially curable	Not curable
Locoregional recurrences (N = 45)	25	20
Diagnosed with:		
clinical-radiological follow-up	16/25 (64%)	12/20 (48%)
self-referral	9/25 (36%)	8/20 (52%)
Second tumors (N = 39)	19	20
Diagnosed with:		
clinical-radiological follow-up	13/19 (68%)	13/20 (65%)
self-referral	6/19 (32%)	7/20 (35%)

Conclusions. Clinical and radiological follow-up identifies a greater percentage of potentially curable recurrence/second tumor than symptom-driven follow-up. If this reflects on better survival needs to be defined in further analysis on larger data. Stratification of patients risk could improve diagnosis and define individualized strategies.

B15 CORRELATION BETWEEN SERUM MAGNESIUM LEVELS AND SKIN TOXICITY DURING CETUXIMAB TREATMENT IN SQUAMOUS CELL CARCINOMA OF HEAD AND NECK CANCER (SCCHN): THE ROLE OF WEEKLY INTRAVENOUS MAGNESIUM SUPPLEMENTATION

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Background. Cutaneous rash and hypomagnesemia are the most frequent adverse events cetuximab related. Their severity is

proportional to treatment dose and duration and they can prejudice adequate drug administration, quality of life and outcomes of patients.

Magnesium stabilizes DNA and RNA, reduces free radical effects and is a key component of different biochemical reactions. Without proper levels of magnesium, all parts of the body, including the skin, fall into a state of deficiency and are prone to disease. Preclinical *in vivo* models demonstrated correlation between magnesium deficiency and cutaneous disease.

Methods. This is an observational, prospective, monoinstitutional, ongoing, phase II clinical trial to evaluate if in locally advanced or recurrent/metastatic SCCHN the maintenance of adequate serum magnesium levels can reduce cetuximab related skin toxicities. From October 2012 to date we evaluated 10 patients (pts) of whom 7 men and 3 women. We administered weekly intravenous magnesium sulfate 30 meq prophylaxis and we realized periodical serum magnesium dosage.

Results. Median age was 62.4 years (range 42-73). All patients received cetuximab, 3 pts in combination with radiotherapy and 7 pts in association with chemotherapy. They all received weekly intravenous magnesium sulfate prophylaxis. No pt developed G3-G4 skin rash, only two pts (20%) developed G2 acneiform rash that needed oral and topic antibiotics and steroids, the others (80%) showed only dry skin and G1 skin rash with spontaneous resolution. All the patients maintained sufficient magnesium serum levels with good treatment adherence in dose and timing.

Conclusions. Even if these are preliminary data, our study could support the importance of weekly magnesium infusional supplementation not only to maintain magnesium serum levels but also to reduce incidence and severity of cetuximab related skin toxicity in head and neck cancers. Our results might be useful to relieve patient's discomfort and prevent severe cutaneous complications during treatment but they need further validation.

B16 SINGLE BONE METASTASIS FROM LACRIMAL GLAND TUMOR: A CASE REPORT

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Background. Lacrimal glands are a very unusual site of primitivity and secondary bone metastases are very rare. Lacrimal gland lesions represent 10% of orbital lesions and may be divided in inflammatory, lymphoproliferative, and epithelial lesions. Epithelial malignant tumors seems to have similarity to salivary gland tumours so we can use the same antiblastic treatment. The aim of our case report is to describe the clinical, radiological, pathological and therapeutic aspects for a patient with single bone metastases from a primary ductal adenocarcinoma of the lacrimal gland.

Methods. A 71-years-old man came with back pain and anterior superior iliac spine pain irradiated to the left buttock and groin ipsilateral. His medical history was only of prostatic hypertrophy in specific treatment. The patient performed MRI of the lumbar spine showed an extensive osteoblastic lesion that affected the left portion of L1, with infiltrative-destructive phenomena marginally involving the spinal canal. On successive examination the patient showed right exophthalmos reported as present from several years.

Results. The patient was therefore subjected to bone CT-guided biopsy with removal of infiltrating carcinoma, with apocrine aspects of necrosis and calcification, positive for cytokeratin 7 and androgen receptor, negative for TTF-1, cytokeratin 20, CDX2, PSA, RE and RP. A total body CT showed, at the right orbit level, the presence of a solid hypotenuse lesion of about 23x17 mm that was removed surgically and showed evidence of adenocarcinoma of the lacrimal gland positive for androgen receptors and intense complete membrane immunoreactivity for Her-2 neu in 40% of neoplastic cells. For L1 lesion pt underwent embolization, but refused surgery and for this reason he received only one shot of radiotherapy (8 Gy). He also started a BAT (androgen total blockade) with leuprorelina/ciproterone. After a follow-up of 11 months the disease remains localized only at L1 with a partial response.

Conclusions. In conclusion we presented a very rare case of single bone metastasis from lacrimal gland tumor in optimal control with BAT, surgery and radiotherapy.

B17 QUALITY OF LIFE OF ELDERLY PATIENTS RECEIVING WEEKLY CARBOPLATIN AND PACLITAXEL CHEMOTHERAPY PLUS CETUXIMAB FIRST-LINE FOR METASTATIC SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

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Background. A phase III trial demonstrated that cetuximab is the first agent to improve survival when added the platinum-based chemotherapy for metastatic squamous cell carcinoma of the head and neck. The safety and tolerability of a combination of weekly paclitaxel and carboplatin and the epidermal growth factor receptor (EGFR) monoclonal antibody cetuximab for the first-line treatment for metastatic squamous cell carcinoma of the head and neck in elderly population were investigated.

Patients and methods. Patients >70 years of age with histologically confirmed metastatic squamous cell carcinoma were enrolled. Other eligibility criteria included: measurable disease (using RECIST), Karnofsky performance status (KPS) >60% and adequate hematologic, hepatic and renal functions. Patients received paclitaxel (80 mg/m^2), carboplatin AUC 2 and cetuximab (400/250 mg/m^2) weekly. Treatment was continued for a maximum of six cycles of chemotherapy. After six cycles, patients who had at least stable disease received cetuximab monotherapy until disease progression or unacceptable toxicity. The European Organisation for Research and Treatment of Cancer QoL Questionnaire-Core 30 (QLQ-C30) and QLQ-Head and Neck 35 (QLQ-H&N35) module were used to assess QoL.

Results. From September 2010 to September 2012 were evaluated 40 patients with metastatic squamous cell carcinoma of the

head and neck. Patients were scheduled to complete the questionnaires at screening or baseline, on day 1 of every cycle. The analysis of the responses to the questionnaires from patients shows that the pattern of chemotherapy used provides excellent control of symptoms related to the disease. Common grade 3/4 adverse events were acne-like rash (18%), asthenia (20%) and neutropenia (10%).

Conclusions. This analysis shows an important clinical benefit of chemotherapy regimen proposed in the population included in the study. Relevant results in terms of overall survival, PFS, in response rates and disease control.

Session C • Melanoma

C1* SEQUENTIAL TREATMENT WITH IPILIMUMAB AND BRAF INHIBITORS IN PATIENTS WITH METASTATIC MELANOMA: DATA FROM THE ITALIAN COHORT OF IPILIMUMAB EXPANDED ACCESS PROGRAMME (EAP)

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Background. Ipilimumab and vemurafenib have recently been approved as single agents for the treatment of unresectable or metastatic melanoma. Currently, limited data exist on the sequential treatment with these agents in patients (pts) with the BRAF mutation; here we evaluate the efficacy outcomes of pts enrolled in the EAP in Italy who sequentially received a BRAF-inhibitor and ipilimumab, or vice versa.

Methods. Ipilimumab was available upon physician request for pts aged ≥16 years with unresectable stage III/stage IV melanoma who had either failed systemic therapy or were intolerant to ≥1 systemic treatment and for whom no other therapeutic option was available. Ipilimumab 3 mg/kg was administered intravenously every 3 weeks for 4 doses. Tumour assessments were conducted at baseline and after completion of induction therapy using immune-related response criteria. Patients were considered for this analysis if they tested positive for the BRAF mutation and had received a BRAF-inhibitor before or after ipilimumab treatment.

Results. In total, 855 Italian pts participated in the EAP from June 2010 to January 2012 across 55 centres. Out of 173 BRAF positive pts, 93 (53.7%) were treated sequentially with both treatments: 48 pts received a BRAF inhibitor upon disease progression with ipilimumab and 45 pts received ipilimumab upon disease progression with a BRAF inhibitor. As of December 2012, median overall survival was 14.5 months (11.1-17.9) and 9.7 months (4.6-14.9) for the two groups, respectively (p = 0.01). Among the 45 BRAF inhibitors pretreated pts, 18 (40%) had rapid disease progression (median overall survival: 5.8 months) and were unable to complete all four induction doses of ipilimumab, while the remaining 27 (60%) pts had slower disease progression (median overall survival: 19.3 months) and were able to complete the therapy with ipilimumab.

Conclusions. These preliminary results suggest that, in BRAF-mutated pts, starting the sequential treatment with ipilimumab can provide a better survival than the reverse sequence. These findings deserve confirmation in a prospective study.

C2* STEVIE: A SINGLE-ARM, OPEN-LABEL, MULTICENTRE STUDY TO EVALUATE THE SAFETY OF THE HEDGEHOG PATHWAY INHIBITOR VISMODEGIB IN PATIENTS WITH ADVANCED BASAL CARCINOMA (BCC): INTERIM ANALYSIS

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Aim. Even if most cases of BCC can be managed by surgery, in some patients with advanced disease surgery could be inappropriate. Vismodegib is a first-in-class Hedgehog pathway inhibitor approved for advanced BCC (aBCC: locally advanced or metastatic) in the US, based on the pivotal study ERIVANCE BCC. STEVIE is a pre-approval safety study of vismodegib in aBCC.

Materials and methods. aBCC enrolled patients receive oral vismodegib 150 mg, once-daily until progressive disease, unacceptable toxicity or withdrawal. Safety is assessed by Common Terminology Criteria for Adverse Events v4.0. Overall response rate is assessed according to Response Evaluation Criteria in Solid Tumours, v1.1. Recruitment is ongoing.

Results. This analysis (data cut-off: 17May 2012) included 150 patients with locally advanced (N = 138) or metastatic (N = 12) BCC with potential for ≥3-month follow-up, from six European countries and Canada. Locally advanced patients had lesions considered inoperable (54.3%), or surgery contraindicated (45.7%). Median treatment duration was 144 days (range 2-302). The most common treatment emergent adverse events (TEAEs, ≥20% of patients) included muscle spasms (53.3%), alopecia (42.7%), dysgeusia (36.0%), ageusia (27.3%), and asthenia (26.7%). Most TEAEs were mild or moderate in severity. Serious TEAEs occurred in 22 patients (14.7%). Patients discontinued treatment (25.3%) due to adverse events (N = 10), patient request (N = 9), death (N = 8), disease progression (N = 4), investigator request (N = 4), or other (N = 3). Deaths were due to disease progression (N = 2) or adverse events not considered related to study drug by the investigator (N = 6; pneumonia, multi-organ failure, rectal cancer, cardiac arrest, chronic obstructive pulmonary disease, non-Hodgkin's lymphoma). Initial preliminary best overall response was confirmed for 124 patients. Of these 19.4% patients had complete response, 55.6% partial response, 21.8% stable disease and 3.2% progressive disease.

Conclusions. This interim analysis from STEVIE confirms a similar vismodegib safety profile to ERIVANCE BCC study. Updated results will be presented.

C3* ITALIAN COHORT OF IPILIMUMAB EXPANDED ACCESS PROGRAMME (EAP): EFFICACY, SAFETY, AND CORRELATION WITH MUTATION STATUS IN METASTATIC MELANOMA PATIENTS

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Background. Ipilimumab was the first agent approved for the treatment of unresectable or metastatic melanoma to show a survival benefit in randomised phase III trials. Efficacy and safety of ipilimumab treatment outside of clinical trials and the correlation with BRAF and NRAS mutation status were evaluated.

Methods. Ipilimumab was available upon physician request for patients (pts) aged ≥16 years with unresectable stage III/stage IV melanoma who had either failed systemic therapy or were intolerant to ≥1 systemic treatment and for whom no other therapeutic option was available. Ipilimumab 3 mg/kg was administered intravenously every 3 weeks for 4 doses. Tumour assessments were conducted at baseline and after completion of induction therapy using immune-related response criteria. BRAF and NRAS mutation status was retrospectively collected for all available patients. Patients were monitored for adverse events, including immune-related AEs, using Common Terminology Criteria for Adverse Events v.3.0.

Results. In total, 855 Italian pts participated in the EAP from June 2010 to January 2012 across 55 centres. With a median follow-up of 6.5 months (range 0.5-30), the disease control rate among 833 pts evaluable for response was 34.3%: 28 pts (3.4%) with complete response, 83 (10.0%) with partial response and 175 (20.9%) with stable disease. As of December 2012, median progression-free survival and overall survival were 3.3 months and 7.2 months respectively, with 1-year survival rate of 36%. The Table shows mutation status for available patients. Disease control rates were comparable among pts with BRAF positive tumors and BRAF wild-type (37.5% vs 39.5%) and among pts with NRAS positive tumors and NRAS wild-type (57.1% vs 49.3%). Survival curves were also comparable between groups. 399 pts (46.7%) had a AEs of any grade, with 286 (33.5%) considered IrAEs. IrAEs were reversible with protocol specific guidelines.

Conclusions. Based on EAP data, ipilimumab is an effective and safe treatment for pretreated pts with metastatic melanoma regardless of BRAF and NRAS mutation status.

C3* - Table

	Mutated	Wild-type	Total
BRAF	173 (36.9%)	296 (63.1%)	469
NRAS	14 (17.1%)	68 (82.9%)	82

C4 DENDRITIC CELL VACCINATION IN METASTATIC MELANOMA PATIENTS: A TWELVE-YEAR MONOINSTITUTIONAL EXPERIENCE

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Background. Since 2001, we have been treating metastatic melanoma patients with autologous dendritic cells (DC) loaded with autologous tumor lysate or homogenate. Results from our published phase I/II open-label, single-arm clinical study showed a clinical benefit (CR + PR + SD) of 55.5% for the 27 evaluable patients, with a median overall survival (OS) of 16 months. Patients who developed antitumor immunity after the treatment had a better outcome (median OS 22.9 vs 4.8 months). Additional 55 patients were treated in a Compassionate Use Program (CUP) utilizing the same treatment protocol. Herein, we report safety and efficacy data for all the 82 patients with metastatic melanoma treated at our Institution either in the clinical study or in the CUP.

Patients and methods. To enter the CUP patients were required to have progressing metastases from melanoma and no alternative therapeutic options. The response to treatment was retrospectively assessed according to RECIST 1.1 criteria for all patients. No concomitant anticancer treatment was allowed, except palliative radiotherapy. Immunoresponsivity was defined as development of a positive delayed-type hypersensitivity skin test (DTH) to at least one of the vaccination antigens after at least four vaccine administrations.

Results. Adverse events (AEs) were observed in 39/82 (47.6%) patients; none led to treatment discontinuation. Most were self-limiting local reactions to the vaccine (10/82; 12.2%) or fever after adjuvant IL-2 given after each vaccine administration (12/82; 14.6%). Only two G4 AEs were observed: both were non-symptomatic subsegmentary pulmonary embolism not likely related to study treatment. The responses observed among 71/82 evaluable patients who received at least four vaccine doses were as follows: 2 (2.4%) CR, 2 (2.4%) PR, 31 (37.8%) SD, 36 (43.9%) PD, for an overall clinical benefit of 42.6%. Median OS was 12.01 months.

DTH was made on 54 (65.9%) patients. Among these, OS was better for immunoresponsive patients (22.76 months vs 8.06 months; $p = 0.0036$; median follow-up 71 months).

Conclusions. These data strongly confirm the results of our previous phase I/II study: dendritic cell vaccination has a very favorable safety profile and good clinical efficacy. The survival benefit is essentially restricted to immunoresponsive patients.

C5 EFFICACY AND SAFETY DATA FROM ELDERLY PATIENTS WITH PRETREATED ADVANCED MELANOMA IN THE ITALIAN COHORT OF IPILIMUMAB EXPANDED ACCESS PROGRAMME (EAP)

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Background. Ipilimumab was the first agent approved for the treatment of unresectable or metastatic melanoma that showed an overall survival benefit in randomised phase III trials. Here we evaluate the safety and efficacy of ipilimumab treatment outside of clinical trials in elderly (>70 years old) patients (pts) enrolled in the EAP in Italy.

Methods. Ipilimumab was available upon physician request for pts aged ≥16 years with unresectable stage III/IV melanoma who had either failed systemic therapy or were intolerant to ≥1 systemic treatment and for whom no other therapeutic option was available. Ipilimumab 3 mg/kg was administered intravenously every 3 weeks for 4 doses. Disease evaluation was performed at baseline and after completion of induction therapy using immune-related response criteria. Patients were monitored for adverse events (AEs), including immune-related AEs, using Common Terminology Criteria for Adverse Events v.3.0.

Results. Out of 855 Italian pts participating in the EAP from June 2010 to January 2012 across 55 centres, 193 (22.6%) were over 70 years old (median 75; 70-88). Of these, 132 pts (68.4%) received all 4 doses of ipilimumab, 24 (12.4%) 3 doses, 17 (8.8%) 2 doses and 20 pts (10.4%) received 1 dose. With a median follow-up of 7.6 months (range 1-26), the disease control rate among 188 pts evaluable for response was 38.3%, including 4 pts (2.1%) with a complete response, 24 (12.8%) with a partial response and 44 (23.4%) with stable disease. As of December 2012, median progression-free survival and overall survival were 3.7 months and 8.9 months respectively, with 1-year survival rate of 38%. In total, 96 pts (49.7%) reported an AE of any grade, which was considered treatment-related in 69 pts (35.7%), with a safety profile comparable to the general population. Grade 3/4 AEs were reported by 19 pts (9.8%) and drug-related in 11 pts (5.7%). AEs were generally reversible with treatment as per protocol-specific guidelines with a median time to resolution of 2.0 weeks.

Conclusions. Based on the data from EAP, ipilimumab is a feasible treatment in the elderly population; efficacy and safety results were similar to those observed in the general population.

C6 CORRELATION BETWEEN EFFICACY AND TOXICITY IN PATIENTS WITH PRETREATED ADVANCED MELANOMA TREATED WITHIN THE ITALIAN COHORT OF THE IPILIMUMAB EXPANDED ACCESS PROGRAMME (EAP)

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Background. Ipilimumab was the first agent approved for the treatment of unresectable or metastatic melanoma that showed an overall survival benefit in randomised phase III trials. Early clinical studies explored the potential relationship between immune-related adverse events (irAEs) associated with ipilimumab and antitumor activity but no definitive conclusion has been reached. Here, we evaluated the possible correlation between efficacy of ipilimumab treatment and irAEs in patients (pts) enrolled in the EAP in Italy.

Methods. Ipilimumab was available upon physician request for pts aged ≥16 years with unresectable stage III/stage IV melanoma who had either failed systemic therapy or were intolerant to ≧1 systemic treatment and for whom no other therapeutic option was available. Ipilimumab 3 mg/kg was administered intravenously every 3 weeks for 4 doses. Tumour assessments were conducted at baseline and after completion of induction therapy using immune-related response criteria. Patients were monitored for adverse events (AEs), including immune-related AEs (irAEs), using Common Terminology Criteria for Adverse Events v.3.0.

Results. In total, 855 Italian pts participated in the EAP from June 2010 to April 2012 across 55 centres. Among 833 evaluable pts, 278 pts (33.4%) reported an irAE and 555 (66.6%) did not. As of December 2012, the disease control rates among pts with or without irAEs were 35.3% and 33.9% respectively. We noted that there was a difference in the distribution of pts with or without irAEs among pts who experienced a fast progression, thus not being able to receive at least 3 cycles, and pts with slow progres-

sion. In fact, due to the mechanism of action of the drug and consequent delayed onset of irAEs, pts with irAEs among fast and slow progressors were 22% and 37% respectively. Therefore, median overall survival was evaluated by adjusting the 2 groups for this factor and results showed a comparable survival between pts who reported an irAE and pts who did not (10.0 vs 9.7 months respectively).

Conclusions. This exploratory analysis of EAP data suggest that activity and efficacy of ipilimumab is not related with the occurrence of irAEs.

C7 FREQUENCIES OF BRAF/NRAS MUTATIONS IN A LARGE SERIES OF PATIENTS WITH ADVANCED MELANOMA

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Background. The prevalence of BRAF and NRAS mutations may vary during melanoma progression. The aim of this study was to evaluate prevalence and distribution of pathogenetic mutations in BRAF and NRAS genes among melanoma patients with different geographical origin within the same Italian population.

Methods. Genomic DNA from 513 consecutively-collected patients with advanced melanoma (AJCC stages III and IV) was screened for somatic mutations in BRAF gene (exon 15). For a large fraction of patients whose DNA was available (354/513; 69%), mutation analysis was also carried out in coding sequences of NRAS gene. PCR products corresponding to coding exons and intron-exon junctions were analyzed by direct sequencing using an automated approach.

Results. Overall, a total of 749 tumor samples (451 primary tumors and 298 metastases) from 513 consecutively-collected patients with advanced melanoma was screened for BRAF and, at lower extension, NRAS mutations by automated DNA sequencing. Among tissues, 236 paired samples of primary melanomas and synchronous or asynchronous metastases were included into the screening. Mutations were detected in 49% primary melanomas and 51% metastases, for BRAF gene, and 15% primary tumors and 16% secondaries, for NRAS gene. An heterogeneous distribution of mutations in both genes was observed among the 451 primary melanomas according to patients' geographical origin: 61% vs 42% ($p = 0.0372$) BRAF-mutated patients and 2% vs 21% ($p < 0.0001$) NRAS-mutated cases were observed in Sardinian and non-Sardinian populations, respectively. Consistency in BRAF/NRAS mutations among paired samples was high for lymph node (91%) and visceral metastases (92.5%), but significantly lower for brain (79%; $p = 0.0227$) and skin (71%; $p = 0.0009$) metastases.

Conclusions. Our findings about the two main alterations occurring in the different tumor tissues from patients with advanced melanoma from Italian population may be helpful in improving the management of such a disease.

C8 NODAL LOCALIZATIONS FROM MERKEL CELL CARCINOMA WITH NO IDENTIFIABLE PRIMARY SITE AND DISTANT METASTASES: A SINGLE-INSTITUTION EXPERIENCE

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Background. Merkel cell carcinoma (MCC) is an aggressive cutaneous neuroendocrine carcinoma. In sporadic cases nodes represent the only site of disease, without primary tumor or distant metastases. This particular entity can be due to a spontaneous regression of the primary tumor, inadequate staging or primary nodal hypothesis. No standard treatment exists in this setting. We report our multimodal management.

Methods. Among patients (pts) with histological diagnosis of MCC managed at European Institute of Oncology, in Milan, between October 1995 and April 2013, we selected those with exclusive nodal involvement without evidence of primary tumor. In these pts we considered: age at diagnosis, nodal sites of disease, Ki 67%, TTF1, CK 20, CT-scan, fluorodeoxyglucose (FDG) positron emission tomography (PET), somatostatin receptor scintigraphy (SRS), 68Gallium-PET-CT, lymphadenectomy, curative radiotherapy, chemotherapy. Then we evaluated relapse-free survival (RFS), progression-free survival (PFS), median overall survival (mOS) and median follow-up.

Results. Among a total of 107 pts, 32 had the above mentioned characteristics. Median age was 63 years. A CT/MRI was performed in 27 pts, FDG-PET in 16, SRS or 68Gallium-PET-CT in 13 pts. All patients underwent excisional biopsy. Lymphadenectomy was performed in 14, in 4 of them combined with chemotherapy, in 2 with radiotherapy, and in 6 with both. Out of the pts not undergone lymphadenectomy, 6 underwent chemotherapy + radiotherapy, 3 chemotherapy alone and 9 no antitumor treatment. With a 39-month median follow-up, median RFS for pts undergone lymphadenectomy was not reached; median PFS for pts without lymphadenectomy was 7 months (95% CI: 4.5-NE). For all pts median OS was 132 months (95% CI: 16.3-NE).

Conclusions. Nodal alone unknown primary MCC represents an undefined entity. Therapeutic approach is heterogeneous and should be individualised after multidisciplinary discussion. Our analysis seems to confirm previous observations by others that OS of pts with stage IIIB is better for unknown than known primary. No clear correlation was observed between prognosis and the evaluated variables. Better outcomes in the lymphadenectomy group could be due to a positive selection of patients.

C9 BEYPRO1: A PHASE II SINGLE-ARM STUDY FOR THE TREATMENT AFTER RECURRENCE OF ADVANCED MELANOMA PATIENTS HARBORING THE V600BRAF MUTATION AND PRETREATED WITH VEMURAFENIB, WITH THE ASSOCIATION OF VEMURAFENIB PLUS FOTEMUSTINE

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Background. Vemurafenib, a ^{V600}BRAF kinase inhibitor, achieves a remarkable clinical response rate and a statistically significant improvement in overall survival (OS) in patients (pts) with unresectable stage III and IV melanoma. However, clinical resistance to this agent eventually arises in most patients. In a phase I study of vemurafenib, among 48 pts with progressive disease (PD) 18 pts continued vemurafenib >30 days after local therapy of PD lesions: median OS had not been reached at a median follow-up of 15.5 months from initiation of vemurafenib, with a median treatment duration beyond initial PD of 3.5 months. Conversely, in pts who stopped vemurafenib after PD, median OS was 1.4 months (Kim et al., ASCO 2011). These findings suggest that one possible approach to improve the prognostic outlook in pts progressing during vemurafenib treatment may be continuing the drug in combination with chemotherapy. Vemurafenib resistance is not caused by acquisition of secondary BRAF mutations but rather by up-regulation in some cell populations of other signals of MAPK pathway with the creation of heterogeneous cell populations partly resistant to BRAF inhibition, and a cytotoxic drug such as fotemustine (FTM) might act on those proliferating clones. FTM was chosen as chemotherapeutic agent because it has shown an effect on melanoma brain metastases: in a phase III study conducted by Avril et al. (JCO 2004) comparing FTM with dacarbazine, the median time of occurrence of brain metastases was approximately three times longer in the FTM group (22.7 months) than in the dacarbazine group (7.2 months).

Methods. Patients progressing on vemurafenib will be enrolled in the study. Thirty pts are expected to participate in this trial. The primary objective is to assess the activity of vemurafenib plus FTM in pts harboring the ^{V600}BRAF mutation and recurred while on treatment with vemurafenib and the primary endpoint is progression-free survival. Treatment with FTM plus vemurafenib will be continued until PD or unacceptable toxicity.

Results. Enrolment started in January 2013 and 9 pts have already been enrolled in the study during the first 4 months. The remaining pts are expected to be enrolled by the 2 participating centers by the end of 2013.

Conclusions. Data from this study will allow to preliminarily assess the activity and safety of vemurafenib in combination with fotemustine in patients harboring the ^{V600}BRAF mutation and recurred while on treatment with vemurafenib.

C10 MULTIPLE TUMOR PHENOTYPES AND MALIGNANT MELANOMA: THE ROLE OF GENETIC TESTING FOT MITF, PTEN AND CDKN2A

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Background. It is well known that synchronous and/or metachronous multiple primary melanomas (MPMs) occur in clearly hereditary settings as well as in familial and sporadic settings. However, no evidence exists about their co-occurrence in patients with multiple cancer phenotypes, a setting in which genetic susceptibility plays a significant role. Inside the multiple tumor phenotypes, multiple primary melanomas occurring in familial or sporadic settings constitute an interesting case study for the analysis of cancer susceptibility. In this study, we focused on the co-existence of MPMs and other types of tumors evaluating the genetic characterization underlying the context of high susceptibility to the development of multiple cancer phenotypes.

Material and methods. We retrospectively evaluated the prevalence of benign and malignant neoplasms occurred in a group of 49 patients with multiple primary melanomas (MPMs) and compared the results with a group of 58 randomly age- and gender matched controls with single primary melanoma (SPM) and a group of 52 age- and gender randomly matched healthy patients. Mutational analysis of specific genes was performed when clinical data and family history were suggestive for familial/hereditary setting.

Results. Individuals affected by MPMs were distinguished by a statistically significant higher mutation frequency and a higher prevalence of other neoplasms. Of 27 diagnosed malignancies, basal cell carcinoma was the most frequent (N = 10, 37.1%), followed by colorectal adenocarcinoma (N = 5, 18.5%) and prostate adenocarcinoma (N = 3, 11.1%). In addition to malignances, we also detected 10 benign tumors. Genetic testing revealed germline mutations affecting PTEN, MITF E318K, CDKN2A, MC1R genes.

Conclusions. Our data highlight the importance of strict cancer surveillance in individuals with MPMs and the role of appropriate genetic counseling and testing in selected patients. Selected candidates should undergo genetic testing, not only for CDKN2a, CDK4, MC1R, but also for MITF E318K and PTEN, in order to plan personalized clinical and instrumental screenings and follow-up strategies; the latter must be assessed basing on mutational status: it is prudent to have a heightened level of suspicion in the clinical management of mutation carriers.

C11 UNEXPECTED HIGH FREQUENCY OF HYPERCHOLESTEROLEMIA IN METASTATIC MELANOMA PATIENTS TREATED WITH BRAF INHIBITORS

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Background. BRAF inhibitors have certainly changed the scenario of the medical therapy of advanced melanoma. The rapid and impressive activity, even on large tumor burdens, in 50-60% of patients with a tumor shrinkage in approximately 80% of patients represents a result never seen before in stage IV melanoma. The toxicity profile is characterized by LFTs alterations, flu-like syndrome, arthralgias, skin maculopapular rash, development of cutaneous squamous cell carcinomas/keratoacanthomas and benign skin lesions (papilloma, keratosis).

Patients and methods. In our experience with vemurafenib into international and EAP clinical trials, we identified a significant number of patients developing hypercholesterolemia, with an increase of total cholesterol and LDL-cholesterol. Two cases

of cholelithiasis, one of which symptomatic and inducing acute abdomen requiring urgent cholecystectomy, were observed. Therefore, we have evaluated prospectively the incidence of hypercholesterolemia in 50 patients treated with vemurafenib as compassionate use, in presence of basic normal serum cholesterol levels.

Results. In particular, we have focused on a monocenter case history of 50 patients treated with vemurafenib from May 2012 to February 2013. We observed a significant increase in cholesterolemia in 11 patients (22%), 2 of which have consequently been taking statins and one nutritional supplement (Armolipid), according to the entity of increase (more than 300 mg/dL) and associated cardiovascular and/or cerebrovascular risk factors. In most cases an improvement in cholesterol levels was obtained with an adequate diet.

Conclusions. After the registration of vemurafenib also in Italy, we strongly suggest in the clinical practice the evaluation of the serum lipid profile, in order to check the increasing cholesterol levels during the biological treatment and the consequent start of an adequate pharmacological control. The biochemical and metabolic mechanisms underlying this alteration in lipid metabolism are being investigated. We will be able to show more data and details on a larger series of patients at the Congress.

C12 BRAF PREVALENCE AND INHIBITION IN METASTATIC MELANOMA: EXPERIENCE OF THE NATIONAL CANCER RESEARCH CENTRE OF BARI

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Background. Constitutive activation of the MAP kinase pathway caused by BRAF mutations is detected in about 50% of melanomas. Several clinical trials in metastatic melanoma (MM) have shown the effectiveness of BRAF inhibitors, which led to a significant survival improvement over 1 year. Beyond clinical trials, these drugs are not yet marketed in Italy and are only available in compassionate use programs.

Patients and methods. We retrospectively evaluated the clinical data of all patients (pts) with MM referred to our Department of Oncology, National Cancer Research Centre of Bari, between January 2011 and March 2013, in order to define their BRAF status and to analyze outcomes of anti-BRAF therapy. Data were extracted from pts records. Eighty-six pts with MM were tested for BRAF mutations; median age was 57 yrs (25-83), sex M/F 42/44; 93% from the Puglia region. The primary site was cutaneous in 80% of pts, unknown in 10%, mucosal in 5% and ocular in 5%.

Results. BRAF mutation was found in 49 pts (57%) (45 V600E, 4 V600K) including 38 cutaneous, 6 unknown primary, and 2 mucosal; rare BRAF mutations (D594G, K601E, G469A) were found in 3 patients. Ocular MM presented no mutations. Forty-three pts were treated with BRAF inhibitors (vemurafenib or dabrafenib) of which 26 pts (60.5%) as first-line. M staging was M1a in 5 pts, M1b in 8 pts, and M1c in 30 pts (70%). Metastatic sites included lung (58%), soft tissue (47%), lymph nodes (56%), liver (35%), brain (23%), bone (21%), adrenal gland (7%) and spleen (4%). We reported 3 CR (7%), 21 PR (49%), 5 SD (12%), 9 PRO (21%); 5 pts (11%) were too early to evaluate. Median PFS was 6 months (range 1-17+). Overall median OS was 9 months (range 1-17+), 9 months for first-line (1-13+) and 10 months (1-17+) for subsequent lines. OS after anti-BRAF failure was 3 months (0-10).

Conclusions. BRAF mutation prevalence, effectiveness of anti-BRAF therapies and PFS of this MM population in Puglia are similar to those found in international trials. OS seems to be shorter than that reported in literature. This may be due to the majority of pts having M1c status, including 10 pts with brain lesions. The forceful disease flare after BRAF inhibitor failure suggests that a great effort should be made in order to tailor the use of the different options available today for MM by defining a useful sequential strategy.

C13 NEW TREATMENT APPROACHES IN MELANOMA: OUR EXPERIENCE

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Background. The anti-CTL4 (ipilimumab) and BRAF inhibitors (vemurafenib and dabrafenib) have changed the clinical landscape in melanoma. These new drugs offer effective treatment for metastatic melanoma, but with limitations: ipilimumab benefits only a minority of those treated, with no means to identify them prospectively; the efficacy of BRAF inhibitors is tied to the presence of an activating mutation in BRAF, and so is more predictable. However, acquired resistance develops within months. There is a lack of information on the means to select patients for treatment in order to improve outcomes. Uncertainty remains as to the optimal sequencing of kinase inhibitors and ipilimumab.

Materials and methods. From January 2011 until now, we treated 35 metastatic melanoma patients (pts), 23 M and 12 F, average age 61, (46-83), ECOG PS 1 (0-2). In 32 pts first-line chemotherapy was performed (fotemustine, dacarbazina, CDDP+TMZ), in 1 pt vemurafenib, in 2 pts no therapy was performed. We used 2nd-line therapy with ipilimumab in 6 pts, and BRAF inhibitors (vemurafenib and dabrafenib) in 5 pts.

Results. We observed 2 cases with prolonged overall survival in pts treated with ipilimumab. They had spread visceral metastases, even bone metastases, (generally associated with poor prognosis). One pt had BRAF mutated melanoma, and was previously treated with vemurafenib, with progression after 11 cycles: he obtained a disease stabilization with ipilimumab for 18 months.

Conclusions. In our experience, integrated treatment plays an important role in the metastatic melanoma. Although in the literature there are studies about the low efficacy of ipilimumab after BRAF inhibitors, we observed an excellent OS in a patient with BRAF mutated melanoma, treated with ipilimumab after vemurafenib.

Session D • Neuroendocrine tumours

D1* CANCER-ASSOCIATED-FIBROBLASTS IN NEUROENDOCRINE NEOPLASMS: A ROLE IN CANCER PROGRESSION

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Background. Tumor microenvironment has recently emerged as an important target for cancer therapy. In particular, cancer-associated-fibroblasts (CAFs) secrete soluble factors that enhance tumor growth and invasion through the epithelial-to-mesenchymal transition, which ultimately promotes heterotopic metastatization. Neuroendocrine tumors (NETs) are malignancies arising from the diffused endocrine system that produce functional peptides. They recruit fibroblasts within the lesional sites and affect their transcriptional profile, despite their role in tumor progression is yet unknown.

Methods. We established primary cultures of CAFs from enterochromaffin cell (ECL) hyperplasia, G1, G2 or G3 NETs and from GISTs. Fibroblasts from the perilesional tissue of NETs and WI-38 lung fibroblasts were used for control. Adherent cells were immunostained for CD34, CD45, CD56, CD73, CD90 and CD105. H720, H727, H835, BON1, CM and QGP1 NET cell lines were cultured with CAF conditioned medium (CM) and their viability was assessed by MTS test. NET cell proliferation was evaluated by staining with CFSE NET cells co-cultured with CAFs in the presence or not of inserts and by flow-cytometry.

Results. CAFs were identified for their expression of mesenchymal markers and absence of hematopoietic and neuroendocrine markers. We linearized CAFs from an ECL hyperplasia, three cell lines from G1, G2 and G3 NETs and from a GIST. Two lines were obtained from perilesional tissue of G1 and G3 NETs. MTS test showed a time-dependent decrease of cell viability of NET cells in the presence of CM from WI-38 cells, normal perilesional fibroblasts and from GIST. A significant increase of NET cell viability up to 170% and 130% was found in H727, H720 and H835 lung carcinoid cell lines respectively cultured in the presence of CM from NET and ECL hyperplasia. CFSE assays confirmed the proliferation effect on cells stimulated by NET CAFs and, at a lesser extent, by CAFs from ECL hyperplasia. Fibroblasts from healthy tissue and from GIST failed to induce the proliferation effect, likewise in the presence of cell-to-cell interactions.

Conclusions. CAFs stimulate the proliferation of NET cell lines by the secretion of soluble factors rather than by physical interactions. This mechanism is absent when tumor cells are incubated with normal fibroblasts, thus implying that major modifications of the transcription profile of CAFs take place during NET tumorigenesis and ultimately drive their progression.

D2* PRIMARY TUMOUR RESECTION IMPACT ON SURVIVAL IN PATIENTS WITH CARCINOID SYNDROME (CS). ANALYSIS OF 139 PATIENTS WITH WELL DIFFERENTIATED NEUROENDOCRINE TUMORS (WDNETS) FROM DATABASE OF ISTITUTO NAZIONALE TUMORI MILANO

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Background. The tumours causing CS arise from enterochromaffin (EC) or enterochromaffin-like (ECL) cells and can originate throughout the digestive system. About 10% of NET pts developed CS clinically evident. Serotonin is most often hyper-secreted by the EC/ECL cell in the gut, where it is normally used to regulate intestinal movements and in such condition is evident an increase in urinary 5-hydroxyindoleacetic acid (5-HIAA) levels. The overproduction of serotonin determines the typical CS: skin flushing, chronic diarrhoea, bronchoconstriction, and right heart disease (CHD), which accounts for 95% of cases. Atypical CS is rare, associated with foregut NETs and histamine hyperproduction. It is characterized by flushing, salivation, bronchoconstriction, lacrimation and hypotension.

Materials and methods. We analyzed 1100 NET pts, followed between 1979 and 2012 in our Institution, identifying a cohort of 139 consecutive pts with typical (98%) or atypical (2%) CS.

Aim. To assess the clinical features and survival of WDNETs pts with CS.

Results. Median age was 53 years, male/female 67/72. All histological types were classified as WDNET and the majority were GEP (77%), distinct by sites: Midgut/Foregut/Hindgut/Primary unknown: 60/53/6/20. Liver involvement was found in 115 pts: synchronous (89%); metacronous (11%). Primary tumor resection was performed in 95% of midgut (57), in 55% of foregut (29) and 100% of hindgut (6) patients. The most common symptoms were flushing/diarrhea/CHD in 43.5%/37%/7% of cases. Cromogranin/5-HIAA pathological levels, were reported in 59.5%-47.5% of patients. Significant difference in median overall survival (mOS) was found for age (cut-off = median age 56 years), $p < 0.05$, but not for gender. Median OS was 93 months (mos) (95% CI 74-135 range), 5 and 10 years survival rates were 66% and 43%, respectively. Significant difference in mOS was evident considering carcinoid/ pancreaticNETs/primary unknown, 130/62/46 mos, respectively ($p < 0.05$). Primary tumor resection improves survival independently of histology: 141/37 mos in resected/not resected pts, respectively ($p < 0.05$).

Conclusions. Liver involvement in advanced stage was the main feature related to CS appearance. The resection of primary tumour was an independent and favourable prognostic factor related to survival in syndromic WDNETs. Impact evaluation of surgery and locoregional treatment in pts with only liver metastases is ongoing.

D3 EVEROLIMUS AND LONG-ACTING REPEATABLE (LAR) OCTREOTIDE AS FIRST-LINE TREATMENT FOR NEUROENDOCRINE TUMORS: EFFICACY DATA IN PNET AND NON-PNET PATIENTS. I.T.M.O. (ITALIAN TRIALS IN MEDICAL ONCOLOGY) GROUP

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Background. Everolimus has shown antitumor activity in pancreatic neuroendocrine tumors. We aim to assess efficacy and safety of everolimus in combination with octreotide LAR in patients with well differentiated gastroenteropancreatic and lung NETs.

Material and methods. We performed a phase II, multicenter trial. Patients with advanced well differentiated, previously untreated NETs of the gastroenteropancreatic tract and of the lung received octreotide LAR 30 mg every 28 days and everolimus 10 mg per day continuously. The primary endpoint was Objective Response Rate (ORR).

Results. A total of 50 pts (58% males) were enrolled. The median age was 60.5 years (range 25-76). Primary tumor site was pancreas in 14 (28%), unknown in 14 (28%), lung in 11 (22%), ileum in 9 (18%) and jejunum and duodenum in 2 (4%) of patients. Thirteen (26%) pts had carcinoid syndrome. The ORR, calculated on the Intention-to-Treat (ITT) population, was 20.0% (95% CI 8.9-31.1): 14.3% (2/14) in pNET pts and 22.2% (8/36) in non pNET patients. Thirty-six patients (72%) achieved stable disease (SD). All CR and all PR as well as 91.7% of SD had a duration ≥6 months. Clinical benefit (CR+PR+SD) was 92%. At a median follow-up of 277 days, the median time to progression (TTP°) was 16.3 months (95% CI 10.7-20.1): 17.2 months in pNET patients. Overall survival could not be assessed. Treatment-related adverse events (AEs) were mostly of grade 1 or 2; the only grade 4 AE was mucositis in 1 patient, while grade 3 AEs included skin rash in 1 case, stomatitis in 4 cases (8%) and diarrhea in 11 cases (22%).

Conclusion. Everolimus in combination with octreotide LAR has shown to be active and well tolerated in advanced NETs, both in pancreatic and non -pancreatic primary sites.

Acknowledgements. The Authors thank the Italian Trials in Medical Oncology (I.T.M.O.) group and Novartis Pharma for their provided support.

D4 5-FLUOROURACIL/CAPECITABINE AND OXALIPLATIN (FOLFOX/XELOX) SUITABLE TREATMENTS FOR PROGRESSING G1-G2 NEUROENDOCRINE TUMORS

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Background. No second-line therapy for metastatic neuroendocrine tumor (NET) has gained wide acceptance, beyond the usual regimens based on streptozocin and doxorubicin or 5-fluorouracil. Oxaliplatin plus 5-fluorouracil (FOLFOX) or oral capecitabine (XELOX) have been evaluated in limited phase II studies in NET. We evaluate our experience in metastatic well differentiated G1-G2 NET patients (pts) treated with these chemotherapy regimens.

Materials and methods. From October 2005 to February 2013, eighteen consecutive NET pts with progressive disease were treated with FOLFOX or XELOX after failure of somatostatine analog (SSA) therapy and/or chemotherapy, targeted therapy, Peptide Receptor Radionuclide Therapy. The primary tumor site was pancreas in 5 pts, gastrointestinal tract in 7 pts, lung in 3 pts, and unknown in 3 patients. Patients received oxaliplatin e.v. 85 mg/m^2 i.v. g1, 5-fluorouracil 2800 mg/m^2 e.v. 48h gg1-3 q21 (FOLFOX) or oxaliplatin e.v. 130 mg/m^2 i.v. g1 and capecitabine 1000 mg/m^2/die os gg1-14 (XELOX). Patients were followed for evidence of toxicity, response assessed using RECIST criteria, and survival.

Results. Four (22.2%) out of 18 pts had a partial response, 9 pts (50%) showed stable disease, and 5 (27.8%) pts showed progressive disease. Median number of cycles was 5 (2-10). At a median follow-up of 46 months, median OS is 24 months (10 patients are still alive). Median progression-free survival was 8.23 months, while 1 patient is still in treatment. G1-G2 toxicities were diarrhea, nausea, asthenia, neutropenia, neurotoxicity; main G3-G4 toxicities were neurotoxicity (5%) and diarrhea (11%).

Conclusions. FOLFOX or XELOX showed interesting activity and efficacy in pretreated patients with progressive NET, also after many previous treatments, with acceptable toxicity.

D5 CHEMOTHERAPY WITH CAPECITABINE PLUS TEMOZOLOMIDE (CAP-TEM) IN PATIENTS WITH NEUROENDOCRINE TUMOURS (NET): AN ITALIAN MULTICENTER RETROSPECTIVE ANALYSIS

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Background. Everolimus and sunitinib have been recently approved for treatment of well/moderately differentiated (WHO 2000) pancreatic-NET (pNET). However, a combination of capecitabine (CAP) and temozolomide (TEM) has been successfully used as first-line treatment in pNET. This is an Italian multicenter retrospective analysis to evaluate activity and toxicity of CAP-TEM regimen in patients with advanced NET.

Material and methods. The patients received oral CAP 1500 mg/m^2/day over 14 days bid plus oral TEM 150-200 mg/m^2/day on days 10-14 of each 28-day cycle. The MGMT methylation status and TS polymorphisms in tumour tissue and peripheral blood are currently ongoing.

Results. Since March 2012, 26 patients were treated (54% males, median age 51 yrs): 50% had a pNET, 31% lung, 11% gastrointestinal (GI) and 8% unknown. According to 2010 WHO classification, among gastro-entero-pancreatic, Ki67 was 2-20% (G2) in 63% of tumours, >20% (G3) in 32% with two "low G3" (Ki67 21-30%), and unknown in 5%. Among lung NETs, 71% were atypical carcinoids, and 29% typical (Travis' classification). As for clinical features 87% (13/15 patients) were FDG-PET/CT positive. Nineteen patients (73%) were progressive on different therapies: peptide-receptor-radiotherapy (58%), and everolimus (26%). Partial response (PR) occurred in 21% (4/19) patients (95% CI: 6-46), stable-disease (SD) in 63% (12/19) (95% CI: 38-84). The two "low G3" responded. Disease control rate (PR+SD) was 84% (95% CI: 60-97). Two PR patients had G2 pNET (Ki67 9%, and 19% respectively), and two lung NET, one typical and one atypical carcinoid. The median time-to-progression (TTP) was 8 months (95% CI: 6-N.E.). One case of grade 3 hyper-

triglyceridemia, and one of grade 4 thrombocytopenia occurred, both temporary. All 4 patients showing PR had genotype 2R/3R investigated for the 28 base pair (bp) variable number of tandem repeats (VNTR) in the 5'UTR of the TS-gene, and MGMT-gene inactivation by epigenetic silencing. The correlation data among TS, MGMT, and the clinical outcome will be presented at the meeting.

Conclusions. This analysis showed that CAP-TEM therapy can be active and well tolerated in pre-treated patients with advanced NET of different origins. On this basis, we designed a prospective phase II trial with the same regimen in patients with G2 or "low-G3" NET, with a concomitant exploratory analysis of the methylation status of MGMT gene and TS genetic polymorphisms.

D6 IRINOTECAN-BASED REGIMEN AS SECOND-LINE CHEMOTHERAPY IN PATIENTS WITH METASTATIC NEUROENDOCRINE CARCINOMAS: EXPERIENCE IN NINE CASES

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Background. The role of a second-line chemotherapy for neuroendocrine tumors (NETs) remains unknown, especially for the small number of patients with this disease that does not allow to build specific prospective trial. Irinotecan alone or in association with platinum derivates has shown some efficacy in patients treated for small cell lung cancer which has pathological similarities with neuroendocine carcinomas (NECs).

Patients and methods. Nine patients (pts), five males/four females, median age 60 years (range 43-76), with metastatic NECs were treated with irinotecan-based regimen as second-line therapy. The sites of the primitive NEC were as follows: three pancreatic, three rectal, two gastric and one laryngeal; all but one pts had liver metastases, moreover three pts had bone metastases, two peritoneal, two lung, two nodal metastases and one patient had splenic metastases. All these pts were treated with a 1st-line chemotherapy with a platinum derivate (seven cisplatin and two carboplatin) in association with etoposide. Five pts were treated with a FOLFIRI regimen (irinotecan 180 mg/m^2 IV over 60' d1, leucovirin 100 mg/m^2 IV over 2 hours d1,2 followed by FU 400 mg/m^2 bolus d1,2 and FU 600 mg/m^2 continuous infusion over 22 hours d1,2); two pts were treated with a modified FOLFIRI regimen (with FU 2400 mg/m^2 continuous infusion over 46 hours), one patient with XELIRI regimen (irinotecan 250 mg/m^2 IV over 90' and capecitabine 1000 mg/m^2 bid for 14 days every 3 weeks) and one patient received another regimen at different doses (irinotecan 300 mg/m^2 IV over 90' d1, leucovirin 250 mg/m^2 d1 and FU 3200 mg/m^2 continuous infusion over 46 hours every 3 weeks). Tumor response was assessed according to RECIST criteria every 3 months.

Results. Median number of treatment cycles of irinotecan-based 2nd-line chemotherapy was 9 (range 5-16). Partial response according to RECIST criteria was seen in one patient (11%) and stable disease in 6 patients (67%). Median time to progression was 6.5 months (range 2-16.5).

No grade 3-4 toxicities were found, except for one case of grade 3 neutropenia.

Conclusions. Although the number of patients treated is limited by the rarity of the disease, Irinotecan-based chemotherapy is safe and potentially efficient in 2nd-line treatment of metastatic NECs.

D7 ACTIVITY AND SAFETY OF A COMBINATION OF THREE DRUGS INCLUDING CISPLATIN (THE CLOVER REGIMEN), FOR POORLY DIFFERENTIATED NEUROENDOCRINE CARCINOMAS (NEC)

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Background. No standard treatment has been established for NEC; the usual recommended treatment is based on the strategy for small cell lung carcinoma. The aim of this study is to evaluate the response of NEC to the combination of three drugs, including cisplatin.

Material and methods. We reviewed 21 NEC patients treated since November 2008 to January 2013 in our two institutions. Six patients (pts) initially were treated with the scheme A: epirubicin (30 mg/m^2 die 1,2,3) fluorouracil (500 mg/m^2 die1,2,3) and temozolomide (200 mg/m^2 die 1,2,3) every 21 days. Subsequently, because of toxicity, the regimen was modified into scheme B: cisplatin (25 mg/m^2 die 1,2,3), capecitabine (2000 mg/m^2 die 1,2,3,4,5) and dacarbazine (200 mg/m^2 die 1,2,3).

Results. The median age was 58 (36-80) years. Primary tumor site was: pancreas 7 (33%), lung 5 (24%), colon-rectum 5 (24%), unknown 3 (14%) and stomach 1 (5%). There were no pts with carcinoid syndrome. Ten (50%) pts underwent surgery of primary site. 40% of pts were pretreated with somatostatine analogues, 30% with chemotherapy (platinum regimen) and two pts received peptide receptor radionuclide therapy. The response rate was 25% and we observed: 0 CR, 6 (29%) PR, 8 (38%) SD and 7 (33%) PD. Overall survival is 13 months (range 1-29), and progression-free survival was 6 months (range 1-11). With the combination epirubicin, fluorouracil and temozolomide 3 pts discontinued treatment after 1 or 2 cycles for toxicity: one pt discontinued treatment for skin rash G3, one pt for myocardical infarction, one pt for G3 renal failure. In the group treated with cisplatinum capecitabine and dacarbazine, grade 3-4 hematologic adverse events were seen in 2 patients (14%) and grade 3-4 non-hematologic adverse events were seen in 3 patients (21%), but no patient discontinued treatment due to toxicity or died of adverse events.

Conclusion. The combination chemotherapy of cisplatinum, capecitabine and dacarbazine is effective and feasible, and it should be considered as a treatment option for NEC.

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Session E • Continuous care in the cancer patient

E1* ESOPO: EPIDEMIOLOGICAL STUDY OF PAIN IN ONCOLOGY. PAIN EXPERIENCE IN CANCER PATIENTS. A NATIONWIDE RESEARCH

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Background. Pain is one of the most common and feared symptoms in cancer patients. The Italian law 38/2010 recognizes the right of citizens to receive the best pain relief treatments. The aim of this research, the largest ever made in Italy, is to evaluate the patient experience of illness with a peculiar focus on pain perception.

Materials and methods. The research is a survey based on a questionnaire which has been constructed by assembling internationally validated scales of measuring and discussed with 20 focus groups with experts and patients. A pre-test on 200 patients was carried out in order to have it validated. The questionnaire contains 65 questions and 6 of these are related to information registered in the clinical folder. The questionnaire was filled out by the patients with the help of a facilitator (nurse, doctor in training, psychologist, volunteer). Processing of the results is still ongoing and in this abstract we propose some data from the descriptive analysis.

Results. The survey was carried out between January 2012 and January 2013 in 53 italian hospital oncology units (16 in the North; 13 in the Center; 11 in the South and 13 in the Islands). A total of 4057 questionnaires were returned. The clinical setting was represented by day-hospital in 79.5% and inpatient ward in 20.5%. The sample was done by 58.4% of women, 39.5% of patients over 65 and 54.7% of patients with KPS 90-100. The more frequent cancers were: breast (25.3%); colon-rectal (15.6%); lung (13.1%); uterine and ovarian (8.9%); prostate (4.7%). The 64.3% of patients had advanced disease (27.8% was on first-line treatment). The 41.3% was receiving "around the clock" analgesic therapy based on minor opiates (14.8%) or major ones (16.5%). A medium-high intensity of pain (NRS >4) in the previous 30 days was reported by 41.7% of patients. The 38.1% of patients had experience of breakthrough pain in the previous week and 75.4% found a satisfactory relief from pain therapy. The 56.8% considers the oncologist very concerned with patient pain and 59.5% reports of having received analgesic therapy whenever asked for. The 78.5% of patients claims to have the utmost confidence in own oncologist and/or the team.

Conclusions. This is the biggest research conducted in Italy on epidemiological and sociological aspects of pain in cancer patients treated in oncological settings. In the conference more analytical and interpretative data will be provided.

E2* APREPITANT (AP) VERSUS DEXAMETHASONE (D) FOR PREVENTING DELAYED EMESIS INDUCED BY ANTHRACYCLINES PLUS CYCLOPHOSPHAMIDE (A+C) CHEMOTHERAPY (CT) IN BREAST CANCER PATIENTS: A DOUBLE-BLIND, MULTICENTER, RANDOMIZED STUDY

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Background. A combination of AP + a 5-HT3 receptor antagonist + D and AP alone is recommended, respectively, for the prophylaxis of acute and delayed emesis induced by A+C CT in breast cancer patients. In the registrative study the role of AP in delayed emesis was not defined because prophylaxis of acute emesis was different between the two arms, and the superiority of AP on delayed emesis could be the consequence of a dependent effect on the different results achieved in acute phase. Aim of this study was to compare the efficacy of AP versus D in preventing delayed emesis in pts receiving the same prophylaxis of acute emesis.

Methods. A randomized double-blind study comparing AP versus D was completed in naïve breast cancer pts treated with A+C. Before CT, all pts were treated with intravenous palonosetron 0.25 mg and D 8 mg, and oral AP 125 mg. On days 2 and 3 pts randomly received D 4 mg bid or AP 80 mg qd. Primary endpoint was rate of complete response (no vomiting, no rescue treatment) from days 2-5 after CT.

Results. From September 2009 to July 2012, 580 pts were enrolled; 551 were fully evaluated, 273 in arm D and 278 in arm AP. Day 1 complete response rates were similar: 239/273 (87.6%) in D arm and 236/278 (84.9%) in AP arm. From day 2-5, complete response was the same with both antiemetic prophylaxes (79.5%), and all secondary endpoints (complete protection, total control, no vomiting, no nausea, score of FLIE) assumed similar values. During the delayed phase, incidence of insomnia (2.9% vs 0.4%) and heartburn (8.1% vs 3.6%) was significantly superior in D arm.

Conclusions. In breast cancer pts submitted to A+C CT and receiving the same antiemetic prophylaxis for acute emesis, D and AP present similar efficacy and toxicity.

E3 IMPACT OF HOME ARTIFICIAL NUTRITION ON QUALITY OF LIFE AND SURVIVAL IN ADVANCED CANCER PATIENTS

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Introduction. The decision to start the Home Artificial Nutrition (HAN) in advanced cancer patients depends not only on presence of malnutrition and avoiding death from cachexia, but also on the influence of the HAN on the patient's quality of life.

Aim. To analyze the impact of the HAN on survival and quality of life in advanced cancer patients assisted at home by ANT Foundation in Bologna.

Materials and methods. A nutritional flow-chart for the individuation of patients candidate to HAN was drawn using the Malnutrition Screening Tool for the assessment of nutritional risk, and the Palliative Prognostic Score for the evaluation of expectancy of life if risk or presence of malnutrition. When the expected 30 days survival was >70%, the following selection criteria were verified by the nutritionist before starting the HAN: a) attendance of malnutrition and/or negative protein-energy balance; b) survival ≥6 weeks; c) psycho-physical and environmental conditions suitable for the HAN; d) informed consent of the patient. The Karnofsky Performance Status (KPS), evaluated at the start and after one month from the beginning of the HAN, has been used for the assessment of the quality of life.

Results. From July 1990 to July 2012, the ANT Foundation assisted 29,348 advanced cancer patients at home in Bologna. HAN was started in 618 patients. Mean survival after the beginning of HAN was 20.4 ± 23.8 weeks for enteral nutrition (285/618 patients) and 15.8 ± 18.6 weeks for parenteral nutrition (333/618 patients). 78% of patients (484/618) survived = 6 weeks. The duration of life was strongly related ($r = 0.291$; $p < 0.0001$) with KPS evaluated at the study entry (52 ± 9.6). KPS had decreased in 73 patients (12%), unchanged in 414 (67%) and increased in 131 (21%) when re-evaluated after one month of HAN. Survival was significantly higher ($p < 0.0001$) in KPS increased group (28.1 ± 26.2 wks) when related with KPS unchanged (16.3 ± 19.6 wks) and KPS reduced (8.9 ± 11.7 wks) groups.

Conclusions. The study showed a significant correlation between survival and KPS at the start of HAN, confirming the accuracy and usefulness of KPS as a prognostic index in the decision-making process for the start of HAN. The correlations between survival and KPS changes, after one month of HAN, showed that the survival increased proportionally to the improvement of the quality of life.

E4 CHEMOTHERAPY AT THE END OF LIFE: A DECREASING ATTITUDE IN THE METROPOLITAN AREA OF BOLOGNA

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Background. The use of anti-cancer drugs in the last weeks of life in advanced cancer patients (ACP) is considered a marker of poor quality of care for the substantial lack of benefit in the face of negative consequences for patients, families and health systems. In 2003-2005 a retrospective study ("study 1") in the metropolitan area of Bologna showed that 22.7% of ACP treated with at least one line of chemotherapy (CT) and subsequently dead, had received the last cycle in the last month of life. Following this observation a prospective research program (MIRTO project*), currently in its final phase, was activated with the goal of reducing the percentage of patients who receive CT at the end of life through a) raising awareness among prescribing oncologists and b) an early and integrated collaboration with the Palliative Care Network. Parallel to this project a retrospective study (study "Registro") with the same characteristics as the "study 1" on ACP who were not enrolled in the MIRTO project, was carried out.

Methods. The study "Registro" is based on the collection of data obtained retrospectively from the medical records of ACP who died in 2009-2011, living in the province of Bologna and followed at the Medical Oncology (MO) Unit of the Azienda Ospedaliero-Universitaria of Bologna or followed by the home care program of the no-profit ANT Foundation.

Results. During the study period 1385 ACP were recorded: 452 pts by MO and additional 933 by ANT. Altogether 762 ACP (55.0%) had received at least one line of CT before dying. Principal tumours were lung (27%), colorectal (16%) and breast (10%). The treatment was initiated or continued in the last month of life in 96 pts (12.6%). This incidence is significantly lower than that observed in the "study 1" ($p = .00001$). These patients were female in 51%, had median age of 69 years (35-86) and median KPS 70 (50-90). CT was of 1st-line in 52% and of 2nd/3rd-line in 44%. The activation of home care programs by MO grew by 68.7% from "study 1" to "study Registro".

Conclusions. In the present study the administration of CT at the end of life decreased compared to 6 years ago. The increased awareness in the oncologists and closer integration with the local Palliative Care Network and first of all the home care program are likely at the basis of this result.

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E5 CHEMOTHERAPY IN THE LAST 30 DAYS OF LIFE

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Background. Literature about chemotherapy in the last 30 days of life is generally poor; we analysed patients with cancer who received chemotherapy in their last month of life.

Patients and methods. The study involved all patients treated in our oncological department between 2010 and 2011; our attention focused on patients receiving chemotherapy in their last month of life.

Results. During the covered period, 4137 pts were visited; 1305 pts received chemotherapy; 469 pts died, 116 pts received chemotherapy in their last month of life (23% of dead). We analysed age, Performance Status, type of cancer, line of chemotherapy before last treatment; type of chemotherapy and cause of death. Median age was 66.7 years (range 36-84); 69% of patients were males. ECOG performance status was respectively 2 in 43%, 1 in 31.9%, 3 in 17.2% and 0 in 7.8% of patients. Prevalent solid tumor types: lung (31%), pancreatic (13.8%), stomach and head and neck (8.6%), breast (7.9%), colon (6%), ovary (3.6%) and esophagus cancers (2.6%). All patients present-

ed metastatic disease: 42% were in first-line, 32.8% in second-line, 16.4% in third-line, 6.2% in fourth-line and 2.6% in fifth-line. Infusion regimen administered was weekly paclitaxel in 19%, cisplatin and gemcitabine in 10.3%, weekly gemcitabine in 6.9%, irinotecan and 5FU in 6%, other regimens from 5.6% to lower. Cause of death: progressive disease in 51.7%, toxicity in 6%, sudden death in 6%; other causes are not known.

Conclusions. 23% of patients dead were treated with chemotherapy within one month of death. Percentage is in line with existing results. Lung cancer tumor type is overrepresented in our analysis; also literature reports 43% of lung pts receiving chemotherapy in the last month of life. Pancreatic cancers are treated in PS2 and in second-line of chemotherapy and this is not in compliance with current guidelines. It is commonly acknowledged that age, performance status, tumor sensitivity, survival prognosis and comorbidities should be considered in every chemotherapy decision-making, nevertheless some studies show that age is not a crucial factor. At present individual clinician is the only predictor for continuing chemotherapy in the last 4 weeks of life. This retrospective study suggested evaluating appropriateness criteria for each cancer treatment on a larger scale, involving a study at Istituto Tumori Toscano.

E6 CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING IN ITALIAN CANCER CENTERS: RESULTS OF CINVDAY, A PROSPECTIVE, MULTICENTER STUDY

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Background. Guidelines consistency for preventing chemotherapy-induced nausea and vomiting (CINV) remains low (29% in Pan European Emesis Registry study) and very low (11%) in highest emetogenic risk regimens. Aim of this study was to evaluate guideline-consistency of CINV prophylaxis for acute emesis in clinical practice in Italy.

Patients and methods. This was a prospective, observational, multicenter study. Patients scheduled to receive chemotherapy in a single pre-specified day were included. Data on patients characteristics (demographic and clinical), type of cancer therapy and antiemetic therapy prescribed for acute emesis were collected on electronic data capture forms. Chemotherapy regimens and antiemetic prophylaxis were categorized according to MASCC 2011 guidelines. The study was approved by local Ethics Committees.

Results. From June to November 2012, a total of 502 patients were enrolled at 26 study sites. Median age of the patients was 62 years (range 27-87). Colorectal cancer and breast cancer were the most common malignancies. Chemotherapy regimens were: HEC (23.7%), MEC (40.6%), LOW (31.3%) and MINIMAL (4.4%). Overall guideline consistency was 19.3%. Consistency was higher (45%) if the various 5HT3 receptor antagonists were considered equivalent and interchangeable in MEC regimens. Among HEC and MEC regimens, 10% of the patients did not receive any 5HT3 antagonists. NK1-receptor antagonists were used in 8% of therapies.

Conclusions. Our study indicates that antiemetic guideline inconsistency remains an issue in oncologic Italian clinical practice. The use of consistent antiemetic therapy was lowest in patients in HEC or MEC risk groups. Strategies to improve guideline adherence are needed.

E7 COMPARISON OF THREE DIFFERENT PROGNOSTIC SCORES FOR TERMINAL CANCER PATIENTS: INTERIM ANALYSIS OF A PROSPECTIVE COHORT STUDY

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Background. To forecast life expectancy in terminal cancer patients, clinical prediction is often inaccurate and multidimensional scores are often used. We carried out a prospective cohort study in two distinct palliative care Units to compare 1) the accuracy of three different prognostic scores: the Palliative Prognostic (PaP) Score, the Objective Prognostic Score (OPS) and the Palliative Prognostic Index (PPI); 2) the accuracy of the Clinical Prediction of Survival (CPS) estimated by two experienced physicians and dedicated nurses.

Materials and methods. At the time of in hospital admission, clinical and laboratoristic data of 238 advanced cancer patients were collected from April 2011 to August 2012. Pap Score, OPS and PPI were calculated and CPS was estimated by the study team. Survival was evaluated by Kaplan-Meier curves and accuracy was established by ROC analysis.

Results. The median survival was 15 days (range 0-502), while the estimated survival using the Kaplan-Meier method was 31% at 30 days and 18% at 60 days. The PaP score was the most accurate instrument (AUC = 0.81) in predicting the 30-day survival. CPS estimates'accuracy was similar among physicians and nurses (AUC = 0.78 vs 0.76) although nurses' CPS had the greatest correlation with the actual survival. In 40 % of cases the clinicians' CPS was underestimated.

Conclusions. Accurate prognostication is crucial for decision-making even in terminally ill cancer patients. The PaP Score had the highest prognostic accuracy in the survival prediction. When blood test samples are not available, the PPI may be also a reliable prognostic score. In contrast with the literature data clinicians underestimated the prognosis. Combining the use of multidimensional instruments with a survival forecast made by trained professionals with personal expertise may lead to a very accurate prognostic characterization.

E8 OVERALL COMPLEXITY EVALUATION OF ONCOLOGIC PATIENTS: A PRACTICAL EXPERIENCE IN A DAY-HOSPITAL

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The "overall complexity" refers to the burden of medical, welfare, psychological and social problems relating to each patient. High overall complexity influences outcomes and quality of life of oncologic pts, implies deviations from standard protocols, needs individualized interventions. Piedmont Oncologic Network (PON) proposed an evaluation instrument of global complexity of oncologic pts; it investigates 4 areas (biological, psychological, social and care) with a scoring system allowing to identify levels of need of intervention. "Complex" pt: score 3 in in at least one of non-biological areas; or score 2 in at least 2 of the 4 areas. We evaluated the impact of the Global Complexity System (GCS) in everyday pt care. We used a 2 steps system to collect data: information was collected by the psychologists (P) during the weekly plenary session (doctors, nurses, social workers, dieticians, P); if some complexity indicator was present P completed evaluation. An intervention project was set up by the whole team. In 2012 we evaluated all our Day-Hospital pts: 351 pts. The mean time needed for the GCS was 15 minutes. In biological area 144 pts (41%) had score >1 and 69 (20%) >2 (short life expectancy 40, comorbidities 13, weight loss 13). In psychological area 108 (31%) had score >1 and 65 (19%) >2 (anxious-depressive symptoms 56 pts, mental disorder 7). In social area 76 (22%) had score >1 and 35 (10%) >2 (small families 12, lack of caregiver 6, disabled family members 5, under age children 5, economic or housing problems 5). In care area 59 pts (17%) had score >1 and 20 (6%) >2 (poor family collaboration 14, inadequate expectations 5). GCS identified as "complex" 77 pts (22%): 46 (60%) had a psychological support, 10 (13%) a social and caring intervention; for 28 (36%) no intervention was done (pt refusal or organizational difficulties). GCS could be easily used. GCS is effective in identifying subgroups who needed prompt psychological, social and care support, even we think that some of social and care indicators partially overlap. We need to improve the interventions with better integration between the hospital professionals and also with volunteer services and primary care system. We are also interested in evaluating if for each grade of biologic complexity the presence of high complexity score in the other areas affects the frequency and severity of complications to oncologic therapies and the number of hospital admissions.

E9 RAPID SCREENING TESTS (RSTS) AS A PROGNOSTIC TOOL FOR ELDERLY CANCER PATIENTS (PTS)

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Background. Comprehensive Geriatric Assessment (CGA) may help to evaluate the functional status of elderly patients; however, because it is time-consuming, RSTs have been proposed. However, the predictive and prognostic value of RSTs is still unclear. The aim of this study was to correlate overall survival (OS) with the results of three rapid tests, G8, VES-13 and aCGA in cancer patients aged over 70.

Materials and methods. From April 2009 to April 2012, 530 outpatients aged over 70, 263 males and 267 females, were evaluated. During the first oncologic visit, they were assessed by a trained oncogeriatric team using a dedicated, expressly developed web-based software (www.oncoger.ro.it) including several tests (G8, VES13, aCGA, MNA, LIFE4, comorbidity index). The study involved patients with a histologically confirmed diagnosis of a solid or hematologic tumor not receiving previous chemotherapy. Survival curves were drawn using Kaplan-Meier method and compared with log rank test; multivariate analysis was performed according to Cox regression method.

Results. The tests identified frail patients as follows: VES-13 69%, aCGA 50%, G8 68.5%. Frailty was significantly associated with poor OS, with different hazard ratios (HRs) for each test. HRs for death of frail vs non-frail pts were: for aCGA 1.45 (95% CI 1.09-1.89, $p = 0.008$), for VES-13 1.55 (95% CI 1.12-2.00, $p = 0.005$) and for G8 2.57 (95% CI 1.66-2.93, $p < 0.0001$). In the multivariate analysis including the 8 items of the G8 test, appetite loss (HR 1.44, $p = 0.002$), weight loss (HR 1.28, $p = 0.003$), and personal perception of poor health (HR 1.58, $p = 0.002$) were significantly associated with a higher risk of death. Furthermore, G8 is the only geriatric RST that significantly predicted the risk of death when included in a multivariate analysis with other potential prognostic tools (LIFE4 and MNA).

Conclusions. 1) Frailty, as identified by RSTs (VES-13, aCGA, G8), is statistically associated with poor OS; 2) G8 presents the most meaningful HR for OS; 3) appetite loss, weight loss and personal perception of poor health are significantly associated with short OS. Our data show that RSTs and in particular G8 represent a useful prognostic tool for the assessment of geriatric patients with cancer.

E10 INFLUENCE OF PATIENT PERCEPTIONS AND PREFERENCES FOR THE TREATMENT OF BREAKTHROUGH CANCER PAIN: RESULTS OF A RANDOMIZED DOUBLE-BLIND CROSS-OVER STUDY BETWEEN FENTANYL PECTIN NASAL SPRAY (FPNS) WITH ORAL TRANSMUCOSAL FENTANYL CITRATE (TFC) IN CANCER PATIENTS

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Introduction. Breakthrough cancer pain (BTCP), defined as a transient exacerbation of pain that occurs either spontaneously, or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain, has been reported to affect 60-95% of cancer pain patients. An important barrier to the effective management of BTCP is patient adherence. In general, patients will adhere to a medication only if they find it efficacious, tolerable, socially acceptable and easy to use. This study investigated the difference in tolerability and therapy management that lead patients to choose the use of fentanyl nasal spray with respect to the oral formulation.

Methods. For newly enrolled patients, the main study consisted of four phases: 1) screening; 2) open dose-titration phase with randomization 1:1 between FPNS and TFC; 3) 2-week, crossover; 4) 4-week, end-of-treatment phase. Patients were stratified on the basis of ECOG performance status, number of metastatic sites, fixed-schedule opioid regimen in use. Exclusion criteria were problems with the oral mucosa, such as xerostomia and mucositis. The primary endpoint is patient preference assessed at 4 weeks. Other endpoints included physician preference, safety, QoL.

Results. Of 46 randomized pts, 40 completed the preference questionnaire. In the primary analysis, FPNC was preferred by 80% of pts, TFC by 15% and 5% had no preference. The most common reasons for pts preference were better QoL and methods of use. Indirectly was observed a better management of the therapy for the BTCP with FPNS and need of lower dose to FPNS.

Conclusions. Patient-reported outcome is also applicable to the treatment of cancer pain and can be a mode of study to improve the adherence of patients to the same.

E11 MUCOSITIS PREVENTION AND TREATMENT IN HEAD AND NECK CANCER PATIENTS TREATED WITH (CHEMO)RADIATION: REPORT OF AN AIOM-AIRO SURVEY

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Background. There is a limited number of therapies reaching a high level of recommendation for mucositis prevention and treatment in head and neck cancer (HNC) patients receiving radiation therapy with/without concurrent chemotherapy. In daily practice, however, several strategies are employed with a limited evidence for efficacy.

Materials and methods. We conducted a 21 items electronic survey among Italian radiation and medical oncologists, aimed to assess standard of care in preventive and therapeutic strategies regarding mucositis in HNC, involving also nutritional aspects and pain treatment employed. The survey was launched with the support of Italian Medical Oncology and Radiation Oncology Societies (AIOM and AIRO).

Results. We collected 111 answers (51% medical and 49% radiation oncologists). CTCAE scale is shown to be employed by 55% of the physicians in assessing mucosal toxicity. The highest predictive factors for mucositis development are considered active exposure to oral stressors (smoke, alcohol), planned radiotherapy on oral cavity and oropharyngeal mucosa, concurrent use of radiosensitizing chemotherapy. Gastrostomy is prophylactically placed in less than 10% of the patients, mainly due to weight loss before treatment. Preventive antimicotic or antibiotic drugs are prescribed by 46% of the responders (mainly local or systemic antimicotic drugs). Alkalinizing mouthwashes or coating agents are frequently adopted (70% of the cases). Among therapeutic intervention, systemic fluconazole is administered by 80% of the physicians, while the antibiotics most frequently employed are penicillins, cephalosporins or fluoroquinolones (20% each). Mucositis induced pain is mainly treated by weak followed by strong opioids. Pain during swallowing is considered as breakthrough pain by 69% of the responders.

Conclusions. Pattern of mucositis prevention and treatment varies among Italian Centers, with some uniform conducts in nutrition strategies, use of antimicotic and painkillers.

E12 PATIENT'S PERCEPTION OF SIDE EFFECTS OF ANTICANCER TREATMENT: AN OBSERVATIONAL STUDY

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Background. It is widely recognised that the perception of side effects of anticancer therapy may be substantially different among patients and physicians. As a consequence, within the context of patient-doctor communication, the process of therapeutic decision making could be improved by better knowledge of patient's point of view.

Aims. To evaluate patient's perceptions of physical and non-physical side effects of contemporary anticancer therapy and their association with clinical and social features of the patients.

Methods. This prospective observational study enrolled 464 consecutive cancer patients receiving outpatient chemotherapy at the Department of Oncology, University Hospital of Udine, Italy, from 2009 to 2012. Participants were asked to rank their side effects in order of distress by using two sets of cards naming physical and non-physical effects, respectively. The association between the first five cards chosen and clinical or social features of patients was estimated by calculating Odds Ratios (OR) through uni- and multi-variate logistic regression.

Results. Patients ranked the non-physical side effect "Affects my family or partner" first (40.1% of the total population). "Constantly tired" (32.5%) and "Loss of hair" (20.7%) were ranked second and third, respectively. These concerns were selected as the most important in the majority of the subgroups. Interestingly, marital status was the predominant characteristic in driving patients' perception, being associated with several side effects (constantly tired, loss of appetite, affects my work, affects my social activities, infertility, diarrhea).

Other significant factors influencing patients' perception of side effects included age, disease characteristics and ongoing anticancer therapy.

Conclusions. This study has identified crucial factors that may influence patients' perception of anticancer treatments side effects. Therefore, these results could be used to improve patient-doctor communication and to educate patients regarding potential toxicity of treatment.

E13 MULTIDISCIPLINARY (MTD) OSTEO-ONCOLOGY CENTER (OOC): FIVE YEARS EXPERIENCE AT ISTITUTO NEUROTRAUMATOLOGICO ITALIANO GROTTAFERRATA

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Background. Bone metastases (BM) are a primary cause of morbidity in cancer patients (pts) and the most frequent malignancy of the bone. Treatment of BM is complex and, because of possible complications (pathological fractures, pain, spinal cord compression, hypercalcemia), requires a MTD approach involving different specialists. To ensure a comprehensive assessment of cancer pts with BM, in Italy have been recently created several OOCs: in this abstract we report our five years experience.

Materials and methods. At our Institution, in June 2007, was created an OOC. Through coordination of an oncologist was formed a MTD team consisting of different specialists: oncologists, radiotherapists, palliativists, radiologists, nuclear medicine specialists, orthopedics, physiatrists, psychologists and nurses. Once a week a meeting took place between MTD team members and pts: this first MTD visit reduced the loss of time for physicians and pts and allowed the scheduling of diagnostic/therapeutic interventions tailored to the individual patient. Each patient was required to fill out questionnaires on pain and quality of life and, subsequently, was visited by the oncologist, the palliativist, the physiatrist and the radiation oncologist. After 3-5 days, the patient was recalled for a second visit in which doctors explained the planned care pathway.

Results. From June 2007 to April 2013 we visited 567 pts and 843 team consultations were made. Mean characteristics of pts: median age 71 yrs (48-85 yrs), M301:F266; main primary tumors were prostate (30%), breast (22%) and lung cancers (24%). At the first visit 456 pts (80%) reported pain with a median intensity (evaluated by NRS) of 5.3 (range 2-9). 236 patients (42%) were treated with palliative radiotherapy (RT) and bisphosphonates. A total of 41 vertebroplasties were performed. Thirty pts (5%) were treated for pathological fractures: 10 pts underwent surgery, 14 pts were treated with palliative RT, 6 pts received both treatments; 14 pts had spinal cord compression: 10 pts were treated with palliative RT only, four pts underwent decompressive surgery followed by RT. Each patient completed an anonymous satisfaction questionnaire. A total of 340 questionnaires were filled out: 320 pts (94%) declared their full satisfaction.

Conclusions. Our data confirms the efficacy of MTD approach of BM. Based on our experience, the OOC offers comprehensive and effective responses to the multiple care needs of cancer patients.

E14 GRANULOCYTE COLONY-STIMULATING FACTOR (G-CSFS) IN THE PREVENTION OF FEBRILE NEUTROPENIA (FN) IN BREAST CANCER (BC) PATIENTS: THE FEWER THE BETTER?

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Background. Docetaxel (TXT)-based chemotherapy (CT) is associated with high incidence of FN in BC. Primary prophilaxis with pegfilgrastim (PEG G-CSF) as a single dose, or filgrastim/lenograstim (G-CSF) in multiple injections, up to 10-11, is widely recommended. Nevertheless, in clinical practice pts usually receive few doses of G-CSF, even if the effectiveness of this schedule is unknown. This analysis retrospectively compares the efficacy of 3 prophylactic schedules of FN in BC pts undergoing CT.

Material and methods. All pts with early BC who received primary or secondary prophylaxis for FN during neoadjuvant or adjuvant TXT-based CT were enrolled. We recorded baseline characteristics, occurrence of FN and the schedule used to prevent FN. Three schedules were identified: PEG G-CSF administered as single dose (schedule A); G-CSF short course, considered as administration of less than 5 doses (schedule B); G-CSF long course, considered as administration of 5 doses or more (schedule C).

Results. We included 218 patients. 130 pts received schedule A, 82 pts schedule B, 6 pts schedule C. For pts receiving G-CSF as primary prophylaxis, the incidence of a following FN was 1.7% in schedule A, 2.9% in the other 2 groups (B+C). No changes in dose-intensity and frequency of CT were recorded in these 3 groups. In secondary prophylaxis, the incidence of FN was 6.6% for schedule A, 10.5% for schedule B; none of the pts treated with schedule C had FN. Two pts treated with schedule B delayed CT due to FN. Table 1 summarizes baseline characteristics of pts with FN.

Conclusions. G-CSF short and long courses are associated with higher risk of FN compared to PEG G-CSF when used in primary prophylaxis. The use of G-CSF short course as secondary prophylaxis is not recommended, while PEG G-CSF should be preferred in this setting.

E14 - Table 1
Patients characteristics

Characteristics	Primary prophylaxis	Secondary prophylaxis
Patients with FN (N)	4	3
Age (years):		
Median	52	55
Range	33-67	48-66
PS 0-4	0	0
Comorbidities yes 1/no 0	0	0
Chemotherapy, regimen (N):		
TEC	3	1
TXT	1	1
TC	0	1
Schedule (N):		
A	2	1
B	1	2
C	1	0

TEC: TXT-epirubicin-cyclophosphamide; TC: TXT-cyclophosphamide.

E15 ANALYSIS AND COMPARISON IN NATIONAL TERRITORY AND IN THREE REGIONS OF THE USE OF OPIOID ORAL DRUGS DURING 2011 AND 2012 FIRST SEMESTERS

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Italy is the European tail-end when it comes to analgesic narcotic drugs consumption for severe and middle pain.

In order to spur the use of these drugs, along with various initiatives addressed to sanitary operators, in June 2009 Italian Ministry of Health introduced a law to simplify their prescription (especially non-injective opioid drugs).

This remarkable study, following an international excursus and observation of the last years Italian trend detecting a good tendency -still very far from European standards-, is intended to monitor drug prescriptions on Italy whole territory and particularly on Friuli Venezia Giulia (Northern Italy), Abruzzo (Central Italy) and Calabria (Southern Italy) territories, using articulate data of the first six months of the year 2011 and comparing them with those of the first six months of the year 2012.

We particularly monitored, for each territory, the following parameters: cost, units, unitary costs, Daily Definite Doses (DDD) for each therapeutic class, active principle and administration way.

The most used drugs in Italy resulted to be codein + paracetamol association and tramadol, both for low-medium pain (over 60% of prescriptions).

The research underscores a national trend of growing consumption of these narcotic drugs, comparing first semester of 2011 with first semester of 2012. In this period the increase is 697,345 units (+10.76).

There has been a cost increase of 16,214,413 euro (+24.35%), while the DDD increased of 2.05 (+11.59%).

Further accounts and articulate data for each Region will be available on the extended version of the work.

E16 OSTEONECROSIS OF JAW (ONJ) RELATED TO BISPHOSPHONATE (BP) TREATMENT: EIGHT-YEAR PHARMACOVIGILANCE EXPERIENCE

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Background. Osteonecrosis of jaw (ONJ) has been reported since 2003 in patients receiving BP as treatment of metastatic bone lesions of solid tumours, of myeloma and of osteoporosis. After first severe ONJ cases were observed in our department on 2005, an institutional ONJ multidisciplinary team was created. Oncologists, haematologists, maxillofacial surgeons, radiologists, nurses, pharmacists, nuclear medicine specialists, rheumatologists, data managers collaborated to improve diagnosis, management and prevention of this "new" disease, becoming a referral centre also for oncologists, haematologists and oral care specialists of neighbour area. Prevention protocols (OPT X-ray and dental visit before start of BP therapy; patient education; dental follow-up) were adopted by our institution on November 2005. We present our eight-year experience of diagnosis and pharmacovigilance.

Materials and methods. We reviewed charts of all patients with diagnosis of ONJ after BP therapy observed between August 2005 and April 2013 at our centre, from two sources: i) cases observed at our hospital, Oncology-Hematology Department (among 485 patients treated with BPs in the period); ii) cases included in patient population at risk of ONJ and submitted to team referral visit by other hospitals or dentists.

Results. We registered 41 ONJ cases, all reported to Italian Drug Safety Surveillance System (AIFA). Out of 41, 18 were patients from our Oncology-Hematology Department (13 among patients who started BP therapy before November 2005, and 5 among patients receiving prevention protocol before beginning BPs); other 23 cases were referred to our ONJ team by other hospitals or by area dentists. Patients characteristics: 16 men (39%) and 25 women (61%), median age 66 years (range 46-86); 24 (59%) dead and 17 (41%) still alive at April 2013. Disease: breast cancer in 17 (41%), prostate cancer in 8 (19%), myeloma in 8 (20%), other tumor type in 4 (10%), osteoporosis in 4 (10%). Delivered drugs: zoledronic acid in 24 (59%), pamidronate in 11 (27%), ibandronate for metastatic disease in 2 (5%), ibandronate for osteoporosis in 1 (2%), alendronate in 2 (5%), clodronate in 1 (2%).

Conclusions. The rate of ONJ in our Oncology-Hematology Department sharply declined after adoption of prevention protocols, whereas new cases from other hospitals and referred by dental practitioners became numerically overwhelming.

E17 ANALYSIS OF THROMBOSIS-ASSOCIATED RISK FACTORS IN CANCER OUTPATIENTS: THE IMPORTANCE OF MULTIPARAMETRIC EVALUATION FOR A DECISION MAKING OF A PROPHYLACTIC APPROACH

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Background. Venous thromboembolism (VTE), a common and potential fatal complication in pts with advanced cancer, is a negative predictor of survival and a leading cause of death. Current international guidelines don't recommend routine prophylaxis in outpts with advanced cancer undergoing chemotherapy (CT) but suggest to carefully consider those with high risk of VTE. A number of clinical risk factors for cancer-associated VTE have been identified and considered in a 5 parameter-based (body mass index, platelet and leucocyte counts, hemoglobin value and tumor site) scoring system, the Khorana score, which has been utilized to indicate the need of a prophylactic approach. We prospectively applied this score in consecutive cancer outpts beginning CT as well as an implementation, based on the analysis of 6 addictional factors (sex, age, use of central venous catheter, CT-agents, antiangiogenetic drugs, erythropoiesis stimulating agent) to evaluate their impact in the assignment of pts into different risk groups.

Materials and methods. We studied adult pts, followed at our Outpt Department from August 2011 to December 2012, with advanced cancers (breast, NSCLC, colorectal, pancreatic/gastric, urogenital, LNH, Hodgkin's disease, HD, and MM), receiving a first- or second-line standard CT outside of experimental clinical trials. We stratified pts into three risk groups (score 0 = low; score 1-2 = intermediate; score 3-4-5 = high) considering both the Khorana scoring system and its implementation.

Results. 169 pts were analyzed (103F/66M, median age 62.3, range 35-80 yrs). The type of tumors were as follows: 38 breast, 32 colorectal, 31 LNH, HD and MM, 27 urogenital, 22 NSCLC and 19 pancreatic/gastric. With the Khorana scoring system 49 pts were assigned to the low risk group (score = 0), 87 pts to the intermediate risk group (57 pts with score = 1, 28 with score = 2), 16 pts (9.4%) were assigned to the high risk group (9 pts with score = 3, 4 with score = 4, 3 with score = 5). When we considered 11 parameters 37 pts were assigned to the high risk group, so that their percentage shifted to 21.8%.

Conclusions. A more precise and comprehensive quantification of VTE risk, especially in view of the recently suggested identification of new independent factors, is mandatory for a correct decision making of an antithrombotic-prophylactic approach.

E18 AN EFFECTIVE AND SAFE TWO-DRUG COMBINATION REGIMEN FOR CANCER RELATED CACHEXIA

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Background. Cancer progression is characterized by loss of lean body mass (LBM), inflammatory status, metabolic derangements and poor quality of life (QoL) which result in cancer-related anorexia/cachexia syndrome (CACS).

Aim. The aim of the present study was to test the safety and efficacy of a combination treatment (including nutraceuticals, i.e. quercetin, alpha lipoic acid and curcumin) with carnitine + celecoxib for the treatment of CACS. Primary efficacy endpoints were: increase of LBM, resting energy expenditure (REE) and improvement of QoL, particularly fatigue. The following were assessed as secondary endpoints: physical performance (tested by grip strength and 6-min walk test, 6MWT), appetite, chronic inflammatory variables (IL-6 and CRP), performance status (PS) and Glasgow prognostic score (GPS).

Patients and methods. Outpatients with advanced cancer at different sites with CACS (i.e. loss of body weight >5% of the pre-illness (or ideal) weight in the last 3 months) received L-carnitine 4 g/day plus Celecoxib 300 mg/day plus nutraceuticals/antioxidants, i.e., quercetin 300 mg/day, lipoic acid 300 mg/day, carbocysteine 2.7 g/day, curcumin 2 g/day (i.e. 400 mg/day of active curcuminoids extract (Meriva, Indena, Milan, Italy). Treatment duration was 4 months.

Results. From June 2011 to October 2012, 80 patients with advanced cancer (all stage IV) at different sites were enrolled: 70 completed the treatment and were evaluable (mean age 65 ± 9.6, range 32-82 years). Ten patients did not complete the treatment for death due to disease progression. Results showed a significant increase of LBM and a significant improvement of QoL (by EORTC-QLQ-C30), and particularly fatigue (by MFSI-SF). Moreover, an improvement of physical performance assessed by 6MWT and ECOG PS as well as a decrease of inflammatory parameters (IL-6 and CRP) and GPS were observed. The treatment was very well tolerated (no grade 3-4 toxicities occurred) and no patient discontinued the treatment due to severe adverse events.

Conclusions. The results of the present study showed that a combined treatment with anti-inflammatory, anabolic/metabolic agents plus antioxidants was able to improve the main nutritional, metabolic and physical activity variables as well as QoL of cachectic cancer patients with an optimal safety and cost-benefit profile, so that it may be suggested in the clinical practice as treatment for CACS.

E19 "SIMULTANEOUS CARE": FROM THE COLLABORATION BETWEEN ONCOLOGY AND PALLIATIVE CARE DEVELOPMENT OF AN ORGANIZATIONAL MODEL CENTRED ON THE PATIENT AND FAMILY

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Background. Despite modern treatment advances, approximately 50% of all cancer patients die from their disease. For these patients the focus eventually has to shift from cure or life prolongation to palliation. Palliative cancer care aims at improving a patient's subjective well-being, that includes symptoms control, continuity of cure, family support.

Patients and methods. Since February 2002 we have formed, inside the Unit of Oncology, a palliative care team, located in our Day Hospital (DH) aimed at patients receiving palliative chemotherapy and those in an advanced stage of disease, who underwent only supportive care (BSC "Intermediate Phase Project"). Since August 2005, we conducted a quantitative analysis of the activity.

Results. We followed 743 patients (169 BSC, 574 BSC + CT); mean daily supportive cares were 9.75; total number of invasive procedures 247 (paracentesis, thoracentesis, Tenchoff catheters). The visits were 3724, (73% planned, 27% in emergency). The activated palliative services assistance were 542 (home care ADI/UOCP = 78%; inpatients Hospice = 22%). The deaths were 709 (154 in hospital, 499 at home or in hospices, 56 in nursing home or other settings). Average length of taking charge: 3.6 weeks for exclusive BSC, and 14.1 weeks for BSC + CT ("simultaneous care"). For 239 pts was activated psycho-oncological support ("Family Protection Project"). Patients who died in hospital were provided with end-of-life care.

Conclusions. Palliative care can be defined as the prevention and relief of suffering. Suffering has four components: physical, psychological, social, and spiritual. When defined this way, palliative care can be pursued simultaneously with usual oncologic approaches to treat cancer. This approach might be described as patient-centered care. The goals are dynamic, changing in emphasis as the disease evolves over time.

In our experience "simultaneous and continuous care", based on the close collaboration between the different professional figures involved in the care pathway (in the hospital and in home care setting), is the most appropriate approach that allows to offer the patient and the family a constant reference particularly in the transition from active treatment to palliative care and subsequent terminal phase of illness. This strategy allows to reduce the accesses to the emergency department and the inappropriate hospitalizations.

E20 MULTIDISCIPLINARY OSTEONCOLOGY CENTER IN THE MANAGEMENT OF PATIENTS WITH BONE CANCER DISEASE

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Background. Bone cancer disease (BCD) is responsible for high morbidity in cancer patients. In January 2005 we founded a multidisciplinary Osteoncology Center comprising 17 dedicated experts, thus offering multidisciplinary care for patients with BCD.

Methods. The primary objectives of the Center is patient care, research and training. The center offers mono and multidisciplinary care (primitive and secondary tumors and management of patients with CTIBL). By March 2013 our team of experts in oncology, palliative care, orthopedics, radiotherapy, physiatrics, nuclear medicine and radiology, with backup support from an oncology nurse and data manager, had seen 2849 patients and carried out 3653 monodisciplinary and 2514 multidisciplinary visits.

Results. Among patients with bone metastases, 40% had breast cancer as primary tumor, 9% lung, 6% sarcoma, 3% neuroendocrine and colorectal respectively, 2.8% prostate, and 36.2% other cancers. High-risk lesions (27%), and first (9%) or uncertain diagnosis (33%) of BCD were the main reasons for referral to the Center. Sixty-six percent of patients reported pain, with a median intensity score of 4.04 (BPI questionnaire). The BPI questionnaire of 70 patients, before and after 7 days of the multidisciplinary visit, showed a decrease of at least 2 points of maximum pain in 49% of patients, of average pain in 46.4%, and of minimum pain in 76.9%. Furthermore it was observed a pain relief of at least 2 points in 61.1% of patients. An anonymous questionnaire completed by 1468 patients at the end of their multidisciplinary appointment showed that 98% were very satisfied with the service provided.

Conclusions. Although the outcome of patients and the full economic impact of this new organizational model have still to be analyzed, the high level of satisfaction expressed by patients confirms the usefulness of this multidisciplinary approach to the treatment of bone metastases.

E21 NEPHRO-ONCOLOGY: AT A CROSSROAD BETWEEN DIFFERENT SPECIALTIES. TWO-YEAR EXPERIENCE OF A NEPHRO-ONCOLOGY AMBULATORY

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Background. The recent development of targeted agents (TAs), the impact of these drugs on kidney function, the issues relative to presence of co-morbidities, to treatment discontinuations and dose reductions, and to direct or undirect renal toxicities, as well as the lack of prospective data on pts with end-stage CKD or under dialysis, have pushed the development of a novel subspecialty: Nephro-Oncology. Its main fields of interest include: direct and undirect renal toxicity form cytotoxic chemotherapy, TAs, and/or contrast medium, electrolyte disturbances, Ca^{++}/P alterations, hypertension, as well as the management of nephrectomized patients. Here we report on a 2-year experience of a dedicated Nephro-Oncology ambulatory.

Materials and methods. This ambulatory is run by a nephrologist once a week within the Oncological Day-Hospital, to allow a privileged interaction between specialists, and a more convenient access to pts data. To date, we have followed 148 cancer pts with CKD on active antitumor treatment (Tx), as well as 46 untreated cancer pts with CKD. Twenty and 27 of them have been nephrectomized for a localized or a metastatic cancer, respectively, the latter being also on active Tx; among treated pts, 19 had either NSCLC or SCLC, 20 gastric cancer, 12 prostate cancer, 14 bladder cancer, and 21 other tumors.

Results. Among the 27 nephrectomized RCC pts, we had only 3 Tx discontinuations (2 cases due to direct kidney toxicity, and 1 case due to undirect kidney toxicity). Among all 47 previously nephrectomized RCC patients with a median follow-up of 13 months, no progression of the underlying CKD was observed (vs an expected percentage of 63% at 3 years). Just on out of 15 cancer pts treated with CDDP discontinuated Tx due to renal toxicity. In 5 out of whole population of 148 CKD cancer pts, an episode of acute kidney failure (AKI), not due to oncological Tx, has been reported, but all of them restarted an active oncological Tx after the resolution of AKI. Finally, no cases of AKI due to contrast medium administration was evidenced (vs an expected rate of 50% in high-risk pts, and of 5% in poor-risk pts).

Conclusions. Our preliminary experience clearly demonstrates how a precocious Nephro-Oncological evaluation of cancer pts with concomitant CKD (or at risk for CKD) may improve oncological and renal outcomes, allowing for a correct administration of active Tx. Nephro-Oncology should be pursued further, and randomized controlled trials should be run.

E22 EARLY INTEGRATION OF SUPPORTIVE CARE IN CANCER PATIENTS: THE PISA CANCER CENTER EXPERIENCE

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Background. Recent advances in the treatment of solid tumors and new chances of care create a growing number of treated patients and therefore of treatment-related complications; relevant toxicities or symptoms may require hospitalization of a sig-

nificant number of these patients. Data from other institutions suggest that an integrated model dedicated to symptoms management and supportive therapies may be more effective for cancer patients care and reduce hospital admissions.

Methods. From May 2012 a dedicated supportive-care team has been activated at our institution inside the Day Hospital service offering to outpatients a direct and early management of chemotherapy toxicities or cancer symptoms. The team receives patients without appointment, in order of the severity of case, and gives a mobile phone consult to patients. From March 2013 we have begun to report the activity in an electronic database; we report here the results about the visits performed in the last 10 weeks.

Results. A total of 276 visits have been performed and more than 500 phone calls from patients have been addressed. The majority of patients had metastatic disease and has been receiving medical therapies. Main reasons for access were: toxicities in 100 patients, uncontrolled symptoms in 128 cases, and logistic problems in the remaining 48 cases. The most frequent grade 3-4 toxicities or uncontrolled symptoms detected and treated were: pain in 67 patients; fatigue in 43; fever in 30; increase in liver blood tests in 25; diarrhea in 23; hematological toxicities in 23; nausea/vomiting in 18; respiratory symptoms in 13; skin toxicity in 11; mucositis in 9; renal failure in 3; bowel obstruction in 1 case. Fifty-one patients received i.v. supportive therapy immediately at the unit while 213 had a prescription for domiciliary treatment. In a total of 72 cases blood tests were controlled and in 48 a radiological exam was required. In 5 cases a paracentesis or thoracentesis was performed and 56 patients were also submitted to other specialist consults. For only 25 patients (9%), hospitalization was required, while the other 251 (91%) were fully managed as outpatients; 55 patients needed repeated accesses to the unit.

Conclusions. A careful and dedicated management of supportive care for cancer patients may reduce the need for hospitalizations and optimize patients care. Integrated models for simultaneous anticancer and supportive care at Oncology Unit should be developed and widely adopted.

E23 ACTIVITY AND TOLERABILITY OF OXYCODONE/NALOXONE IN THE TREATMENT OF MODERATE-SEVERE CANCER PAIN IN PATIENTS RECEIVING CHEMOTHERAPY FOR METASTATIC DISEASE: A PROSPECTIVE MONOCENTRIC PHASE II TRIAL

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Background. A recent phase III study showed that the association of oxycodone and naloxone (OXN PR) provides analgesya in cancer patients (pts), as previously demonstrated for chronic benign pain. No data are available for cancer pts receiving chemotherapy (CT). We designed a phase II study to investigate the activity and tolerability of OXN PR during CT for the metastatic disease.

Patients and methods. Fifty-eight consecutive pts receiving CT for metastatic disease (median age 62 years, females 55.2%) were enrolled. Primary tumor: breast 36.2%, gastrointestinal 24.1%, lung/head and neck 15.5%, liver/pancreas 8.6%, other 15.5%; single metastatic site in 22.4%, multiple sites in 77.6%. Patients were stratified according to baseline analgesic therapy (none/NSAIDs vs weak opioids + NSAIDs), oral or i.v. CT, emetogenic power of CT. NRS, constipation and variations in laxative agents use were evaluated at 2, 3, 6, and 9 weeks.

Results. Median starting dose of OXN PR was 10/5 mg twice daily (range 5/2.5-20/10). Over 70% of the pts received OXN PR as first-line treatment. A statistically significant difference in baseline NRS between pretreated and naïve pts was found (6 ± 1.9 vs 4.8 ± 1.6, respectively, $p = 0.02$), as well in starting and final drug dose ranges (10 ± 3.2 vs 6.5 ± 2.6 and 22.5 ± 11.7 vs 15 ± 10.4, respectively, $p < 0.002$). In the whole population OXN PR produced a median reduction of NRS of 5 (range 2-6). The incidence of moderate-severe constipation decreased during therapy, with WHO grade 0 constipation increasing from 48.3% to 58.6%.

Conclusions. Our study shows that OXN PR provides effective pain control in cancer pts regardless of the disease sites, the concomitant use of anti-HT_3 and the route of CT administration. Of interest for clinical practice, a decrease in severity of constipation was observed during treatment, also in pts receiving highly emetogenic CT over a long-term period. In addition, the finding that pts pretreated with a weak opioid and/or with weak opioid/NSAIDs associations exhibited a higher NRS at baseline, also requiring a higher dose of OXN PR for adequate pain control, could suggest the opportunity of using a strong opioid earlier in the global therapeutic approach to cancer pain, to allow a quicker relieve using lower drug doses and to improve patient quality of life.

E24 FACTORS RELATED TO PLACE OF DEATH IN A SAMPLE OF PATIENTS WITH ADVANCED LUNG CANCER ASSISTED BY A HOME PALLIATIVE CARE SERVICE

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Background. Lung cancer is the first cause of death in Western Countries for male cancer patients. Often, patients with advanced lung cancer have disabling symptoms that affect the quality of the end-of-life with both an increase of hospedalizations and hospital deaths. Prior researches show that home care raises the chance for patients to die at home, reduces the need for hospital admissions during the last months of life, and improves the satisfaction of patients and families. The goal of this study was to identify factors related with the place of death in a group of advanced lung cancer patients in at-home care setting.

Material and methods. Sample included 210 advanced lung cancer patients (53% male; medium age 73.97, ds 9.8) assisted at home in Bologna by a home care team and deceased from 1st January to 31st December 2011. Univariate statistical analysis was performed using chi-squared test for the discrete variables. Kruskal-Wallis test was also applied in order to analyze the continuous variables that did not prove to be compatible with a normal distribution (Shapiro-Wilk normality test).

Results. Of the 210 patients examined in Bologna, 112 (53%) died at home, 52 (25%) in hospital and 46 (22%) in hospice. Sta-

tistical analyses show that 8 variables were significantly correlated with place of death. In the last four months of life, patients who died at home received a greater number of home visits by physicians (p = .000), they underwent a lower number of hospital admissions (p = .000) and spent a lower number of days in hospital (p = .000). Patients who died in hospice had a higher survival prognostic factors (KPS ≥70) at the beginning of home care (p = 0.05), most frequently didn't activate both social services (p = 0.02) and formal caregivers (p = 0.01). Patients who died in hospital were less aware of the prognosis (p = 0.01) and got more admissions to ER (p = 0.05).

Conclusions. This study highlights that a network of supportive-palliative care, which consists of a dedicated and structured home care and a good communication including patient involvement in the management of the disease, can decrease both aggressive interventions at end of life and deaths in hospital. These data suggest the need to support health policies oriented to consider palliative home care in order to improve satisfaction of patients and families, reducing healthcare costs. We'd like to extend our study to other Italian regions.

E25 TOTAL PARENTERAL NUTRITION AS NUTRITIONAL SUPPORT IN PATIENTS WITH ADVANCED CANCER AND CACHECTIC STATE. A CASE OF WERNICKE KORSAKOFF SYNDROME (DEFICIENCY OF VITAMIN B1) IN OUR INSTITUTION

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OMS defines malnutrition as the imbalance between cell ratio of nutrients and energy and the amount of these needed by the body to ensure growth and functions. Malnutrition may be related to inadequate intake of nutrients or secondary forms of the disease that alter the metabolism or absorption as it is cancer. In our business unit the use of total parenteral nutrition (NPT) in patients with cachectic state in the advanced stage of the disease or when there is a difficulty in swallowing during the chemotherapy treatment (head/neck and esophagus cancer in the course of radiotherapy). Malnutrition is responsible for the increase in cancer complications, which impact the results of the treatment and the continuation of therapy. In our unit from 03/2011 to 03/2012, 190 NPT were performed; of these, 104 were also fed orally (in small amounts) and 86 performed only parenteral nutrition. Of this last group one patient presented neurological disorders not associated with the underlying disease (peripheral neuropathy/irritability and memory impairment); after thorough investigations which excluded association with the underlying disease, neurological consultation performed by a subsequent indication of blood dosage of Vit B1, which was below the normal range, demonstrating a Wernicke-Korsakoff syndrome, was initiated the therapy with injectable vitamin B1 and vitamin complex with subsequent gradual resolution of the clinical picture. This case has brought to light the possibility of a B1 deficiency associated with parenteral nutrition alone to monitor this phenomenon. From 03/2012 to 03/2013 we performed 386 nutritions, 236 partial and total 150. We analyzed the consumption and nutritional components of the bags and standard products containing vitamin (vitamin B1 and vitamin complex for injection); the team has focused attention on vitamin B1, which occupies a central role in cellular energy metabolism and is the cause of Wernicke-Korsakoff syndrome. To 150 of these parenteral nutritions performed at our department has been added vitamin complex containing B1, with subsequent monitoring of neurologicals symptons and dosage of B1 during nutrition; we have not found other cases of Wernicke-Korsakoff syndrome.

E26 PROLONGED-RELEASE OXYCODONE/NALOXONE (PR OXN) COMBINATION IN CHRONIC CANCER RELATED PAIN TREATMENT: A SINGLE INSTITUTIONAL OBSERVATIONAL EXPERIENCE

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Background. Opioids represent the mainstay of treatment for moderate to severe intensity cancer related chronic pain. Their major side effect is represented by constipation. Combined PR OXN has shown to be effective in malignant and non-malignant chronic pain management reducing also opioids induced constipation (OIC) incidence.

Methods. Patients with moderate to severe cancer related pain, both opioids pre-treated and naïve, receiving PR OXN were weekly observed for an 8 weeks period. PR OXN dose titration was performed before starting observation period. Numeric Rating Scale (NRS) and Bowel Function Index (BFI) were used to evaluate respectively pain intensity and OIC at each weekly visit. Use of adjuvant drugs for pain management was allowed.

Results. From January 2012 to January 2013 a group of 116 pts was observed in our institution. Median age was 67 years (range 41-92), 50.9% female, 56.9% ECOG PS 0-1, 36.4% PS 2 and 6.7% PS 3. 60.3% of pts had metastatic disease, 39.7% has unresectable locally advanced disease. Primary tumor localization was breast (30.2%), genitourinary (25.9%), lung (18.9%), gastrointestinal (17.3%), head and neck (1.7%), gynecological (6%). Bone metastases were present in 63.8% of pts and visceral involvement in 55.2% of patients. 76.7% of pts received chemotherapy, while 23.3% received best supportive care. 51.7% of pts were opioid naïve. 92.2% of pts completed the 8 weeks observation period. Median dose of PR OXN used to obtain pain control was 85 mg/day (range 10-120 mg/day). 69.8% pts used adjuvant drugs for pain management. At baseline evaluation median pain intensity was 7.5 (range 7-9) according NRS and median BFI was 37.5 (range 25-69). At the end of observation period we detected a median reduction in strongest pain of 2.6. Median BFI at final evaluation was 19.6. In opioid pre-treated pts we also observed a marked reduction of constipation form 76% at baseline to 36.5% at final evaluation. Treatment with PR OXN was well tolerated and the most frequent adverse events were dizziness (4.2%) and confusion (2.6%).

Conclusions. Our single institutional observational experience shows that oral PR OXN combination is effective in terms of pain reduction in cancer-related pain management and this treatment has a positive impact on pts quality of life reducing constipation and providing relief from bowel disfunction.

E27 SCRAMBLER THERAPY AND PAIN IN BONE METASTASES PATIENTS

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Introduction. Chronic cancer pain (CCP) affects the 70% of patients with bone metastases. Preliminary results have shown the effectiveness of Scrambler therapy, a neuromodulatory approach using electro-cutaneous nerve stimulation that interferes with pain signal transmission by providing non-pain information. The Scrambler machine is supported by a multiprocessor computers capable of simulating 5 artificial neurons that send signals identified by the central nervous system as "no pain". In this way the Scrambler information can be conveyed to nerve fibres involved in the transmission of acute and chronic resistant pain, but no studies at the moment reveal its efficacy on bone metastases.

Methods. We analyzed 32 pts affected by chronic pain from bone metastases of different type of primitive tumours from July 2008 to December 2012.Two consecutive weeks of treatment (one treatment per day lasting 30 minutes, 5 days a week) (T1, T2) are normally given followed by weekly follow-up for further 2 weeks (T3, T4). Patients are asked to describe their current level of pain in a VAS questionnaire immediately before starting treatment (T0) and after each 30-minute session (T2). At follow-up appointments (T4), the efficacy and duration of the Scrambler's effects are evaluated.

Results. We analyzed the mean values of pain across T0-T2-T4 observing a reduction in pain from 6.13 ± 2.12 to 2.00 ± 2.02 to 2.34 ± 2.03 (Friedman's test, $p < 0.0001$). The mean absolute change in pain scores showed a delta from T0 to T2 of 4.13 and from T2 to T4 of 0.34. At T0 the 28% of pts had mild pain and moderate pain respectively, while 43.75% severe pain. At T2 the pain was for the 68.75% mild, 21.88% absent and only 6.25% showed severe pain. At T4 the proportion of pts with mild pain increased to 71.88%, those with severe pain further reduced to 3.13%. We found that 7/32 pts had no changes in pain at 3 times and 6 pts had a reduction between T0-T2, but an increase at T4. Overall, 23 patients (71.9%) had a reduction in pain between T0-T2. Stratifying patient by site of pain, a statistically significant reduction in pain across the 3 time points, was confirmed.

Conclusions. The data collected showed a statistically significant effect on pain after treatment with Scrambler in patients with bone metastases maintained at 4 weeks.

E28 TAPENTADOL IS ACTIVE IN THE MANAGEMENT OF CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY (CIPN): A PHASE II STUDY

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Background. CIPN is a common dose-limiting side effect of anti-cancer treatment; the incidence of CIPN varies from 30 to 40% of patients receiving chemotherapy and depends on the type of drug, the duration of administration, cumulative dose and pre-existing peripheral neuropathy. Chemotherapeutic agents most commonly associated with neuropathy include platinum-based drugs (cisplatin, carboplatin and oxaliplatin), vincristine, taxanes (paclitaxel and docetaxel), bortezomib, thalidomide, and lenalidomide. Tapentadol is a centrally acting analgesic with 2 mechanisms of action, μ-opioid receptor agonism and norepinephrine reuptake inhibition. We designed a pilot single center phase II study evaluating the effects of tapentadol in managing CIPN.

Materials and methods. From July 2012 to January 2013, 40 patients (30 females and 10 males) were enrolled and divided in: a) patients affected by CIPN refractory to standard treatment and b) patients naïve. The intensity of CIPN was evaluated with Visual Analogue Score (VAS). In the group a tapentadol was administered after at least 2 weeks of standard treatment (gabapentin and steroid). In the group b tapentadol was administered after the appearance of CIPN score VAS >5.

Results. Among the enrolled patients (pts), 15 were affected by breast cancer, 15 by colorectal cancer and 10 by lung cancer. Among all patients included in the study only 5 pts had a personal history of diabetes. In the A group were included 15 patients, in group B were included 25 patients. Tapentadol was administered at a dose of 50 mg BID. The median decrease CIPN intensity at 2 weeks after tapentadol introduction was 95% in group A and 100% in group B. Only 6 patients required a dose increase to 100 mg BID of tapentadol.

Conclusions. Tapentadol has been proven safe and effective in the treatment of CIPN. None of the patients enrolled in the study discontinued treatment for neurotoxicity, while maintaining a good performance status and ability to perform normal daily activities.

E29 AN EXAMPLE OF APPLICATION OF ARTICLE 7-ITALIAN LAW 38: "DUTY TO REPORT THE RECOGNITION PAIN IN THE MEDICAL RECORD": OUR EXPERIENCE IN CARDARELLI HOSPITAL

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Background. On 15th March 2010 the "Law 38" was issued in Italy to ensure the citizens' right of access to palliative care and pain therapy. With the purpose to correctly identify the breakthrough cancer pain (BTcP) in oncologic patients, we conducted an internal audit in our department, in order to evaluate the minimal data setting to be introduced in the medical record, with the aim to systematically register pain and its episodic severe recurrence.

Patients and methods. We have developed a paper and electronic medical record which was reported in a number of useful parameters for the diagnosis and monitoring of baseline pain and BTCP cancer. In the period between June and September 2011 were compiled 74 clinical cards about 34 females and 40 males (age 55.8 ± 15.5). 22.1% of the total population with lung cancer, and 82.4% of them had metastases.

Results. The systematic survey has identified many patients with poorly controlled baseline pain acceptance (36.5%), that reduced at discharge (9.5%), but not yet at an ideal level, that is, the disappearance of pain. 36.4% of patients with exacerbations of cancer pain (BTCP) at discharge are still treated with an NSAID, although many of them, during hospitalization, are rotated in opiate. Still, although there is a trend toward improvement, BTCP at discharge is present in 21.6%. It was also noted that while accepting patients with BTCP being treated with opioids were just 21.2% at the time of discharge, they increased up to 81.3%. Finally, subjects with pain acceptance are better controlled during hospitalization reaching them a baseline pain daily average of 1.0 1.5 points of the numerical scale.

Conclusions. The creation of an internal audit to assess the minimum data to be included in the clinical setting, as well as essential, is useful to establish a methodological process of interaction between doctors and nurses.

E30 COMMUNICATION ABOUT COMPLEMENTARY AND ALTERNATIVE MEDICINE (CAM) USE: RESULTS OF A SURVEY IN TUSCANY SETTING

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Background. The use of CAM has increased in the last years. About this matter there are a lot of missing data due often to an ineffective patient-doctor communication.

Materials and methods. A survey was carried out on patients (pts) followed in three different institutions between March and May 2012: one university and two community hospitals using a modified version of questionnaire by Molassiotis et al. (Ann Oncol, 16: 655-663, 2005). Modifications aimed to investigate motivations that underlie CAM use; source of information; communication skills with the doctor; frequency of use etc.

Results. 483 pts were screened; 74.3% of them accepted to participate. Incidence of CAM use was of 31.1%. Characteristics of pts receiving CAM: 73.2% women, 52.7% aged between 51 and 65 years; level of education was: 9.8% primary school, 17% secondary, 45.5% diploma and 26.8% university degree (0.9% missing data). Motivations that underlied use: 17.9% strenghten the body's defense, 8.9% combat the symptoms, 5.3% reduce the toxicity, fight cancer 3.6%, more than a reason 56.3%, other reasons 5.3%, missing data 2.7%. Source for information: 56.3% relatives or friends, 10.7% other pts, 5.3% media, 18.7% miscellany, 9% missing data. Fifty-one pts (45.5%) don't discuss with their doctor about CAM use. Reasons were unknown in 39.2% of the cases; in 17.7% for patient's anticipation of the doctor disapproval; in 19.6% for absence of occasion for talking about it.

Conclusions. Despite the increasing use of CAM among oncology pts, discussions regarding these treatments in oncology setting is very limited. Doctors' lack of information about CAM may be a barrier to communication and should be addressed with specific medical training on the way to optimize the possible benefits and minimize the potential harms from these therapies.

E31 ADL SCORE AND LEVEL OF ANXIETY AS PROGNOSTIC FACTORS IN THE TERMINAL PHASE OF CANCER

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Background. Prognostic characterization is an essential step in the initial assessment of cancer patients in advanced stages of disease to plan the most appropriate therapeutic program. The objective of this prospective study was to assess the role of clinical variables, including ADL score and anxiety, in predicting survival.

Methods. A total of 238 consecutive advanced cancer patients were included in the analysis. Among other clinical variables, the need for oxygen therapy, the presence of pain (NRS scale), the presence or absence of anxiety (yes/no), level of family support (degree of care during hospitalization, classified as poor/good/excellent), and grade of autonomy (ADL score expressed as a 0 to 6 points) were all evaluated for each patient of the cohort. Moreover, plasma levels of albumin and PCR were also considered. The impact of all those parameters on the 30-day survival was assessed using logistic regression, while the overall survival was estimated with the Cox model.

Results. Median survival was 15 days (range 0-502), the estimated survival using the Kaplan-Meier method was 31% at 30 days and 18% at 60 days. ADL score and anxiety had influence on the 30-day survival (ADL independency OR 0.69, 95% CI 0.59 to 0.81, $p < 0.0001$; for anxiety OR 10.69, 95% CI 1.40-81.46, $p = 0.022$). The other variables analyzed did not show any significant association with survival. Multivariate survival analysis showed that the variables ADL and anxiety were associated with overall survival (HR 0.81, $p < 0.0001$ and HR 1.69, $p = 0.022$ respectively).

Conclusions. Cancer patients' autonomy and their level of anxiety are important parameters to be evaluated on admission to better estimate prognosis in advanced stages of disease. In this context, supportive interventions and an optimal treatment of anxiety could be of value.

E32 A MODEL OF SIMULTANEOUS CARE (SC) FOR PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (MCRPC) DURING FIRST-LINE CHEMOTHERAPY WITH EVERY-3-WEEKS DOCETAXEL (D) PLUS PREDNISONE (PDN): RESULTS FROM A MONOCENTRIC EXPERIENCE

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Background. Patients with mCRPC are often elderly, more prone to develop serious adverse events (AEs) and may show a worst compliance to chemotherapy. To improve the management of pts with mCRPC during first-line chemotherapy with D 75 mg/m^2 administered q21d plus PDN 5 mg bid, we have developed a model of SC which provided for the presence of a multidisciplinary (MTD) team to take care of pts during chemotherapy.

Patients and methods. At our Institution, from January 2010 to January 2013, we recruited 32 pts with mCRPC. Main characteristics of pts: median age 73 yrs (range 68-81), median ECOG PS1 (range 0-2); median baseline NRS pain was 5 (range 3-8). During chemotherapy each patient was followed by a MTD team composed of oncologists, specialist nurses, palliative care experts, psychologists, urologists and radiotherapists; each patient was scheduled for a weekly visit and blood sample during

chemotherapy. All pts were provided a mobile phone number to contact a physician when necessary. Primary endpoints of this study were: evaluation of quality of life (QoL) using FACT-P test, pain evaluation, median overall survival (mOS), proportion of severe AEs, number of treatment-related deaths, hospitalization rate. Secondary endpoints were: treatment's discontinuation rate due to AEs, length of hospital stay for each administration of chemotherapy.

Results. All pts were evaluated for primary and secondary endpoints. 15 pts (47%) showed QoL improvement: the greatest benefit was noted for prostate-specific concerns (appetite, pain, physical comfort and urinary function); no treatment-related deaths occurred; after completion of chemotherapy median NRS of pain was 3 (1-5), 5 pts (16%) had at least one serious AE, 2 pts were hospitalized due to severe AEs; mOS was 20.2 months (17-22 mos). One patient stopped treatment due to chemotherapy-related AEs and the average length of hospital stay was 84 min (range 71-101).

Conclusions. Despite the small number of pts enrolled and the absence of a control arm, data emerged from our experience suggest that this model of SC is potentially able to improve the management of pts with MCRPC, ameliorating their QoL and reducing the rate of serious AEs. Although a direct comparison with data emerged from TAX327 trial cannot be made, our results seem slightly better than those emerged from the previously mentioned study: a larger randomized trial could better define the role of SC in this setting.

E33 MRGFUS TREATMENT FOR THE PAIN PALLIATION OF BONE METASTASES

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Background. Bone painful metastases are a frequent complication of cancer. Magnetic Resonance-guided Focused Ultrasound Surgery (MRgFUS) has emerged as a non-invasive thermal ablation technique of oncological lesions. It allows the precise ablation of the tumor tissue by focusing the acoustic energy precisely at the target volume, while MR permits the real-time monitoring of temperature rise. At G. Giglio Hospital of Cefalù in collaboration with Institute of Molecular Bioimaging and Physiology (IBFM), National Research Council (CNR), Laboratorio di Tecnologie Oncologiche (LATO), a clinical protocol for the MRgFUS treatment of painful bone metastases started in May 2010. Protocol purpose is the evaluation of safety and efficacy of MRgFUS in bone metastases treatment. This work reports about the outcomes of the first five treatments.

Methods. The MRgFUS treatments had as primary aim the patient pain palliation. For this purpose, this technology takes advantage of the bone's high acoustic absorption of ultrasound energy that produces the destruction of periosteal innervations. Moreover in two clinical cases in which the bone was completely eroded by the tumor, it was possible to focus the ultrasound beam to directly ablate the (soft) cancerous tissue in order to destroy the tumor itself. For each patient, the variation in pain level was evaluated using the Visual Analogue Scale (VAS) and to follow the metabolic and morphologic evolution of the lesion, each patient underwent a FDG PET/CT exam before and after the treatment. Quantitative analysis on PET/CT images was performed by calculating the SUV parameter by a threshold based semi-automatic method with partial volume correction.

Results. All treated patients had a significant pain relief within ten days after the treatment without any change in drug therapy. In that cases in which the treatment had also therapeutic purpose of the tumor, PET/CT monitoring confirmed FGD uptake reduction in correspondence of ablated regions.

Conclusions. The outcomes of the first five treatments confirmed the efficacy of MRgFUS in pain palliation from bone metastases. Moreover PET/CT results indicate that, when the lesion is directly accessible to the ultrasound beam, the MRgFUS technique represents also a valid treatment option in a multidisciplinary approach for local control of disease to obtain a global clinical benefit maintaining a good level of patient's QoL.

E34 THE ASSESSMENT OF MALNUTRITION AND THE EFFECTS OF NUTRITIONAL TREATMENT IN CANCER PATIENTS

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Background. Many cancer patients suffer from a complex syndrome characterized by asthenia, anorexia, weight loss and biochemical alterations, which lead up to malnutrition and to a global impairment of the quality of life. Therefore, the evaluation and monitoring of nutritional status is mandatory, not only at the beginning of the diagnostic workup/treatment, but also throughout its whole duration. The aim of this study is to ascertain the entity of the nutritional risk and monitoring the nutritional status of patients affected by cancer, in order to reduce potential complications, and improve the quality of life.

Patients and methods. We enrolled in three months all the patients with supramesocolic digestive system or lung neoplasms, at their first access for day-hospital chemotherapy in our Cancer Unit. Assessment of nutritional risk (with anthropometry, evaluation of nutritional needs and intake, blood chemistry), fatigue and appetite (with the validated NRS 02-fatigue questionnaire) was made by a dietician involved full-time in the project. Treatment consisted of a dietary plan, food education and facultative prescription of high protein-hypercaloric supplements. Patients were assessed during their first oncologic examination (T0) and at one month after the beginning of chemotherapy (T1).

Results. We evaluated 57 patients, the mean age (SD) was 69.9 (9.0) years. The results of the nutritional parameters are so reported: weight (kg) 68 ± 13.1 in T0 and 69 ± 12.9 in T1 (p

<0.01); BMI (kg/m^2) 24.1 ± 3.9 in T0 and 24.4 ± 3.8 in T1 (p = 0.01); CMB (circumference arm in cm) 27 ± 3.6 in T0 and 27 ± 3.3 in T1 (p = n.s.); hand grip dx (kg) 26 ± 9.0 in T0 and 28 ± 8.8 in T1 (p <0.001); fatigue NRS 7 ± 1.3 in T0 and 6 ± 1.2 in T1 (p = 0.001); VAS (Visual analogic scale) appetite (0-10) 7 ± 2.3 in T0 and 7 ± 2.4 in T1 (p = n.s.); calorie intake (kcal) 1554 ± 310 in T0 and 1724 ± 32 in T1 (p = 0.001); protein intake (g) 67 ± 19.7 in T0 and 75 ± 19.1 in T1 (p <0.01); water intake (L) 1.022 ± .423 in T0 and 1.341 ± .427 in T1 (p <0.001).

Conclusions. This study shows how nutritional management may not only maintain but also increase weight, muscle strength, food/water intake and decrease fatigue. Fatigue improvement may be explained by weight gain and muscular energy increase. In conclusion, assessing and monitoring the nutritional status of cancer patients throughout their treatment seems an effective strategy in order to prevent malnutrition and fatigue.

E35 A NEW MULTIDISCIPLINARY DEPARTMENT UNIT (DOM) FOR END-STAGE CANCER PATIENTS IN PALLIATIVE CARE: PRELIMINARY RESULTS

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Background. In recent years, as for high medical specialization, shifts to home care and tendency of segmentation in care delivery, continuity of care has become one of the most important goals in Oncology. Planned care pathways within hospital, from the diagnosis to the end of life, can lead to less frequent accesses of end-stage cancer patients to emergence unit and to a better quality of life of patients (pts) and families. Vercelli Hospital has pursued these targets by providing end-stage pts with continuing palliative care in a new 8-bed care unit (DOM) in Medical Department.

Methods. From July 2012 to April 2013 in DOM 76 cancer pts were admitted, after clinical evaluation in Oncology Unit, whose medical team provided medical assistance at DOM, ensuring continuity of care. Their conditions were: end-stage cancer; survival prediction ≤30 days; ECOG PS = 3-4; resident in Vercelli District. DOM database and registers were analysed.

Results. One hundred and seventeen patients were hospitalised in DOM, 78 from Oncology (78; 66%), (40 female, 38 male); the average age was 77 (77 for male, 73 for female). Most common primary cancer sites in these pts were lung (25%), colon (25%), pancreas (15%), gastric (11%), breast (9%), genitourinary (8%), esophageal (5%), soft tissue sarcoma (2%). Metastatic cancers were 56 (72%), those with peritoneal carcinomatosis 3(4%). Twenty-eight pts (41%) had liver mestatases, 13 (19%) lung, 12 (18%) brain, 8 (12%) bones, 28 (41%) widespread. All pts had anorexia and high grade (3) cachexia; 20 (26%) pts had restlessness and disorientation. The visual analogue scale(VAS) has been used to assess and monitor pain: on entry 40 had VAS 9 (51%), 20 VAS 6 (26%), 18 VAS 4 (23%); on the 3rd day all pts (100%) had VAS ≤4. The average lenght of hospitalisation in DOM was 9 days. The average number of days required to make a request for admission to DOM was 6 days. After request, movement from the Department of Oncology to DOM took 1 day. Only 2 pts were released from DOM still alive.

Conclusions. DOM has offered palliative ad psychological care to elderly, metastatic cancer patients nearing the end of life, residents in Vercelli. They came from Oncology Unit of the same Hospital, in which they were hospitalised on average for 7 days. The transfer to DOM was very quick. All symptoms were controlled ensuring good quality of life. Many grants were given by patients relatives also by mass media.

E36 EFFICACY OF TAPENTADOL FOR MANAGING SEVERE PRURITUS RELATED BIOLOGICAL CANCER TREATMENTS: MULTICENTRIC EXPERIENCE

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Background. Severe pruritus affects a large proportion of the cancer patients treated with anti-EGFR antibodies and tyrosine-kinase inhibitors. Tapentadol is a centrally acting analgesic with 2 mechanisms of action, μ-opioid receptor agonism and norepinephrine reuptake inhibition. We designed a multicentric study to assess tapentadol for the management of pruritus induced by biological treatments.

Material and methods. In this multicentric study we enrolled 30 patients with metastatic solid tumours treated with biological drugs between November 2012 and February 2013. Intensity of itch was evaluated by Visual Analogue Scale (VAS) score. The primary endpoint was change in median VAS score during treatment with biological drugs. All patients were enrolled in the failure of standard therapies for itch. All patients received tapentadol 50 mg cpr bid.

Results. Median VAS was 9.00 at baseline and 1.00 after 3 days of treatment. Twenty-five patients responded to tapentadol. the only side effect was nausea G1 resolved in a week.

Conclusions. Tapentadol showed excellent efficacy in the control of pruritus associated with the use of biological drugs. It is not a minor reduction on the quality of life of pain associated with hand-foot syndrome typical of TKI inhibitors.

E37 INCIDENCE OF OSTEONECROSIS OF THE JAW (ONJ): 5 YEARS EXPERIENCE OF THE ONCOLOGY OF ISERNIA

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Background. Osteonecrosis of the jaw (ONJ) is a rare but severe disease. ONJ is a complication described in 2003 in cancer patients receiving bisphosphonates (BPs). Major risk factors for ONJ are tooth extractions, major dental surgery in the course of BP therapy, duration of administration and type of BP; other potential risk factors are: concomitant use of corticosteroids, antiangiogenetic drugs, diabetes, peripheral vasculopathy.

Patients and methods. From January 2008 through 2012 we treated with zoledronic acid (ZOL) 177 patients with bone metastases: 38% (67) had a breast cancer, 18% (32) prostate cancer, 12% (21) lung cancer, 9% (16) colorectal cancer, 3% (6) bladder cancer, stomach and kidney cancer, 2% (4) multiple myeloma,

sarcoma and larynx cancer, 2% (2) thyroid, penis, melanoma, esophagus, pancreas and ovary cancer, 1% (1) lymphoma and adrenal cancer. Of these, 3 patients had a double tumor (breast and thyroid cancer, prostate cancer and multiple myeloma, colon and penis cancer). All patients, before treatment with ZOL, had undergone dental visit ± orthopantomography of the jaws and had not undergone either tooth extractions or major dental surgery in the course of BP therapy.

Results. In our series ONJ has been reported in 2.8% of patients (5 cases). Specifically, ONJ was observed in 4% of patients with breast cancer, 6% of prostate cancer and 25% of patients with multiple myeloma. The mean number of months of treatment was 36 months (range 5-57). In 2 cases ONJ was associated with a treatment with antiangiogenetic drugs; both patients with prostate cancer assumed concomitant therapy with corticosteroids; no combination therapy for the other patient with breast cancer.

Conclusions. Despite preventive measures (dental exams) 2.8% of patients had ONJ. According to the literature the frequency of ONJ varies with: treatment duration (greater than 24 months), concomitant use of corticosteroids, antiangiogenetic drugs and type of cancer.

E37 - Table

Patients	Primary cancer	N of months of infusions before ONJ diagnosis	Concomitant drugs
1	Prostate	5	Corticosteroids
2	Prostate and multiple myeloma	57	Corticosteroids
3	Breast	34	Antiangiogenetic
4	Breast	44	Antiangiogenetic
5	Breast	41	None

E38 SORAFENIB-INDUCED NEPHROTIC SYNDROME IN ADVANCED HEPATOCELLULAR CARCINOMA AND OTHER RISK FACTORS

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Background. To date only three cases of sorafenib-induced nephrotic syndrome have been reported, all in patients with metastatic renal cell carcinoma. In patients with hepatocellular carcinoma, the presence of diabetes and the use of immunosuppressant nephrotoxic drugs can increase the risk.

History. A 59-year-old man developed in August 2011 a nephrotic syndrome two weeks after the beginning of sorafenib for a single metachronous vertebral metastasis of hepatocellular carcinoma. Three years before he had undergone orthotopic liver transplantation because of a multifocal hepatocellular in HCV and alcohol-related cirrhosis. He was receiving cyclosporine and he was also diabetic with a moderate chronic renal failure. The patient developed progressive peripheral edema with a nephrotic 24 hours-proteinuria of 7.5 g and a severe ipoalbuminemia. Diuretics were immediately started and sorafenib was stopped; successively patients developed acute pulmonary edema needing admission to Intensive Care Unit. Patient also received steroids, cyclosporine was reduced and mycofenolate mofetil was started. Then patient gradually recovered and proteinuria and edema decreased. Renal biopsy was not performed due to increased bleeding time. He died 4 months later because of systemic disease progression.

Discussion. Asymptomatic proteinuria and hypertension are common dose-related side effects of vascular endothelial growth factor (VEGF) inhibitors, mainly bevacizumab and sunitinib. Possible pathogenic mechanisms can be a decreased nitric oxide blockage or a perturbation of podocyte-endothelial VEGF axis; however often a renal parenchymatous damage is lacking and the concomitant use of nephrotoxic agents drugs can have an additional pathogenetic role. In randomized trials of sorafenib for advanced hepatocellular carcinoma, hypertension was present in up to 28% of patients while there are no data about proteinuria or nephrotic syndrome. No specific preventive interventions are to date available to prevent anti-VEGF renal damage; however close monitoring of renal function can allow to interrupt the damage by promptly interrupting the drug.

Conclusions. When starting sorafenib in patients receiving nephrotoxic drugs or with pre-existing renal damage particular attention should be paid to the monitoring of proteinuria and renal function.

E39 ULTRASOUND GUIDED SUBCLAVIAN VEIN PUNCTURE IN CENTRAL VENOUS PORT-A-CATH IMPLANTATION FOR THE PREVENTION OF ACUTE CATHETER RELATED COMPLICATIONS: OUR EXPERIENCE

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Background. The aim of the present paper is to report our personal experience in totally implanted venous catheter system (Port-a-Cath) using ultrasound-guided puncture of subclavian vein instead of blind puncture or surgical vein cannulation in patients with solid tumors eligible for receiving chemotherapy. Ultrasound-guided puncture of subclavian veins may significantly improve the feasibility, safety and patient comfort by correct evaluation of vascular anatomy, vein collapse, variations with breaths, and the relations with clavicle and the subclavian artery. This technique is particularly helpful in those cases in which the vein puncture is challenging because of patient habitus (e.g. obese patients), difficult anatomy of the clavicular region or a particular shape of the vein that may need multiple blind needle passes. Serious complications include hematomas, arterial injury and pneumothorax.

Patients and methods. One hundred and fifty-three patients (N = 153) underwent ultrasound guided port-a-cath implantation from March 2008 to April 2013. The procedure was performed in angio suite with bland conscious sedation. Imaging of the subclavian vein was performed with a 7.5 Mhz linear ultrasound probe in B-mode. Puncture was performed under ultrasound control. In some cases the patient was placed in Trendelenburg position to reduce the collapse of the subclavian vein during inspiration; after vein cannulation, the catheter was advanced through a peel-away sheet under fluoroscopy guidance in order to obtain correct position of the tip at the atriocaval junction.

Results. Port-a-cath implantation was successful in all cases. No complications such as hematoma or pneumothorax were observed and a significant reduction of time of the procedure was obtained.

Conclusions. As reported by other Authors, our experience confirms that the use of ultrasound in venous access significantly improves technical success allowing to reduce time of the procedure directly visualizing the vein of its anatomical relationships, avoiding major complications and failures, and significantly reducing costs.

E40 VALIDATION OF A QUESTIONNAIRE ON COMMUNICATION AND RELATIONAL DYNAMICS BETWEEN CAREGIVER AND WORK TEAM IN THE TRANSITION FROM ACTIVE THERAPY TO PALLIATIVE TREATMENT

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Background and aim. In medical oncology the transition from active to palliative treatment is a critical and hard moment for the patient, the family and the new care providing team. In this phase crucial factors including communication, psychological and relational issues have to be considered. The palliative treatment must provide sensible and suitable tools to investigate, at an early stage, issues related to communication and to the family's problems. Our study is aimed to define and validate a questionnaire capable to explore the information and relational domain between caregivers and operators, thus allowing a prompt psycho-oncological support when needed.

Material and methods. A monocentric, observational and transversal study including 70 caregivers of patients has been conducted in two different phases (definition/validation). In the first step the Focus Group technique has been utilized; the qualitative follow-up outcome has represented the conceptual platform from which the first version of questionnaire has been developed. Subsequently, an assessment of the completeness and of the statistical description of each item, reliability and internal consistence of each item and of the complete scale (Chronbach alpha), correlation matrix multitrait/multiitem, internal consistency and discriminant validity of the selected items (item-global assessment correlation with other scales and indicators FSQ) has been performed.

Results. The first version of the questionnaire includes 7 questions and the answers are coded using the Likert scale with 4 points. Statistical analysis points out that such tool has good validity, discriminatory power, internal consistence and reliability: Chronbach's alpha for the global questionnaire = 0.78 (0.83 and 0.62 for dimension 1-information, and dimension 2-relationship, respectively). The two dimensions (information/relationship) are insufficiently related to one another (Spearman's rank correlation coefficient 0.37, $p < 0.001$), showing, in keeping with our working hypothesis, that they explore different domains.

Conclusions. We have defined a simple questionnaire to identify the communication and relational needs of the cargivers in this phase of transition. Data generated on the whole study population, aimed to validate this tool, are in course of processing and final results will be presented at the meeting.

E41 RETROSPECTIVE ANALYSIS OF PATIENTS WITH CANCER PAIN EVALUATED INSIDE PISA MEDICAL ONCOLOGY CONSULTATION PAIN THERAPY SERVICE

Ginocchi L., Brunetti I.M., Antonuzzo A., Vasile E., Lucchesi M., Galli L., Caparello C., Vivaldi C., Ferrarini I., Biasco E., Farnesi A., Marconcini R., Bondi F., Tollapi L., Poli P., Ricci S., Falcone A.

AOUP Santa Chiara, Pisa

Background. Cancer pain afflicts many patients, both in early and metastatic disease, undergoing anticancer therapies.

Material and methods. From January 2012 until today about 325 patients were evaluated inside Pisa Medical Oncology consultation pain therapy service. We retrospectively analyzed data from 40 of these patients throughout information collected from medical records.

Results. Forty patients (19M/21F) with a median age at diagnoses of 63 years (range 32-89) were included into analysis. ECOG performance status was 0 in 18 patients, 1 in 18, 2 in 4. Primary site of cancer was: colo-rectal (6), esophageal-gastric (3), chordoma (2), sarcoma (2), breast (9), pancreas (5), parotid (1), ovary (3), lung (3), kidney (1), prostate (5), ureter (1); 1 patient had occult primary tumor. Thirty-five (87.5%) patients have metastatic disease, mainly involving bone (17), nodes (14), lung (13), liver (6) and peritoneum (5); 29 (72.5%) of them received anticancer therapies. Oncologic pain was classified as: neuropathic (mostly in spine) in 17 (42.5%) patients, nociceptive (mostly abdomen) in 11 (27.5%), and mixed (mostly in skeletal muscle and abdomen) in 12 (30%), with a median intensity scored (evaluated with numerical rate scale (NRS)) of 4 (range 2-8). Twenty (50%) patients (18 with metastatic disease; 8 with mixed pain, 8 with neuropathic and 4 with nociceptive) experienced breakthrough pain (BTP), but only 10 (50%) patients received adequate therapy as needed. After the first visit in pain therapy visit, BTP therapy was introduced in 7 patients and replaced in 7. Only 1 patient added BTP treatment after the second visit and 2 patients after the third one. After a median number of 2 accesses in pain therapy visit room (range 1-7), BTP was solved in all patient (19 with medical therapy, 1 with analgesic pump system).

Conclusions. To relieve cancer pain is a pivotal feature during oncologic patient life. Many patients experience BTP, due to tumor disease, cancer treatment (chemo-radiotherapy and/or surgery) or other conditions. Providing a pain therapy consultation service for outpatients inside our Division of Oncologic, we have improved patients care especially regarding BTP.

E42 THE MULTIDISCIPLINARY TEAM FOR SIMULTANEOUS CARE. OUR EXPERIENCE

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E42 - Table

Patients	68						
Visits (median)	3						
Chemoterapy use (%)	Yes	No					
	(62)	(38)					
Diagnosis (%)	Colon	Breast	Other	Lung	HCC	H&N	Pancreas
	(17)	(9)	(22)	(23)	(6)	(12)	(8)
Time to home care-first visit	45.6 days						
Dead	24						
Location of death (%)	Hospice	Hospital	Home				
	(29)	(12.5)	(58.5)				
Hospice service	Received						
	20						
Nutritional visit	12						
Hospitalization	Pts	Days	Median				
	12	79	7 days				

Early integration of palliative care in cancer patients has recently gained attention. The objective of simultaneous care is multidimensional vision and improved survival. In fact there are many factors causing disabilities and needing monitoring: disease management (diagnosis, prognosis, symptoms, treatment's toxicities), psychological and social factors, practical difficulties such as the performance of daily activities, death anticipation, end of life management, choice of optimal timing for recovery to hospice services or supporting the decision to die at home. In this context, becomes essential to ensure the continuity of care between Hospital, attending physician, territorial services rehabilitation and palliative care. Our group consists of 4 oncologists, 2 palliative care physicians, 1 psychologist and 2 nutritionists. The aim of this project is cancer patient with metastatic and incurable disease and his range of life expectancies. The multidisciplinary team encourages a better relationship between physicians, thought the synergies, in order to reduce discomfort for the patient and increase the effectiveness of therapeutic outcome. The nutritional evaluation has been assessed through the Minimal Nutritional Assessment (NMA): the method measures the body mass index and thus the potential risk of malnutrition. This method is able to distinguish between disease or outcomes of malnutrition. The nutritionist participates in the elaboration of therapeutic program evaluating nutritional status and dietary plane custom processing. He evaluates patient's adherence and results. Palliative physician uses ESAS during each visit monitoring symptoms, patient adherence and the results. Psychologist supports patients during the course of illness, especially in the final phases. The Table presents data from January 2012 to March 2013.

E43 SAFETY OF OXYCODONE/NALOXONE PROLONGED-RELEASE TABLETS FOR CANCER PAIN: A RETROSPECTIVE EVALUATION

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Background. Opioid-induced side effects as constipation can have a major negative impact on patient's quality of life. This retrospective study evaluated the analgesic efficacy of prolonged-release oral oxycodone when co-administered with PNR oral naloxone (OXPNR), and its impact on opioid-induced constipation in patients with severe chronic pain.

Methods. From 03/2011 to 03/2013, 47 patients with stage IV cancer disease and moderate-to-severe pain requiring opioid therapy were evaluated. Characteristics of pts were as follows: male/female: 24/23, median age 63 years (range 20-83), genitourinary cancer: 14 pts, lung cancer: 10, pancreas/biliary ducts: 6, breast cancer: 3 pts; colon-rectum: 2, gastric cancer and sarcoma one pt each. Forty-four pts were on chemotherapy and 3 on hormone therapy. Eleven pts in treatment with OPR at median dose of 30 mg/die (range 10-80 mg/die) were switched to OXPNR due to onset of toxicities, 36 patients started OXPNR at the onset of pain (dose ranged from 10 mg to 80 mg/die). Pain was evaluated using the Brief Pain Inventory (BPI-SF) and constipation symptoms due to opioid treatment using the Bowel Function Index (BFI).

Results. Constipation grade 1 was observed in 2/36 (5.5%) pts receiving OXPNR. No other OXPNR related toxicities were observed. In the 11 pts starting with OPR, a switch to OXNPR was done because of the onset of constipation grade 2 in 6 pts (54%) and of nausea grade 2 in 5 pts (45%). In the group of patients switching from OPR to OXNPR no other toxicities related to OXNPR were observed.

Conclusions. In our experience OXPNR provides adequate pain control without onset of severe toxicities, in particular we did not observe constipation of any grade and no patient required the use of laxatives compounds. OXPNR is well tolerated and efficacious in cancer pain.

E44 EVALUATION OF BODY MASS INDEX (BMI) IN DAY HOSPITAL CANCER PATIENTS: RESULTS OF A MONOINSTITUTIONAL SURVEY

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Background. Risk of venous thromboembolism (VTE) is elevated in cancer and several risk factors have been described. Identification of high risk patients for VTE and prophylaxis could improve morbidity, mortality, delivery of cancer therapy and quality of life. It is well known the Korana risk model for VTE in cancer patients that includes five variables: site of cancer, platelet count, hemoglobin level, leukocyte count and BMI of 35 or more. We decide to evaluate BMI in all subsequent patients coming to our day hospital for chemotherapy or supportive thera-

pies, so to evaluate the relevance of this factor for VTE risk in our patients.

Material and methods. From January to December 2012, we collected demographic data of all patients who accessed to our day hospital to receive chemotherapy or supportive therapies. BMI was calculated from weight and height (Quetelet index). Patients were classified according to five categories: underweight (BMI <18,5), normal range (BMI 18.5-24.99), overweight (BMI 25-29.99), moderately obese (BMI 30-34.99), severely obese (BMI = 35).

Results. A total of 328 patients accessed to our day hospital in 2012, 43.6% male and 56.4% female; mean age 63.3 (range 29-83). Primary site of cancer: breast 32%, lung 20.7%, colorectal 19.2%, pancreatic 6%, gastric 4.9%, other site 17.2%. According to BMI categories 21/328 (6.4%) resulted underweight, 175/328 (53.4%) normal, 91/328 (27.7%) overweight, 34/328 (10.4%) moderately obese and only 7/328 (2.1%) severely obese. In this last category, considered a risk factor for VTE, 6/7 patients are female, median age 59.4. The only man in this group was affected by lung cancer, 4/6 women were affected by breast cancer and the last 2 patients by gynecologic cancer. In all primary cancer site categories there is a prevalence of normal BMI, with the exception of endometrial cancer with 2/2 patients severely obese.

Conclusions. Considering the results of our survey we could conclude that among Italian day hospital cancer patients dominate normal weight people. The small percentage of severely obese cancer patients in our survey suggest that a BMI = 35 could not be a relevant risk factor for calculate risk score for developing a venous thromboembolic event. Despite the small number of patients with BMI = 35, it is interesting to note that our data confirm the well-known pathogenetic role of fat and estrogens in developing cancer.

E45 ANTIANGIOGENETICS AND HYPERTENSION: A FEASIBLE EXAMPLE OF MULTIDISCIPLINARY APPROACH

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Background. The most common anti-angiogenetic drugs (AAG), such as bevacizumab, sorafenib, and sunitinib are well known to induce or to worse a pre-existing blood hypertension (HTN), whose predictive role is still debatable. Despite the increasing number of AAG-treated patients (pts), a standardized approach to AAG-induced HTN (AAG-HTN) has not been clearly defined. The aim of this work is to propose a model of multidisciplinary management for all AAG-treated patients.

Patients and methods. In our hospital, a multidisciplinary team composed by oncologists and HTN-specialized physicians has been constituted. Before starting an AAG-based therapy, each patient is sent to the "Center for diagnosis and management of hypertension" where cardiovascular risk (CVR) and target organ damage are evaluated according to ESH/ESC guidelines. In particular, all pts undergo: physical examination, ECG, heart ultrasonography and laboratory exams. Blood pressure is evaluated by office monitoring, 24-hour ambulatory monitoring, and daily home monitoring. This clinical-instrumental evaluation is performed before starting AAG, 4 weeks after and 4 weeks after its withdrawal. AAG-HTN is treated according to literature, preferring angiotensin receptor blockers and ACE-inhibitors to other drugs.

Results. Between 01/03/2012 and 13/05/2013, 18 AAG-treated pts were sent to the multidisciplinary team (male/female 12/6, median age 67 yrs, range 49-83). Up to date, the median follow-up is 12 weeks (range 1-52w). A pre-existing HTN was documented in 14 patients, and 1 patient out of 7 with a follow-up longer than 4 weeks developed a worsening of a pre-existing HTN.

Conclusions. The increasing number of AAG-treated pts, the increased overall survival deriving from AAG-based regimens, and the frequent finding of an elevated CVR also in these subjects suggest a multidisciplinary approach. Despite the shortness of the follow-up, our experience demonstrates that the global management of these pts is feasible and useful. A coordination between the multidisciplinary team, in terms of timing and setting of the various accesses to hospital, makes more tolerable the additional time spent by pts, thus allowing a better adherence. Our aim is to perform a prospective evaluation of pts and to verify the impact of this model on the management and prevention of AAG-related CV events.

E46 "SALOTTI ROSA": A PROJECT REALIZED FOR BREAST CANCER PATIENTS AT GUASTALLA HOSPITAL ONCOLOGY

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Background. In Oncology we assist to the impairment of body and mind in the same way. The emotional and psychological components therefore play a vital role and the management of emotions takes on the same importance as the management of organic disease. Changing in physical aspect is the external indicator of illness and "lifesaver" therapies in this situation must affect in the same way doctors, nurses and patients. Many chemotherapeutic drugs and new molecules induce dermal toxicity from general skin dryness-xerosis-palmoplantar eritrodistesia, rushes, dermatitis, skin fissures. Our service following the guidelines from "The Oncologist" (Lynch TJ et al., Oncologist 2007). In addition to clinical advice how to treat cutaneous effects of terapies, adequate information about how to remove blemishes with make-up and using topical treatments can improve the quality of life of patient and assure therapy continuation. The "Salotti Rosa" meetings were born from the collaboration between professionals in the Oncological Hospital of DH Guastalla: doctors, nurses and psychologists.

Methods. Thanks to our initiative, 7 awareness-raising meetings of Dermatocosmetica line have been established from 17/02/2012 to 29/04/2013, towards the problems of Oncology. The patients were divided into small groups of 7 people; in these groups, thanks to the collaboration of a skilled esthetician, patients were educated to make-up and imperfection-coverage techniques, through the use of appropriate products and to the preparation of products for face and body with natural substances available on daily basis.

Results. The viewpoints of 40 women, who participated in the event, were collected and all agreed upon the positive experience

and the need to feel "a little more pleasant" in order to better accept the condition of cancer illness.

Conclusions. A good-looking appearance, hiding imperfections, improvement in skin pallor and redness, caused by radiation therapy, help to feel better, to feel "less sick". These aspects mustn't be underestimated especially in Oncology, where the quality of life has assumed a co-starring role during organic disease treatments.

E47 SIMULTANEOUS CARE IN ONCOLOGIC PATIENTS WITH ADVANCED DISEASE: A RETROSPECTIVE ANALYSIS AND ONE EXAMPLE OF PROGRESSIVE PALLIATIVE CARE

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Background. Oncologic therapy and early palliative care can ameliorate the quality of life for patients and their family but this approach is not always used.

Methods. We reviewed all consecutive advanced cancer patients (pts) from November 2012 to April 2013.

Results. There were 34 in-patients and 69 out-patients, 51 M and 52 F; median age was 75 years (41-93). Primary tumors were: colorectal 15, esophago-gastric 10, hepato-pancreatic 10, breast 18, lung 17, gynaecological 12, genito-urinary 9, lymphoma 6, others 6. Out of 34 in-patients 5 were receiving chemotherapy and 3 hormone therapy. 65/69 out-patients were receiving specific therapies (51 chemotherapy, 14 hormone therapy). All of them received supportive care. At the discharge from the hospital for 24/34 pts (70.5%) care settings were home palliative care (14 pts), hospice (7 pts), intermediate care (3 pts). Out of 69 out-patients 12 (17%) received simultaneously curative therapies and palliative home care by a specialist equipe. We report the case of a woman 76-years-old affected by advanced NSCL cancer living far from the hospital. She was given two previous lines of chemotherapy and stereotactic radiotherapy because of cerebral metastasis. To date she is receiving the third-line of treatment with the collaboration of home care team and her general practitioner. We can have a twice weekly communication with her family to control toxicity of therapy, thus reducing the need to access to the hospital or to the emergency services.

Conclusions. From this analysis we note that the involvement of palliative care team is rather late in the process of patient care with difference between in-patients and out-patients. The particular case reported shows that progressive palliative care can enhance patient and caregiver comfort and be integral part of quality care. We hope earlier palliative care specialists involvement for patients with advanced disease still in active treatment to avoid compartimentalized medical care. To extend this experience we are projecting a closer integration among the hospital, palliative care specialists and caregivers through direct contacts and update phone communications after periodical briefings and personalized treatment plans.

E48 IMPRESSIVE LOW ACUTE + CUMULATIVE OXALIPLATIN NEUROTOXICITY WITH THE ASSOCIATION OF A FIXED OXALIPLATIN INFUSION TIME (3 HOURS) + GLUTATHIONE (GSH) IV PREMEDICATION + ORALLY BIOTAD ® POST-MEDICATION

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Background. Oxaliplatin related neurotoxicity is the main limitation for its usage. Two distinct syndromes have been reported so far: an infusion-rate-dependent acute neurosensory complex and a cumulative sensory neuropathy. Acute neurotoxicity (incidence varying from 81.5 to 98%) is related to voltage-gated calcium-dependent sodium channels changes. Chronic neurotoxicity is due to the impairment of cellular transportation and the reduction in metabolism of dorsal root ganglia cells. GSH is able to prevent the initial accumulation of platinum adducts in dorsal root ganglia. Moreover GSH inactivates reactive oxygen species generated by platinum compounds that play an important role in neuronal apoptotic cell death. Vitamin C and E potentiate the action of GSH and facilitate its bioavailability. Thioctic acid prolongs action of GSH, vitamin C and E. We present here results of a consecutive group of oxaliplatin treated pts with: over 3 hours oxaliplatin infusion + association of GSH plus vitamin C, E and thioctic acid in the prevention of oxaliplatin-induced neurotoxicity.

Patients and methods. Thirty consecutive pts have been studied: 18 males and 12 females, mean age 63 years. Oxaliplatin-based chemotherapy regimens were FOLFOX4, GEMOX, XELOX. The patients received: oxaliplatin given as a 3-hours infusion, GSH 1.5 g/m^2 over a 15 minute period immediately before oxaliplatin, GSH 600 mg iv or im on days 2 and 3. Starting from day 2 and for the duration of the treatment, the patients received orally: GSH 50 mg + Vitamin E 10 mg + Vitamin C 120 mg + Thioctic acid 30 mg (biotad ®). Toxicities were evaluated according to the NCI CTC.

Results. Twenty-two patients received FOLFOX4, 6 XELOX and 3 GEMOX; 1 patient was treated with FOLFOX4 and XELOX. Totally cycles administered have been: 154 FOLFOX4 (median 7), 38 XELOX (median 6) and 16 GEMOX (median 4). Median cumulative dose of oxaliplatin was 680 mg/m^2, in detail: 680 mg/m^2 for FOLFOX4, 780 mg/m^2 for XELOX and 400 mg/m^2 for GEMOX. The acute neurological toxicity was as follows: G1 perioral paresthesia: 2. Cumulative toxicities were the following: G3 paresthesias: 1, G1 paresthesias: 12. Oxaliplatin dose reduction has not been necessary.

Conclusions. Our protocol for oxaliplatin treated patients (pre-medication with GSH iv + 3 hours oxaliplatin infusion time + orally continuative Biotad® post-medication) has been able to obtain a virtually absent acute neurotoxicity and a very low cumulative neurotoxicity.

E49 CONTINUITY OF CARE FOR CANCER PATIENT: PRELIMINARY DATA OF A SINGLE CENTRE EXPERIENCE

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Background. Home care (HC) for cancer pts can be a way, that may improve quality of life. It can lead to important outcomes: integration of hospital and community assistance, implementation of pts centered care, reduction of unnecessary emergence unit admissions, achievement of cost savings in health care system. This study presents preliminary results of continuity of care path developed for pts receiving home care and referred to Vercelli Oncology unit.

Methods. Aim was to find out effective standard discharge and HC provision procedures. Project work (PW) was divided into four phases: establishment of multidisciplinary Oncology Specialised Team (OST), PW definition, implementation, outcome; data processing PW had 4 work packages (WP): WP1 identified pts needs in HC, determined standard care plan keypoints and developed a home medical record; WP2 settled a HC model, improved discharge planning from hospital to home, established methodology for creating personalised care plans; WP3 established to integrate OST, hospital and district assistance planning a fast way for pts; WP4 will analyse effectiveness of interventions. Home medical care was provided to pts discharged from the Oncology unit, according to their medical and social needs. Phone medical counseling/assistance service was offered.

Results. Patients needs were assessed by a multidisciplinary team representative of hospital and community institutions: oncologist, psychologist, anaesthesist, family doctor, nurse. From January to March 2013 we followed eight pts, discharged with a nursing record planning of home care interventions, received 12 home visits. Six were male (71%), 2 female (29%); average age was 83, median age 85. Five (71%) received palliative care, 1 (14%) adjuvant, 1 adjuvant suspended by toxicities. Regard to diagnosis there were: 3 pancreas (44%), 1 prostate (14%), 1 breast (14%), 1 lung (14%), 1 sarcoma (14%) cancer. They had a pts clinical record including side-effects symptoms management guidelines and daily diary. We measured and recorded treatment toxicity at home during visits using ECOG; 7/8 pts (87%) were ECOG 3; all had a strong will to receive HC. Two of them died, the others are still alive. Nobody was hospitalized.

Conclusions. Preliminary data are positive. Hospitalization was avoided for all pts keeping their wishes ensuring continuity of care at home. We will carry on our trial because we think that strategy can contribute to reduce costs maintaining good quality of life for cancer patients.

E50 QUALITY OF LIFE DURING INTRA-PERITONEAL THERAPY WITH CATUMAXOMAB

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Background. The Edmonton Symptom Assessment Scale (ESAS) has been developed for the assessment of daily symptoms in cancer patients receiving palliative care. It allows an overall assessment of the quality of life by assessing not only the pain but also other dimensions such as the sensory-discriminative, the motivational-affective and the cognitive-evaluative one. It consists of nine visual numerical scales (0 to 10) that assess pain, fatigue, nausea, depression, anxiety, drowsiness, anorexia, malaise, dyspnoea; it also provides a tenth symptom indicated as another, which can be added by the patient.

Material and methods. A 47-years-old woman with refractory ascites from metastatic bilateral breast cancer attained to our Unit for treatment with catumaxomab. She was previously treated with almost four chemotherapy lines and with repeated abdominal drainages with intra-peritoneal infusion of carboplatin with only partial benefit. In April 2013 she started intra-peritoneal treatment with catumaxomab at the four fixed doses of ten, twenty, fifty and 150 mcg after positioning of a peritoneal catheter. The day of admission in our Unit and the day after each infusion, we administered the ESAS questionnaire; the same questionnaire was then administered 7 and 21 days after the last infusion of catumaxomab. Our goal was to monitor and optimize the management of possible side effects as well as the assessment of any changes in quality of life.

Results. The day of admission the patient has assigned at each scale a score of 0; after both the first and the second infusion a score of 3 was assigned to fatigue, a score of 5 to malaise and one of 7 to fever. After the third and fourth infusion the quality of life was stable but worsened seven days after the last infusion: the score for fatigue was 8 and the score for malaise 5. However, 21 days after the last infusion there was an improvement in the quality of life with a score of 0 assigned to each scale.

Conclusions. In our opinion ESAS is an effective and reliable tool for assessing the quality of life in cancer patients. Catumaxomab is a valid therapeutic option for patients with refractory ascites as it ensures a chance for cure without interfering with the quality of life.

Session F • Gynaecological tumours

F1* PULMONARY METASTASES IN GYNAECOLOGICAL CANCER: A SINGLE INSTITUTION EXPERIENCE

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Background. Gynaecological tumors rarely develop lung metastases. The treatment options are chemotherapy, radiotherapy or surgery, alone or in combination. Lung metastases incidence depends: 1-34% for ovarian cancer with a 5-year survival rates, range 17-36% for patients with the prerequisites for pulmonary resection. Lungs metastases are common also in endometrial cancer (2.3-8.3%, 80% metachronic and 20% synchronic). Metastases unilaterality is a positive prognostic factor with a DFI >24 months. Pulmonary metastasis in cervical cancer is fairly common and 96% of cases occur within 2 years of primary tumor. Incidence (median 33%) relates to disease stage while isolated lung metastases incidence, after primary radical hysterectomy, is 11.3% in positive pelvic lymph nodes. Resection of lung metastases plus chemotherapy showed a 5-year survival rate of 46%.

Material and methods. Nineteen women affected by pulmonary metastases from a primitive gynaecological cancer were selected for metastasectomy in the last 2 years. The inclusion criteria are: 1) primary tumor removed, no pelvic recurrence (II-look LPS or PET/TC recommended), 2) resectable lesions, disease free-margin, 3) no extrapulmonary disease, 4) sufficient pulmonary function, 5) no other therapy available.

Results. Our starting results are encouraging but observation is still ongoing in order to obtain a longer follow-up.

Tumour	Patients	Median age	DFI
Uterus-cervix	16	56 yrs	39.6 ± 6.6 m
Ovaries	3	46 yrs	12.6 ± 0.6 m
Tumour	**NED**	**AWD**	**DOD**
Uterus-cervix	8	3	5
Ovaries	2	1	0
Total	10	4	5

Conclusions. Thoracic surgery techniques increase the accuracy of FIGO staging, the tumor debulking and the median survival rate. Surgery may be preceded by neoadjuvant chemotherapy or be followed by adjuvant chemotherapy or can be interval debulking. Our preliminary results evidenced that the surgical treatment of lung metastases originating from female genital tract tumours (mainly endometrial carcinoma) is associated with a high long-term survival. It is recommended that patients with resectable lung metastases from uterine malignancies undergo metastasectomy. Carefully selected patients, especially those with a DFI of more than 12 months, would have potential survival benefits.

F2* CBDCA/PACLITAXEL OR CDDP/PACLITAXEL IN ADVANCED CERVICAL CANCER

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Background. Cisplatin (CDDP) + paclitaxel is the current first-line choice for stage IVB, recurrent, or persistent cervical cancer (CC). However, carboplatin (CBDCA) + paclitaxel has showed similar efficacy compared to CCDP + paclitaxel in a phase III study. This systematic review compares indirectly the efficacy of CDDP/taxane vs CBDCA/taxane in the treatment of advanced CC.

Material and methods. A systematic search in PubMed, EMBASE, Web of Science and The Cochrane Library was performed to identify relevant studies. Trials that were conducted in advanced CC patients treated with CCDP/taxane and CBDCA/taxane and reporting objective response rate (RR), progression-free survival (PFS), time-to-progression (TTP) and overall survival (OS) were pooled in this pooled analysis. Data on RRs were aggregate by using Comprehensive Meta-Analysis software with a random-effects model; PFS and OS were summarized descriptively.

Results. Eighteen (3 phase III, 7 single-arm and 1 randomized phase II, 6 retrospective and 1 prospective series) studies containing 1,204 advanced CC patients treated with CDDP/taxane or CBDCA/taxane-based chemotherapy were considered. Eight studies included CBDCA/taxane arms, 9 CDDP/taxane arms and 1 was a phase III trial that compared CDDP/paclitaxel with CBDCA/paclitaxel. Only in 1 study a docetaxel-combination was adopted, the remaining included a paclitaxel-based combination. The calculated median PFS, median OS and pooled objective RRs were 6.9 months, 12.87 months and 49.3% for CDDP + paclitaxel combinations and 5 months, 10 months and 49.3% for CBDCA + paclitaxel combinations. Only difference in PFS, but not that in OS, was significantly in favour of CCDP/paclitaxel chemotherapy (T-test). Response rates were similar (43.9 vs 40%) with both combinations in CDDP-pre-treated patients. In CDDP naïve patient RRs were 68.3% and 59.1% for CBDCA-based vs CDDP-based chemotherapy respectively (p not significant). Analysis of OS according to CDDP exposure was not possible for lack of data.

Conclusions. CBDCA + paclitaxel represents a viable alternative, and its efficacy is comparable to CDDP + paclitaxel for the treatment of advanced CC.

F3* EFFECTIVENESS OF ORAL LOW-DOSE CYCLOPHOSPHAMIDE (MO-CTX) IN HEAVILY PRE-TREATED RECURRENT OVARIAN CANCER (ROC) PATIENTS: A RETROSPECTIVE, MULTICENTER STUDY

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Introduction. Metronomic chemotherapy (MC) has proved to be effective in various cancers. The aim of this multicenter, retrospective study was to evaluate the efficacy of MO-CTX on heavily pre-treated ROC patients.

Patients and methods. Retrospective analysis of pre-treated ROC patients, previously treated with = 2 chemotherapy regimens, who received treatment with MO-CTX 50 mg/day. The endpoints were response rates (ORR), progression-free disease (PFS) and overall survival (OS).

Results. Forty-seven patients with advanced, RECIST-measurable ovarian cancer were included. Of these, 29 (61.7%) were platinum sensitive (PS), and 18 (38.3%) platinum refractory/resistant (PR). Median age was 72 years (range 40-80); patients with a performance status 0-2 were included. There was a mean of 4 previous lines of chemotherapy, range 2-9. All patients had received prior chemotherapy with platinum and a taxane. Most had received treatment with topotecan, gemcitabine, or liposomal doxorubicin. Applying RECIST criteria, the efficacy data were as follows: ORR 23.4%; stable disease (SD) was observed in 11 patients (23.4%), for a rate of clinical benefit (CB) of 46.8%. At 6 months, median PFS and OS were 5, and 11 months, respectively. In PR disease, ORR was 12.9%. The median number of cycles administered was 5 (range 2-35). No severe adverse effects were reported. Only one patient had G3 asthenia and G2 nausea/vomiting and one was shown not to tolerate oral administration of CTX due to gastritis, and was triaged to intravenous route.

Conclusions. MO-CTXis a safe and effective regimen for heavily pre-treated ROC patients, in terms of ORR and long lasting CB.

F4 HUMAN EPIDYDIMAL PROTEIN 4 (HE-4) IN MONITORING RECIDIVA OF OVARIAN CANCER

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Aims and background. Human Epididymis Protein 4 (HE-4) is a 25 KD single peptide chain which shows low expression in epithelia of respiratory and reproductive tissues, but high expression in ovarian cancer tissue. It was recently approved by the Food and Drug Administration to monitor recurrence or progressive disease in epithelial ovarian cancer in conjunction with CA125. As a single tumor marker, HE-4 had the highest sensitivity for detecting ovarian cancer, especially in stage I disease, and correlates with clinical response to therapy.

Patients and methods. Basal serum samples were collected from 40 recidival ovarian cancer patients (mean age 63, range 38-82 years) to measure HE-4 and CA125 concentrations. HE-4 and CA125 were measured by chemiluminescent immunoassay on Cobas6000 (Roche-USA) and on Centaur XP (Siemens-Germany) rspectively. Ratio CA125/HE-4 and Mann-Whitney test were used for statistical investigation.

Results. Thirty-two patients out of 40 were affected by serous histological type, and 8 patients were affected by undifferentiated ovarian cancer. We excluded 5 cases out of 32 serous, in which the concentration of both markers was normal.

The median concentrations of HE-4 in serous and undifferentiated histological type were 132.60 pmol/L (range: 46.30-649.80 pmol/L) and 155.10 pmol/L (range 30.70-351.10 pmol/L) respectively.

The median concentrations of CA125 in serous and undifferentiated histological type were 167.4 U/mL (range 7.80-780.4 U/mL) and 21.85 U/mL (range 1.00-37.70 U/mL) respectively.

Ratio CA125/HE-4 was calculated for every patient in serous (median = 0.92) and undifferentiated (median = 0.12) groups. The Mann-Witney test shows RATIO statistical significative difference between serous histological type group and undifferentiated histological group, $p = 0.007$.

Conclusions. HE-4 and RATIO CA125/HE4 could play an important role on follow-up of recidival undifferentiated ovarian cancer, instead of CA125 which doesn't show a significative level increasing.

F5 INCIDENCE OF OSTEOPOROSIS RELATED TO GYNECOLOGIC MALIGNANCIES: RETROSPECTIVE STUDY ON PATIENTS TREATED AT THE ONCOLOGY DEPARTMENT OF NOVARA

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Introduction. Studies have shown reduced bone mineral density in patients with advanced cervical cancer without bone metastasis, pointing out high risk for osteoporosis of these patients.

Objective. Primary objective of our analysis is to estimate the osteoporosis incidence among women affected by gynecologic malignancies followed at the Oncology Department of Novara, who were not yet in menopause at the time of surgery or at the first cycle of chemotherapy.

Methods. This is a retrospective, monocentric study conducted on patients with gynecologic malignancies followed at the Oncology Department of Novara between 2000 and 2012. None of the patients had reached menopause at the time of intervention or at the first cycle of chemotherapy. We evaluated how many patients were scanned by DEXA and how many had positive results for osteopenia or osteoporosis. We also reported skeletal events related to osteoporosis diagnosed with back-lumbar-sacral X-ray, computed tomography, magnetic resonance imaging or total body bone scan.

Results. Only 60 out of 335 patients with gynecologic malignancies met the inclusion criteria of our study. The age range was 29-54 years, with a median age of 45 years. Twenty-nine patients had an ovarian cancer (48.3%), 22 (36.7%) had a cervical cancer and 9 had an endometrial cancer (15%). Only 20% of patients have made a DEXA. Six patients (10%) had osteoporosis documented by at least one radiological method and 3 were osteopenic. Among patients with osteoporosis, 5 were suffering from ovarian cancer (3 with stage III disease, one with stage IV and one with stage Ic) and one had a cervical cancer in stage IIa. Five out of 6 have developed skeletal events.

Conclusions. The size of the problem is of clinical interest: 10% of patients who underwent surgery or chemoradiotherapy developed osteoporosis at an early age. In contrast to literature, risk is likely to be higher in patient affected by ovarian cancer. It seems to be correlated with advanced stage of disease, at least for the ovary. It's important to note that 83.3% of osteoporotic patients developed skeletal events. According to previous studies calcium and alkaline phosphatase levels were normal. Probably clinicians are not sufficiently sensitive in detecting the problem: in these patients the assessment of bone metabolism should be investigated with greater accuracy.

F6 CONCURRENT CHEMORADIOTHERAPY (CCTRT) WITH WEEKLY CISPLATIN (WCDDP) IN LOCALLY ADVANCED CERVICAL CANCER (LACC) PATIENTS: 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 with RT. This study is aimed to report the toxicities and the clinical outcomes of pts treated with wCDDP plus RT for LACC in our institution.

Material and methods. Between May 2001 and January 2013 we treated a consecutive series of 60 patients. The treatment consisted of whole pelvic external RT (plus RT boost in patients with parametrial invasion) and brachytherapy (B) in selected cases, those with good clinical response to external RT. CDDP was given weekly at the dose of 40 mg/m^2 for a total of 4-6 courses, starting on day 1 of RT.

Results. Main pts characteristics were: median age 54 yrs (range 30-79); median PS 0 (range 0-2); FIGO stage Ib2 in 6 pts, IIa in 5 pts, IIb in 21 pts, IIIa in 2 pts, IIIb in 18 pts, IVa in 5 pts, IVb (without visceral metastasis) in 3 patients. Histology was squamous in 53 pts, adenocarcinoma in 6 pts, NAS in 1 patient. Patients treated with external RT alone received a median total dose of 60 Gy (range 43.2-67), plus which was 48 Gy (range 40-62) for those receiving B too. The treatment was completed in 77.4% of the patients. The median number of delivered CT courses was 5 (range 1-6). Grade 3 toxicities consisted of anemia (1 pt), neutropenia (4 pts), diarrhoea (2 pts), constipation (1 pt), and vomiting (2 pts). No grade 4 toxicities were observed. No grade 3-4 late toxicity was observed. Among the 58 evaluable pts, the response rate was 89.6% (40 CR and 12 PR). After a median follow-up of 41.5 mos, the 3-year OS and DFS were 74.5% and 68.9% respectively, with median OS and DFS not reached.

Conclusions. Our experience of cCTRT in LACC pts appears superimposable to the literature data and confirms the good activity and tolerability of this combined CT-RT treatment in clinical practice.

F7 A SAFE AND EASILY APPLICABLE PROTOCOL OF DESENSITIZATION FOR HYPERSENSITIVITY REACTION TO PACLITAXEL

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Background. Hypersensitivity reaction (HSRs) to paclitaxel has been observed in less than 10% of pts treated with adequate premedication (antistamines and corticosteroids) and often required a permanent discontinuation of this drug, replaced by a less effective treatment.

Patients and methods. We treated with a desensitization protocol, derived from that previuosly published by Feldweng AM et al., 3 pts affected by advanced ovarian cancer and that have experienced severe HSRs to paclitaxel. The pts were premedicated with ranitidine 150 mg po twice daily, dexamethasone 20 mg iv 12 and 6 h before the infusion, chlorphenamine maleate 10 mg iv, 1 h before too. The protocol was a 12-step desensitization that combines gradual increases in the rate of infusion and concentration of the paclitaxel, administering the total dose in 6 h. The target dose was calculated based on the pt's BSA. The three infusion solutions -A, B, and C- contained X/100, X/10, and X mg of taxane, respectively, diluted in 250 mL of saline 0.9%. Solution A was used for steps 1 to 4, solution B for steps 5 to 8, and solution C for steps 9 to 12. The rate of the infusion was adjusted every 15 min, with each step delivering approximately twice the dose of the previous step. The final step 12 maintained a constant rate of infusion to deliver the remainder of the total taxane dose. Given the little dose of paclitaxel and the slow rate of the first step, particular attention has been paid to fill all the peripheral or central venous catheters with the solution, so that the first contact between drug and blod was made at the correct dosage.

Results. All our pts have experienced severe HSRs to paclitaxel during the first exposure. The first pt had rush, flushing, broncospasm and hypotension; the second pt had a shock during drug infusion; the third pt had flushing, severe hypothension and chest pain. Before the desensitization, the pts have failed alternative treatments. We administered 21 desensitization protocols in total. The first desensitization for each pt was conducted in the medical intensive care unit; subsequent desensitizations were performed in oncology unit, with rescue medication placed by the bedside. No HSRs occurred.

Conclusions. The protocol was a safe and effective strategy for re-administration of paclitaxel in pts with prior severe HSRs even in second level hospital if administerd by an allergist specially trained in drug desensitization.

F8 NEOADJUVANT POLICHEMOTHERAPY (PCT) WITH PACLITAXEL, IFOSFAMIDE AND CISPLATIN (TIP) IN LOCALLY ADVANCED SQUAMOUS CELL CERVICAL CARCINOMA. EXPERIENCE OF A SINGLE INSTITUTION

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Background. The management of locally advanced squamous cell cervical cancer includes chemoradiotherapy or neoadjuvant

cisplatin based chemotherapy followed by surgery that may offer specific advantages. However, giving neoadjuvant chemotherapy might have a similar benefit but have less side effects than giving the treatments at the same time.

Aim. To evaluate efficacy and to describe the toxicities associated with TIP chemoregimen.

Patients and methods. From March 2009 to April 2013 we enrolled 34 patients (pts) with locally advanced squamous cell cervical carcinoma. Median age was 52 years (25-77 yrs). The majority of pts had clinical FIGO IIb stage. PCT was given every 3 weeks and for total 3 courses: paclitaxel (175 mg/m^2) day 1, cisplatin (50 mg/m^2) day 1, mesna (5000 mg/m^2) plus ifosfamide (5000 mg/m^2) in continuously 24 hours iv infusion day 2. Primary prophylaxis of febrile neutropenia with filgrastim from day 4 to day 8 was given in all patients. Tumor extension was assessed clinically and by abdominopelvic MRI and PET WB at baseline and after 3 courses. Response rates were determined according to RECIST criteria. Toxicity was graded according the NCI common toxicity criteria. All patients were offered psychological support.

Results. All pts were evaluated for response and toxicity. Post-PCT pathological response was: CR 7 pts (20 %), PR 19 pts (56 %), SD 6 pts (18%), PD 2 pts (6%). Thirty-two pts (94%) underwent surgery after neoadjuvant PCT. Bone marrow suppression and asthenia were the most common toxicity (grade III/IV haematological toxicities: anemia 24%, thrombocytopenia 18%; have not been reported cases of febrile neutropenia due to the use of G-CSF); asthenia was observed in 84% of pts (grade III/IV 22%); emesis was observed in 9 pts (no grade III-IV toxicities); only one neurotoxicity (grade III) was demonstrated in a diabetic patient. For one or more of these reasons, treatment was delayed or withdrawn in 5 pts (15%).

Conclusions. In our experience paclitaxel, ifosfamide and cisplatin are an effective chemoregimen in treating locally advanced squamous cell cervical carcinoma and have an acceptable toxicity profile.

F9 WEEKLY BEVACIZUMAB AND PACLITAXEL IN HEAVILY PRETREATED PATIENTS WITH SEROUS OVARIAN CARCINOMA AND BRCANESS PHENOTYPE

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Introduction. The efficacy of chemotherapy for recurrent/progressive ovarian cancer (OC) mostly relies on platinum sensitivity. The addition of bevacizumab in both platinum sensitive and resistant disease has been shown to produce a survival advantage. Recent studies demonstrated a correlation between BRCA dysfunction and increase of tumor angiogenesis. The aim of this study is to evaluate safety of bevacizumab in patients with BRCAness phenotype.

Methods. We recruited three heavily pre-treated ovarian cancer patients. One of them carries a recognized mutation in BRCA-1. The other two presented a BRCAness phenotype as shown by Tan et al. (JCO, 2008). All patients, previously undergone at least 4 treatment lines, received a schedule containing bevacizumab 7.5 mg/kg every three weeks plus weekly paclitaxel 80 mg/m^2 until disease progression or unacceptable toxicity. CT scan, CA 125 evaluation were performed at baseline and repeated every 9 weeks. IL1b, IL2, IL6, IL8, IL10, IL12, IL17a, IL17f, VEGF, GCSF, IFN-gamma and FGF were evaluated in patients serum at baseline and after the third chemotherapy course by ELISA.

Results. All patients are still under treatment. Mean baseline Ca125 was 121 U/mL and dropped down to 10.3 U/mL after 3 treatment courses remaining stable at 10.5 U/mL after 6 courses. A patient achieved a complete response, two patients a partial response according to RECIST. One grade three (cutaneous) and one grade two (neutropenia) adverse events were reported. Serum VEGF level was reduced in all patients after 3 treatment courses. Furthermore we found a ten-fold increase in both IL1b and IL8 in the patient who achieved the complete response.

Conclusions. Our preliminary data indicate that bevacizumab-paclitaxel combination is safe and active in this particular setting and may modify patients immunologic/inflammatory balance as demonstrated by changes in circulating cytokines.

F10 EARLY ONSET VASCULITIS IN BRCA1 HEREDITARY OVARIAN CANCER PATIENT DURING ANTIANGIOGENETIC THERAPY

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Introduction. Several clinical trials have demonstrated that the addition of bevacizumab to chemotherapy in ovarian cancer produces a survival benefit. A correlation between BRCA mutation and increase of tumor angiogenesis has been hypothesized. We describe a case report of BRCA-1 hereditary ovarian cancer that developed cutaneous toxicity during antiangiogenic therapy.

Methods. A medline search was conducted to review the literature for cases of vasculitis correlated to antiangiogenic therapy. We report a case of a 46-years-old woman with BRCA1 related hereditary ovarian cancer, who had undergone 6 previous lines of chemotherapy, treated with weekly paclitaxel 80 mg/m^2 and bevacizumab 7.5 mg/kg every three weeks from November 2012.

Results. In January 2013, after three treatment courses, the patient showed grade 3 cutaneous toxicity characterized by dyschromia, dry skin, onycho-dystrophy, burning sensation, dysesthesia localized on hands and feet. Therefore, the search of inflammatory markers demonstrated an increase of VES and PCR and subsequently hand skin biopsy showed "notes of small vessel vasculitis". This toxicity has never been reported in bevacizumab-treated patients while cutaneous toxicity has been reported for paclitaxel but with different alterations (dermatitis and folliculitis). The patient showed partial response according to RECIST. Currently she is still on treatment with maintenance bevacizumab.

Conclusions. Chemotherapy plus bevacizumab is becoming a standard care in ovarian cancer; however clinician should be aware of potentially unusual adverse events related to its unique mechanism of action.

Session G • Genitourinary tumours

G1* VEGF AND VEGFR POLYMORPHISMS MAY AFFECT CLINICAL OUTCOME AND RESPONSE IN ADVANCED RENAL CELL CARCINOMA PATIENTS RECEIVING FIRST-LINE TREATMENT: IT IS A MATTER OF CHOICES OR BIOLOGY?

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Background. For the last few years sunitinib has been considered the standard treatment for first-line metastatic renal cell carcinoma, but in 2010 a new drug pazopanib has been approved for treatment in this setting. Recent data from the COMPARZ and PISCES study seem to suggest a non-inferiority of pazopanib confronted with sunitinib in PFS and OS and a patients preference for pazopanib if we consider quality of life parameters. We previously reported how VEGF and VEGFR polymorphisms have a predictive role in patients treated with first-line sunitinib. The aim of our study is to investigate whether polymorphisms of VEGF and VEGFR can influence PFS and OS when patients are treated either with sunitinib or pazopanib as first-line treatment.

Methods. Ninety-seven histologic samples of mRCC patients were tested for VEGF-A, VEGF-C and VEGFR-1,2,3 single nucleotide polymorphisms (SNPs). Patients progression-free survival (PFS) and overall survival (OS) were analyzed for first-line treatment.

Results. Nineteen patients were treated with pazopanib while 78 received sunitinib. In patients treated with sunitinib VEGF A rs833061 resulted significant in PFS (CC+CT vs TT, p <0.0001) and OS (p <0.0001). VEGF A rs699947 was significant for PFS (AA+AC vs CC) (p = 0.0001) and OS (p <0.0001). VEGF A rs2010963 was significant in PFS (CC vs CG vs GG, p = 0.0001) and in OS (p = 0.0045). At multivariate analysis rs833061, rs2010963 and rs68877011 were significant in PFS. rs833061 and rs68877011 were independent factors in OS. In the pazopanib treated groups of patients VEGF A rs833061 resulted significant in PFS (TT vs CC + CT, p = 0.002).

Conclusions. In our analysis patients with CC or CT polymorphism of rc833061 had a favourable PFS and OS if treated with sunitinib, instead patients treated with pazopanib seem to have benefit if with TT polymorphism, A polymorphism rs699947 and G polymorphism of rs2010963 seem to have a better PFS and OS in first-line with sunitinib. Patients with C polymorphism of rs6877011 and G polymorphism of rs307822 seem equally to have a favourable impact in first-line therapy with sunitinib. Our data seem to suggest that biology could have a role in the choice of first-line treatment for mRCC patients. Further data will be presented at the meeting.

G2* ASSESSMENT OF CLINICAL OUTCOMES (CO) AND PREDICTIVE FACTORS (PRE) IN A COHORT OF CASTRATION RESISTANT PROSTATE CANCER (CRPC) PATIENTS TREATED WITH ABIRATERONE ACETATE (AA) IN A NAMED PATIENT PROGRAM (NPP). PRELIMINARY RESULTS FROM A MULTICENTER ITALIAN STUDY

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Background. AA provided a survival advantage compared to placebo, in pts who had received docetaxel for CRPC (De Bono, 2011). Before the regulatory authority approval, AA was made available in Italy through a NPP supervised by the local ethic committees. The present retrospective study is aimed to assess PRE and CO in an unselected CRPC population which received AA outside clinical trials.

Methods. We retrospectively reviewed the clinical records of all pts treated with AA for CRPC by NPP in our Institutions. For each pt we have recorded the pre and post-AA clinical history, the AA treatment details and outcomes. We have also assessed the ability of a series of selected 22 clinical factors to predict AA response through a logistic regression analysis. Continuous variables were categorized by quartiles and chosen for the initial model after a univariate chi-square analysis.

Results. To date we have collected a consecutive series of 164 pts from 15 Italian hospitals. The median age was 72 yrs (range 52-89). The median baseline PSA was 151 ng/mL (range 0.33->100,000); 79% and 17.1% of the pts showed bone and measurable lesions respectively. The median duration of AA treatment was 22 wks (range 1-102); 60 treatments are ongoing. Grade 3-4 toxicities were anemia (6 pts), thrombocytopenia (1 pt), nausea (1 pt), fatigue (7 pts), bone pain (3 pts), dyspnoea (1 pt), constipation (2 pts), hypertension (1 pt), and hypokaliemia (1 pt). A PSA reduction >50% was observed in 42.6% of the patients. Having a performance status (PS) 0-1 [(exp(beta) 4.641; p = 0.011], a previous ormonotherapy lasting >40 months [(exp(beta) 3.296; p = 0.020], baseline hemoglobin >12 g/dL [(exp(beta) 2.591; p = 0.073], no visceral organ involvement [(exp(beta) 1.939; p = 0.096] resulted to be independently predictive of a PSA reduction >50%. The median PFS and OS were 6 mos and 15 mos, respectively; the 1-year PFS and OS rates were 24.7% and 57.5%, respectively.

Conclusions. Our preliminary results have confirmed the efficacy of AA in second-line CRPC outside clinical trials. Patients with good PS, good hemoglobin levels, long-lasting hormosensitivity, and without visceral organ involvement have higher probability to achieve a biochemical response to AA. Data collection from other Hospitals is ongoing.

G3 THE MANAGEMENT OF PATIENTS WITH CASTRATE RESISTANT PROSTATE CANCER (CRPC): RESULTS OF AN ITALIAN CONSENSUS ADOPTING THE DELPHI METHODOLOGY

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Background. CRPC encompasses an heterogeneous patient population with different prognosis. This study aimed to find the position of different specialists concerning the management of CRPC patients.

Material and methods. Using the Delphi method, the Advisory Board (the Authors) developed 19 groups of statements that were presented to the panelists. They had to indicate the extent to which they agree or disagree as follows: "1 = strongly disagree" to "5 = strongly agree". The disagreement consensus was declared when >66% of answers were 1+2, whilst the agreement consensus was declared when >66% of answers were 3+4+5. A total of 210 participants completed a 1st statements-list, while 123 participants completed a 2nd statements-list.

Results. The first statement was whether rising PSA alone during androgen deprivation therapy (ADT) is sufficient enough to change the treatment. The panel disagreed with this assumption, while there was agreement that the decision should be made on the basis on the PSA kinetics. Neither Gleason score nor the type of ADT were powerful enough to influence the clinical decision making process. With respect to the CRPC patients that are candidates to cytotoxic therapy, there was agreement that they should be metastatic patients with either symptomatic or asymptomatic disease. Chemotherapy was not recommended in non-metastatic patients irrespective of the PSA kinetics. The third statement was when the CRPC patient is addressed to another specialist, all participants agreed that metastatic patients (symptomatic or asymptomatic) are the best candidate. Concerning when the new hormone therapies (such as abiraterone and MDV) should be administered in patients with CRPC, all specialists believe that they should be administered in chemotherapy naïve patients. Oncologists and urologists would prescribe them also after chemotherapy while only a weak consensus was obtained among the radiation oncologists. Urologists and radiation oncologists, but not oncologists, would administer them concomitantly with chemotherapy. No consensus was obtained on the administration of these drugs in asymptomatic chemotherapy naïve CRPC patients.

Conclusions. Although the management of CRPC is challenging, urologists, oncologists and radiation oncologists are often in agreement with respect to the clinical approach to be adopted.

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G4 RISK OF TYROSINE KINASE INHIBITORS-RELATED FATIGUE IN CANCER PATIENTS: A META-ANALYSIS OF RANDOMIZED CLINICAL TRIALS

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Background. The impact of tyrosine kinase inhibitors (TKIs)-related fatigue on cancer patients (pts) quality of life and adherence to treatment regimens is substantial and under-recognized. We performed an up-to-date meta-analysis to determine the incidence of fatigue in pts with cancer treated with sorafenib (SO), sunitinib (SU) and pazopanib (PZ).

Patients and methods. PubMed databases were searched for articles published from January 1966 to April 2013. Eligible studies were selected according to PRISMA statement. Summary incidence and 95% CI were calculated. Fatigue was defined by the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) criteria.

Results. Fifteen studies were included in this analysis. A total of 6996 pts was enrolled: 2260 (32.3%) had renal cell carcinomas (RCC), 1691 (24.1%) non-small cell lung cancers, 1290 (18.4%) breast cancers, 823 (11.8%) hepatocellular carcinomas, 362 (5.2%) soft tissue sarcomas, 304 (4.3%) gastrointestinal solid tumors, 165 (2.4%) neuroendocrine tumors and 101 (1.5%) melanomas. Of them, 3728 (53.3%) pts were assigned to treatment arms and 3268 (46.7%) to placebo or control arms. Stratifying studies by TKI, we reported an incidence of all-grade fatigue of 41.4% (95% CI 38.7-44.3) for SU, 39.7% (95% CI 35.6-43.9) for PZ and 26.62% (95% CI 24.7-28.6) for SO. The differences among incidences of all-grade and high-grade fatigue were significant for SU vs SO ($p < 0.001$) and PZ vs SO ($p < 0.001$) but not for SU vs PZ ($p = 0.52$). As for high grade fatigue, the incidence was 8.97% (95% CI 7.48-10.72) for SU, 7.18% (95% CI 5.28-9.21) for PZ and 4.74% (95% CI 3.89-5.85) for SO. The overall incidence of fatigue was 35.67 (95% CI 33.02-38.4) in pts with RCC and 32.06% (95% CI 30.26-33.91) in non-RCC pts ($p = 0.03$). In regard to RCC pts, incidence of all-grade fatigue was highest with SU (54.13%, 95% CI 49.07-59.11%), followed by SO (31.87, 95% CI 28.12-35.89) and PZ (18.97%, 95% CI 14.87-23.87). The differences were significant for SU vs SO ($p < 0.001$, RR 1.7, 95% CI 1.46-1.97), SU vs PZ ($p < 0.001$, RR 2.86, 95% CI 2.2-3.67) and SO vs PZ ($p < 0.001$, RR 1.68, 95% CI 1.28-2.2).

Conclusions. Treatment with SO, SU and PZ is associated with an increased incidence of fatigue in pts with cancer. Early and appropriate management is required in order to avoid unnecessary dose reductions and transitory or definitive treatment discontinuations.

G5 HYPERTENSION (HTN), HYPOTHYROIDISM (HYPO) AND HAND-FOOT SYNDROME (HFS) AS POTENTIAL BIOMARKERS IN PATIENTS RECEIVING FIRST-LINE SUNITINIB (SU) OR SORAFENIB (SO) IN METASTATIC RENAL CELL CARCINOMA (MRCC): DATA FROM AN ITALIAN MULTICENTRE SURVEY ON 1120 PATIENTS

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G5 - Table

TKI	Side effect	N (%)	RR		PFS			OS		
			%	p	mos	HR	p	mos	HR	p
SU	HTN	330 (42)	49	<0.001	16.3	0.67	<0.001	35.3	0.60	<0.001
	No HTN	463 (58)	32		7.4	(0.6-0.8)		18.4	(0.5-0.7)	
	HFS	185 (23)	52	<0.001	20.2	0.55	<0.001	45.1	0.45	<0.001
	No HFS	630 (77)	36		8.4	(0.5-0.7)		19.9	(0.4-0.6)	
	HYPO	351 (64)	50	0.03	17.0	0.68	<0.001	37.4	0.65	<0.001
	No HYPO	195 (36)	40		9.5	(0.5-0.8)		24.7	(0.5-0.8)	
SO	HTN	39 (30)	28	1.0	9.7	0.76	0.15	26.3	0.66	0.05
	No HTN	92 (70)	28		6.7	(0.5-1.1)		15.9	(0.4-1.0)	
	HFS	55 (43)	30	1.0	9.7	0.63	0.01	26.3	0.63	0.02
	No HFS	74 (57)	29		7.0	(0.4-0.9)		15.8	(0.4-0.9)	
	HYPO	14 (32)	33	0.7	16.1	0.47	0.02	44.8	0.59	0.21
	No HYPO	30 (68)	23		8.7	(0.2-0.9)		24.3	(0.3-1.3)	

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Background. HTN, HYPO and HFS are TKIs adverse events; since correlation with outcome is unclear, they were investigated as clinical biomarkers in a large data set from 30 Italian Institutions.

Methods. HTN (systolic or diastolic blood pressure ≥140 or ≥90 mmHg), HYPO (TSH ≥3.77 mM/mL) and HFS (any grade) were correlated with RR, PFS and OS. X^2 test and KM method, compared by log-rank test, were used for statistical analysis.

Results. Among 1120 pts, 869 were treated with SU, 142 with SO. For evaluable pts, the incidence of HTN, HYPO, HFS and the correlation with outcome is reported in the Table.

Conclusions. In SU treated pts, HTN, HYPO and HFS were significantly associated with a better RR, PFS and OS; in the small cohort of SO treated pts, HFS was associated with lower risk of progression and death, while HTN was less clearly correlated with outcome; of note in SO treated pts, the incidence of HYPO (32%) was higher than expected and this subset experienced also longer PFS; however the small number of pts does not allow conclusions.

G6 ANTIANGIOGENIC TARGETED AGENTS IMPROVE OVERALL SURVIVAL IN METASTATIC RENAL CELL CARCINOMA (MRCC). A META-ANALYSIS OF PUBLISHED TRIALS

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Background. Current available targeted agents (TAs) for treatment of mRCC have improved progression-free survival and overall response rate compared to interferon or placebo. Despite this, none reported a significant improvement of overall survival (OS). This meta-analysis aims to investigate the effect of TAs on OS in a large cohort of patients enrolled in phase III trials.

Methods. MEDLINE/PubMed was searched for randomized phase III trials that compared TAs with non-TAs in mRCC. The search terms were sunitinib or sorafenib or bevacizumab or pazopanib and renal cancer. No limits of time were included. Data extraction was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Statistical analyses were conducted to calculate the summary hazard ratio (HR), and 95% Confidence Intervals (CIs) by using random-effects or fixed-effects models based on the heterogeneity of included studies.

Results. A total of 3,469 patients from 5 phase III randomized controlled trials (RCTs) were included, 1,801 received TAs and 1,668 were treated with non-TAs. The overall reduction of the risk of death was 13% (HR: 0.87; 95% CI, 0.80- 0.95; p = 0.001), not heterogeneity was found (Chi2 = 0.75, p = 0.94, I2 = 0%). When studies were divided by the class of drug, the reduction of the risk of death was 14% for the VEGFR inhibitors (HR: 0.86; 95% CI, 0.77-0.97; p = 0.01), and 12% for the VEGF inhibitors (HR: 0.88; 95% CI, 0.78-1.00; p = 0.04). No significant heterogeneity was found in both cases.

Conclusions. This analysis first reports a positive improvement of OS by TAs. Considering the high rate of patients crossover from the control arm to the TAs reported in all the included studies, this benefit, even if small, may be considered highly significant.

G7 PROGRESSION-FREE SURVIVAL BUT NOT OVERALL RESPONSE RATE (ORR) PREDICTS BENEFIT OF SUBSEQUENT LINES OF THERAPY IN METASTATIC RENAL CELL CARCINOMA (MRCC)

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Background. The aim of this study is to analyse the relationship between the PFS or the ORR with the overall survival (OS) or the progression-free survival (PFS) at subsequent line of therapy in a cohort of 281 patients with mRCC and treated with three lines of targeted agents.

Patients and methods. For each line of therapy, the median PFS and the ORR were evaluated. Patients were divided based on the PFS above or below the median value or the response to line of therapy. These classes were related to the PFS, and the OS reported in subsequent line: the post progression-PFS (PPPFS) and -OS (PPOS), respectively.

Results. The median PFS at first-line (PFS1) was 11.7 months (95% CI, 10.8-12.6); the partial responses were reported in 45.5%, the stable disease in 42.5% and the progression of disease in 12.0% of patients. The median PFS at second-line (PFS2) was 6.7 months (95% CI, 5.7-7.7); the partial responses were reported in 22.7%, the stable disease in 49.8% and the progression of disease in 27.5% of patients. The median PFS at third-line was 6.1 months (95% CI, 5.3-6.9); the partial responses were reported in 11.2%, the stable disease in 58.1% and the progression of disease in 30.7% of patients. The PFS1 above or below the median value was able to predict the PPOS (30.5 vs 24.0 months; p = 0.012) and the PPPFS2 (9.0 vs 5.4 months; p = 0.001). The response at first-line was unable to predict PPOS2 reporting a median OS of 30.5 months for PR, 26.4 months for SD and 24.0 months for PD. Similarly, this was also unable to predict PPPFS2 reporting a median PFS2 of 7.1 months for PR and SD and 4.0 months for PD with a significant difference only between PD and PR (p = 0.001) or SD (p = 0.009). The PFS2 above or below the median value was able to predict the PPOS (17.4 vs 10.4 months; p = 0.003) and the PPPFS (7.1 vs 4.7; p = 0.038). The response at second-line was substantially unable to predict PPOS reporting a median OS of 15.2 months for PR, 13.1 months for SD and 11.0 months for PD with a significant difference between PR and PD (p = 0.013). Similarly this was unable to predict PPPFS2 reporting a median PFS3 of 6.6 months for PR, 6.4 for SD and 3.8 months for PD without significant differences.

Conclusions. The PFS at first- and second-line is an useful prognostic factor able to predict patients who may have major benefit at second- and third-line, respectively.

G8 TARGETED THERAPIES (TTS) IN METASTATIC RENAL CELL CARCINOMA (MRCC): ROLE OF THE SITE OF DISEASE AS A PROGNOSTIC FACTOR

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Background. The prognostic role of metastatic sites in mRCC patients (pts) treated with TTs is not clearly understood. Aim of this study was to investigate whether metastatic sites were statistically associated to progression-free survival (PFS) and overall survival (OS).

Patients and methods. We retrospectively collected data of consecutive mRCC pts treated with TTs at Istituto Nazionale Tumori of Milan. All pts received at least one targeted agent including: sunitinib, sorafenib, bevacizumab plus interferon-alfa, pazopanib, everolimus, temsirolimus or axitinib. Multivariate Cox regression models were used to estimate hazard ratios (HRs) and to test the association between predictors and PFS and OS. In the first model metastatic sites categorized into liver, lung, brain, bone, lymph node and other site were contemporary introduced as binary predictors; in the second model the previous predictors and the Motzer score were evaluated. Statistical significance was reached when p value was less than 5%. Survival was estimated through the Kaplan-Meier method.

Results. From January 2004 to October 2012 a total of 366 mRCC pts were treated with TTs at our centre and a total of 358 (97.8%) pts were evaluated. After a median follow-up of 56.1 months (range 1.0-93.2 months) median PFS was 11 months (95% CI 8.1-12.0) and median OS was 24.2 months (95% CI 20-27.8). Metastatic sites were associated to the PFS as follows: lymph nodes (HR: 1.43; 95% CI 1.12-1.83, p = 0.004); liver (HR: 1.41; 95% CI 1.05-1.90, p = 0.021); bone (HR: 1.26; 95% CI 0.96-1.65, p = 0.091); brain (HR: 0.81; 95% CI 0.46-1.43, p = 0.474); other sites (HR: 1.07; 95% CI 0.83-1.38, p = 0.589). Number of metastatic sites was statistically associated to the PFS (HR: 1.16; 95% CI 1.04-1.29, p = 0.008). Metastatic sites were associated to the OS as follows: lymph nodes (HR: 1.73; 95% CI 1.31-2.29, p <0.001); liver (HR: 1.71; 95% CI 1.23-2.37, p = 0.002); bone (HR: 1.48; 95% CI 1.10-1.98, p = 0.009); brain (HR: 1.21; 95% CI 0.64-2.28, p = 0.568); other sites (HR: 1.09; 95% CI 0.81-1.47, p = 0.568). Number of metastatic sites was statistically associated to the OS (HR: 1.27; 95% CI 1.13-1.44, p <0.001).

Conclusions. mRCC pts with liver, lymph nodes and bone metastases treated with TTs had poorer outcome than pts with metastases to other sites. Liver, lymph nodes and bone metastases may be considered independent negative prognostic factors.

G9 DOES PATHOLOGIC COMPLETE RESPONSE AFTER NEOADJUVANT CHEMOTHERAPY AND RADICAL CYSTECTOMY CORRELATES WITH SURVIVAL IN PATIENTS WITH BLADDER CANCER? A COMPREHENSIVE META-ANALYSIS

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Background. Neoadjuvant chemotherapy and radical cystectomy (RC) are the best treatment for muscle invasive bladder cancer (BC). Pathological complete response (pCR) is associated with increased overall survival (OS) in rectal and breast cancer patients. The aim of this analysis was to evaluate if pCR is associated with a better outcome also in muscle invasive BC.

Material and methods. A systematic search in PubMed, ISI Web of Science, Cochrane Register of Controlled Trials and EMBASE for publications reporting outcome of patients with and without pCR after neoadjuvant cisplatin-based polychemotherapy and RC, was performed. Primary outcome reported as relative risk (RR) was OS. Secondary endpoints were relapse-free and cancer-specific survival (RFS and CSS) other than distant and locoregional RFS. Meta-analysis was performed using the fixed-or random-effects model. Overall heterogeneity was assessed for RFS and OS with forest plots and the Q test.

Results. A total of 13 trials were included and data from 855 patients, who have undergone neoadjuvant chemotherapy and RC without any postoperative treatment, were analyzed. The overall pCR rate was 27.8%. Patients who achieved a pCR in primary tumours as well as in lymph nodes present a RR for OS of 0.45 (95% CI 0.36-0.56; p <0.00001). The number need to treat to prevent one death was 3.7 (absolute risk difference -26%). The summary RR for RFS was 0.19 (95% CI 0.09-0.39; p <0.00001).

Conclusions. Patients with locally advanced BC who achieved a pCR (a pT0N0 stage) after neoadjuvant chemotherapy have a better OS and RFS than those who did not get a pCR.

G10 DOCETAXEL (DOC) TREATMENT IN VERY OLD (80 YEARS) PATIENTS WITH CASTRATION RESISTANT PROSTATE CANCER (CRPC): UPDATED RESULTS OF AN ITALIAN MULTICENTER RETROSPECTIVE STUDY (DELPHI STUDY)

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Background. A diagnosis of CRPC is frequently made in very old pts (= 80 years). In these cases, fear of high toxicity degree usually limits chemotherapy use due to both pts frailty and several comorbidities occurrence. Moreover, if treated, these pts usually receive an adapted chemotherapy, often with a weekly schedule, which in TAX327 trial failed to show survival advantage compared to mitoxantrone. The present retrospective study is aimed to assess the clinical outcomes (CO) in this very elderly CRPC population.

Methods. In this multicentric retrospective study, after Ethical Committee approval, we have reviewed the clinical records of all = 80 yrs CRPC pts from participating institutions, treated with DOC in clinical practice, recording the pre- and post-DOC clinical history, the DOC treatment details and outcomes.

Results. To date we have collected a consecutive series of 106 pts from 23 Italian hospitals. The median age was 82 yrs (range 80-90). The median baseline PSA was 92 ng/mL (range 3-2981); 83% of the pts had bone metastases, while nodal, lung and liver metastases were observed in 38%, 8%, and 7% of the pts, respectively. Median Cumulative Illness Rating Scale score was 3 (range 0-11), median Activity Daily Living index score was 0 (range 0-5), median Instrumental Activities of Daily Living score was 0 (range 0-5). The DOC was administered on 3-week or weekly schedule basis (42%/58%). A PSA reduction >50% and an objective response were observed in 57% and 7% of the pts, respectively. Grade 3-4 toxicities were: anemia (2%), neutropenia (11%), thrombocytopenia (2%), fatigue (10%), diarrhea (4%), renal (2%), and febrile neutropenia (1%). The median PFS and OS were 6 mos and 20 mos, while the 1-year PFS and OS rates were 17.1% and 70.3%, respectively.

Conclusions. This data suggests that DOC treatment, both on 3-week or weekly schedule, is able to produce good survival outcomes, comparable to pivotal trials (18 mos), also in highly selected very older (= 80 yrs) CRPC pts. Data collection is ongoing from other hospitals.

G11 SAFETY OF TARGETED THERAPIES (TTS) IN METASTATIC RENAL CELL CARCINOMA (MRCC) PATIENTS IN HAEMODIALYSIS (HD)

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Background. On the basis of few published data, sunitinib and sorafenib can be safely administered to patients (pts) with mRCC and end-stage renal disease on HD. Limited data regarding the use of mTOR inhibitors on HD are available, even though no influence of HD on serum concentration of these drugs has been reported. Aim of this study was to investigate the safety and tolerability of TTs in pts with mRCC on HD in an Italian population.

Patients and methods. Between July 2006 and December 2012, 37 pts with mRCC undergoing HD were treated with sunitinib, sorafenib, temsirolimus or everolimus in 17 Italian Institutions. We retrospectively reviewed the medical records of these pts to evaluate the administered doses of TTs and the treatment-related toxicities.

Results. Twenty-six males/11 females with a median age of 63 years (range 47-81) were analyzed. All pts were under HD, in 18 cases as a consequence of a bilateral nephrectomy. Sunitinib and sorafenib were administrated as first-line TTs in 24 pts: sunitinib at 50 mg daily for 4 weeks followed by a 2-week break in 6 pts, 37.5 mg daily in 7 pts, 25 mg daily in 2 pts and 12.5 mg daily in one patient with the same schedule. Sorafenib was administrated at 800 mg daily, continuously, in 4 pts, at reduced dose of 400 mg in 3 pts and 200 mg daily in one patient. Everolimus was administered at 10 mg daily, continuously, in 5 pts and at 5 mg in one pt; 7 pts received temsirolimus at 25 mg weekly. Everolimus was administered as second-line treatment in 5 pts and as fourth-line in one patient. Temsirolimus was given as first-line treatment to 5 pts, as third-line to 2 pts. None of the pts had to change the number of dialysis sessions during TTs treatment. No unexpected adverse event (AE) and no grade 4 haematological or non-haematological toxicity were reported. The most common grade 1-2 non-haematological treatment-related AE with TTs was fatigue (20/37 pts). A grade 3 dyspnea, due to interstitial pneumonia, in one pt treated with temsirolimus and a grade 3 cardiac ischaemia in one pt treated with sorafenib led to treatment discontinuation. The most frequent grade 1-2 haematologic toxicity was anemia (27/37 pts). A grade 3 anemia and thrombocytopenia were observed in 2 pts during treatment with everolimus and sunitinib without any need to discontinue treatment.

Conclusions. These data indicate that, in pts with mRCC in HD, TTs are not contraindicated, leading to no unexpected toxicity and showing a safety profile.

G12 CLINICO-PATHOLOGICAL FEATURES AND PROGNOSIS OF PATIENTS WITH LATE-RELAPSING (>5 YEARS) RENAL CELL CARCINOMA AFTER CURATIVE SURGERY: RESULTS FROM LATER STUDY

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Background. Late relapse of renal cell carcinoma (RCC) after radical initial nephrectomy is not a rare event. The aim of this study was to describe the late relapse of RCC, defined as 5 or more years after the primary tumour's excision in a series of RCC patients.

Patients and methods. Patients who developed metastatic RCC over 5 years after curative surgery were enrolled in this retrospective analysis. Data were collected from 17 Italian centers involved in the treatment of RCC. MSKCC risk class was assessed before starting first-line treatment with sunitinib. Overall survival (OS) was estimated with the Kaplan-Meyer method with 95% CI.

Results. Of the 2457 metastatic RCC pts screened, 282 pts (11%) experienced a late relapse (>5 yrs) and were included in this analysis. The median age was 66 yrs (range 29-88) and 202 pts (72%) were male. Median time to recurrence was 7.9 yrs (range 5.1-35.0). Pathological subtypes were clear cell RCC in 267 pts (95%) and non-clear cell RCC in 15 pts (5%), including 11 with papillary RCC (4%). At first diagnosis, Fuhrman's nuclear grade was G1 in 14 pts (5%), G2 in 178 pts (63%), G3 in 83 pts (29%), G4 in 7 pts (3%); micro-vascular and fatty infiltration was present in 34 (12%) and 36 (13%) pts, while sarcomatoid differentiation was identified in 11 pts (4%). In 20 pts (7%) the first relapse consisted of a single metastasis that was treated with surgery. The most frequent sites for late relapse was lung (59%), followed by lymph nodes (31%), bone (21%), adrenal gland (18%), pancreas (17%), kidney (16%), liver (15%), soft tissue (9%), brain (7%), and thyroid (3%). Median OS from relapse was 59.5 (4.6-87.9) months. Prognostic categories using MSKCC score were good in 64%, intermediate in 30% and poor in 6% of patients. For each group median OS were 69.5, 43.5 and 21.1 months, respectively ($p < 0.001$). One hundred and thirty-eight (49%) and 104 (37%) pts received a second- and third-line treatment, respectively.

Conclusions. Patients with late relapsing RCC present a different metastatic spread of disease including frequently adrenal gland, pancreas and kidney, with a consistently favorable prognosis. These data should be considered in the long-term therapeutic strategy and management of these patients.

G13 EFFICACY OF FIRST-LINE TYROSINE KINASE INHIBITORS IN PATIENTS WITH LATE RECURRENCE (>5 YEARS) OF CLEAR CELL RENAL CELL CARCINOMA: RESULTS FROM LATER STUDY

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Background. The effect of vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs) in patients (pts) with late recurrence of renal cell carcinoma (RCC) is not well-known. Aim of this retrospective study was to investigate the efficacy of first-line VEGFR TKIs in late-relapsing metastatic RCC patients.

Material and methods. Data were collected from 17 Italian centers. MSKCC prognostic categories were assessed before starting first-line treatment with VEGFR TKIs. Overall survival (OS) and progression-free survival (PFS) were estimated with the Kaplan-Meyer method with 95% CI and curves were compared with log-rank test.

Results. A total of 2457 pts were screened and 267 pts (11%) were treated with VEGFR-TKIs for late-relapsing RCC and were included in this retrospective analysis. The median age was 66 years (range 29-87) and 194 (73%) of pts were male. Median time to recurrence was 7.9 years (range 5.1-35.0). Median OS was 45.5 months and median PFS was 18.0 months. Motzer prognostic category was good in 62% of pts, intermediate in 32% and poor in 6%. Median OS in these groups was 69.7, 43.5 and 16.9 months, respectively (p <0.001). Median PFS was 25.7, 11.0 and 3.6 months, respectively (p <0.001). One hundred and ninety-one pts were treated with sunitinib, 56 with sorafenib and 20 with pazopanib as first-line therapy. As for sunitinib, median PFS was 19.73 months and median OS was 43.3 months, with a DCR of 90.5% (47.6% partial responses, 1% complete responses and 41.9% stable diseases). When stratified by Motzer score, median PFS was 25.7, 11.4 and 3.6 months (p <0.001) and median OS was 52.2, 40.2 and 16.9 months (p <0.001), respectively. Sorafenib-related median PFS was 13.9 months and median OS was 47.7 months. DCR was 91%, with 46.4% of partial responses and 44.6% of stable diseases. Patients stratified by Motzer score showed a median PFS of 29.0, 9.1 and 3.9 months (p <0.001) and a median OS of 77.7, 23.3 and 7.1 months (p <0.001), respectively. When pazopanib was the first-line therapy, median PFS was 14.4 months and median OS was 40.8 months, with a DCR of 90.0% (65.0% of partial responses and 25.0% of pts with stable disease).

Conclusions. Patients with late relapsing RCC treated with first-line VEGFR TKIs showed consistently longer PFS and OS and dramatically higher DCR than reported in previous studies with TKIs. Our data should be considered in the long-term management of these patients.

G14 PROGNOSTIC SIGNIFICANCE OF FDG-PET/CT AFTER TWO CYCLES OF FIRST-LINE CHEMOTHERAPY IN ADVANCED TRANSITIONAL CELL CARCINOMA

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Background. A risk-adapted treatment for advanced transitional cell carcinoma (TCC) is lacking and it may guide trial designs with novel agents/combinations for early-recognized unresponsive patients (pts). [18F]fluorodeoxyglucose Positron Emission Tomography/computed tomography (FDG-PET/CT) is increasingly used by many centers for (re)staging in TCC. We prospectively assessed the value of FDG-PET/CT after 2 cycles of upfront chemotherapy.

Methods. In a single-center trial, pts with newly-diagnosed advanced/metastatic TCC receiving first-line MVAC underwent CT and FDG-PET/CT at baseline, a restaging with FDG-PET/CT after 2 cycles only, and a CT and/or FDG-PET/CT at the end of treatment. EORTC criteria for metabolic response were applied. The endpoints were progression-free (PFS) and overall survival (OS). PFS and OS rates were estimated with the Kaplan-Meier method; univariable (UVA) and multivariable (MVA) Cox models were also fitted, adjusted for pre-specified factors.

Results. Thirty-one pts were accrued in the time-frame 05/2010-10/2012. All of them received MVAC regimen and had an ECOG-PS 0. After 2 cycles of MVAC, 6 pts (19.3%) had a complete (CR) and 17 (54.8%) a partial metabolic response (PR), 4 pts had stable disease (SD). Median FUP was 18 months (IQR: 10-47). Those with metabolic response (CR+PR) had a median (95% CI) PFS = 8.0 (7-11) mos compared to 3.0 (2-5) mos in patients without response (p = 0.024). Early PET responders had a significant difference in 8-month PFS (p <0.0001) and 15-month OS (p = 0.016 at Klein test). A significant association was observed between early PET response and PFS in both UVA and MVA (p = 0.027 and p = 0.023, respectively (Table).

Conclusions. PET response after 2 cycles of first-line MVAC seemed to confer an independent prognostic impact on PFS and might even affect OS.

G14 - Table.
Cox models for progression-free survival

	Univariable			Multivariable		
	HR	95% CI		HR	95% CI	
PET response						
No (SD, PD) vs Yes (CR, PR)	2.87	(1.13, 7.31)	0.027	3.88	(1.21, 12.42)	0.023
Visceral disease						
Yes vs No	3.16	(1.29, 7.70)	0.012	3.77	(1.41, 10.04)	0.008
Nodal/soft tissue disease						
Yes vs No	3.43	(0.73, 16.08)	0.118	1.62	(0.25, 10.36)	0.611

G15 TARGETED THERAPIES (TT) FOR METASTATIC RENAL CELL CARCINOMA (MRCC) IN THE REAL WORLD SETTING: AN ITALIAN MULTICENTRIC SURVEY OF 1120 PATIENTS

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Background. This survey was aimed to evaluate the outcome of TT in mRCC pts in the community setting.

Methods. Individual data of 1120 pts treated with TT from mid 2007 to December 2012 in 30 Institutions were reviewed.

Results. Median follow-up was 16 mos (range 1-85), median age 65 yrs (range 23-90), histology was clear cell in 78% and nephrectomy was performed in 88% of the cases. Main metastatic sites were lung (63%), lymph nodes (40%), bone (31%), liver (20%). Overall survival (OS) was 69%, 50%, 36%, 27%, 19% at 1, 2, 3, 4, 5 yrs, respectively, without difference in relation to the number of pts treated per center (median 37, range 6-98). First-line tx was sunitinib (SU) in 869 pts (77%), sorafenib (SO) in 142 (12.5%), temsirolimus in 46 (4%), others (6.5%). Median PFS of first-line (mPFS1) SU was 10.7 mos and that of SO 7.9 mos ($p = 0.004$). Dose reduction of SU and SO was required in 48% and 39% of the cycles, respectively; 269 pts (24%) received <2 cycles of SU/SO mostly for rapid progression and/or deterioration and had a mOS of 5 mos. Second-line tx was performed in 48% of the pts: SO 186 (17%), everolimus (EV) 149 (13%), SU 126 (11%), temsirolimus 26 (2.3%), chemo-immunotherapy 33 (3%), others 1.4%. mPFS2 was 6.9 mos for SU, 4.7 mos for SO, 4.0 for EV; SU vs SO $p = 0.018$, SU vs EV $p = 0.008$. 219 pts (19.5%) received 3 lines of tx: VEGFi-VEGFi-mTORi (A) 85 pts (39%), VEGFi -mTORi-VEGFi (B) 65 pts (30%), VEGFi-VEGFi- VEGFi (C) 27 pts (12%), others (various schedules of chemo/immunotherapy) 42 pts (19%) (D). mOS of the group was 40 mos: 45 (A), 39 (B), 45 (C), 35 (D), respectively; A vs B $p = 0.4$, A vs D $p = 0.009$. Presently, first-line tx is ongoing in 167 pts (15%) (median duration 18 mos, range 2-71), second-line tx in 67 pts (6%). About 5% of the pts survived at least 12 mos after stopping TT (median time from end of TT 50 mos, range 13-61). 210 pts (19%) died within 30 days after the last dose of tx.

Conclusions. i) In the community setting PFS and OS reproduced data of clinical trials; ii) no variation according to center volume was found showing a widespread expertise; iii) about 40% of pts became long survivors, mostly after subsequent lines of tx and 5% even after stopping tx; iv) 24% of pts were refractory to tx; v) 19% of pts died within 1 mo after stopping tx; vi) further studies are needed to better identify the different subsets of pts in order to improve the efficacy of TT.

G16 EXPECTED OVERALL SURVIVAL (OS) BENEFIT IN CASTRATION RESISTANT PROSTATE CANCER (CRPC). POTENTIAL IMPLICATIONS FOR CLINICAL TRIALS' DESIGN

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Background. In a few years, several new drugs were approved by regulatory authorities for the treatment of patients affected by CRPC on the basis of an advantage in OS demonstrated in pivotal trials. Unfortunately, lacking comparison studies between the different therapeutic strategies, the choice of the best treatment in this setting of patients is difficult. We used a meta-analytical approach to evaluate if the comparison of the results of the trials, in absence of head-to-head studies, may drive to biased survival estimations.

Methods. Twenty-three randomized clinical trials (RCT), including 17,640 patients, were identified. Hazard ratios (HR) with 95% confidence intervals (CI) were extracted and cumulated according to a random-effect model. Sensitivity analyses according to: 1) therapeutic strategy (TS, chemotherapy versus hormonal versus immunotherapy versus other), 2) comparison (chemotherapy versus placebo versus other), and 3) disease setting with regard to treatment with docetaxel (DOC), were performed. Testing for heterogeneity was performed as well.

Results. A significant heterogeneity for the 3 sensitivity analyses was found ($p < 0.0001$). The cumulative HR in favor of (any) experimental arm was 0.91 (95% CI 0.84-0.99, $p = 0.028$). A significant interaction according to the chosen TS was found ($p < 0.0001$): an OS significant differences were more likely to be determined in RCT evaluating hormonal drugs (HR 0.76, 95% CI

0.64-0.92, p = 0.005), versus studies testing immunotherapy (HR 1.16, 95% CI 0.86-1.56, p = 0.31). With regard to comparison, a significant interaction (p <0.0001) was found in favor of RCT having placebo as control (HR 0.86, 95% CI 0.76-0.97, p = 0.015), versus studies evaluating chemotherapy (HR 1.00, 95% CI 0.84-1.19, p = 0.99). A significant interaction according to DOC-treatment was also found (p <0.0001), suggesting that in the post-DOC setting, a significant OS benefit was more likely to prove (HR 0.77, 95% CI 0.66-0.90, p = 0.001).

Conclusions. This meta-analysis suggests that the OS results comparison across the clinical trials may drive biased conclusions in absence of head-to-head studies. Therefore, to design clinical trials in order to assess the efficacy of a new therapeutic strategy in CRPC, the expected OS benefit must be estimated evaluating the choice of the comparator, the type of treatment strategy and the phase of the disease in relation to the administration of DOC.

G17 ENUMERATION AND MOLECULAR PROFILING OF CIRCULATING TUMOR CELLS (CTCS) IN UROTHELIAL CANCER (UC) BEFORE AND DURING SYSTEMIC TREATMENT

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Background. CTCs provide clinically relevant information in different tumor types and represent promising tools in UC, for which multimodal decision making and innovative tools for patient selection are desperately needed. However, optimal approaches to detect and characterize CTCs remain open questions.

Materials and methods. We prospectively evaluated CTCs in two populations of UC pts with either muscle-invasive (M0) or metastatic disease (M+) being enrolled in INT-sponsored phase 2 trials of neoadjuvant sorafenib, cisplatin, and gemcitabine, of second-line anti-TGFß receptor ALK1 PF-03446962, or receiving standard first-line chemotherapy. Five mL of whole blood were filtered by ScreenCell® Cyto device and CTC status was assessed with centralized scoring by referral pathologists. Additional 5 mL of whole blood were processed to exploit epithelial- and tumor-associated surface markers as catcher antigens (AdnaTestSelect® kit) and the expression level of a panel of markers (*EPCAM*, *MUC1*, *HER2*, *CEA* and *EGFR*) was evaluated by multiplex PCR. Assays were done at baseline and during treatment for all pts (overall, 240 assays).

Results. In the time-frame 07/2012-03/2013, 16 M0 pts and 23 M+ pts were enrolled. At baseline, ScreenCell detected = 1 CTC in 89% and 94% of M0 and M+ patients, respectively (median CTC: 6; range 1-95), while PCR signals = specific cut-off values were observed in 5/16 M0 and 13/23 M+ cases, with distinct patterns for the different biomarkers.

Setting	Detected cases	EPCAM+	MUC1+	HER2+	CEA+	EGFR+
M0	5	5	1	1	0	0
M+	13	11	7	5	2	2

Discordant results between biomarkers profile and CTC number trend were observed in 6/10 M+ cases and consisted in substantially unchanged *EPCAM* expression levels despite an increase in CTC number during treatment, suggesting a different sensitivity in reflecting treatment-related changes. However, three M0 patients with favorable pathological response to neoadjuvant treatment (pT0/downstaging to pT <2) showed a stepwise reduction in CTC number before cystectomy.

Conclusions. The present combined techniques for CTC detection seem to be promising compared to currently available patho-biological information in UC, though additional follow-up data are necessary to analyze associations with clinical outcome.

G18 EARLY RESULTS OF A PHASE 2 STUDY OF NEOADJUVANT CISPLATIN AND GEMCITABINE PLUS SORAFENIB (S-CG) FOR PATIENTS WITH MUSCLE-INVASIVE TRANSITIONAL CELL CARCINOMA OF THE BLADDER (INT52/10, NCT01222676)

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Background. Despite surgery with curative intent, about 50% of patients (pts) with muscle-invasive transitional cell carcinoma of the bladder (MIBC) die for distant metastases. Improvements with neoadjuvant chemotherapy are still limited. A rationale exists for inhibiting the RAF/MEK/ERK pathway, the VEGFR1-3, and PDGFR in urothelial cancer. The S-CG combination is being investigated in an ongoing open-label, single-group, single-center, phase 2 trial.

Methods. Chemonaïve pts with T2-4N0 MIBC were given 4 cycles of cisplatin 70 mg/m^2 on day 1 and gemcitabine 1000 mg/m^2 on day 1 and 8, every 3 weeks. Sorafenib 400 mg q12h was administered daily from day 1 until surgery (radical cystectomy). Patients were evaluated with computed tomography (CT) and positron emission tomography (PET)/CT scan. An optimal 2-stage Simon's design is applied whereby 6 pathologic complete responses (pT0, primary endpoint) should be observed in 24 patients before moving to full enrollment of 45 cases. Residual carcinoma *in situ* with no evidence of concurrent invasive tumor (T1-T4) was considered as pT0. Intention-to-treat analysis was applied. 5 mL of blood samples were collected at baseline and at each cycle for exploratory circulating tumor cell (CTC) analysis by the AdnaGen® kit and ScreenCell® Cyto devices.

Results. Twenty-one pts were enrolled from 04/11 to 03/13. Thus far, 17 completed the treatment and are evaluable. Median age was 61 yrs (IQR: 54-66). Eleven had T2, 9 T3, and one a T4 disease. Fifteen pts underwent radical cystectomy; 6 pts (35.3%, 95% CI 14.2-61.7) had a pT0 and 3 pts a pT <2. G1-2 hand-foot syndrome (HFS) occurred in 4 pts, rash in 2, and diarrhoea, increase of liver transaminases, fatigue and hypertension in one patient each. Grade 3 adverse events were thrombocytopenia in 7 pts (41.2%), fatigue in 2 pts (11.7%), HFS, anemia and hypertension in one pt each (5.8%). CTC evaluations were carried out in 11 pts. 4 pts with pT <2 response were evaluable for CTC (range 7-21 cells by ScreenCell®) and all of them had a stepwise reduction prior to cystectomy.

Conclusions. S-CG combination is tolerable and endowed of substantial antitumor activity that justifies full study enrollment in pts with MIBC. Preliminary results on the contribution of sorafenib were obtained and warrant further investigation on a larg-

er sample size. Mature results on the CTC and further biomarker analyses with longer follow-up will be available in October 2013.

G19 CLINICAL OUTCOME (CO) EVALUATION OF ELDERLY (>75 YEARS) CASTRATION-RESISTANT PROSTATE CANCER (CRPC) PATIENTS TREATED WITH ABIRATERONE ACETATE: PRELIMINARY RESULTS OF AN ITALIAN MULTICENTER ANALYSIS

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Background. Prostate cancer predominantly affects old men, with a median age at diagnosis of 68 years. Due to the increased life expectancy, management of prostate cancer in elderly adults (aged >75 years) represents a major public health problem. This patients population may not receive optimal therapy for their disease, if decisions are made based on chronological age alone. Clinical trials are rarely designed specifically for elderly. Evidence suggests that healthy senior adults have similar treatment outcomes to their younger counterparts. Abiraterone acetate (AA) significantly improved overall survival of mCRPC pts after chemotherapy in all age groups.

Methods. Sixty-six pts with advanced CRPC received AA (1000 mg, orally once daily) plus prednisone (5 mg, orally twice daily) from 2011 to 2013 in 3 Italian Institutions. The present study is aimed to compare CO in elderly and younger CRPC population treated with AA.

Results. At the baseline, characteristics were: 29 elderly pts with a mean age of 79 years (range 75-86) and median PS 1 (0-2) and main sites of disease: bone 27 pts (93%), lymph nodes 13 pts (45%), prostate 8 pts (28%), liver 3 pts (10%) and lung 3 pts (10%); 37 younger pts with mean age of 64 years (range 54-74) and median PS 1 (0-2) and main sites of disease: bone 32 pts (89%), lymph nodes 15 pts (40%), prostate 9 pts (24%), liver 3 pts (8%) and lung 2 pts (6%). All patients had received prior docetaxel. No G3-4 toxicities (fluid retention or oedema or hypokalemia or cardiac events) have been observed neither in younger nor in elderly. Grade 1 peripheral oedema occurred as frequently in either groups. A G3 increase alanine aminotransferase (ALT) was observed in a younger patient, and hemorrhagic gingivitis in an elderly patient. Median time to progression (PSA, objective or symptomatic) in elderly was 11.35 months (95% CI 9-13.7) and in younger was 9.35 months (95% CI 7.04-11.18).

Conclusions. In our experience, CO was similar in elderly and in younger, and the therapy was well tolerated in either subgroups. Therefore, the fear of inducing an increased toxicity in a patient simply because elderly, should not limit the choice of treatment and the therapeutic approach should be fundamentally the same in the healthy elderly and their younger counterparts.

G20 CASTRATE RESISTANT PROSTATE CANCER (CRPC) AND THE MODULATION OF ITS MANAGEMENT: RESULTS FROM AN ITALIAN CONSENSUS

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Background. Oncologists, urologists and radiation oncologists have been interviewed regarding CRPC definition and its management in case of metastatic or not metastatic patient.

Material and methods. Using the classical Delphi method, the Advisory Board (the Authors) developed 19 groups of statements that were presented to the panelists. They had to express their level of agreement/disagreement for each sentence ranging from "1 = strongly disagree" to "5 = strongly agree". The disagreement consensus was declared when >66% of answers were 1 + 2, whilst the agreement consensus was declared when >66% of answers were 3 + 4 + 5. If a consensus was not achieved, the question was deemed to have no agreement. A total of 210 participants completed a 1st statements-list, while 123 participants completed a 2nd statements-list.

Results. All specialists agreed on the CRPC definition: 3 consecutive rises of PSA resulting in 2 ≥50% increases over the nadir and PSA >2 ng/mL, failure of at least 2 ADT lines; progressions of bone lesions (≥2 new or extrabone lesions >2 cm diameter).

There was a strong agreement on the parameters that have to be considered when evaluating therapy response: PSA and its derivate change, RECIST criteria, symptoms change (bone pain score) and performance status variation (not helpful for the radiation oncologists). Specialists strongly agreed on the factors related to the therapy: age, presence or absence of metastases, presence or absence of symptoms, PSA values and its kinetics. All specialists also agreed on switching therapy when a sierologic, radiologic and/or symptomatic progression is detected. When asked about the management of a patient with biochemical progression but no metastasis, there was a consensus in treating the patient, and was also accepted that the PSA kinetics is the key parameter. Furthermore it was evidenced that the pressure of the family has not the power to influence the specialists motivation to treat or not.

Conclusions. In general specialists showed agreement on the CRPC definition and the patients characteristics driving the therapy choose (some disagreement was showed on Chromogranin A level). Specialists agreed that a patient with only biochemical progression should be treated on the basis of its PSA kinetics.

With an unrestricted grant by Ipsen.

G21 CLINICAL, PHARMACODYNAMIC AND PHARMACOGENETIC EVALUATION OF DOCETAXEL PLUS PREDNISONE IN COMBINATION WITH METRONOMIC CYCLOPHOSPHAMIDE AND CELECOXIB AS FIRST-LINE TREATMENT IN METASTATIC CASTRATION RESISTANT PROSTATE CANCER (MCRPC)

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Background. Docetaxel (D) is the standard first-line treatment in mCRPC. D has been combined with various agents that demonstrated additive/synergistic activity in preclinical studies in an effort to further improve outcomes, but to date, overall survival (OS) has not been extended compared with D plus prednisone (P). Metronomic chemotherapy has been studied for its anti-angiogenic property: phase II trials have demonstrated clinical activity and good toxicity profile. The aims of the present study were to evaluate the clinical activity, pharmacodynamic/pharmacogenetic profile of the new D-based combination with metronomic cyclophosphamide (CTX) and celecoxib (C), as first-line treatment in mCRPC.

Methods. From March 2006 to April 2010, 41 patients (pts) received D (60 mg/m^2 i.v. every three weeks up to 12 cycles) and, from day 2, P 10 mg/day, C 400 mg/day and CTX 50 mg/day continuously until disease progression. Primary endpoint was progression-free survival rate (PFSR) at 6 months. Plasma vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) were detected by ELISA at different time points. Blood samples were collected at day 1 (pre-treatment) for DNA extraction. Real-time PCR-SNP analysis of VEGF-A [-2578A/C (rs699947), -154A/G (rs1570360), -634C/G (rs2010963) and -936C/T (rs3025039)] were performed.

Results. In 39 evaluable pts we observed a PSA decrease = 50% in about 82% of pts. Main grade 3 adverse events were: neutropenia (5%), thrombocytopenia, diarrhoea, stomatitis and onycholysis (2.5%). PFSR at 6 months was 87%. Median PFS and OS were 14.9 months (95% CI, 9.2-15.3) and 33.3 months (95% CI, 23-35.6), respectively. A significant increase of PFS was found in those pts who, after the first cycle of treatment, had plasma levels of VEGF >129 pg/mL (16.5 vs 11.1 months, p = 0.042) and of bFGF >13 pg/mL (20.8 vs 12.2 months, p = 0.0314). Moreover, pts with the VEGF -1154AA genotype showed a significant shorter PFS (11.1 months) if compared to the VEGF-154AG/GG pts (23.7 months; p = 0.0028).

Conclusions. The combination of D and metronomic cyclophosphamide plus celecoxib and P was effective in pts with mCRPC and showed favorable toxicity. The -1154A/G VEGF polymorphism, VEGF and bFGF plasma levels after the first cycle of chemotherapy may represent useful pharmacogenetic/pharmacodynamic markers to predict a better outcome. Randomized phase III clinical trials are needed to verify these preliminary findings.

G22 SAFETY AND EFFICACY OF EVEROLIMUS GIVEN AT 10 MG/DAY IN ADVANCED RENAL CELL CARCINOMA (RCC) PATIENTS WITH STAGE III TO V CHRONIC KIDNEY DISEASE (CKD)

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Introduction. Everolimus is commonly used as an immunosuppressant in renal transplant recipients; most recently, it was also registered for the treatment of advanced RCC patients pre-treated with tyrosine kinase inhibitors. The two indications are very different, especially when it relates to the dose, almost 5 times higher in patients with metastatic RCC (10 mg/day). Data on safety and efficacy of everolimus in patients with RCC (usually nephrectomized) and concomitant CKD are limited by the extremely restrictive selection criteria used in the pivotal RECORD-1 trial.

Materials and methods. We retrospectively evaluated the trend of renal function, electrolytes, proteins and fat values (before initiation of therapy, and then at 3 and 5 months) in 40 patients with advanced RCC and different stages of CKD treated with everolimus. We also correlated this trend with everolimus tolerability profile, as well as antitumor efficacy parameters, such as disease control rate (DCR) and progression-free survival (PFS). Furthermore, toxicity has been evaluated in accordance with the Common Toxicity Criteria of the National Cancer Institute (NCI-CTC), version 3.0.

Results. Only 4 patients with stage III CKD at the beginning of treatment showed a worsening of renal function under treatment with everolimus (already evident at 3 months), without the need to discontinue or temporarily interrupt treatment; however, in two of them, everolimus was dose-reduced to 5 mg/day for acute renal toxicity (AKI). Furthermore, there was no evidence of significant electrolyte disturbances, while alterations in glucose and lipid metabolism, as well as a decline in hemoglobin (consistent with the known toxicity profile) were observed.

Conclusions. Everolimus proved to be active and safe also in RCC patients with concomitant stage III to V CKD.

G23 EFFECT OF CHOLESTEROL AND TRIGLYCERIDE INCREASES ON TIME TO PROGRESSION IN RENAL CLEAR CELL CANCER PATIENTS TREATED WITH EVEROLIMUS

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Background. An increased level of cholesterolemia (C) and triglyceridemia (T) secondary to an impairment of lipidic metabolism is a well known side effect of all mTOR inhibitors including everolimus (E). We assessed the value of C and T increase as a factor predicting the efficacy of E in metastatic clear cell renal cancer.

Methods. We retrospectively evaluated 128 patients (96 male, 32 female; median age 64 years ± 11.76) with metastatic clear cell renal cancer who received a second (75 patients)/third-line (53 patients) with E after at least one tyrosine-kinase inhibitor (TKI). From routinely performed blood test, we retrieved the value of total C and T the day before the first E administration and during the entire duration of treatment. Among others, parameters of metabolic syndrome (i.e. variations of glycemia, blood pressure and BMI before and after treatment start), as also response to E and first-line treatment were evaluated. Time to progression (TTP) and survival were evaluated.

Results. Among the potential predictive factors considered, only the co-increase of C and T (>20% compared to the baseline) within 2 months (median time: 40 days ± 12.37) from treatment start correlated with outcome. Median TTP in 58 patients with total early C-T co-upraise was statistically significant longer than in 70 patients without co-upraising (12 vs 6 mos, p = 0.031). Interestingly, both response to E and response to a first-line correlated with an improvement in TTP (12 vs 6 mos with p <0.001 and 16 vs 8 months with p = 0.032 respectively). These results were also confirmed in the multivariate analysis (CT co-increase p = 0.010; response to E p <0.001; response to a first-line p = 0.004). Conversely, the single upraise of C or T was not correlated with statistically longer TTP (7 vs 6.5 mos, p = 0.314 and 12 vs 6 mos, p = 0.127). Considering E-second line population only, median TTP in the 29 patients with total early C-T co-upraise was higher than in 29 patients without co-upraise with favourable trend but not statistically significant (15 vs 8 mos, p = 0.095) while in E-third line population this difference was smaller and not statistically significant (10.4 vs 6 mos, p = 0.134). Finally C-T co-upraise did not correlate with improved median overall survival (17 vs 14 mos, p = 0.092).

Conclusions. Early C-T upraise predicts E efficacy in renal clear cell cancer.

G24 CUMULATIVE TOXICITY RELATED TO TIROSINE KINASE INHIBITORS (TKI) IS AN INDEPENDENT PREDICTIVE FACTOR IN METASTATIC RENAL CELL CARCINOMA (MRCC)

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Background. Previous studies have shown that TKI-induced arterial hypertension, hypothyroidism and hand-foot syndrome are predictive factors in mRCC. We aim to demonstrate whether cumulative toxicity developed by patients treated with TKI as first-line therapy for mRCC is an independent predictive or prognostic factor.

Materials and methods. Patients suffering from mRCC and consecutively treated with first-line TKI at our Institution were checked for any grade of arterial hypertension, hypothyroidism and hand-foot syndrome. Data about sex, age, performance status, risk-class according to Motzer score, type of prescribed TKI were also collected. Progression-free (PFS) and overall survival (OS) were estimated using Kaplan-Meier method and compared by log-rank test. Cox-analysis was used to find factors related to PFS and OS. Patients were divided into two groups: low-toxicity (0 or 1 toxicity) and high-toxicity (2 or 3 toxicities).

Results. A total of 53 (33 male and 20 female) patients were included in our analysis; median age was 59 years. 67.9% were treated with sunitinib, 24.5% with sorafenib and 7.5% with pazopanib. The ECOG-PS was 0 for 35 patients (66%), 1 for 14 (26.4%) and 2 for 2 (3.9%). The Motzer class was good in 28.3%, intermediate in 41.5% and poor in 3.8% According to Motzer classification the median OS was not reached in the good prognostic group; it was 25.1 months for intermediate-group and 1.9 months for poor-group (p = 0.022). Median PFS was 12.2 months. A total of 8 patients (15.1%) developed hypertension during the treatment, 17 (32.1%) developed hypothyroidism and 31 (58.5%) developed hand-foot syndrome. Based on toxicity, 74% of patients were in the low-toxicity group and 26% in the high-toxicity group. The median PFS for low-toxicity group was 8.7 compared to 29.2 months for high-toxicity group (p = 0.005). The median OS for low-toxicity group was 36.9 months while this was not reached in the high-toxicity group (p = 0.12). Cumulative toxicity was confirmed to be an independent predictive factor when compared to ECOG-PS (HR: 0.27, 95% CI 0.11-0.66; p = 0.005) or Motzer score (HR: 0.27, 95% CI 0.09-0.82; p = 0.021).

Conclusions. mRCC patients who experienced cumulative toxicity during first-line therapy with TKIs have longer PFS compared to those who did not. Cumulative toxicity was also found to be an independent predictive factor for PFS.

G25 PERIPHERAL NEUTROPHIL COUNT AND INFLAMMATORY SIGNS STRONGLY CORRELATE WITH OUTCOME IN PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (MCRPC)

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Introduction. Prostate cancer represents the most common malignancy in men. Preclinical and clinical evidence suggests that inflammation may play a role in the progression of many type of cancers, including prostate cancer. The aim of this study is to evaluate the association between different baseline patients characteristics (with focus on white blood cell count as inflammatory index) and outcome in patients with metastatic castration-resistant prostate cancer (mCRPC).

Material and methods. We retrospectively evaluated 46 consecutive mCRPC patients treated at our institution. All patients

underwent docetaxel plus prednisone front-line treatment. Baseline patients characteristics (peripheral neutrophil, lymphocyte and monocyte count as well as neutrophil-to-lymphocyte ratio, age, Gleason score (GS) and PSA) were collected from medical records. Median values of the different variables were considered as cut-off values. Our intent is to assess if these baseline characteristics are associated with first-line progression-free survival (PFS) and overall survival (OS). Kaplan-Meier curves and log-rank test were used for survival comparisons. Multivariate analysis was performed with the forward stepwise method. SPSS statistical package was used for statistical analysis.

Results. Median PFS and OS of the whole group were 8.16 and 34.97 months respectively. In our analysis lower neutrophil count is correlated with longer OS (34.97 vs 19.47 months; p = 0.016). So we developed a prognostic model based on neutrophil count and monocyte count and we found that the contemporary presence of high number of both neutrophils and monocytes significantly correlates with shorter PFS (p = 0.047) and OS (p = 0.013). Furthermore, we found that an elevate GS (a well-known prognostic factor) is associated with an higher peripheral neutrophil count (p = 0.029). Multivariate analysis confirmed the association between GS <9 and longer PFS (HR: 0.34, 95% CI 0.14-0.80; p = 0.01) and underlined the strong relation between a low neutrophil count and longer OS (HR: 0.09, 95% CI 0.01-0.74; p = 0.02).

Conclusions. The strong correlation between peripheral neutrophil count and both OS and GS underlines the role played by systemic inflammation in patients outcome. Additional studies should prospectively validate this model and should define clinical meaning and therapeutic implications of these data.

G26 PSA DECREASE DURING ENZALUTAMIDE TREATMENT IN CASTRATION-RESISTANT PROSTATE CANCER (CRPC) PATIENTS: RESULTS FROM NAME PATIENT PROGRAM (NPP) IN 4 ITALIAN INSTITUTIONS

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Background. Enzalutamide targets multiple steps in the androgen-receptor-signaling pathway, the major driver of prostate-cancer growth. Enzalutamide significantly prolonged the survival of CRPC pts after chemotherapy. Aim of this study is to investigate clinical activity of enzalutamide (reduction in PSA level ≥50% from baseline) in pts with CRPC progressing after docetaxel in NPP.

Patient and methods. Between September 2012 and April 2013, 66 pts with CRPC received enzalutamide in 4 Italian Institutions. Demographic characteristics, previous treatment history, extent of disease, PSA level at baseline, after 1 month and the best reduction in PSA level were collected in 36 patients. Treatment was continued until disease progression or unacceptable toxicity. Percentages and mean ± standard deviation are calculated for categorical and continuous variables respectively. The Fisher exact test is used to evaluate the association between the PSA reduction ≥50% and predictor variables.

Results. The median age was 74 years (range 55-86), 83% of the pts have an ECOG PS 0-1. Thirty-six percent of the pts had visceral disease; only 28% underwent radical prostatectomy and 31% adjuvant prostatectomy. Twenty-two out of thirty-six pts (61%) received only one line of hormonal therapy before docetaxel. Enzalutamide is administered at 160 mg daily orally to 44% of pts as second-line treatment, to 33% as third-line and to the remaining 23% as fourth-line. At baseline, the mean PSA level was 289 ng/mL (range 5.37-1540). After one month of enzalutamide treatment, 81% of pts achieved a reduction of PSA level, while 59% of pts obtained a PSA reduction ≥30%. The best value of PSA level was achieved after a median of 34 days. In our population, median PSA reduction was of 44% (range 0-98). A reduction ≥50% of PSA from baseline level was registered in 14/32 (44%) of patients. No unexpected adverse event (AE) and no grade 4 haematological or non-haematological toxicity were reported. The most common grade 1-2 non-haematological treatment-related AEs were fatigue (7/36) and hot flashes (4/36). At the time of analysis 11/36 pts discontinued enzalutamide for PD and 5/36 pts died.

Conclusions. In 44% of pts treated with enzalutamide in NPP a reduction ≥50% of PSA level was registered. A lower risk of progression disease (48% vs 78%) was observed in pts with PSA decline ≥50%, during enzalutamide treatment.

G27 ASSOCIATION OF A PANEL OF TISSUE BIOMARKERS EXPRESSION WITH SURVIVAL PARAMETERS IN TWO SUBSETS OF LOCALLY-ADVANCED AND METASTATIC UROTHELIAL CANCERS UNDERGOING PERI-OPERATIVE AND FIRST-LINE PLATINUM-BASED THERAPY

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Background. Progress in developing new effective treatments for urothelial carcinoma (UC) has been stagnant for more than 20 years. Information on the prognostic role of drugable pathways for selection and treatment of patients (pts) is needed.

Materials and methods. Samples from primary tumor and/or metastases were evaluated for expression of a panel of biomarkers (BMKs) by immunohistochemistry (IHC) including: ERCC1, EGFR, HER2/neu, VEGFR, PDGFR, p53, p63, cKIT, PTEN. Two cohorts were selected: pts with locally advanced (T2-4±N+M0) UC receiving peri-operative cisplatin-based chemotherapy (CT) (cohort 1) and metastatic pts receiving first-line platinum-based CT (cohort 2). IHC results were assessed according to standard protocols and dichotomized as positive (= 1+ for either ERCC1, EGFR or HER2/neu) or negative for study purposes. Tumor was deparaffinized and specific antigen retrieval determined for individual antibodies. Fisher exact test was

used to evaluate the association with response for pts with measurable disease. Cox regression model evaluated staining with PFS and OS in uni/multivariable analysis (UVA/MVA) controlled for prognostic variables [treatment setting, nodal status (cohort 1), Bajorin score (cohort 2)].

Results. From 03/2000 to 03/2013, 86 cases were retrieved (N = 30 in cohort 1 and N = 56 in cohort 2). Full panel was not available for all patients. Rates of staining positivity were: 37/63 (59%) ERCC1, 34/50 (68%) EGFR, 41/53 (77%) HER2/neu, 45/62 (72%) VEGFR, 11/56 (18%) PDGFR, 26/48 (54%) p53, 41/48 (85%) p63, 9/47 (19%) cKIT, and 11/38 (29%) PTEN. BMKs were uniformly distributed (p always >0.05) and no association between staining and response was found in assessable patients. Median follow-up was 29.5 mos (IQR: 12-51). Expression of PDGFR significantly associated with poorer PFS in UVA [HR: 3.70 (1.58-8.66), p = 0.0025] and MVA [HR: 2.90 (1.21-6.93), p = 0.0166]. P63 positivity associated with better OS in UVA [HR: 0.336 (0.12-0.88), p = 0.0280] and at the limit of significance in MVA [HR: 0.37 (0.13-1.05), p = 0.0626]. BMKs were independent each other and with clinical variables.

Conclusions. A significant proportion of UC pts harbor potentially drugable targets. Unclear information on how these signals affect prognosis compromise clinical translation. New signals were obtained in relation to prognosis of UC, partly discordant with available literature. Further studies are required to corroborate the clinical meaning of these BMKs.

G28 EVEROLIMUS AS SECOND-LINE THERAPY FOR METASTATIC RENAL CELL CARCINOMA. AN OBSERVATIONAL, RETROSPECTIVE STUDY FROM THE CAMPANIA REGION

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Background. Everolimus is approved for treatment of patients (pts) with metastatic renal cell carcinoma (mRCC) who have progressed on prior VEGFr-TKI (Vascular Endothelial Growth Factor receptor - Tyrosin Kinase Inhibitors) therapy. However, how a new drug is used in practice may not always reflect the way that drug was used on registrative, randomized study, potentially affecting its broad efficacy and safety profiles. Observational studies can provide valuable clinical information about the safety and effectiveness of cancer therapies and represent an additional, real-world source of clinical information.

Patients and methods. An observational, retrospective study conducted in Italy by 10 Centres from the Campania Region considered mRCC patients starting everolimus (Eve) immediately after failure of initial VEGFr-targeted therapy. Study endpoints were activity (according to RECIST 1.1), efficacy (progression-free survival-PFS: time from first dose to progression or death from any cause, estimated with the Kaplan-Meier method), and tolerability (adverse event type and grade according to CTC-AE v.3.0).

Results. One hundred pts, progressing after first-line sunitinib (99%) or pazopanib (1%) were recorded. Seventy-one were males and 29 were females, with median age 64 years (range: 41-75). Nineteen pts had a partial remission of disease, 62 had a disease stabilization, and 19 had a disease progression. Eighteen pts were still on Eve, 67 discontinued Eve for radiologic progression, 12 for clinical progression, and 3 because of untolerable toxicity. The median PFS estimate was 8 months (95% CI 6.7 to 9.3), with 26.3% of pts estimated to be free from progression at 12 months from Eve initiation. Grade ≥3 adverse events were stomatitis (11%), diarrhea (3%), hyperglycemia (2%), infection (2%), non-infectious pneumonia (2%), fatigue (2%).

Conclusions. Heeding the possible under-reporting by participating physicians in routine clinical practice, as compared with the randomized RECORD-1 trial, anyway Eve demonstrated a longer median treatment duration and a better safety profile than the pivotal phase 3 trial. The observed 8-month PFS and favourable safety profile were similar to those of the CHANGE Eve real-life study (median PFS: 7 months; Staehler, 2012). Thus, these results support the use of everolimus for patients with mRCC who have failed a single VEGFr-TKI.

G29 POOLED ANALYSIS OF EFFICACY OF SECOND-TO-THIRD LINE CHEMOTHERAPY NATIONWIDE FOR PATIENTS WITH ADVANCED TRANSITIONAL-CELL CARCINOMA (TCC)

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Background. Progress in developing new effective treatment and strategies in advanced TCC has been stagnant in the last decades. While upfront chemotherapy (CT) confers >50% RR, PFS and OS are still dismal. While vinflunine (V) is approved by the EMA for progressive TCC after platinum-based therapy, the US FDA has no approved agents.

Patients and methods. We retrospectively queried all pts receiving second- and third-line regimens in Italy in the time-frame 2003-2013. Inclusion criteria included failure of one or two prior CT regimens for metastatic disease and no exclusion of specific salvage regimens, including targeted agents. Distribution of treatments and outcome parameters were the primary endpoints.

Results. We identified a total of 160 eligible pts across 8 centers nationwide. Median age was 67 years (IQR 39-82), most frequent sites of disease at relapse were: nodes 71%, lung 29%, bone 26% and liver 19%. Median Bellmunt score (BS) available in 141/160 pts was 1, 62 pts (44%), 55 pts (39%), 19 (13%) and

5 pts (4%) had BS 0, 1, 2 and 3 respectively; median time-to-relapse to first-line was 2 months (95% CI 1.57-3.10). Regimens used as upfront CT were cisplatin-gemcitabine (CG) in 65 pts (41%), carboplatin-G in 50 pts (31%), MVAC in 25 pts (16%), and single-agent CT in 19 pts (12%). In second-line 42 pts (26%) received paclitaxel (P), 40 (25%) V, 21 pts (13%) pazopanib (PZP), 10 (6%) MVAC, 47 pts (29%) other drugs alone or combined. 75/160 pts (47%) received a third: 19 (25%) P, 15 (20%) PZP, 11 (15%) MVAC, 30 pts (40%) miscellaneous. Overall RR in second-line was 19% (CI 95% 13.1-24.8), 21% in third-line (95% CI 15.5-19.7%); median PFS was 2.8 (95% CI 2.30-3.13) and 2 months (95% CI 1.87-2.80) in second- and third-line respectively, median OS was 16 months (95% CI 14.8-17.6) and 20 months (95% CI 17.7-21.7), respectively. Patients treated with P and V in second-line showed a median PFS of 2.7 (95% CI 2.37-2.90) and 3.3 (95% CI 2.20-4.13) months while OS was 13.5 (95% CI 11.1-14.2) and 13.4 (95% CI 12.0-16.7) months respectively.

Conclusions. These findings aligned with published survival estimates of salvage therapies in the community oncology practice and underscored the need of a uniform approach to this disease. P and V were the most commonly used regimens, showing comparable results. Of note, almost half of pts received up to three lines of CT with not negligible responses. This cohort will serve to prospectively validate modern prognostic scores.

G30 SEQUENTIAL TARGETED THERAPY (TT) WITH SUNITINIB-SORAFENIB (SU-SO) VERSUS SORAFENIB-SUNITINIB (SO-SU) IN METASTATIC RENAL CELL CARCINOMA (MRCC): RESULTS FROM A LARGE SERIES OF PATIENTS

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Introduction. Up to now, there is no clear consensus on the most appropriate sequencing of drugs following disease progression in mRCC. This study was performed to investigate the correlation between progression-free survival (PFS) and overall survival (OS) in a consecutive series of mRCC pts treated with the sequence SU-SO versus SO-SU.

Methods. Characteristics and outcome of 125 pts affected by mRCC treated with SU-SO or SO-SU at the Istituto Nazionale Tumori in Milan were collected between November 2005 and January 2012. The Kaplan Meier curves were used to describe the survival distributions and the log-rank test to detect a statistical significance between survival distributions (p value <0.05); correlation between PFS and OS was measured with the Kendall's Tau non parametric index.

Results. The main characteristics of 104 (83.2%) pts treated with the SO-SU sequence were: ECOG PS 0/1/2 56 (53.8%)/47 (45.2%)/1 (1%); clear-cell histology 88 (84.6%); previous nephrectomy 98 (94.2%); according to Motzer criteria 38.5% were low risk, 53.9% intermediate risk and 7.7% poor risk. The main characteristics of 21 (16.8%) pts receiving SU-SO were: ECOG PS 0/1/2 10 (47.6%)/10 (47.6%)/1 (4.8 %); clear-cell histology 17 (81%); previous nephrectomy 20 (95.2%); according to Motzer criteria 14.3% were low risk, 61.9% intermediate risk and 23.8% poor risk. Median follow-up was 66.6 months (range 6-84) in the SO-SU arm and 37.1 months (range 4-60.1) in the SU-SO treatment. At the time of analysis 88/125 (70%) pts were dead and 98/125 (78%) pts reached the disease progression. No statistical difference in PFS was observed for the two treatment groups: median PFS for SO-SU was 26.1 months (95% CI 21.8-34.0), while for SU-SO was 20 months (95% CI 10.0-33.0); no statistical difference in OS was observed for the two treatment groups: median OS for SU-SO was 27 (95% CI 10.0-nd), while for SO-SU was 35.3 months (95% CI: 26-44.4). For both SO-SU and SU-SO treatment sequences a low positive correlation between PFS and OS was observed, respectively $\tau = 0.13$ and $\tau = 0.15$.

Conclusions. These data suggest that the sequence SO-SU compared to the sequence SU-SO has comparable efficacy in terms of PFS and OS. No strong evidence of a correlation between PFS and OS was demonstrated.

G31 DOCETAXEL (DOC) FOR TREATMENT OF YOUNG (<60 YEARS) CASTRATION RESISTANT PROSTATE CANCER (CRPC) PATIENTS. PRELIMINARY RESULTS OF AN ITALIAN MULTICENTER RETROSPECTIVE STUDY (CYCLOP STUDY) ON CLINICAL OUTCOMES (CO) AND PREDICTIVE FACTORS (PRE)

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Background. Prostate cancer is mainly diagnosed in pts over 65 yrs of age, so CRPC is rarely observed in pts ≤60 years. CO of these pts are not clearly defined but there is a common feeling of a worse prognosis for such younger pts. The present study is aimed to assess CO and PRE in this specific population.

Methods. In this multicentric retrospective study, after Ethical Committee approval, we have reviewed the clinical records of all ≤60 yrs CRPC pts from participating institutions, treated with DOC, both in clinical trials and in clinical practice. We recorded the pre- and post-DOC clinical history, the DOC treatment details and outcomes. We have also assessed the ability of a series of selected 18 clinical factors to predict DOC response through a logistic regression analysis. Continuous variables were categorized by quartiles and chosen for the initial model after a univariate chi-square analysis.

Results. To date we have collected a consecutive series of 114 pts from 19 Italian hospitals. The median age was 57 yrs (range 41-60). The median baseline PSA was 78.5 ng/mL (range 1-2721); 87% of the pts had bone metastases while 45%, 10%, and 14% showed nodal, liver and lung metastases, respectively. All but 10 pts received DOC with a 3-week standard schedule: the median number of received DOC courses was 8 (range 1-14). The main grade 3-4 toxicities were anemia (4 pts), neutropenia (16 pts), febrile neutropenia (1 pt), peripheral neuropathy (2 pts). A PSA reduction >50% was observed in 54% of the pts while

13% and 6% of the cases showed a partial and complete response, respectively. Having a Gleason score (GS) <8 [(exp(beta) 3.630; p = 0.029], a hemoglobin initial value >12 [(exp(beta) 2.881; p = 0.053], no nodal involvement [(exp(beta) 1.767; p = 0.141], resulted to be independently predictive of a PSA reduction >50%. The median PFS and OS were 7 mos and 21 mos, while the 1-year PFS and OS rates were 16.9% and 73.9%, respectively.

Conclusions. From these preliminary results, we failed to confirm a worse prognosis for younger CRPC since their survival outcomes are similar to those observed in the pivotal trials. Low GS, absence of nodal involvement and good hemoglobin levels are the only predictive factors. Data collection from other Hospitals is ongoing.

G32 CABAZITAXEL AND ABIRATERONE ACETATE IN METASTATIC DOCETAXEL-REFRACTORY CASTRATION-RESISTANT PROSTATE CANCER (MDR-CRPC): WHICH AGENT FIRST?

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Background. Cabazitaxel (Cbz) and abiraterone acetate (AA) are both efficacious treatment options for patients with progressive mDR-CRPC. However, no published data exist for patients treated with both these drugs to understand possible differences in treatment sequency. Aim of our study was to analyze data in a real world scenario.

Material and methods. An intention-to-treat (ITT) analysis of activity data deriving from all consecutive patients with mDR-CRPC treated in our Units with prednisone plus Cbz, AA or both was performed. Primary endpoint of the study was median progression-free survival (mPFS), evaluated according to Prostate Cancer Working Group 2 (PCWG2) criteria.

Results. Here we report characteristics and activity data of the first 62 patients analyzed: 7 treated with Cbz, 32 with AA and 16 with both drugs. The median age of our study population was 71.5 years (range 55-87), median Gleason Score 8 (range 4-9) and median ECOG PS 0 (range 0-3); visceral disease was present in 37 cases (59.7%). The mPFS, according to Kaplan Meier method (KM), was 4.7 months (mos) for patients treated with Cbz, 8.6 months for cases treated with AA and 8.2 mos for cases treated with both agents. Of the 16 patients treated with both drugs, 12 received a sequence Cbz-AA and 4 a sequence AA-Cbz for an overall median PFS of, respectively, 5.6 and 4.0 months.

Conclusions. In our limited experience, both Cbz and AA were confirmed as active drugs in the mDR-CRPC setting and seem to be active also when utilized sequentially. Of course, these data should be verified in prospective studies to avoid potential selection biases.

G33 PSA FLARE PHENOMENON IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER PATIENTS TREATED WITH CABAZITAXEL: A RETROSPECTIVE ANALYSIS OF OUR EXPERIENCE

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Background. "PSA flare" is an initial increase in serum PSA from baseline observed in about 20% of patients receiving chemotherapy for metastatic castration resistant prostate cancer (mCRPC). This phenomenon is described during the first 8 weeks of treatment and there seems to be no correlation with prognosis. Cabazitaxel (C) is a new taxane approved for the treatment of mCRPC patients progressed after or during a docetaxel (D) containing regimen. We evaluated the PSA flare incidence and trend in patients treated with C.

Patients and methods. Twenty-six patients with mCRPC treated with C (25 mg/m^2 every 3 weeks) were retrospectively analyzed. Patients characteristics and disease history were collected; PSA evaluation was performed before the start of chemotherapy and then every 3 weeks. Treatment response was evaluated according with the recommendations of Prostate Cancer Working Group 2 (PCWG2).

Results. Twenty patients received a C based chemotherapy as a second-line treatment (of these, 5 patients progressed during D treatment) and 6 patients received more than 2 chemotherapy lines before C. Patients median age was 69 years (60-79); ECOG PS was 0-1 in all patients. Metastatic disease involved only bone in 61.5%, bone and lymph nodes in 27%, bone, nodes and visceral tissues in 7.7%. Median number of C cycles administered were 5.7 (range 3-12). Chemotherapy is ongoing in 6 patients. Median PSA at the beginning of chemotherapy was 210 ng/dL (27-1407). We observed an initial PSA increase followed by a subsequent decrease only in 2 patients (7.7%). One patient developed a PSA flare (84.6 % compared to baseline) during the first cycle of chemotherapy; the duration was 6 weeks. In the other patient, PSA rose from baseline to a maximum of 52% at the sixth week of therapy. In this case the PSA drop occurred after 15 weeks.

Conclusions. Some Authors reported a PSA surge syndrome in about 16% of patients treated with C. In our experience PSA rise is lower, about 7% of patients and high PSA serum level was observed even after 12 weeks of treatment. C should not be withdrawn in case of an initial PSA rise. According to PSAWG2 recommendation, cytotoxic chemotherapy should be continued through early PSA rise for a minimum of 12 weeks unless other evidence of progression.

G34 TARGETED THERAPY (TT) FOR ADVANCED BELLINI DUCTS CARCINOMA: EFFICACY RESULTS IN A RETROSPECTIVE ANALYSIS

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Background. Collecting ducts carcinoma (CDC) is a rare and very aggressive renal pathology, affecting about 1% of the renal cell cancer (RCC) patients (pts). So far, only limited data are available to demonstrate efficacy of chemotherapy in the ad-

vanced setting. Aim of our study was to evaluate the efficacy of targeted therapy (TT) in advanced CDC.

Patients and methods. We retrospectively analysed data collected from medical charts of pts affected by advanced CDC, treated with TT at Istituto Nazionale Tumori of Milan. All patients underwent CT and bone scan before and after surgery. All pts received TT including sunitinib, sorafenib and temsirolimus. After starting therapy, radiological assessment was repeated every 2-3 months. Response to treatment was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Disease control was defined as the absence of progressive disease (PD).

Results. From December 2004 to April 2013, 499 patients with advanced renal cell carcinoma were treated at our Institution. Eleven pts (2%) had a histologically confirmed CDC. Median age was 57 years (range 33-79), males:females was 8:3. All pts were diagnosed with metastatic disease. Ten pts received total nephrectomy as first approach, only one resulted unsuitable for surgery and the diagnosis was made with a renal biopsy. At the beginning of the treatment, 5 pts presented an ECOG performance status (PS) 0, 3 pts had PS 1 and 3 pts PS 2. Two pts received temsirolimus, 6 pts sorafenib, 2 pts sunitinib and 1 pt received pazopanib as first-line treatment. Two pts, 1 treated with sorafenib and 1 with temsirolimus, achieved a disease control lasting 33 and 6 months respectively. At PD, these pts received a second line treatment with sunitinib, which added 10 and 9 months in terms of stable disease. Overall survival for these pts was 49 and 19 months, respectively. The remaining 7 pts experienced a rapid PD to first-line therapy, with an overall survival lasting 1 to 4 months. At the time of this analysis, 2 pts were still receiving sorafenib as first-line treatment. Treatment related adverse events (AEs) were manageable and consisted of fatigue, diarrhoea, hand-foot syndrome, hypertension and anemia. No patient discontinued therapy because of AEs.

Conclusions. TT may play a role in selected patients with advanced CDC. Further studies are promptly needed to identify biomarkers potentially predictive of response to TT.

G35 BRAIN METASTASES IN PATIENTS RECEIVING TARGET THERAPIES FOR ADVANCED RENAL CELL CARCINOMA AT MEDICAL ONCOLOGY UNIT OF BOLOGNA (S. ORSOLA-MALPIGHI HOSPITAL)

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Background. Treatment of metastatic renal cell carcinoma (mRCC) has really changed in the past few years thanks to target therapies (TKi). In the literature, brain metastases (BMs) are reported to occur in 2% to 17% of patients (pts) with mRCC. The aim of this analysis was to evaluate the incidence and characteristics of patients with brain metastases from RCC treated with target therapy.

Methods. From March 2007 to April 2013, 65 consecutive pts affected by mRCC were analyzed. Patients characteristics were: 53 (81.5 %) males, 12 (18.5%) females; median age 55 years (range 34-79); KPS 100 (range 60-100). A clear renal cell histology was observed in 59 (90.8%) pts, other histology in 6 (9.2%). Fifty-six (86.1 %) pts underwent surgery, 49 (75.4 %) pts were treated as first-line, and 16 (24.6 %) were pretreated. Median follow-up was 42 months (range 1-73).

Results. Four (6.1%) pts showed BMs at diagnosis, and 9 (13.8%) pts progressed with brain metastases; median time to unset was 14 months (range 6-27) from TKi start. Multiple BMs were observed in 2 (15.4%) pts, single lesion in 11 (84.6%) pts. Patients characteristics were: 13 (100%) males; median age 61 years (range 46-74), KPS 100 (range 60-100), clear renal cell histology 12 (92.3 %) pts, other histology 1 (7.7 %) patient. Twelve (92.3%) pts underwent nephrectomy and 11 (84.6%) pts showed lung metastases. Histology Fuhrman G3 was observed in 12 (92.3%) patients. In 5 (38.4%) pts BMs were symptomatic. Seven (53.8%) pts underwent Gamma-Knife treatment, 3 (23.1 %) external radiotherapy, 1 (7.7%) surgery and 2 (15.4 %) only antiedema therapy. Median overall survival was 20 months (range 3-68), with 6 (46.1%) pts alive. Using Kruskal Wallis Test, a statistically significant correlation was found between BMs and histology Fuhrman G3 ($p < 0.009$) and duration time of TKI treatment over 14 months ($p < 0.007$).

Conclusions. The occurrence of BMs during mRCC pts treatment is a significant event. The assessment of these pts requires systematic evaluation and CT-scan brain, particularly in pts with histology Fuhrman G3 and long time duration of TKi therapy.

G36 ABIRATERONE ACETATE IN CASTRATION-RESISTANT PROSTATE CANCER (CRPC) PATIENTS: PRELIMINARY EVALUATION OF CLINICAL ACTIVITY IN 3 ITALIAN INSTITUTIONS

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Background. Abiraterone acetate (AA) has demonstrated an interesting activity in clinical trials in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). AA significantly improved overall survival of mCRPC pts after chemotherapy.

Material and methods. Sixty-six pts with mCRPC received AA (1000 mg, orally once daily) plus prednisone (5 mg, orally twice daily) from 2011 to 2013 in 3 Italian Institutions. The aim of this study was to evaluate clinical activity of AA (time to progression and reduction in PSA level = 50% from baseline) in pts with mCRPC.

Results. At the time of AA beginning, median age was 79 years (54-86), median PS was 1 (0-2), median baseline PSA level was 118.65 ng/mL (range 2.98-7982.00); main sites of disease were: bone 59 pts (89%), lymph nodes 28 pts (43%), prostate 17 pts (26%), liver 6 pts (9%) and lung 5 pts (7%). All patients had received prior docetaxel; 25 pts received >2 lines of chemotherapy regimens. Median duration of treatment was 8.7 months (range 1.3-16.5). No G3-4 haematological toxicities have been observed. No G3 fluid retention or oedema or hypokalaemia or cardiac events were observed; grade 1 peripheral oedema accounted for most of these events. A G3 increased alanine aminotransferase (ALT) was observed in one patient, and in another patient an hemorrhagic gingivitis was reported. A confirmed PSA

levels decrease >50% was found in 35 pts (53%). According to RECIST criteria 4 out of 17 pts evaluable obtained a CR and 5 pts a PR. Median time to progression (PSA, objective or symptomatic) was 10.07 months (95% CI 9.92-10.21).

Conclusions. AA showed clinical activity (time to progression or reduction in PSA) in pts with mCRPC who had disease progression after docetaxel-based chemotherapy, with a low frequency of treatment-related side effects. For survival analysis the duration of follow-up was too short.

G37 SECOND-LINE TREATMENT IN METASTATIC PATIENTS WITH NON-CLEAR CELL RENAL CARCINOMA (NCC-RCC): RETROSPECTIVE ANALYSIS OF A 22 PATIENTS COHORT

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Background. Renal cell carcinoma (RCC) more than one single disease consists of various tumor types, each one with a different histology and clinical course. Histologies include clear cell, papillary types I/II, chromophobe, collecting duct and unclassified renal carcinoma. The sarcomatoid variant (SV) represents a phenotype of RCC that can be present in any subtype, usually showing an aggressive biological behavior. Patients with SV or Ncc-RCC have been included in RCC clinical trials, although such patients represent minority components. There is no specific recommendation for Ncc-RCC. First-line prospective dedicated studies are ongoing. No second-line data have been reported.

Methods. All pts with metastatic Ncc-RCC treated in first-line from 2007 to 2013 at our Institution were retrospectively analysed. Clinical data, prognosis classifications and treatments were assessed; PFS after first- and second- line treatments and OS were calculated.

Results. Twenty-two pts with metastatic Ncc-RCC were identified. Median age at diagnosis was 62, sex ratio 16M/6F. Histological subtypes were: papillary type I/II (39%), chromophobe (18%), unclassified (13%) and sarcomatoid (30%). Nephrectomy had been performed in 18 pts (82%). Most pts presented with synchronous metastatic disease (82%). Metastatic sites were respectively: lung 12 (55%), 17 lymph node (77%), 5 bone (23%), 6 liver (27%). Prognostic classification by MSKCC was good in 9, intermediate in 5 and poor in 8 patients. Median OS was 16.2 months, 9/22 pts are still alive. As first-line treatment, pts received: sunitinib (9), temsirolimus (7), sorafenib (3), pazopanib (1), bevacizumab based regimen (2). Median first-line PFS is 13.0 months. Eleven (50%) pts received a second-line treatment after first-line failure. Second-line treatment included VEGFR-TKI (9) including sunitinib (6), sorafenib (3) or mTOR inhibitor (2). Median second-line PFS is 16 months. Median PFS in papillary type I/II and chromophobe is 18 months and in unclassified and SV is 2 months.

Conclusions. This is a report on Ncc-RCC patients. Median second-line PFS is better in patients with papillary or chromophobe (16 months) than unclassified and SV (2 months). The optimal treatment approaches for patients with Ncc-RCC remain to be fully explored. Definitive recommendations will require subtype specific clinical trials or, lacking that, a registry of treatment results for patients with these relatively uncommon tumors.

G38 VERY OLD PATIENTS WITH METASTATIC RENAL CELL CARCINOMA TREATED WITH SUNITINIB: THE MAXIMUM TOLERATED OR THE MINIMUM EFFECTIVE DOSE?

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Background. Renal cell carcinoma (RCC) is the third most common genitourinary cancer. Sunitinib, an orally available tyrosine kinase inhibitor, is one of the main therapeutic first-line options for metastatic RCC patients. There is a lack of data about its use in patients older than 75 years, who are often excluded from studies for fear of serious toxicity without a survival benefit.

Methods. In our Institute, from 2008 to 2012, we enrolled 18 patients, median age was 77.6 years (range 71-88 yrs). 94% of pts had a clear cell carcinoma, 83% had a surgery on primary tumor, 22% had a metastatic disease at diagnosis and the median time to the onset of metastases was 13.2 months. All patients had 0-1 performance status and 72% of them received sunitinib as first-line treatment. Four pts started sunitinib with the standard dose of 50 mg/day at the known schedule but three of them reduced to 37.5 mg/day after the third cycle. Nine patients started at a personalized dose of 37.5 mg/day and six reduced the dose at 25 mg/day or modified the schedule. Five patients started with 25 mg and 2 of them continued the treatment at modified schedule. Median number of cycles administered was 9.5 (range 2-18).

Results. Eighteen patients were evaluable for objective response rate; overall response was 89% (16 pts) including 33% (6 pts) of partial response (PR), 39% (7 pts) of stable disease $\geq$6 months and 17% (3 pts) with a complete response. Progressive disease was observed only in 1 pt and the treatment was discontinued. Time to progression (TTP) was 19.6 months (95% CI 8.1-32.6). Overall survival was 33.9 months (95% CI 29.6-). The main toxicity requiring dose reduction or schedule modification was haematologic (46%) and was observed when standard or the first reduction dose was given; no toxicity more than G1 was observed in the group treated with the 25 mg/die dose level. No treatment interruption occurred with any dose.

Conclusions. Our results suggest that sunitinib in very old patients is associated with a TTP similar to those reported in the registration study and prolonged overall survival also with the 25 mg/day 4 weeks ON/2 weeks OFF schedule. Physiologic metabolic modification related to age could justify this trend. Although we need more data, nonetheless we have to hypothesize that a minimal dose can be therapeutic and it has to be considered as an effective option in very old patients with metastatic RCC.

G39 SORAFENIB-MEDIATED APOPTOSIS OF BLADDER CANCER CELLS REQUIRES TYROSINE PHOSPHATASE ACTIVATION

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Background. Sorafenib-induced apoptosis is inhibited by orthovanadate, a specific tyrosine phosphatase inhibitor, suggesting the existence of a cross-talk between tyrosine-kinases and -phosphatases in regulating sorafenib-mediated cancer cell death. Aim of our study was to evaluate the molecular mechanisms responsible for the pro-apoptotic effects induced by sorafenib in bladder cancer (BC) cell lines.

Patients and methods. The viability of BC cell lines was tested by MTT assay. Apoptosis was determined by Annexin-V/PI staining and cytofluorimetric analysis. The cathepsin B (CTB) activation was evaluated by western blot using an anti-CTB antibody (Ab); the CTB proteolytic activity was determined using the fluorogenic Z-Arg-Arg-AMC peptide and the fluorescence of the hydrolyzed 7-amino-4-methyl-coumarin was detected by a SpectraMax Gemini XPS microplate reader. Sorafenib-induced dephosphorylation was evaluated by immunoprecipitation and blotting on lysate from sorafenib-treated BC cells by using anti-CTB and pTyr Abs.

Results. We found that 20 mM of sorafenib strongly reduced the viability and induced time- and dose-dependent apoptosis of BC cells. Sorafenib by triggering tyrosine-dephosphorylation of CTB increased both its fragmentation and enzymatic activity. Finally, sorafenib-induced apoptosis was completely inhibited by a CTB inhibitor and sodium orthovanadate.

Conclusions. Sorafenib by triggering tyrosine-phosphatase activation stimulates CTB-dependent tyrosine dephosphorylation and apoptosis of BC cells. Overall, these results strongly suggest the tyrosine-phosphatases as novel targets in sorafenib-induced apoptotic cell death of BC cells.

G40 'EARLY' SECOND-LINE CHEMOTHERAPY WITH VINFLUNINE IN ADVANCED AND/OR METASTATIC TRANSITIONAL CELL CARCINOMA OF THE UROTHELIUM (TCCU): PRELIMINARY RESULTS OF AN ONGOING PROSPECTIVE PHASE II TRIAL

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Background. Vinflunine has recently been approved in Europe as monotherapy in patients (pts) with advanced TCCU who relapse after a first-platinum-based CT. Basing on clinical and biological considerations, the concept of 'anticipated' CT treatment before evident disease progression (PD) appears of interest. We designed a phase II study to assess activity and safety of vinflunine given as an 'early' second-line CT in this patients population.

Patients and methods. Seventeen consecutive pts were enrolled and treated: 70% were males, median age 56 years (range 44-77), ECOG PS ≤1 in 69% of pts, dominant visceral metastatic disease in 52% of pts, ≥3 metastatic sites in 41%. After 3-6 cycles (median 4) of cisplatin (or carboplatin) plus gemcitabine, pts were switched to 3-weekly vinflunine, regardless of the response to their first-line CT (PR in 23%, SD 59%, PD 18%). Starting dose was 320 mg/m^2 in all but one patient, who entered at 280 mg/m^2 because of bulky liver disease and previous pelvic radiotherapy. All pts were treated in the outpatient setting up to disease progression, intolerable toxicity or treatment refusal.

Results. A total of 121 cycles were given (median 6, range 4-9). The objective response rate (RR) of 47% was achieved, with 1 CR (in a woman with oligomestatic liver disease), 7 PR, and 6 SD lasting >16 weeks, for an overall CB rate of 82%. Median PFS was 6 months (range 4-9+). Vinflunine dose was reduced by 25% in 3 pts at the 3rd, 5th and 6th cycle due to G3 neutropenia; grade 3 constipation occurred in one patient at the 2nd cycle; other side effects were expected and manageable. No significant differences in the toxicity profile was observed in the 5 pts >70 years.

Conclusions. Our preliminary data confirm the clinical activity of vinflunine as second-line treatment for metastatic TCCU, also in pts with visceral and plurimetastatic disease, with globally acceptable toxicity. The ORR and PFS values we observed are encouraging, also suggesting an improved therapeutic index of the drug when given at an 'early' point of the sequential therapeutic strategy in such a disease setting. The accrual is in progress; a prospective analysis of quality of life and of factors potentially predictive of response is ongoing.

G41 BEST RESPONSE (BR) MAY BE PREDICTIVE OF PROGRESSION-FREE SURVIVAL (PFS) IN PATIENTS WITH METASTATIC RENAL CELL CANCER (MRCC) TREATED IN FIRST-LINE WITH TYROSINE KINASE INHIBITORS (TKI)

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Background. TKIs have quite recently brought innovation in the treatment of mRCC. Although their efficacy and tolerability have been proven in many trials, currently there is no certain data about predictive markers (both clinical and biological) of response. In this retrospective study we analyzed the correlation between BR and PFS in a cohort of patients subjected to first-line TKI treatment for mRCC.

Patients and methods. A 2-year follow-up was requested to enter the analysis. Between 2007 and 2011, 42 patients affected by mRCC started a first-line treatment in four hospitals in Palermo. Patients MSKCC risk groups were: good 9/42, moderate 25/42, poor 8/42. Patients received the following treatment: 36 patients received sunitinib, 6 patients received sorafenib. BR response was defined as the smallest diameter reached in tumor burden (TB) during the course of treatment. Kaplan-Meier survival and log rank test were performed using MedCalc® software.

Results. 7/42 patients were not evaluable for response as interrupted treatment due to inacceptable toxicity; 4/42 patients did

not respond to treatment at the time of the first evaluation, thus were not included in the analysis; 31/42 patients were evaluable for response and were included in the analysis. Analysis showed median PFS in PR group to be 22 months vs 8 months in SD group ($p = 0.0002$).

Conclusions. In our study, patients affected by mRCC experiencing PRs to TKI treatment in first-line appeared to have a better outcome in terms of PFS compared to patients experiencing SDs. These data do not reflect what we have seen in gastro-intestinal stromal tumors (GISTs). Although the treatment approach to GIST is very similar to mRCC, in the first case patients who experience PRs appear to have very similar outcomes to patients who experience SDs. Limits to this study are retrospectivity, small amount of cases, and short follow-up. Time-to-BR evaluation may improve the efficacy of the analysis. Also, it cannot be concluded that a longer PFS is associated to a longer OS. Further studies will certainly follow.

G42 METASTATIC RENAL CELL CARCINOMA TREATED WITH ANTI-ANGIOGENETIC THERAPY IN COMMON CLINICAL PRACTICE: A RETROSPECTIVELY MONOCENTRIC ANALYSIS FOCUS ON PATIENTS WITH POOR SURVIVAL

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Background. The development of anti-angiogenetic therapy produced a change in the treatment of metastatic renal cell cancer (mRCC). During the past decade, VEGF targeted therapies have become standard treatment. This study was aimed to analyze a population of mRCC treated with target therapies (TT) in common clinical practice.

Methods. We retrospectively analyzed data from the clinical records of 61 patients (pts) with mRCC treated with TT from February 2007 to April 2013 at Oncology Unit of Ferrara, especially focusing on characteristics of 17 pts with overall survival less than 1 year.

Results. Median age was 64 (range 40-81); 80.3% pts were male and 86.9% pts had undergone nephrectomy. Histology was clear cell (CC) in 90.2% patients. Median overall survival (mOS) was 22.4 months (range 1.2-114). ECOG performance status was ≥2 in 18% of pts; MSKCC risk score (54 evaluable pts) was poor in 14.8%, intermediate in 63% and good in 22.2% of patients. Eighteen pts (29.5%) had ≥3 metastatic sites. Considering 17 pts (27.8%) with OS less than 12 months compared with 44 pts (72.2%) with OS more than 12 months we observed a higher frequency of non-CC histology (23% vs 4.5%), ECOG PS ≥2 (35% vs 11.3%), MSKCC high risk (29% vs 6.8%), a higher frequency of pts who have not performed nephrectomy (23% vs 9%). Nine pts (52.9%) had ≥3 metastatic sites. Evaluating blood tests, we observed a higher frequency of anaemia (64.7% vs 38%) and neutrophilia (23.5% vs 11.9%); no significant difference in platelet count and hypercalcaemia. In the group of poor survival pts, sunitinib was first-line treatment in 16 pts (94.1%) and pazopanib in 1 pt (5.9%). Median progression-free survival (mPFS) was 4.4 months (range 0.72-10.8). Seven pts (41.2%) experimented disease progression or death after 1 cycle of therapy. Sunitinib was first-line treatment in all 5 pts with MSKCC high risk; mPFS was 2.4 months (range 0.4-4.1). Performing a multivariate analysis prior nephrectomy, CC histology, ECOG PS and MSKCC risk score confirmed to be independent prognostic factors.

Conclusions. Overall, the outcomes of pts treated in routine clinical practice were similar to comparable groups reported by literature. ECOG PS and MSKCC risk score confirmed to be the best predictors for the outcome, particularly in pts with poor survival. According to high variability of our results, more studies are needed in order to identify biologic markers predicting the response to targeted therapies.

G43 SAFETY AND EFFICACY OF ABIRATERONE ACETATE (AA) AND GNRH ANTAGONIST (DEGARELIX) IN PATIENTS WITH CASTRATION RESISTANT PROSTATE CANCER (CRPC): WORK IN PROGRESS

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Introduction. Abiraterone acetate (AA) is a potent and selective irreversible inhibitor of both 17-alpha-hydroxylase and C-17,20-lyase CYP17 activity, two critical enzymes in extragonadal and testicular androgen synthesis. Abiraterone treatment in non-castrate men showed that initial androgen suppression was soon overcome by a compensatory surge in luteinizing hormone. For this reason, the administration of AA has been associated with the use of GnRH agonists. GnRH antagonist bind directly to GnRH receptors and block the effect of GnRH on the pituitary, producing immediate suppression of LH, FSH and testosterone. The most common adverse events related to AA were hypertension and cardiac disorders; degarelix showed a better cardiovascular safety compared to GnRH agonists.

Materials and methods. Metastatic CRPC pts were enrolled in this study; at the time of writing the abstract nine pts were enrolled. AA 1000 mg per day and prednisone 5 mg bid were administered orally; degarelix is administered at a loading dose of 240 mg sc, subsequent to the maintenance dose of 80 mg sc monthly. Primary endpoints are to assess the amount of reduction of serum testosterone, monitoring the serum concentration of LH and the safety profile. The secondary endpoints are progression-free survival and PSA response.

Results. From April 2013 to date have been included in the study nine CRPC patients. Main pts characteristics were: median age 67 years (56-81); baseline mean PSA value 168 ng/mL (12-1000); baseline mean testosterone value 0.4 ng/mL (0.1-0.8); baseline mean LH value 1.2 mUI/mL (0.1-3). The most common sites for disease were bone (6 pts), lung (2 pts), lymph nodes (4 pts) and skin (1 pt). All patients were previously challenged with at least two chemotherapy regimens (docetaxel and cabazitaxel) and one hormone therapy. The most common cardiovascular comorbidities were hypertension (3 pts), cardiac ischemia (2 pts) and arhythmias (3 pts). To haematological monitoring after 15 and 30 days the PSA value was 80 ng/mL (6-600) and 50 ng/mL (4-420) respectively; the testosterone value was 0.1 ng/mL (0.01-0.2) and 0.01 ng/mL (0-0.1) respectively and LH value was 0.8 mUI/mL (0.1-1.2) and 0.3 mUI/mL (0.0-0.8) respectively.

Conclusions. The use of antagonists in combination with AA could guarantee an improvement in the therapeutic strategy of CRPC. Not the secondary is likely manageability of therapy especially for patients with significant cardiovascular comorbidities.

G44 ESTRAMUSTINE PLUS CHEMOTHERAPY IN ADVANCED REFRACTORY PROSTATIC CANCER (ARPC): A LOCAL EXPERIENCE

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Background. Metastatic prostate cancer progressive after first- or second-line antiandrogen treatment and after first-line chemotherapy with docetaxel has poor prognosis and remaining options are limited. The single agent activity of estramustine(EMP), vinorelbine(VNR), etoposide (ETO) and their combination are well established in ARPC. We therefore combine EMP with chemotherapy in patients (pts) with ARPC to determine the antitumor activity (response rate and clinical benefit) of oral EMP in combination with VNR and ETO or in combination with docetaxel (rechallenge). Secondary endpoints are time to tumor progression, duration of response and toxicity.

Material and methods. Sixteen pts with ARCP with bidimensional measurable or evaluable (biochemical progression) disease, performance status <2 and adequate haematological, hepatic and renal function have been treated between January 2004 and December 2011 with EMP 15 mg/kg, VNR 25 mg/m^2 day 1 and 8, ETO 100 mg/m^2 day 1, 2, 3 every 3 weeks or with docetaxel (at the same dosage) until disease progression or appearance of non-tolerable toxicity.

Results. Baseline data, activity data and toxicity are available in fifteen patients. Patients with median age 70 years (range 52-87) were treated for a median of six cycles (range 1-7). Nine pts had bone, 3 lymph nodes, 1 bone and lung metastases, 1 pelvic relapse and 5 biochemical (PSA) progression only. Decrease in PSA >80% was seen in 11 patients. Out of 11 pts with measurable disease, 1 had complete response, 5 had partial response and 2 had stable disease with clinical benefit (improvement in performance status, pain, feeling of well being). Three had early disease progression with death. The median PFS was 8 months and the median survival was 16 months. The haematological toxicity was moderate. Additional non-haematological toxicities experienced include mild asthenia, alopecia and stomatitis.

Conclusions. The present experience showed that EMP in combination with chemotherapy is an effective and well tolerated regimen in pts with ARPC previously treated with chemotherapy (at low economic price).

G45 CASTRATE LEVEL OF TESTOSTERONE (T), PATTERN OF PROGRESSION DURING CASTRATION WITH GNRH AGONISTS (A) AND RESCUE WITH GNRH ANTAGONIST DEGARELIX (D) IN PATIENTS WITH METASTATIC PROSTATE CANCER (MPC)

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Background. For years, treatment of pts with MPC has been T suppression with A. D offers an alternative to A, as previously shown (Klotz L, BJU Int, 2008; Crawford ED, J Urol, 2011). Compared with A in first-line, D resulted in faster PSA and T suppression, no surge or microsurges, improvement in PSA PFS, decreased risk of PSA failure in pts crossed over from A to D. Castration resistance (CR) is defined as a progressive disease with T at castrate level, historically <50 ng/dL. Although modern methods have shown median T level in surgical castrated men is 15 ng/dL, and <20 ng/dL has been recently proposed as new cut-off of efficient castration (Djavan B, BJU Int, 2012), pts with rising PSA during A, and T >20 and <50 ng/dL are considered castrate resistant, but they may still be responsive to a more efficient T ablation. Aim of this study was to evaluate modifications of PSA and T after switching from A to D pts with rising PSA and T <50 ng/dL.

Patients and methods. CR was defined as 3 consecutive rises in PSA during A, despite a T <50 ng/mL and after withdrawal of an anti-T if associated with A. After evidence of CR, we switched pts to D at dose of 240 mg (induction) and then 80 mg every month. PSA and T were measured baseline and after 3 mos. PSA response (PSAR): decrease >10%; PSA stabilization (PSAS): rise/decrease <10%, PSA progression (PSAP): rise >10%.

Results. From 10/2012, we enrolled 13 pts with MPC in progression to A and T <50 ng/dL. Median age 78 (65-86), median PS 1 (0-2), sites of metastases: bone 12, nodes 3, lung 2, local 2. In 11 evaluable pts (2 pts too early), baseline T was <20 ng/dL in 5 pts (45%) and >20 and <50 ng/dL in the remaining 6 pts (55%). After 3 mos of D, T was <20 ng/dL in all pts (100%). All 5 pts with baseline T <20 ng/dL progressed, whereas in the 6 pts with baseline T >20 and <50 ng/dL we observed 4 PSAR, 1 PSAS and 1 PSAP. Overall, 5 (45%) out of 11 pts with baseline T <50 ng/dL, considered castrate resistant to A, had a PSA control after switching to D.

Conclusions. In a very hard setting of pts, we confirm the most efficient T ablation and PSA control with D compared to A. Although T <50 ng/dL is still considered the threshold of efficient castration, <20 ng/dL seems a more realistic cut-off. Patients with T >20 and <50 ng/dL and rising PSA during A should be considered with caution because of a possible retention of sensitivity to a more profound T ablation.

G46 ABIRATERONE-BASED THERAPY IN METASTATIC CASTRATE-RESISTANT PROSTATE CANCER PATIENTS HEAVILY PRETREATED

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Background. The aim of this study was to evaluate the activity and tolerability of abiraterone acetate (AA) in patients with metastatic castrate-resistant prostate cancer (CRPC) previously treated with more than three lines of chemotherapy.

Material and methods. Patients received 1 g of AA (administered as four 250 mg tablets) orally once daily with prednisone in a dose of 5 mg orally twice daily. The primary endpoint was PSA response.

Results. Twenty-six patients were enrolled: a PSA response was observed in 16 patients (61.5%, 95% CI 0.41-0.81). Median

time to PSA progression was 7.3 months and after a median follow-up of 10.1 months all patients were alive. The treatment was generally well tolerated, side effects secondary to mineralocorticoid excess resulting from blockade of CYP17 were largely controlled with prednisone.

Conclusions. AA seems to be an effective and well-tolerated treatment option for patients with metastatic CRPC regardless of the number of chemotherapy lines previously administered.

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H1* FIRST-LINE PEMETREXED PLUS CISPLATIN FOLLOWED BY MAINTENANCE PEMETREXED VS CARBOPLATIN-PACLITAXEL PLUS BEVACIZUMAB FOLLOWED BY MAINTENANCE BEVACIZUMAB (ERACLE) IN ADVANCED NON-SQUAMOUS NSCLC: A QUALITY OF LIFE-ORIENTED, MULTICENTER RANDOMIZED PHASE III TRIAL OF THE GOIM (GRUPPO ONCOLOGICO ITALIA MERIDIONALE)

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Background. The role of chemotherapy (CT) for advanced NSCLC is debated and mainly palliative with similar results for efficacy and survival among different regimens. Histotype, maintenance therapy and quality of life (QoL) have been explored to improve the outcome of these patients (pts). Histology is crucial for the treatment choice. For large-cell and adenocarcinoma cisplatin (C) and pemetrexed (P) achieve better results while in pts with non-squamous (NS) NSCLC bevacizumab (Be) improves survival if added to carboplatin (Ca) and paclitaxel (T). Maintenance therapy has become a possible therapeutical option. As new strategies impact on safety and long-term outcome, a better knowledge of QoL could optimize the management of lung cancer patients. EQ-5D is a standardized QoL questionnaire to provide a simple measure of health for clinical and economic appraisal, consisting of a 5-domain and visual analogue scale (VAS). ERACLE trial, a randomized phase III study (NCT01303926), was designed to compare the QoL during the above mentioned first-line CT regimens.

Patients and methods. Patients with stage IIIB/IV NS-NSCLC (ECOG 0/1) were randomized (1:1) and stratified by Centre and disease stage. ARM A received 6 cycles of C (75 mg/m^2)-P(500 mg/m^2) q3w, followed by P maintenance at the same dose; ARM B received Ca AUC 6-T (200 mg/m$^{2)}$ plus Be (15 mg/kg) q3w for 6 cycles followed by Be maintenance. Co-primary endpoints were EQ5D Index (EQ5D-I) and EQ5D-VAS (Euro-QoL questionnaire) at baseline, after 3rd, 6th cycle and at 12th and 18th week during maintenance. Secondary endpoints were QoL over time, activity and safety of CT arms.

Results. From 1/2011 to 3/2012, 118 pts were enrolled. Demographics were well balanced; overall 74% male, 79% PS 0 and 94% stage IV. QoL results (mean change from baseline): EQ5D-VAS = 1.82 (95% CI 8.60-12.24; p = 0.73) and EQ5D-I = 0.15 (95% CI 0.01-0.29), were statistically significant in favour of ARM A if determined by EQ5D-I. Disease control rate was 88.3% in ARM A vs 78.6% in ARM B. PFS was superior in ARM A (HR 0.62, p = 0.03).

Conclusions. A significantly better health profile by EQ5D-I was observed in ARM A at 12 weeks as compared to ARM B. No significant difference was seen by EQ5D-VAS between arms. Time-to-event analysis showed a better outcome for ARM A while toxicity was as expected. A reliable QoL assessment is important and strongly suggested in clinical trials evaluating maintenance therapy in lung cancer patients.

H2* BIOMARKER ANALYSES FROM THE RANDOMIZED PHASE III TORCH TRIAL OF FIRST-LINE ERLOTINIB FOLLOWED BY SECOND-LINE CISPLATIN/GEMCITABINE (CG) VERSUS FIRST-LINE CG FOLLOWED BY SECOND-LINE ERLOTINIB IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS

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Background. TORCH was a randomized phase 3 trial comparing first-line erlotinib followed at progression by cisplatin/gemcitabine vs the standard reverse sequence in unselected pts with advanced NSCLC. Overall survival (OS) was the primary endpoint; 900 pts were planned. The study was terminated early, after the accrual of 760 pts, because the first interim analysis showed inferiority of the experimental arm. Tumor samples, available for 317 (41.7%) cases, were analysed for *EGFR* activating mutations, *KRAS* mutations and *EGFR* gene copy number (GCN).

Patients and methods. *EGFR* exon19 deletions were identified using PCR fragment analysis on macro-dissection enriched tumor DNA, with positive cases confirmed by sequencing. *EGFR* exon 21 and *KRAS* codons 12/13 were analysed by sequencing. Mutations were confirmed in independent PCR products and *EGFR*L858R negative cases were confirmed further by MassARRAY (Sequenom). *EGFR* GCN was evaluated by FISH and classified by Colorado system.

Results. Results of *EGFR* and *KRAS* mutational status and *EGFR* GCN were available for 275 (36.2%), 276 (36.3%) and 196 (25.8%) patients, respectively. Mutations were found in 14.2% for *EGFR* and 26.4% for *KRAS*; 52.0% of pts had high *EGFR* GCN tumors. No significant imbalances between arms were noted. *EGFR* mutations were significantly more common among females, East Asians and never smokers. *KRAS* mutations

were less common among never smokers. There was no interaction between any biomarker and treatment efficacy for OS. For progression-free survival (PFS) and objective response with first-line treatment, only *EGFR* mutations, but neither *KRAS* mutations nor *EGFR* GCN showed significant interaction with treatment. Patients with *EGFR* mutations had improved first-line PFS with erlotinib (HR 0.60, 95% CI 0.30-1.20) compared to *EGFR* wild type (WT) patients (HR 2.07, 95% CI 1.58-2.71; interaction p = 0.006). Response rate was 25% with first-line chemotherapy in both *EGFR* WT and mutated pts, while response with first-line erlotinib was 5% and 42%, respectively. Among *EGFR* wild-type patients with known *EGFR* GCN, there was no interaction between *EGFR* GCN and treatment efficacy.

Conclusions. Patients with EGFR mutation can be effectively treated by erlotinib followed by second-line chemotherapy, while *EGFR* wild-type patients derive a detriment from this sequence. *KRAS* mutations and *EGFR* gene copy number did not show a significant interaction with the efficacy of the two treatment sequences tested.

H3* TREATMENT DECISIONS FOR ELDERLY PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) IN ITALIAN CLINICAL PRACTICE: RESULTS FROM THE RIGHT3 PROJECT BY ITALIAN ASSOCIATION OF MEDICAL ONCOLOGY (AIOM)

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Background. In 2004, Italian Association of Medical Oncology (AIOM) created the RIGHT (Research for the identification of the most effective and highly accepted clinical guidelines for cancer treatment) program. The third step of the program, RIGHT3, aimed to evaluate the concordance between AIOM lung cancer guidelines and clinical practice in Italy. Description of treatment decisions for elderly patients with advanced non-small cell lung cancer (NSCLC) was among the indicators. According to 2009 AIOM guidelines, single-agent chemotherapy with a third-generation agent was a reasonable choice for elderly patients with advanced NSCLC, whilst evidence about use of platinum-based treatment in the elderly population was judged potentially affected by selection bias and not conclusive.

Materials and methods. RIGHT3 was a retrospective observational study conducted in a sample of 53 Italian lung cancer centers, representative of 230 AIOM centers. Patients with NSCLC diagnosis who had their first visit at the oncology center during 2010 and followed-up for at least 6 months were included. Proportion of elderly patients with stage IV disease receiving chemotherapy was among the 14 indicators evaluated.

Results. Overall, 306 pts with stage IV NSLSC were enrolled, and 299 were evaluable. Of these, 91 (30.4%) were older than 70. In the elderly subgroup, 81 pts (89%) were treated with first-line chemotherapy. In detail, a single-agent treatment was administered in 28 (34.6%) cases, and a combination chemotherapy in the other 53 cases (65.4%). Among pts receiving platinum-containing doublets, carboplatin was more frequently used than cisplatin: carbo-gemcitabine (16 pts), carbo-pemetrexed (12 pts), cisplatin-pemetrexed (8 pts), cisplatin-gemcitabine (7 pts), carbo-vinorelbine (4 pts) were the 5 most frequently used regimens. Thirty pts (33%) received a second-line chemotherapy: single-agent in 23 cases, combination chemotherapy in 7 cases.

Conclusions. First-line platinum-based combination chemotherapy was commonly used in elderly patients with advanced NSCLC in 2010 by the Italian Lung cancer centers involved. First-line single-agent treatment, recommended by AIOM 2009 guidelines as the treatment choice with highest level of evidence, was used only in a minority of patients.

H4* PRETREATMENT EVALUATION OF T790M MUTATION AND ITS CORRELATION WITH RESPONSE TO TYROSINE KINASE INHIBITORS (TKIS) OR CHEMOTHERAPY IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS WITH ACTIVATED EGFR MUTATIONS

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Background. Preclinical data have shown that the T790M mutation confers resistance to reversible TKIs (gefitinib, erlotinib) but not to irreversible TKI (afatinib).

Aim. The aim of this study was to investigate, in advanced NSCLC patients harboring an activated EGFR mutation, the correlation between T790M mutation and the clinical outcome in patients positive for T790M mutation treated with reversible TKIs (erlotinib, gefitinib) or irreversible TK-I (afatinib) or chemotherapy compared to patients negative for T790M mutation treated with the same agents.

Patients and method. We screened 317 patients (pts) for EGFR mutations using PCR/sequencing method. The tumor tissue of EGFR mutated patients was analyzed for T790M mutation using a highly sensitive LNA-PCR/sequencing method. Response to treatment (RR), progression-free survival (PFS) and overall survival (OS) were evaluated retrospectively in these patients.

Results. Using standard procedure 49 pts (15.4%) had an activating EGFR-mutation on exon 19 or 21, 2 pts (0.6%) had an insertion on exon 20 and 4 pts (1.2%) had both exon 19 or 21 mutation and the T790M mutation. Forty-two out of 51 patients with EGFR mutations (82.3%) were successfully analyzed for T790M mutation using LNA-PCR/sequencing method. The T790M mutation was detected in 17 (40.5%) pts with higher incidence in never or former smokers, adenocarcinoma and female. Data analysis was feasible in 39 pts, 18 (46.1%) pts with the T790M mutation. In our study, pts mutated for T790M had lower RR (22.2%) to TKIs than those wild-type for T790M (33.3%) but had longer PFS and OS (median PFS 7.9 months vs 7 months, re-

spectively; median OS 16.1 months vs 11.14 months, respectively). Patients positive for T790M were sensitive to afatinib and obtained better PFS compared to patients negative for T790M (median PFS 4.7 months vs 3.15 months, respectively) but on the contrary the OS was lower (median OS, 16.29 months vs 18.15 months, respectively). Notably, pts with T790M mutation had more response to chemotherapy (44.4%) compared to pts without T790M mutation (18.2%) and had longer PFS (median PFS 8.17 months vs 6.1 months, respectively) and OS (median OS 21.8 months vs 12.4 months, respectively).

Conclusions. The pre-treatment T790M mutation in NSCLC pts with EGFR-activating mutations may be more common than expected using high sensitivity methods and identifies a subset of patients with a relatively more favorable prognosis.

H5* DIFFERENT MICRO-RNA EXPRESSION IN LUNG ADENOCARCINOMA WITH MOLECULAR DRIVER EVENTS

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Background. Oncogenic driver alterations identify several types of lung adenocarcinoma with different prognosis and sensitivity to targeted agents. MicroRNAs (miRNAs) are a new class of non-coding RNAs involved in gene expression regulation. How miRNAs are dysregulated in lung cancer with ALK translocation, EGFR or KRAS mutation is largely unknown.

Aim. In the present study we aimed to investigate miRNAs expression according to the presence of specific molecular driver and to correlate miRNAs deregulation with patient outcome.

Material and methods. The study was conducted in a cohort of 67 lung adenocarcinoma patients (pts) including 17 ALK+ tumors, 11 ALK-/EGFR mutation+, 15 ALK-/KRAS mutation+, 24 ALK-/EGFR and KRAS wild-type and defined as triple negative cases. Matched normal lung tissues from 18 cases representative of the entire cohort were also included onto the analysis. RNA was isolated from formalin-fixed paraffin-embedded tissue (FFPE), using the Recover ALL kit (Ambion). NanoString nCounter system platform was used to generate the miRNA profile. We used Limma to test for differential expression analysis of data. Among the miRNAs evaluated, the miR-515 family expression between tissues was validated by RT-qPCRs, analyzed using the parametric t-test (unpaired, 2-tailed for validation).

Results. miRNA expression profile clusters distinctly ALK+ pts from ALK- and normal lung tissue. Within the ALK- group we found specific miRNAs subsets able to sub-stratify KRAS versus EGFR careers clustering sharply triple negative versus EGFR mutation+ and triple negative versus KRAS mutation+. miRNAs belonging to the miR-515 family seems to be the most deregulated in the ALK+ versus ALK-. Although their expression is stably high in normal tissues and ALK+ class, they are highly downregulated in KRAS mutated versus EGFR mutated and versus triple negative (p value <0.001 for all comparisons).

Conclusions. miRNAs profile significantly differs in lung cancer pts with ALK translocation, EGFR mutations and KRAS mutations. Putative targets of deregulated miRNAs are under investigation to better define differences in driver-dependent pathway activation.

H6 BEYOND THE EPIDERMAL GROWTH FACTOR MUTATION: DO WE HAVE RELIABLE FACTORS TO PREDICT THE OUTCOME OF PATIENTS WITH LUNG ADENOCARCINOMA RECEIVING FIRST-LINE TYROSINE KINASE INHIBITORS? A SENSITIVITY AND META-REGRESSION ANALYSIS OF RANDOMIZED TRIALS

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Background. It has been widely demonstrated that activating mutations of the epidermal growth factor receptor (EGFR) identify a non-small cell lung cancer (NSCLC) patients population with a peculiar sensitivity to EGFR tyrosine kinase inhibitors (TKIs). These agents, rightly applied in this featured molecular context, are demonstrated to significantly improve responses and progression-free survival (PFS) in comparison with chemotherapy, radically changing the prognostic expectancy of those patients harboring this 'druggable' genetic alteration. However, beyond the well validated predictive role of the EGFR mutation, the rationale of a further 'super-selection' of the EGFR mutant patients, on the basis of other demographic and molecular factors to implement the awaited TKIs benefit, deserves to be clarified.

Methods. We conducted a literature-based meta-regression and sensitivity analyses to investigate the differential effect of TKIs according to demographic and molecular factors, analyzing all the randomized clinical trials (RCTs) exploring the benefit of TKIs versus chemotherapy in the first-line treatment of patients affected by EGFR mutant NSCLC.

Results. Eight trials (3,377 patients) were identified (data on the EGFR mutant population were reported for 1,433 patients). Eight RCTs were evaluable for PFS (1,416 patients) and response (1,359 patients); 7 out of 8 for survival (1,075 patients). With regard to PFS, a significant interaction according to ethnicity (Asian versus Caucasian versus mixed) and to drug (gefitinib versus erlotinib versus afatinib), was found (Q 7.979, $p = 0.019$ and Q 9.943 $p = 0.007$); a trend towards significance according to trial design (retrospective versus prospective EGFR analysis) was determined (Q 3.287, $p = 0.07$). With regard to response, a significant interaction according to ethnicity (Q 7.701, $p = 0.021$), to trial design (Q 10.760, $p = 0.001$) and to type of drug (Q 6.508, $p = 0.039$), was found. No difference was observed in term of survival. Although limited by a significant heterogeneity and their retrospective nature, these data suggest the existence of a differential effect in terms of both PFS and response of TKIs according to potential predictive factors.

Conclusions. These results support the rationale to create a clinical-pathologic predictive model, potentially able to further tailor the therapeutic approach, increasing the magnitude of bene-

fit expected from the use of EGFR TKIs in patients with EGFR mutant NSCLC.

H7 INDIRECT COMPARISONS OF HARM/BENEFIT PROFILE OF EGFR TYROSINE KINASE INHIBITORS AS FIRST-LINE TREATMENT IN EGFR MUTATED NSCLC PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background. To date, three EGFR tyrosine kinase inhibitors (TKIs) gefitinib (G), erlotinib (E) and afatinib (A) have been compared to standard chemotherapy as first-line treatment in patients with advanced NSCLC harboring EGFR mutations. We performed a systematic review and meta -analysis in order to estimate through indirect comparisons the relative risk benefit associated to each drug.

Material and methods. The major databases were searched for published and unpublished randomized control trial up to March 2013. Data extraction was performed by two independent reviewers and focused on benefit (ORR, PFS) and selected harm outcomes (diarrhea, rash, nail disorders, hypertransaminasemia). The adjusted indirect comparisons were performed using the random effect method described by Bucher and Glenny approach for hazard ratio (HR) for PFS and relative risk (RR) for the other outcome measures.

Results. All EGFR TKIs fared better when compared with chemotherapy in terms of PFS: overall HR 0.40 (95% CI 0.30-0.54); G vs E HR 1.34 (95% CI 0.63-2.86), G vs A HR 0.74 (95% CI 0.53-1.04), E vs A HR 0.55 (95% CI 0.31-0.99). The relative probability of ORR was G vs E 0.96 (95% CI 0.69-1.34), G vs A 0.79 (95% CI 0.49-1.28), E vs A 0.82 (95% CI 0.49-1.38). Indirect comparisons for safety showed RR for diarrhea G vs E 0.8 (95% CI 0.63-1.01), G vs A 0.32 (95% CI 0.20-0.51), E vs A 0.38 (95% CI 0.24-0.62); for rash G vs E 1.0 (95% CI 0.82-1.22), G vs A 0.31 (95% CI 0.15-0.65), E vs A 0.31 (95% CI 0.15-0.65); for hypertransaminasemia G vs E 2.29 (95% CI 1.63-3.23). Nail disorders affected 57% of patients treated with A, 15% with G, and 4% with E.

Conclusions. Results of our analysis showed that all treatments have similar activity and efficacy while the toxicity profile was less favorable for A with a significant higher risk of diarrhea, rash, and nail disorders. Based on these safety results, we suggest that A may not be the first choice for upfront treatment in EGFR mutated patients. Confirmation is warranted by ongoing prospective head to head RCTs.

H8 AFATINIB IN EGFR MUTANT LUNG CANCER PATIENTS WITH ACQUIRED RESISTANCE TO REVERSIBLE EGFR-TKIS

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Background. Afatinib, an irreversible EGFR-HER2 dual inhibitor, demonstrated superiority versus standard platinum-based chemotherapy as front-line therapy in non-small cell lung cancer patients (NSCLC) harboring activating epidermal growth factor receptor (EGFR) mutations. In pretreated NSCLC, afatinib failed to improve survival when compared to placebo in patients refractory to gefitinib or erlotinib not selected for EGFR status. Aim of the present study was to assess clinical efficacy of afatinib in EGFR mutant NSCLC with acquired resistance to reversible EGFR-TKIs.

Materials and methods. We analyzed a cohort of 97 EGFR mutant lung patients (pts) resistant to EGFR-TKI according to criteria used in the LUX-Lung 1 trial (Miller VA, Lancet Oncol, 2012) and treated with afatinib at the daily dose of 40-50 mg in 12 Italian centers. The drug was given as compassionate use.

Results. The study included individuals with a median age of 62.5 years. The majority were females (N = 63/64.9%), never/former smokers (N = 94/96.9%), with good PS (0-1; N = 90/90.2%) and pretreated with >3 therapy lines (N = 68/70.0%). EGFR status was assessed in tumor tissue obtained at the time of original diagnosis and the majority (N = 64, 66%) harbored a exon 19 deletion. T790M mutation was detected in two cases, including one case with double exon19 and T790M mutation. Among the 95 pts evaluable for toxicity, 54.7% had any grade skin rash, including 11.6% with grade 3, and 50.5% had any grade of diarrhea, with grade 3 recorded in 10.5%. Among the 85 pts evaluable for efficacy, response rate (RR) was 10.6%, with a median progression-free survival and overall survival of 3.9 months and 7.3 months respectively. In 25 pts a tumor biopsy was repeated immediately before starting afatinib therapy and 1 patient out of 5 individuals harboring T790M mutation showed a short extracerebral partial response, with following brain progression.

Conclusions. Our findings suggest that afatinib is modestly effective in EGFR mutant NSCLC with acquired resistance to reversible EGFR-TKIs.

H9 GENE MUTATIONS IN SMALL CELL LUNG CANCER (SCLC) IN AN ITALIAN COHORT OF PATIENTS: EGFR AND MET AS POTENTIAL TARGETS IN LIMITED NUMBER OF PATIENTS

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Background. SCLC accounts for 13-15% of lung cancers. Chemotherapy plays the leading role in the treatment of this cancer type and no target therapies are presently available. We investigated a retrospective series of SCLC for the presence of mutations in the EGFR, MET, BRAF, KRAS, and c-KIT genes and we evaluated correlations with immune-histochemical, clinical and outcome features.

Materials and methods. Molecular analysis by direct sequencing method was carried out on formalin-fixed paraffin-embedded surgical samples and biopsies of patients affected by SCLC collected from 2 Italian Institutions. EGFR, MET, BRAF, KRAS, c-KIT gene mutations were analyzed. Immunohistochemical expression of TTF-1, p63, chromogranin, synaptophysin, CD56 and bcl-2 were also assessed.

Results. We analyzed tissue samples from 113 SCLC patients. Of these, 85 (75.2%) were males; only 3 patients (2.7%) had not-smoking history; 74 patients (65.5%) had extensive disease (ED); 107 (94.7%) and 35 (31%) patients received chemotherapy or chemo-radiotherapy, respectively. Overall, patients showed 63.5% and 35.6% of 3- and 6-months response rate (RR), respectively. Time to progression (TTP) and overall survival (OS) were 6 and 11 months, respectively. All cases were wild-type for BRAF, KRAS and c-KIT (data available for 82 patients). Two (1.8%) patients resulted EGFR-mutated (exon 19 delE746-A750 and exon 21 L858R); both were females, non-smoker and had limited disease (LD). OS of EGFR-mutated patients was 21 as compared to 11 months in wild-type ($p = 0.577$). Five (4.4%) patients were MET-mutated (4 on exon 14: 2 R988C, 1 D990N, 1 D102Y; 1 on exon 17 R1166Q); all were smokers, 3 (60%) were males and 4 (80%) had ED. OS was comparable in MET-mutated and wild-type cases (12 vs 11 months, $p = 0.441$). EGFR and MET mutations were mutually exclusive. No significant correlation was found between mutations and immunohistochemical profile.

Conclusions. Targetable mutations are uncommon in SCLC. EGFR-mutated patients were more likely to be female and non-smoker, and experienced a prolonged OS suggesting a possible positive prognostic effect. MET mutations did not affect survival. Data should be evaluated prospectively in a large cohort of patients, considering a target therapy in EGFR and MET-mutated patients.

H10 DOES KRAS MUTATIONAL STATUS PREDICT FOR CHEMORESISTANCE IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)?

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Background. Clinical implications of KRAS mutation status in advanced NSCLC remain unclear. While KRAS mutations seem to be correlated with resistance to EGFR TKIs (tyrosine kinase inhibitors), their role in predicting benefit from chemotherapy (CT) is still debated. To clarify this point, we retrospectively explored whether KRAS mutations could impact on tumor response, disease control rate (DCR) to first- and second-line CT as well as on progression-free survival (PFS) or overall survival (OS).

Methods. Between June 2009 and June 2012, 340 patients with advanced (stage IIIB/IV) NSCLC were retrospectively reviewed in a single institution (Institut Gustave Roussy). Two hundred and one patients had a biomolecular profile and a platinum-based first-line CT. Patients with NSCLC and an unknown mutational status or with targetable abnormalities (i.e. EGFR, PI3K, HER2, BRAF, FGFR4, ERBB4, PTEN, NRAS, or STK11 mutations; as well as HER2, FGFR1, or MET amplification; ALK translocation), were excluded. We retained two groups: patients with tumors bearing an exclusive KRAS mutation (MUT) and patients with wild-type KRAS and wild-type EGFR (WT). Multivariate analyses with logistic or Cox model were used. Survival curves were calculated with Kaplan-Maier method.

Results. One hundred and eight patients were included in the analysis: 39 in MUT group and 69 in the WT group. Baseline radiological assessment demonstrated more brain and liver metastases in MUT patients (33% vs 13%; $p = 0.01$; 21% vs 7%; $p = 0.04$). DCR in first-line CT was 76% for MUT vs 91% for WT group ($p = 0.04$, in uni and multivariate analysis), regardless the type of platinum-based CT (use of pemetrexed or not). In second-line setting, no difference in DCR was observed ($p = 0.32$) between the two groups. Although no statistically significant differences were found, a slightly shorter PFS (4.8 vs 7.3 months; $p = 0.27$) and OS (10.3 vs 13.2 months; $p = 0.37$) were observed for patients with KRAS mutant tumor.

Conclusion. In all, NSCLC patients with KRAS mutant tumor had a lower DCR after the first-line platinum-based CT, but this difference did not translate in PFS or OS differences in multivariate analysis. The presence of KRAS mutations may configure a more aggressive disease, with greater baseline incidence of hepatic and cerebral metastases.

H11 HER-2 AMPLIFICATION OCCURS IN EGFR-MUTANT LUNG ADENOCARCINOMA WITH ACQUIRED RESISTANCE TO EGFR-TKIS

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Background. Patients with EFR-mutant lung adenocarcinoma develop progression of disease on TKIs therapy after a median of 12 months; this acquired resistance is mainly due to a secondary mutation in EGFR (T790 M) in about 50% of patients, amplification of MET in 15%, PIK3CA mutations in 5%, an unknown mechanism in almost 30% and a SCLC transformation in some patients. Recently, Takezawa et al. pointed-out that HER-2 amplification is a mechanism of acquired resistance to EGFR inhibition in EGFR mutant lung cancers without EGFR T790M mutation. To aid in identification and treatment of these patients we examined a cohort of patients whose cancers were assessed with tumor biopsies at multiple times before and after their treatment with TKIs.

Methods. Forty-one lung adenocarcinomas pts (20 male, 21 female, median age 55 years) with EGFR mutations at 19 or 21 exons received TKIs as first-line of treatment. Thirty-one pts (75%) showed a clinical response and relapsed after a mTTP of

12 months. At the time of relapse a new biopsy was performed, histologic samples were reviewed to re-confirm the diagnosis, EGFR, MET and HER-2 amplification were identified by FISH, while EGFR mutations have been tested by DNA sequencing.

Results. At the time that drug resistance was acquired all 31 pts retained their original activating EGFR mutations, 16 pts developed EGFR T790M resistance mutation with pronounced EGFR amplification in 5, 4 pts developed MET amplification, three were found to have a diagnosis of small cell lung cancer. HER-2 amplification was observed in four pts (13%), with dramatic progression and a median OS of 5 months after treatment with CDDP + pemetrexed. Notably all 4 cases were EGFR T790M negative.

Conclusions. Among pts with acquired resistance to EGFR TKIs the presence of HER-2 amplification defines a clinical subset with a more adverse prognosis and rapid progression. Interestingly, recent data suggest that afatinib combined with cetuximab could have promising activity in pts with acquired resistance due to HER-2 amplification.

H12 DETECTION AND FGFR1 GENE COPY ASSESSMENT OF CIRCULATING TUMOUR CELLS (CTCS) IN ADVANCED SQUAMOUS-CELL LUNG CARCINOMA

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Introduction. Although recent studies evaluated the role of novel biomarkers in squamous-cell lung carcinoma (SQCLC), few data are available on the detection and characterization of CTCs in this non-small cell lung cancer (NSCLC) subtype. Fibroblast growth factor receptor 1 (FGFR1) gene amplification has been documented by fluorescence in situ hybridization (FISH) in about 20% of SQCLC tissue samples, however, this analysis on CTCs is unreported. This study aimed at evaluating the incidence of CTCs on patients with advanced SQCLC based on FGFR1 gene amplification.

Methods. CTCs were isolated from blood samples in patients with SQCLC and in a control group with advanced lung adenocarcinoma (ADK), by using a non-epithelial cell adhesion molecule (EpCAM)-based capture method (AutoMACS, Miltenyi Biotec, Bergisch Gladbach, Germany) and an EpCAM-based technology (CellSearch, Veridex, Raritan, NJ). FGFR1gene copy number was evaluated by FISH using a break-apart FGFR1/CEN8 FISH probe set (Cytocell Aquarius, Cambridge, UK) on CTCs and on corresponding primary tumor when available.

Results. CTCs were detected in 24/26 (92%) SQCLC and in 8/10 (80%) ADK patients with non-EpCAM method. Sixteen of the 24 (67%) SQCLC and 5 of the 8 (63%) ADK CTC positive cases had a CTC count 5 (CTC count range: 1-46 in SQCLC and 1-30 in ADK). Only 2 out of 22 (9%) SQCLC and 1 out of 8 (12%) ADK samples were found positive for CTC using Veridex technology. According to FGFR1 asset, we found that 92% of SQCLC and 100% of ADK had ≥3 gene copy number as average per nucleus. The number of FGFR1 signals per cell ranged from 2 to 11 (median value = 8.1) and from 4 to 11 (median value = 6.7) in CTC from SQCLC and ADK, respectively. In all cases FGFR1 gene copy number per cell was equal to that of Chromosome 8, underlining a high frequency of polysomy (≥3 FGFR1/Chr8 signals per cell). The pattern of FGFR1signal distribution was often heterogeneous within each case. FGFR1 gene copy number in 10 corresponding primary SQCLC tissue samples was significantly lower than that measured in CTCs (mean 3.0 vs 6.5, $p < 0.05$).

Conclusions. Our findings suggest that CTCs are frequent inadvanced NSCLC and often undetectable by EpCAM based techniques. The detection of high FGFR1 gene copy numbers associated with apparent loss of EpCAM expression in CTCs either from SQCLCand ADK suggest the development of a mesenchymal phenotype in these cells which may unveil novel targeted therapeutic strategies.

H13 A PHASE II STUDY OF INDUCTION CHEMOTHERAPY WITH CISPLATIN AND DOCETAXEL FOLLOWED BY CONCURRENT LOW DOSE CISPLATIN AND DOCETAXEL WITH THORACIC RADIATION IN UNRESECTABLE LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

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Background. Concomitant chemoradiotherapy (CHRT) is the standard of treatment in patients (pts) with unresectable locally-advanced non-small cell lung cancer (LA-NSCLC). Despite the high response rate, these pts still have a poor prognosis with a high incidence of distant relapse with a median survival of 18-20 months. Induction chemotherapy (CT) may play a cytotoxic role by eradicating distant micrometastases and reducing distant relapse. Previous trials reported no significant survival benefit and higher toxicity for induction CT prior to CHRT. Recently, two phase II studies reported a feasibility for induction CT prior to CHRT with a good tolerability. The aim of this study was to evaluate the feasibility and tolerability of induction cisplatin-docetaxel followed by concomitant CHRT for LA-NSCLC.

Patients and methods. This is a prospective phase II, multicenter, single arm trial in chemonaïve pts with unresectable stage III NSCLC. Patients received, after two cycles of cisplatin 75 mg/m^2 + docetaxel 75 mg/m^2, concomitant CHRT with cisplatin 25 mg/m^2 + docetaxel 25 mg/m^2 and thoracic radiotherapy (60-68 Gy) in 6-7 weeks. The primary endpoint of this study was the

feasibility of treatment determined by the percentage of pts who have completed all the treatment. We consider this treatment feasible if ≥70% of pts have completed all the treatment. Secondary endpoints included: response rate (RR), toxicity, time to progression (TTP), and survival.

Results. Thirty-seven pts were enrolled. The median age was 60.9 years. Twenty-seven pts (73%) were male, 22 pts (59.5%) had adenocarcinoma, 11 pts (30%) squamous cell carcinoma and 4 (10.5%) undifferentiated NSCLC. Thirty-three (89.2%) pts were evaluable for the primary endpoint. Twenty-four (73%) pts have completed all the treatment planned, 7 (21%) discontinued the treatment due to disease progression and 2 pts (6%) for adverse event. In 31 pts evaluable for toxicity grade 3-4 haematological toxicity was 12.5% and grade 3-4 esophagitis was 6.25%. The activity and efficacy final results will be presented at the meeting.

Conclusions. The preliminary data meet the primary endpoint of the trial showing that induction CT followed by concomitant CHRT using in both phases (induction and concomitant) cisplatin and docetaxel was feasible with an acceptable toxicity.

H14 ALTERATIONS IN CANDIDATE GENES (EGFR, KRAS, BRAF, ALK, MET) AMONG PATIENTS WITH NON-SMALL CELL LUNG CANCER FROM SARDINIA

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Background. Activating alterations of the epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) genes are associated with dramatic tumor responses and favorable clinical outcomes using targeted inhibitors in patients with non-small cell lung cancer (NSCLC).

Methods. Since July 2010, a total of 481 tumor tissues from patients with NSCLC and ascertained Sardinian origin were enrolled. Genomic DNA was isolated and screened for somatic mutations in EGFR, KRAS, and BRAF genes by automated DNA sequencing. Double-colour fluorescence in situ hybridization (FISH) analysis was performed using probes specific for ALK gene rearrangement and MET gene locus.

Results. Overall, 49/481 (10.2%) patients carried an EGFR mutation. Somatic mutations in EGFR gene were equally distributed between exon 19 (49%) and exon 21 (49%), with one mutation only (2%) in exon 18 among the first 294 (0.3%) enrolled patients. No significant difference in distribution of EGFR mutations according to the age at diagnosis was observed [EGFR mutated vs wild-type: median age, 65.3 (range 35-89) vs 65.8 (range, 37-82)]. Females presented a significantly higher frequency of EGFR mutations in comparison to males (23.4% vs 4.3%; p = 0.009). According to the smoking history, a significant preponderance of EGFR mutations were observed in never smokers (46.7%) as compared to former smokers (8.1%) and smokers (2.1%) (p <0.001). Among 286 patients whose somatic DNA was available, we detected 46 cases (16.1%) with KRAS mutation and 3/233 (1.3%) with BRAF mutation. Interestingly, a single NSCLC case carrying both an EGFR and a KRAS mutation was found, in contrast with the general findings that such mutations are mutually exclusive. KRAS mutations were slightly more prevalent in males than females (19.3% vs 11.8%) as well as in smokers (35.1%) than in former smokers (18.7%) or never smokers (5.7%). Among the patients tissues analyzed by FISH analysis, 7/81 (8.6%) presented an ALK gene rearrangement and 5/36 (13.9%) carried a MET gene amplification. Two (20%) out of 10 cases with such alterations presented a concomitant ALK and MET involvement. Correlation with clinical and pathological features in our series is ongoing.

Conclusions. With the exception of a frequency of ALK gene rearrangements slightly higher than expected, the prevalence of the other gene alterations among NSCLC patients from Sardinia is quite consistent with that reported in literature for Western populations.

H15 CLINICAL RELEVANCE OF VEGF, VEGFR, PDGFR, HIF AND ERCC1 GENE POLYMORPHISMS ON THYMIC MALIGNANCIES OUTCOME

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Background. Improving our understanding of the molecular biology of thymic malignancies represents a key challenge in the treatment of these rare tumors.

Methods. The genomic DNA of 57 consecutive patients (31 females and 26 males; 43 thymomas and 14 thymic carcinomas) submitted to total thymectomy at our Institution was extracted from paraffin-embedded tissue. We selected polymorphisms in the following genes: Hypoxia Inducible Factor-1 alpha (HIF1a: rs2057482T>C, rs1951795A>C, rs2301113C>A, rs10873142C>T, rs11158358G>C, rs12434438G>A, rs11549465C>T, rs11549467G>A), Vascular Endothelial Growth Factor-A (VEGF-A: rs2010963G>C, rs699947A>C), VEGF Receptor 2 (VEGFR-2: rs2305948C>T, rs1870377T>A), VEGFR-3 (rs307826T>C,rs307821C>A), Platelet-Derived Growth Factor-A (PDGFR-A: rs35597368C>T) and Excision Repair Cross-Complementing 1 (ERCC1: rs11615A>G). Gene polymorphisms were determined by Real-Time PCR using TaqMan assays.

Results. The allele frequency of PDGFR-A rs35597368 T (95.24%) was significantly higher than general population (86%, p = 0.012), while the frequency of alleles HIF1-A rs2057482C (76.98%), rs1951795C(68.25%), rs2301113A (68.55%), rs10873142T (68.85%), rs11158358C (74.6%), rs12434438A (65.87%), rs11549465C (83.33%) were significantly lower than those of the control group (90%, 87%, 82%, 87%, 86%, 84%, 92%, respectively, p <0.01). VEGFR-3 rs307821C was significantly higher in thymomas vs thymic carcinomas (79.5% vs 72%, p = 0.0371). The following factors were significantly correlated with a better overall survival: VEGFR-3 rs307826T, VEGFR-2 rs1870377T, PDGFR-A rs35597368T/C, HIF1a rs2301113A/C,

rs2057482C/T, rs1951795C, rs11158358G/C and rs10873142T/C, ERCC1 rs11615A ($p < 0.05$).

Conclusions. To the best of our knowledge this is the largest monocentric study analyzing the angiogenetic variants in thymic tumors representing a further asset in the definition of high-risk patients after curative resection. The selection tool deriving from this analysis may allow an optimal use of innovative treatment strategies including targeted antiangiogenic agents such as sunitinib and sorafenib.

H16 CIRCULATING TUMOR CELLS AS NOVEL PREDICTOR OF RESPONSE TO PLATINUM AND PEMETREXED CHEMOTHERAPY IN PATIENTS WITH ADVANCED ADENOCARCINOMA OF THE LUNG

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Background. Circulating tumor cells (CTC) are cells spread from the primary tumor into the bloodstream with a crucial role in the development of distant metastases. CTC have been detected in several cancers and are associated with aggressive disease. The aim of this study is to evaluate the correlation between the numeric variation of CTC in the blood of patients (pts) with advanced adenocarcinoma (ADK) of the lung during chemotherapy (CHT) and the radiological response to explore their potential role as early predictive factor of treatment response.

Materials and methods. Blood samples and CT-scans were obtained at baseline from pts with advanced ADK candidate for first-line CHT (carboplatin/cisplatin and pemetrexed). Blood samples and CT-scans were repeated every 2 cycles. Radiologic responses were assessed with RECIST 1.1. CTC were collected from blood through a filtration-based device (ScreenCell®, Sarcelles, France) able to isolate and sort CTC by size. H&E stain and Immunofluorescence (IF) using CK7 were carried out to enumerate and characterize CTC. Variations in tumor size observed in CT-scans were compared with variations in CTC count.

Results. Baseline CTC and CT-scans were obtained from 25 pts: male/female 18/7, median age 68 years (range 45-81); currently, assessments after at least 2 cycles were acquired from 18 patients. H&E revealed that CTC were morphologically compatible with tumor cells and they were present in all pts at baseline (range 2-25 CTC/mL); furthermore IF showed CK7 positivity. To date, 2 pts achieved partial response (PR), 3 pts showed progressive disease (PD), and 13 pts achieved stable disease (SD) as best response. Variation of CTC count was concordant with variation of tumor size in 13/18 (72.2%); in particular, reduction in CTC count was observed in 7 pts out of 8 (87.5%) with reduced tumor size, while increase in CTC count was observed in 6 pts out of 10 (60%) with increased tumor size. Variations in CTC count and tumor size were concordant in 100% of pts achieving PR or PD as best response.

Conclusions. This study demonstrates the feasibility of isolating CTC in all advanced ADK pts using a size-based low cost technique. Interestingly, the concordance between CTC counts and CT-scans, especially in pts with SD or PD, suggests that CTC may represent a predictive factor of treatment outcome. To our knowledge, this is the first study suggesting a relationship between CTC variation and treatment response in lung cancer.

H17 IMPACT OF AGE ON TREATMENT DECISIONS FOR PATIENTS WITH STAGE I-III NON-SMALL CELL LUNG CANCER (NSCLC) IN ITALIAN CLINICAL PRACTICE: RESULTS FROM THE RIGHT3 PROJECT BY ITALIAN ASSOCIATION OF MEDICAL ONCOLOGY (AIOM)

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Background. In 2004, Italian Association of Medical Oncology (AIOM) created the RIGHT (Research for the identification of the most effective and highly accepted clinical guidelines for cancer treatment) program. The third step of the program, RIGHT3, aimed to evaluate the concordance between AIOM lung cancer guidelines and clinical practice in Italy. Description of treatment decisions for patients with non-small cell lung cancer (NSCLC) in stages I-III was among the indicators.

Materials and methods. RIGHT3 was a retrospective observational study conducted in a sample of 53 Italian lung cancer centers, representative of 230 AIOM centers. Patients with NSCLC diagnosis who had their first visit at the oncology center during 2010 and followed-up for at least 6 months were included. Among the 14 indicators evaluated, here we consider the proportion of pts in early stages receiving lobectomy, the proportion of patients receiving adjuvant chemotherapy after surgery, the proportion of stage IIIB patients receiving concomitant or sequential chemo-radiotherapy. Patients are classified as elderly if older than 70 years.

Results. Overall, 225 pts with stage I-IIIA (70 elderly), and 156 pts with stage IIIB NSLSC (61 elderly) were evaluable. Out of 110 stage I-II pts eligible for surgery (30 elderly), 89 (80.9%) received lobectomy, and 8 (7.3%) received bilobectomy. Proportion of patients receiving lobectomy/bilobectomy was 77.5%/8.8% in younger pts and 90.0%/3.3% in elderly patients. Out of 99 pts in stage II-IIIA who underwent surgery (26 elderly), 58 (58.6%) received adjuvant chemotherapy. Proportion of patients receiving adjuvant chemotherapy was 67.1% and 34.6% among younger and elderly pts, respectively. Patient condition was the most common reason for the exclusion of elderly patients. Out of 156 stage IIIB pts, 43 received combination of chemo- and radiotherapy as first treatment (18 elderly). Of these, sequential treatment was adopted in most pts (88.0% and 83.3% in younger and elderly pts, respectively), whilst concomitant administration was not frequent in both age groups.

Conclusions. Lobectomy was the most common surgery among both younger and elderly patients. Proportion of elderly

patients receiving adjuvant chemotherapy was lower compared to younger subjects. For patients with locally advanced disease treated with chemo- and radiotherapy, sequential administration is much more common than concomitant, both in younger and elderly patients.

H18 NATURAL HISTORY OF MALIGNANT BONE DISEASE IN NON-SMALL CELL LUNG CANCER: PRELIMINARY RESULTS OF A MULTICENTER BONE METASTASIS SURVEY

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Background. As disease-related survival improves, bone metastases become an increasing clinical problem in advanced non-small cell lung cancer (NSCLC). Here we show the results of a multicenter, retrospective survey aimed to explore the impact of tumor bone involvement in this severe, life-threatening disease.

Patients and methods. Data on clinicopathology, skeletal outcomes, skeletal-related events (SREs), and bone-directed therapies for 661 deceased NSCLC patients with evidence of bone metastases were collected and statistically analyzed.

Results. ECOG performance status at diagnosis of NSCLC was 0-1 in 85% of patients. The most frequent stage at diagnosis was IV (79%). Adenocarcinoma was the commonest histotype (69.3%). EGFR status was unknown in 70.4%; in the remaining patients (29.4%) EGFR status was wild type in 74.9% and mutated in 25.1%. Most of the patients received first-line treatment (91.7%): chemotherapy was the preferred first-line treatment in 94.3% and platinum-based one was administered in 59.4%. Tyrosine kinase inhibitors (TKIs) were administered in 30.6% of patients: gefitinib was used in 22.1% and erlotinib in 77.9%. Bone metastases were evident at diagnosis in 57.5% of patients. In the remaining cases median time to bone metastases was 9 months. ECOG performance status in patients with bone metastases was 0-1 in 74.9%. Patients were diagnosed with multiple bone metastases in 78.3%, 74.3% of these were osteolytic. Axial skeleton was interested in 25.1% of cases, pelvic and limb bones in 48.1% and 32.9%, respectively. Bone metastases related pain was reported by 78% of patients. The median value of Verbal Numerical Rating Scale (VNRS) for pain was 4 and it measured >4 in 44.3% of cases. Bisphosphonates were administered in 59.6% of patients. Zoledronic acid was the most used (56.2%) and it was administered before the first SRE in 33.4% of cases. Osteonecrosis of the jaw was reported in only 1.4% of cases. SREs was experienced by 57.7% of patients, 42.5% experienced one SRE, 11.9% two SREs, only 3% at least 3 SREs. The most common first, second and third SRE needed radiotherapy in 71.4%, 79.2% and 61.9% of patients, respectively. Median time to first SRE was 6 months. Median survival after bone metastases diagnosis was 9.5 months and after first SRE was 7 months.

Conclusions. These data confirm the important role of bone metastases as an early, relevant clinical event in the natural history of patients affected by NSCLC.

H19 SRC FAMILY KINASE INHIBITORS ACT THROUGH DIFFERENT MECHANISMS TO COOPERATE WITH EGFR OR MEK INHIBITORS IN NSCLC MODELS

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Background. Src family kinase (SFK) inhibitors have been demonstrated to play an important role in regulating biological process in human tumors, including proliferation, motility, migration, survival and angiogenesis. However, a recent phase II study of the SFK inhibitor dasatinib conducted in patients with metastatic NSCLC failed to demonstrate drug efficacy.

Methods. In this study, we evaluated the activity of different SFK inhibitors in a wide panel of human NSCLC cell lines with different mutation status of epidermal growth factor receptor (EGFR) and Ras genes. We used PC9 and HCC827 (harbouring the EGFR-TKI sensitizing mutation A746_A750del), CALU3 (EGFR and Ras wild-type) H1299, A549 and H460 (Ras mutated), H1975 (EGFR double mutant L858R/T790M, resistant to TKIs). We also generated a cell line with acquired resistance to erlotinib, CALU3-ER. We performed survival assay and Western blot analysis after treatment with three different Src inhibitors (saracatinib, dasatinib and bosutinib) alone or in combination with EGFR TKI or MEK inhibitors.

Results. We first evaluated the sensitivity of NSCLC cell lines to saracatinib, dasatinib and bosutinib. MTT assay showed a different panel of sensitivity to the Src inhibitors, with saracatinib and bosutinib more efficient in EGFR mutated cells, while dasatinib in EGFR wild-type and K-Ras mutated cells. Consistently, saracatinib and bosutinib had a major efficacy in directly inhibiting EGFR activation, while dasatinib efficiently inhibited Src activation, as shown by Western Blot analysis. Based on these data, we tested the combination of saracatinib with the EGFR inhibitors erlotinib and cetuximab in NSCLC cell lines with EGFR mutations, including the erlotinib resistant H1975 cells. Conversely, we tested the combination of dasatinib with the MEK inhibitor selumetinib in NSCLC cell lines with K-Ras mutation. Both combination treatments showed a cooperative effect in inhibiting cell proliferation and signal transduction, as demonstrated by MTT and Western blot assays. We are now evaluating the

effects of these combination *in vivo*, in nude mice xenografted with NSCLC cells.

Conclusions. We demonstrate that SFK inhibitors may act with different mechanisms in NSCLC cell lines, depending on EGFR and/or K-Ras mutational profile. Moreover, our data suggest that the association of anti-Src agents with EGFR or MEK inhibitors could represent an effective therapeutic option for different cohorts of NSCLC patients.

H20 GENDER DIFFERENCES IN LUNG ADENOCARCINOMA

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Background. Primary lung cancer is the most common malignancy after non-melanocytic skin cancer and the leading cause of human cancer deaths worldwide. Lung cancer in women seems to have different characteristics than in men; in fact gender differences are described in terms of epidemiological data, biomolecular and clinical characteristics of the disease with a better outcome in women.

Aim. The aim of the study was to determine if the expression of nuclear/cytoplasmatic androgen receptor (AR), estrogen receptor α (Erα) and progesterone receptor (PR) in patients with metastatic adenocarcinoma may represent prognostic factors.

Patients and methods. We investigated the immunohistochemical expression of nuclear/cytoplasmatic AR, ERα and PR in 62 lung adenocarcinomas and correlated their expression with patients clinico-pathologic characteristics.

Results. Five out of 62 patients (8%) had a positive ERα expression and showed a median survival of 44.5 months compared to 19.3 months in patients with negative expression ($p = 0.03$). Four patients (6.4%) had a positive PR expression with a better outcome in terms of survival (44.5 against 19.3 months, $p = 0.03$).

Eight patients (12.9%) who presented positive n-AR showed a significantly better survival (49.4 vs 19.3 months, $p = 0.03$) and again, 18 patients (29 %) who presented positive c-AR showed a better outcome (median survival = 29.5 vs 16.7 months, $p = 0.04$). The significantly better survival was particularly evident among women with positive nuclear or cytoplasmic AR expression.

At multivariate analysis, the hormonal receptors expression represented a significant independent prognostic factor.

Conclusions. Our data showed that hormonal receptors expression has a significant impact on outcome in patients with metastatic lung adenocarcinoma and should become object of close examination in larger series, also in order to consider the possibility to select the patients with best prognosis that can benefit from a peculiar therapeutic strategy. The better prognosis in women may actually be linked to hormonal interactions.

H21 CHEMOTHERAPY (CT) AND ANTI-EGFR TYROSINE-KINASE INHIBITORS (TKIS) EFFICACY IN WOMEN WITH LUNG ADENOCARCINOMA: CORRELATION WITH EGFR AND K-RAS MUTATIONAL STATUS

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Background. Little is known about the impact of molecular factors on treatment efficacy in women with advanced adenocarcinoma of the lung. We investigated the outcome of female patients (pts) with stage IIIB-IV adenocarcinoma according to *EGFR* and *K-Ras* mutational status.

Patients and methods. Patients treated at least with first-line CT were eligible. Anti-EGFR TKIs were allowed as salvage (II or further line) treatment. *EGFR* (exons 18-21) and *K-Ras* (exon 2, codons 12-13) mutations were evaluated by PCR-SSCP-DNA sequencing and pyrosequencing, respectively. The association of mutational status with clinical variables and treatment benefit was investigated by chi-square test and log-rank test.

Results. 103 consecutive women were screened; *EGFR* and *K-Ras* mutations were found in 30% and 15% of cases respectively. As expected, *EGFR* mutations were more frequent among never or former smokers (38% vs 13%; $p = 0.034$), while *K-Ras* mutations were more frequent among current smokers (30% vs 7%; $p = 0.022$). Seventy-six pts received first-line cisplatin-based CT and were evaluable for analyses. There was no correlation between *EGFR* or *K-Ras* mutational status and response rate (RR) to first-line CT ($p > 0.05$); however, *EGFR* mutant pts experienced significantly shorter median progression-free survival (PFS) compared to wild-type ones (4.4 vs 6.4 months; HR 0.597, 95% CI 0.287-0.975; $p = 0.048$). Thirty-nine pts received salvage erlotinib, most of them (27 pts) as second-line therapy. *EGFR* mutations significantly correlate with higher RR (60% vs 12.5%; $p = 0.004$) and longer PFS (median: 11.4 vs 4.8 months; HR 0.430, 95% CI 0.190-0.976; $p = 0.049$). None of the patients harbouring *K-Ras* mutant tumor achieved an objective response to TKIs; PFS of women harbouring a *K-Ras* mutant tumor treated with TKIs was significantly shorter in comparison with that of wild-type cases (median: 4.0 vs 8.8 months; HR 0.305, 95% CI 0.0154-0.828; $p = 0.038$).

Conclusions. In our series of Caucasian women with advanced adenocarcinoma of the lung, the data suggest that *EGFR* mutations may be associated with lower benefit from first-line platinum-based CT in terms of PFS, stressing the importance of upfront TKIs in these cases. The potential negative predictive role of *K-Ras* mutations in TKIs-treated pts deserves further investigation. Overall survival analysis is ongoing.

H22 TREATMENT WITH CRIZOTINIB IN PATIENTS WITH IV STAGE NON-SMALL CELL LUNG CANCER (NSCLC) WITH ALK TRANSLOCATION. A SINGLE INSTITUTION EXPERIENCE

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Background. Crizotinib is a MET inhibitor, having also an activity on ALK (anaplastic lymphoma kinase) and ROS1 (c-ros oncogene 1) pathways. The ALK translocation is described in 4% of NSCLC and these patients benefit from crizotinib therapy with a RR ranging from 51% to 61%.The drug is already approved by FDA and EMA; waiting for national registration, in Italy crizotinib is still available within controlled clinical trials and expanded access program (EAP).

Material and methods. From June 2010 to February 2013, 155 patients with advanced NSCLC were analyzed for Alk translocation using fluorescence in situ hybridization (FISH) at our institution (AOU San Luigi). The selection criteria were: adenocarcinoma histology, never or ex smoker, EGFR status WT. Main pts characteristics were: 59% males, median age 57.5 years (range 26-76), 77 former smoker (76 patients for more than 15 years). Tissue samples were available from primary tumor and metastases in 78% and 22%, respectively, having 73% cytological material. In 23.2% of the cases Alk translocation was not evaluable due to poor quality and/or quantity issues.

Results. Among the 155 pts, 22 (14%) were ALK translocated: 19 treated within PROFILE clinical trials and 3 patients in the EAP. Seventeen pts are evaluable for response and toxicity: 6 of them received crizotinib as first-line treatment, the others in successive lines. The total number of administered cycles is 235. The reduction of the dose (7% of cycles) was necessary in two pts: in 1 case due to bradycardia and fatigue G3 (in first-line treatment) and in the other one due to neutropenia G3 (in second-line).The observed toxicities were mostly grade 1-2 (fatigue 47%, bradycardia 5.8%, visual disorder 5.8%, anemia 29%, neutropenia 18% and nausea 12%); grade 3-4 was less common. The temporary cessation of treatment was required in 3 pts (range 4-15 days) for grade 3-4 toxicity (mostly neutropenia plus fatigue). No drug interruption for unacceptable toxicity was reported. Progression-free survival (PFS) was equal to 8.9 month; 5 pts are still in treatment. The most common progression sites were brain (37%) and bone (27%).

Conclusions. The introduction of a selection criteria (such as negative EGFR status) leads on an increase of the Alk traslocated pts compared to literature data; this is in any case the recommended diagnostic algorithm recently proposed by the Italian Expert Panel. Efficacy and tolerability profile are consistent with published data.

H23 MOLECULAR FOLLOW-UP OF AN ITALIAN COHORT OF EGFR MUTATED PATIENTS PROGRESSING AFTER TREATMENT WITH ORAL TYROSINE KINASE INHIBITORS

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Background. Tyrosine kinase inhibitors (TKIs) are valuable treatment options for A-NSCLC EGFR mutated patients (pts). Since acquired resistance occurs at disease progression (PD), increasing efforts have led to discover counter- mutations in EGFR exon 20 and C-MET amplifications related to molecular resistance. We evaluated the incidence of these mutations in an Italian cohort of EGFR mutated NSCLC pts who had a PD after an oral TKI treatment.

Material and methods. We evaluated 17 pts, 12 women and 5 men, 15 adenocarcinoma and 2 squamous cell carcinoma. Twelve pts had an EGFR exon 19 deletion and 5 patients a L858R mutation in exon 21. At first PD after a TKI therapy, after previous written informed consent, a second biopsy was performed on the PD site to reassess the EGFR mutational status and c-MET amplification. Exon 20 T790M mutation analysis was performed on 14 pre-treatment and all post-treatment specimens by direct sequencing while c-MET was studied by FISH on 13 rebiopsies. Ten pts received oral TKIs as first-line treatment, while other 7 pts in second-line.

Results. On the second bioptic specimen the T790M mutation was detected in 8 pts (47%), while a c-MET specific amplification was identified in 4 of 13 evaluated pts (31%). In one patient, T790M mutation and c-MET amplification were present in a concomitant fashion while 3 pts exhibited a c-MET amplification without any T790M alteration. Therefore clinical resistance was explained in the present cohort by novel EGFR T790M and/or c-MET molecular alterations in 11 assessed patients (65%). In 2 cases the original EGFR TKI-sensitive mutation found in the first diagnostic specimen evaluated was not detected on the site of disease progression. We had 1/5 pre-treatment EGFR T790M mutations defined by Real Time PCR and 1/the other by direct sequencing. We didn't observe any change in histotype.

Conclusions. EGFR T790M mutations and c-MET amplifications are common in Italian patients treated with oral TKIs that eventually develop drug resistance. Since new generation drugs are currently being developed against EGFR (irreversible TKIs) or c-MET, a "molecular follow-up" will allow to identify pts eligible for future treatment options.

H24 MOLECULAR MECHANISM OF RESISTANCE TO AFATINIB IN EGFR MUTATED (NSCLC) CELL LINES AND POTENTIAL THERAPEUTIC IMPLICATIONS

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Background. Ten to 20% of non-small cell lung cancer (NSCLC) harbor activating mutations in the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) in Caucasian patients (pts). TK inhibitors (TKIs) such as erlotinib or gefitinib have demonstrated longer progression-free survival compared to chemotherapy alone in first-line for advanced EGFR mutated NSCLC patients. Some of these tumors develop drug-resistance due to an acquired mutation (T790M) in EGFR, determining progression of disease. Recent clinical trials (LUX-Lung 1 and 4) have demonstrated the activity of an irreversible EGFR-TKI, BIBW-2992 (afatinib), in pts who failed previous EGFR-TKI treatment in advanced NSCLC carrying EGFR mutation.

Material and methods. Our study aim is to elucidate the

mechanisms of acquired resistance in an *in vitro* model of afatinib resistant clones. A dose-escalation study was performed to establish the H1975 NSCLC cell line (exon21 L58R/exon20 T790M) afatinib-resistant(AR) cells. All exons of EGFR and KRAS were deeply sequenced by Ion PGM™ Sequencer, while the expression of 92 genes of the EGFR pathway was studied by quantitative Polymerase Chain Reaction (qPCR). Concomitantly, protein expression of some genes related to the EGF pathway such as EGFR, AKT and ERK (total and activated form) as well as MRAS and PI3KR1 were investigated by Western Blot.

Results. Although sequence analysis of AR-cells did not reveal any novel mutation, gene expression profiles disclosed an increase of some members of the RAS family (MRAS, KRAS), PIK3R1 as well as an up-regulation (about 100-fold) of SHC3 while EGF was silenced. AR cells showed a higher signal of MRAS and an increase of active ERK1/2 compared to the parental cells. This behavior also persisted in absence of EGF stimulation and in cultures maintained in afatinib-free medium for over 6 months. The absence of novel mutations suggests that other mechanisms are implicated in afatinib resistance. In particular the marked increase of SHC3, an adaptor immediately downstream of EGFR, leads to hypothesize its involvement in the EGFR activation. Furthermore, the EGF down-modulation, together with the MRAS increased expression and ERK1/2 activation, suggests that this cell line may acquire a different way to activate the EGFR pathway.

Conclusions. These preliminary data open new approaching for future development of RAS and PI3K inhibitors as a strategy for delaying or reversing afatinib resistance in EGFR mutant NSCLC patients.

H25 MULTICENTER POST-MARKETING ANALYSIS ON ERLOTINIB IN PREVIOUSLY TREATED NSCLC

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Background. Erlotinib is a potent inhibitor of the EGFR (epidermal growth factor receptor) tyrosine-kinase activity and its efficacy has been demonstrated for the treatment of NSCLC in large randomized trials. The registration study BR.21 (N Engl J Med, 353: 123-132, 2005) showed to prolong significantly OS and PFS in erlotinib arm. The median age of the patients in this study was 61.4 years. We have conducted a prospective observational study, using institutional data of the Onco-AIFA, a web-based national Italian registry of new oncology drugs. The aim of our study was to assess median OS and PFS in clinical practice in comparison to outcome values obtained from the registration study.

Materials and methods. Ten Italian oncology centers (Meldola - 222 pts, Padova - 159, Parma - 145, Pescara - 82, L'Aquila - 64, San Donà di Piave - 61, Cosenza - 42, Bolzano - 38, Trieste - 36, Bassano del Grappa - 11) collected data from the registry to establish the real clinical impact of the drug. The observation period was October 2006-November 2012. Every patient was checked for the length of the treatment and outcomes. For the efficacy/effectiveness comparison assessment we used the RCT outcome measures: OS, PFS with Kaplan-Meier estimates. EGFR was not a mandatory status for drug administration.

Results. A total of 860 patients treated with erlotinib were reviewed (median age 66.8 years, M 61%). Median PFS and OS were 2.4 (95% CI 2.3-2.6) and 5.3 (95% CI 4.7-6.3) months respectively compared to erlotinib arm of the BR.21 study with PFS 2.2 months and OS 6.7 months. We recorded 26 (3%) suspensions of the treatment for toxicity. The median duration of treatment was 2.3 months (range 0.5-49.2) and 1-year survival rate was 33%. Moreover, there was a statistically significant difference in OS between males and females (5.0 vs 6.4 months respectively, $p < 0.001$).

Conclusions. The post-marketing studies in real life practice are needed in order to verify effectiveness and safety in general population and test the validity of the randomized trials. Moreover, the post-progression survival assessment may be crucial to determine the real clinical impact of a drug in combination with other treatments as it is usually missed in the approval RCTs. Our results do not differ particularly from the study BR.21 and the slight difference in OS noticed by us can be explained by the fact that in our study the median age was higher than in the pivotal trial (66.8 vs 61.4 years).

H26 18F-FDG-PET-CT AND SURGERY AS PROGNOSTIC FACTORS IN MALIGNANT PLEURAL MESOTHELIOMA (MPM). A MONO-INSTITUTIONAL EVALUATION OF BOLOGNA MPM GROUP

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Background. The prognostic and classification systems currently in use in MPM, such as the EORTC EPS score and CALGB groups, are limited to some clinical and histological parameters. The aim of our study was to investigate the role of 18F-FDG-PET-CT (PET) baseline and surgery as prognostic factors.

Methods. From April 2002 to December 2012, 48 pts with a certain histological diagnosis of MPM underwent staging by PET scan before surgery or palliative first-line chemotherapy. Patients characteristics were: 44 (92%) men, 4 (8%) women; median age 65 (51-77) years; 45 (94%) pts ECOG PS 0-1, 3 (6 %) pts ECOG PS 2; 18 (37.5%) pts IMIG stage I-II, 30 (62.5%) pts IMIG stage III-IV; histological subtypes: 40 (83%) epithelial, 5 (11%) mixed, 3 (6%) sarcomatoid; surgery: 8 (16%) extrapleural pneumectomy (EPP), 14 (29%) pleurectomy/decortication (P/D), 7 (15%) VATS plus pleurodesis, 19 (40%) any surgical procedures; platinum based chemotherapy was performed in combination with pemetrexed in 39 (81%) pts and with gemcitabine in 9 (19%) patients. According to the EORTC score, 30 (62.5%) pts were classified in the good prognosis group and 18 (37.5%) pts as poor prognosis. The cut-off value of PET baseline SUV-max calculated by ROC analysis was 9 (Adua et al., ASCO, 2013). Overall survival (OS) was evaluated with the Kaplan-Meyer analysis; the Cox regression model was employed for multivariate analysis.

Results. Median OS in all population was 14 months (95% CI 10-18). The OS in epithelial histology was 17 months (95% CI 14-20), in mixed and sarcomatoid subgroup 6 months (95% CI 0-12), in EPP and P/D procedures 17 months (95% CI 14-20) and in any surgical treatment subgroup 12 months (95% CI 9-15). The OS in pts undergoing EPP was 25 months (95% CI 12-38) and in pts who underwent P/D 17 months (95% CI 12-22). PET baseline SUV-max was ≤9 in 32 (67%) pts and >9 in 16 (33%) pts; the OS was 16 months (95% CI 13-19) and 10 months (95% CI 8-12) respectively. In the univariate analysis statistical significance was only reached by histology (p = 0.0038) and surgery (EPP and P/D) (p = 0.0027). In the multivariate analysis, according to age, histology, stage, surgery and the PET baseline SUV-max, only epithelial histology (p = 0.002) and surgery (p = 0.012) achieved statistical significance. PET baseline SUV-max was not statistically significant (p = 0.29).

Conclusions. Our analysis suggests surgery as a possible prognostic factor and shows no prognostic role for PET baseline SUV-max in MPM management.

H27 MALIGNANT PLEURAL MESOTHELIOMA LONG-TERM SURVIVORS: A STUDY ON POPULATION DATA BASE REGISTRIES (LUME STUDY)

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Background. Malignant pleural mesothelioma (MPM) is a rare tumour induced by asbestos exposure. Survival for mesothelioma is very poor and the prognosis rarely exceeds one year. However, during the clinical practice we observe a few patients surviving longer. This suggests the presence of milder phenotypes with a different prognosis.

Material and methods. The database of the project rare cancers in Italy (RITA) and the wider database of the project Surveillance of Rare Cancers in Europe (RARECARE) were searched for mesothelioma long survivors (alive after >3 years from diagnosis). These projects pull together data from 19 and 76 population-based cancer registries (CRs), respectively offering a unique opportunity to study rare cancers such as mesothelioma. CRs were asked to verify the pathological diagnosis and follow-up of mesothelioma long-term survivors to verify that they are real long-term survivors. In addition, in Italy all general CRs and mesothelioma dedicated registries (COR) were asked to verify the number of MPM long-term survivors in the more recent period 2003-2008.

Results. In the period 1995-2002, in the RITA database 127 cases of mesothelioma long-term survivors were identified and 117 were confirmed mesothelioma long-term survivors after the revision of the pathological report and of the follow-up. In the RARECARE database (34 out of the 76 CR contributed to this review) 678 cases of mesothelioma long-term survivors were identified and 578 were confirmed mesothelioma long-term survivors. Long-term survivors (survival time >3 years), in comparison with the other patients (survival time <3 years), included a larger fraction of younger people, and of epithelioid morphology. No major differences were observed between sexes. The collection of information on the number of MPM long survivors in Italy is at present ongoing however, in 23 CRs providing the information already 300 MPM long term survivors were identified.

Conclusions. Our preliminary data suggest that MPM long-term survivors do exist and represent approximately the 11% of MPM cases at population level. A high resolution study is ongoing, in the context of the LUME study, to confirm diagnosis, describe patterns of care for MPM in selected Italian populations, and to study the biological characteristics of MPM long-term survivors. Histological specimen will be collected and exome of available tissues will be deep sequenced to identify common genetic characteristics.

H28 CD133 AND EGFR STATUS MAY REPRESENT MARKERS ABLE TO PREDICT EARLY RELAPSE AND RESISTANCE IN THE TREATMENT OF LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS

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Background. Neoadjuvant chemotherapy represents a consolidate treatment strategy for locally advanced disease but even if radical surgery is obtained many patients (pts) will die for recurrences. The presence of stem cells may be hypothesized as a mechanism of everlasting resistance and CD133 is an epithelial specific marker for their presence. Moreover, CD133 has been previously appointed as platinum resistance.

Methods. All consecutive locally advanced NSCLC patients were enrolled and their tissues were genotyped for EGFR, KRAS, ALK through Direct Sequencing and Fluorescence in situ Hybridization. CD133 was evaluated by immunohistochemistry (IHC) on paraffin-embedded tumor sections. A multivariate analysis was conducted in order to assess relationships between clinical-pathological factors and patients outcome in terms of response rate (RR) and progression-free survival (PFS). Biomarker analyses from mediastinal nodes obtained at diagnosis were focused on EGFR amplification, ALK rearrangement, KRAS and EGFR mutation and CD 133 expression.

Results. From August 2005 to September 2011, 50 consecutive pts with locally advanced NSCLC underwent induction platinum based chemotherapy (CT) followed by surgery. Radiotherapy was performed if pN2. Population was composed by 36 males and 14 females, median age was 64 years. Smoking history was positive in 47/50 patients. Histological subtypes included adenocarcinomas (N = 37), squamous cell (N = 10), sarcomatoid (N = 1). Thirty pts obtained objective response (RECIST) from CT: 2 complete response (4%), 28 partial response (56%), 15 stable disease (30%). Six pts had progressive disease (12%) during CT. Median follow-up is 40 months. Median PFS was 24 months (range 1-54). Twenty-six patients were defined as CD133 positive and 23 pts had high polysomy EGFR. None of the clinical information were significantly associated with RR and PFS, while biomarker analysis suggested that pts with EGFR polysomy and high CD133 IHC expression were correlated with early recurrence HR 2.22 (95% CI 1.02-4.83, p < 0.05).

Conclusions. Although the number of patients is still low to draw any conclusion, there is a strong correlation between CD133 and worse prognosis. This correlation is stronger when EGFR polysomy is present. A prospective study to test this hy-

pothesis is ongoing. The presence of initiating cells may be useful in clinical practice to personalize treatment strategy.

H29 A COST MINIMIZATION ANALYSIS FROM THE ITALIAN NATIONAL HEALTH SYSTEM (NHS) PERSPECTIVE OF NAVO TRIAL 01: ORAL VINORELBINE (NVBO) PLUS CISPLATIN (CDDP) VERSUS PEMETREXED (PEM) PLUS CDDP FOLLOWED BY MAINTENANCE WITH SINGLE AGENT NVBO OR PEM AS FIRST-LINE TREATMENT OF PATIENTS WITH ADVANCED NON-SQUAMOUS NON-SMALL CELL LUNG CANCER (NS-NSCLC)

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Background. Vinorelbine and CDDP are a standard treatment in NSCLC. PEM plus CDDP is recommended in front-line chemotherapy of NS-NSCLC. NAVoTRIAL01 is a randomised phase II study in NS-NSCLC where 100 (arm A) and 51 (arm B) pts were treated with NVBo/CDDP and PEM/CDDP respectively. Overall, Arm A/Arm B reported: disease control rate including combination (4 cycles) and maintenance period of 75.0%/76.5%, median progression-free survival of 4.2/4.3 months and median overall survival of 10.2/10.8 months. In order to analyze the economic impact of these two treatments, a cost minimization analysis was conducted from the perspective of the Italian NHS.

Materials and methods. Specific costs and clinical settings reflecting the Italian practice were considered. Costs included in the analysis were: anti-cancer drugs (AC), administration settings (AS, i.e. outpatient/inpatient/at home), serious adverse events (SAE, defined as involving hospitalization and suspected to be due to AC), concomitant medications (CM, used for curative intent) and blood transfusions (BT). Unit costs used for AC were official ex-factory prices, with further percent deductions enforced by law. The distribution of AS was re-modelled according to the respective frequencies found for the subset of Italian pts participating in NAVoTRIAL01 and DRG and other tariffs (day-hospital or one day admission) for out/in-pt settings were used (no cost was charged when administration was at home). Hospitalization costs were assessed for SAE on the basis of appropriate DRG tariffs.

Results. Average cost per patient (€):

	Arm A	Arm B	A-B
AC	1,763	13,615	-11,852
AS	1,706	344	1,359
SAE	611	569	42
CM	273	223	50
BT	63	44	19
Total	4,413	14,795	-10,382

In detail, the cost for AC in arm A was € 572 in the four-cycle combination period and € 1,191 in the maintenance period; the analogous cost in arm B was € 6,738 and € 6,877 respectively.

Conclusions. Given the reported efficacy outcomes with both regimens, NVBo/CDDP followed by maintenance with NVBo provides substantial savings (€ 10,382 per patient on average), appearing a cost-effective treatment option in advanced NS-NSCLC. Such results should be confirmed by a phase III trial.

H30 ACTIVITY AND SAFETY OF CPBEV REGIMEN (CIS-PLATINUM, PEMETREXED AND BEVACIZUMAB) AS FIRST-LINE THERAPY FOR LOCALLY ADVANCED OR METASTATIC ADENOCARCINOMA OF THE LUNG: FINAL RESULTS OF A PHASE II STUDY

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Background. During the past seven years the paradigms of advanced lung cancer therapy dramatically changed: bevacizumab and pemetrexed, when administered separately in association with platinum salts, demonstrated to improve survival in patients with non-squamous histologies. In the aim to investigate activity and safety of a three-drugs regimen containing both these agents and cisplatinum, we conducted a multi-institutional phase two study.

Material and methods. To satisfy main eligible criteria, patients had to be chemonaïve with stage III-IV non-squamous non-small cell lung cancer expressing an ECOG-WHO PS <2 and without cerebral metastases. We adopt the two-stage of Simon model as statistical design: activity of the regimen, expressed as overall response rate and safety, was the primary endpoint, whereas progression-free and overall survival were secondary endpoints.

Results. Thirty-two patients were enrolled: their main characteristics are: male/female 20/12, median age (years) 59 (rate 36-77), ECOG-WHO PS 0/1 21/11. One hundred and eighty-three cycles of CPBev were administered: main grade 3 adverse events were neutropenia (28%), emesis (19%), asthenia (9%), and hypertension (9%). In terms of response rate we registered 20/32 (62.5%) partial responses, 8/32 (25%) stable diseases, and 4/32 (12.5%) progressive diseases, with a clinical benefit rate of 28/32 (87.5%). The median overall survival of the entire series was 16.9 months; 1- and 2-year survival rates were respectively 61.4% and 32.1%. The median progression-free survival was 9.3 months, with a 1- and 2-year progression-free survival rate of 43.2% and 7%, respectively.

Conclusions. On the basis of our data, CPBev has a good toxicity profile and seems extremely active in advanced non-squamous lung carcinomas. Data concerning outcome parameters are very interesting: CPBev deserves to be compared to actual standard regimens in a phase III trial.

H31 ANALYSIS OF PREDICTIVE FACTORS INVOLVED IN TIME TO BONE METASTASES AND SURVIVAL AFTER BONE METASTASES IN A LARGE SERIES OF ITALIAN NSCLC PATIENTS

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Background. This is a multicenter, retrospective survey aimed to explore the role of some clinico-pathological parameters involved in this severe, life-threatening disease.

Patients and methods. Data on natural history of 661 deceased non-small cell lung cancer (NSCLC) patients (51% aged >64 years) were collected and then selected for univariate and multivariate analysis.

Results. Univariate analysis showed that 7 parameters tested were found to be linked to time to first bone metastases, 2 of them proved to be independent in the multivariate analysis (Table 1). Moreover, we did a univariate analysis in which 14 parameters seem to be correlated to overall survival from bone metastases diagnosis. Multivariate analysis was carried out to assess the independent role of 3 of them (Table 2).

Conclusions. These data confirm the important role of bone metastases as an early, relevant clinical event in the natural history of patients affected by NSCLC.

H31 - Table 1
Parameters linked to time to first bone metastases in univariate and multivariate analysis

Parameters		Median (mos)	Univariate p value
Age	>64	5	7
	<64	7	0.046
ECOG PS at diagnosis	0-1	7	
	>2	2	0.012
Stage at diagnosis	I	16	
	II	19	
	IIIA	12	0.001
	IIIB	7	
	IV	4	
Surgical resection	Yes	11	
	No	6	0.001
First-line treatment	CT	6	
	TKIs	12	0.087
Pelvic bone metastases	Yes	4.2	
	No	8	0.023
Limb bone metastases	Yes	5	
	No	7	0.019

Parameters	HR	Multivariate p value	95% CI
Stage at diagnosis	1.370	0.001	1.2-1.5
Surgical resection	0.727	0.053	0.5-1.0

H31 - Table 2
Parameters linked to time to overall survival from bone metastases diagnosis in univariate and multivariate analysis

Parameters		Median (mos)	Univariate p value
Age	>64	7	
	<64	8	0.008
ECOG PS at diagnosis	0-1	8	
	>2	3.5	0.001
Histology	Adenocarcinoma	8	
	Others	6	0.001
Stage at diagnosis	I	14	
	II	6	
	IIIA	9	0.004
	IIIB	9	
	IV	7	
First-line treatment	Yes	8	
	No	3	0.001
Platinum-based chemotherapy	Yes	8	
	No	5	0.001
First-line TKIs	Yes	12	
	No	6	0.001
ECOG PS at bone metastases diagnosis	0-1	8	
	>2	4	0.001
Number of SREs	0	6	
	1	8	
	2	10	0.001
	3	12.6	
Bone fracture as SRE	Yes	7	
	No	8	0.040
Spinal cord compression as SRE	Yes	7	
	No	9	0.008
Bisphosphonate administration	Yes	9	
	No	5	0.001
Zoledronic acid administration	Yes	9	
	No	5	0.001
Zoledronic acid administration before first SRE	Yes	10	
	No	7	0.001

Parameters	p value	Multivariate HR	95% CI
Histology	0.049	1.296	1.0-1.6
Stage at diagnosis	0.010	1.174	1.0-1.3
Platinum-based chemotherapy	0.002	0.663	0.5-0.8

H32 RE-TREATMENT WITH GEFITINIB OR TREATMENT WITH ERLOTINIB AFTER GEFITINIB FAILURE IN RESPONSIVE NON-SMALL CELL LUNG CANCERS: NEW STRATEGIES TO OVERCOME ACQUIRED RESISTANCE

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Background. Patients (pts) with advanced NSCLC, who initially respond to gefitinib or erlotinib, after a median PFS of 10-16 months, eventually develop acquired resistance to the TKIs. Anecdotal and retrospective reports suggest that EGFR-TKI resistant cancers can respond again to gefitinib or erlotinib after an interval off the TKI. This analysis was undertaken to investigate the impact of gefitinib retreatment after a drug-free interval or erlotinib treatment in NSCLC with acquired resistance to gefitinib, in order to identify the best strategy in this subset of patients.

Methods. We searched published reports including retreatment with gefitinib or treatment with erlotinib after gefitinib failure in responsive NSCLC. Twenty reports were identified (published between 2004 and 2012), including eight reports for gefitinib retreatment and twelve for treatment with erlotinib after gefitinib failure. We used direct data as extracted from the Author's publications for response rate, disease control rate, OS and PFS.

Results. A total of 214 patients were pooled from these studies. In gefitinib retreatment group (85 pts), we reported: PR 17.6%, DCR 65.8%, OS 9.8 months and PFS 2.2 months. In erlotinib therapy, we recorded (129 pts): PR 11.6%, DCR 38.9%, OS 8.9 months and 5.9 PFS months.

Conclusions. To date there is no optimum strategy for patients who experienced progression disease while receiving EGFR TKIs. In this preliminary analysis no significant statistic differences were observed in the two groups, but these data suggest that patients might still retain a certain sensitivity to the EGFR blockade, even after acquisition of resistance.

Table 1

Author	N of pts	RR (pts)	DCR	OS (mos)	PFS (mos)
Asahina H, 2010	16	0	44%	14.7	2.5
Koizumi T, 2007	20	3	45%	12	2
Lee SJ, 2012	1	1	-	-	-
Yano S, 2004	3	0	100%	-	-
Yoshimoto A, 2007	1	0	-	1	1
Kurata T, 2004	1	1	-	NI	NI
Oh IJ, 2012	23	5	75%	11.4	3.4
Tomizawa Y, 2010	20	5	65%	10	-

Table 2

Author	N of pts	RR (pts)	DCR	OS (mos)	PFS (mos)
Cho BC, 2007	21	2	28.6%	5.2	2
Costa DB, 2008	18	1	22.2%	-	2
Garfield DH, 2005	1	1	-	-	-
Gridelli C, 2007	3	3	-	-	-
Testumoto S, 2012	2	-	100%	11.5	10.5
Wu SG, 2008	1	1	-	-	8
Lee DH, 2008	23	1	8.7%	-	3.3
Vasile E, 2008	8	2	62.5%	14.6	5.9
Wong AS, 2008	14	-	35.7%	-	-
Chang JW, 2007	1	1	-	-	18
Sim SH, 2009	16	1	25%	-	1.7
Zhou ZT, 2009	21	2	28.5%	4.5	1.8

H33 THE ROLE OF BONE METASTASES IN EGFR-MUTATED ADVANCED LUNG ADENOCARCINOMA PATIENTS

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Background. Although the introduction of targeted therapy has improved the prognosis of patients with activating mutations of the epidermal growth factor receptor (EGFR) gene, the clinical outcome in a subgroup of these patients remains unacceptably poor. The aim of our study was to analyse the clinical factors potentially influencing the outcome of patients with lung adenocarcinoma harbouring activating EGFR mutations.

Patients and methods. We evaluated 288 advanced non-small cell lung cancer patients undergoing therapy at our Institution between 2010 and 2013. 168 were adenocarcinoma (52.4%) and 33 (19.6%) of these showed EGFR mutations. In 26 patients (79%) the mutation was found in exon 19 and in 7 cases (21%) in exon 21. We retrospectively studied clinical and pathological characteristics and clinical outcomes of the 33 EGFR-mutated advanced lung adenocarcinoma patients.

Results. Sixteen out of the 33 EGFR-mutated advanced lung adenocarcinoma patients (48.5%) presented bone metastases (BMs) at the time of diagnosis and only 3 patients (1%) presented isolated bone disease. At univariate analysis a worse progression-free survival (PFS) was related to presence of bone metastases at time of diagnosis: the median PFS was 7.4 months compared to 10.7 months in patients with or without BMs, respectively ($p = 0.023$). The univariated analysis showed a negative correlation with high level of tumor markers (CEA or CYFRA 21.1) at time of diagnosis and the PFS ($p = 0.016$). These results were confirmed also by the multivariate analysis. No significant relationship was found between PFS and type of mutation, ECOG performance status, sex, smoking status, brain or other visceral metastases.

Conclusion. Our preliminary analysis showed that there are clinical factors, such as the presence of BMs at time of diagnosis and high level of tumor markers (CEA and CYFRA 21-1), that could represent negative prognostic factors in EGFR mutated lung adenocarcinoma patients. These data should be considered in the therapeutic strategy and management of these patients.

H34 DECLINING TREND IN THE USE OF CHEMOTHERAPY NEAR THE END OF LIFE IN PATIENTS WITH ADVANCED LUNG CANCER: A SEQUENTIAL OBSERVATIONAL STUDY

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Background. The use of chemotherapy (CT) in the last weeks of life is considered a poor indicator of quality of care. It is reported expecially in patients (pts) with advanced lung cancer (ALC). In a previous retrospective study carried out in 2003-2005 at our Institution, 34% (41/119) of pts treated with at least one line of CT for ALC and subsequently dead, had received the last drug administration in the last month of life (cohort 1). Following this observation, a number of initiatives have been planned and prospectively taken with the aim of reducing the percentage of pts who receive cancer treatment in the last month

of life through a) promotion of oncologists awareness of the appropriate use of anticancer drugs, b) inclusion of psychologists within the team, c) earlier and more integrated collaboration with the extra-hospital Palliative Care Network and d) multiprofessional and multidimensional evaluation of pts with short-term life expectancy. Parallel to these initiatives, internal audits on the use of CT in the last weeks of life in pts followed by our Institution were periodically conducted.

Methods. The study is based on the audit of medical records of ALC pts treated with at least one line of cancer therapy and dead in the periods 2006-2007 (cohort 2), and 2009-2011 (cohort 3). The data were then compared with each other and with those of the cohort 1.

Results. Ninety-eight and 125 pts were recorded in the cohort 2 and 3, respectively. The treatment was initiated or continued within the last month of life in 28.6% and in 24.8% of pts, respectively. Patients in cohort 3 who received CT in the last month of life were male in 71%, had a median age of 68 (37-83), a median KPS of 70 (50-90), the last anti tumour treatment was of first-line in 35%, second- or third-line in 61% and consisted mainly of single-agent regimens for both i.v. and oral administration route. At the same time in the cohort 3 the activation of home care programs for ALC pts increased by 78.6% and 41.9% as compared with cohort 1 and 2, respectively.

Conclusions. The use of CT in the last month of life in patients with ALC has been declining over the past few years. Increased awareness of the oncologists towards an appropriate use of anticancer treatments in these patients and closer integration with the local Palliative Care Network may have contributed to this result. Nevertheless, patients with ALC still remain at risk of receiving cancer treatments near the end of life.

H35 WHY LUNG CANCER (LC) PATIENTS ARE ADMITTED IN THE ACUTE CARE SETTING? AN ANALYSIS OF CLINICAL ISSUES AND PROGNOSIS

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Background. LC pts frequently need hospital admission during the natural history of the disease due to acute conditions or refractory symptoms. We aimed at having an insight on the characteristics of LC pts admitted in our oncology ward, on their needs and their prognosis in order to re-think the organizational model and clinical procedures.

Patients and methods. Using the electronical medical records (Trakcare ®), we described the consecutive admissions of pts with LC within a 15-month period, with respect to pts characteristics and outcome of admission.

Results. 156 admissions of 108 LC pts were consecutively performed in our department in the examined period. LC pts were 24% of all the admissions in the same period. 62% of the pts was admitted once, 32% twice, 6% three or four times. Males were 69%; median age was 68 (range 38-89); 41% was = 70. 16% had SCLC, 13% had stage III NSCLC and 71% stage IV NSCLC. ECOG PS was 0-1 in 29%, 2 in 22% and 3-4 in 49%. Admissions were urgent in 76% of the cases and were due to cancer-related problems in 78%; in 22% were due to non-cancer related conditions or to treatment toxicity. Admissions were performed within 1 month from diagnosis in 27%, from 1 to 3 months in 13% and over 3 months in 60%. The main reason for admission (85%) was a non-controlled symptom: dyspnea in 28%; neurological symptoms due to CNS involvement in 23%, pain in 17%. Mean hospital stay was 12 days. During hospital stay chemotherapy was performed in 8%, radiotherapy in 6%, an invasive procedure in 32% and medical supportive therapy only in 53%. In 45% pts were admitted in the last 30 days of life: among them, chemotherapy was performed in only one case. Discharge at home was possible in 58%, in hospice in 8%, while death during hospital stay occurred in 34%. The median overall survival was 1.3 months (95% CI 0.9-1.6 months). 30-day survival was 56.9%; 6-month 16.2% and 1-year 3.9%. In a multivariate analysis, PS 3-4 ($p = 0.0001$), skeletal ($p = 0.012$) and CNS ($p = 0.017$) metastases identified pts with a worse prognosis.

Conclusions. Admission of LC pts is often unplanned and due to refractory symptoms, among which dyspnea is the more frequent and troublesome. The prognosis of admitted pts is dismal and in-hospital mortality is high. ECOG PS. has a high prognostic value. Only a minority can be transferred to palliative care services. Palliative treatment and end-of-life support should be provided in the acute care setting.

H36 PROGNOSTIC VALUE OF CELL-FREE HTERT DNA LEVELS IN PLASMA FROM EARLY STAGE NON-SMALL CELL LUNG CANCER PATIENTS

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Background. Prognosis of patients (pts) with non-small cell lung cancer (NSCLC) is poor, even in early-stage disease. Human telomerase reverse transcriptase (hTERT) expression and telomerase activity have been reported as prognostic factors in stage I NSCLC patients, but less is known about the cell-free DNA (cfDNA) concentration of this marker. The aim of this study was to evaluate the prognostic value on disease-free (DFS) and overall survival (OS) of plasma hTERT cfDNA concentration assessed before definitive radiation therapy (RT) in an Italian prospective cohort of early stage NSCLC patients.

Material and methods. Twenty early-stage NSCLC pts (11 stage IA and 9 IIA) were evaluated: median age was 77 years (range 59-88); Male/Female: 10/10; smokers/never smokers: 12/8. All the pts underwent Stereotactic Body RT (SBRT), consisting of 52 Gy in 8 fractions, and were treated with Helical Tomotherapy. Blood samples were collected the first day of SBRT and plasma cfDNA extracted by QIAmp DNA Mini kit (Qiagen, Italy). Several dilutions of the extracted cfDNA were quantified with a previously validated hTERT real-time PCR. Log-rank tests of DFS and OS were computed according to cfDNA levels.

Results. Before SBRT, median value of hTERT cfDNA was 3.5 ng/mL (range 0.2-24.3 ng/mL). After a median follow-up of 12 months from SBRT, 6/20 pts (30%) developed tumour recurrence (2 hilar nodal/mediastinal failures, 3 distant metastases and 1 secondary lung cancer) and 3/20 pts died (15%). Evaluating pts

survival according to cfDNA concentrations, we observed an incresead DFS in pts with hTERT cfDNA <3.5 ng/mL (log-rank test: 9.32, p = 0.002); both DFS and OS were increased in pts with hTERT cfDNA <10 ng/mL (log-rank test: 6.79, p = 0.009 and log-rank test: 10.59, p = 0.001, respectively).

Conclusions. Our results suggest that in early-stage NSCLC pts hTERT concentration >10ng/mL, evaluated before RT, was associated with worse prognosis. The quantification of this laboratory molecular biomarker, mostly considering the non-invasive approach, may have practical clinical implications and its possible prognostic significance needs to be further explored also in the follow-up.

H37 MAINTENANCE CHEMOTHERAPY WITH PEMETREXED IN MALIGNANT PLEURAL MESOTHELIOMA

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Background. Maintenance chemotherapy with pemetrexed is not the standard treatment of choice in patients with locally advanced or metastatic epiteliomorfe malignant pleural mesothelioma (EMPM). We would assess the safety and efficacy of a treatment with pemetrexed until progression disease after 4 or 6 cycles of induction therapy with or without platin.

Material and methods. From July 2008 to September 2012, 21 patients (18 males and 3 females with a median age of 67 years, range 58-84) with locally advanced or metastatic epiteliomorfe malignant pleural mesothelioma (EMPM) were enrolled. In all patients histology was epiteliomorfe malignant mesothelioma. Only 15 patients (71.4%) had a PS 0 whereas 6 (28.6%) had a PS 1. All patients received an induction therapy with or without platin. Each patient received an average of 5.6 cycles of induction chemotherapy. Then all patients received a maintenance chemotherapy with pemetrexed 500 mg/m^2 intavenously over 10 minutes every 3 weeks. Each patient received an average of 7.3 cycles of maintenance chemotherapy. All patients received folic acid and vitamin B12 supplementation to improve safety.

Results. At the time of analysis all patients were evaluable for response. Fourteen patients (66.6 %) had a partial response and two of these underwent surgery and obtained a complete response. Six patients (28.5%) had a stable disease. The median overall survival was 13 months, while median progression-free survival was 11 months. Grade 2-3 of WHO haematological toxicities (anemia and neutropenia) occurred in 4 patients (19%). We also observed grade 2-3 of WHO gastrointestinal toxicities (diarrhea, nausea and vomiting) in 2 patients (9.5%). Grade 2 of lack of appetite and asthenia occurred in 3 patients (14.3%).

Conclusions. Our data show that a maintenance chemotherapy with pemetrexed in EMPM resulted in a moderate overall survival (13 months). These results indicate that patients with EMPM could benefit from a maintenance treatment with pemetrexed.

H38 FIRST-LINE TREATMENT WITH METRONOMIC ORAL VINORELBINE IN ELDERLY PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER: SECOND STEP RESULTS OF A PHASE II TRIAL (MOVE TRIAL)

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Background. Metronomic oral vinorelbine could be a safe option for elderly patient with advanced non-small cell lung cancer (NSCLC). Metronomic chemotherapy leads to a cytostatic action shifting treatment target from cancer cell to tumor neo-angiogenesis. Moreover, metronomic administration of drugs has the potential to increase drug-related therapeutic effect without worsening safety profile.

Patients and methods. Thirty-two (M/F 27/5) chemotherapy naïve elderly (= 70 yrs), PS 0-2 patients with stage IIIB-IV NSCLC were prospectively enrolled. Median age was 79 (range 70-86) yrs with low differentiated tumors and predominantly squamous histology. PS distribution was 0-1 (12)/2 (20) with a median of 3.5 (range 1-5) serious (cardiovascular, pulmonary, renal or metabolic) co-morbid illnesses. Study treatment consisted of oral vinorelbine 50 mg three times weekly (Monday-Wednesday-Friday) restless. Primary endpoints were overall response rate (ORR), clinical benefit (CB) and safety. As per protocol we present the second interim analysis results.

Results. Patients received a median of 6 (range 3-24) cycles. ORR was 15.6% with 4 partial and 1 complete responses; 16/32 experienced stable disease lasting more than 12 weeks leading to an overall CB of 65.6%. Median time to progression was 6.4 (range 2-21) and median overall survival 9.2 (range 3-26) months. Treatment was well tolerated with rare G3/4 toxicity (three episodes of G3 diarrhoea, two of not-febrile G3 neutropenia and two of G3 fatigue). Regardless of severity main toxicities observed were anemia in 39%, fatigue in 39%, diarrhoea 16%, nausea in 9% and vomiting in 7% of patients.

Conclusions. Metronomic oral vinorelbine is safe in elderly patients with advanced NSCLC with an interesting activity mainly consisting in long-term disease stabilization. Preliminary survival data are encouraging. Study accrual will continue to a total of 43 patients.

H39 TUMOR-RELATED SYMPTOMS (TRS) ASSESSMENT IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) TREATED WITH GEFITINIB OR ERLOTINIB: PRELIMINARY RESULTS OF AN OBSERVATIONAL STUDY

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Background. Edmonton Symptoms Assessment Scale (ESAS)

is a validated tool in palliative care, which evaluates physical symptoms through a numeric scale (0-10). Symptoms improvement as a predictive factor for response rate (RR) in pts with advanced NSCLC treated with tyrosine-kinase inhibitors (TKIs) has not yet been evaluated. To this purpose, we performed an observational retrospective study.

Methods. Patients with advanced NSCLC treated with gefitinib or erlotinib were eligible. Primary outcome was the association between treatment response and tumor-related symptoms (TRS)(pain, asthenia, dyspnea) improvement. ESAS was performed at day 1 and 14 of each 28-d cycle. Symptoms scores were divided into: not clinically relevant (0-4, NCR) and clinically relevant (5-10, CR). Sample size estimation was 115 to 165 pts to be needed for the expected difference in the primary outcome. Differences between symptoms groups were analyzed with the paired-data McNemar-test. All the associations were estimated using the Chi-Square test. Kaplan-Meier method was used for survival calculation. Uni- and multivariate survival analysis were carried out using the Cox regression model.

Results. At present, we report data about 89 consecutive pts; median age: 69 years, 70% males, ECOG PS 0-1 88%, smokers 71%, EGFR-mutated 19%. Treatment was gefitinib (20%) or erlotinib (80%). RR: RC/RP 14%, SD 22%, PD 64%. Median follow-up was 7 months. 63% of pts had at least one CR TRS at baseline. A significant reduction ($p < 0.0001$) of TRS was observed among these pts (Table). Our preliminary data show a significant association between dyspnea/asthenia and RR ($p = 0.01$). At the multivariate analysis, TRS improvement correlates with both PFS and OS. Also related with survival were PS, EGFR status (PFS) and RR (OS).

Conclusions. Our preliminary data show that TRS improvement is significantly associated with treatment response and appears to be a prognostic factor during treatment with TKIs.

TRS	Basal score = 5 (%)	Nadir* score (%)
Pain	53	19
Asthenia	66	30
Dyspnea	57	23

*Lower score registered per patient.

H40 CISPLATIN IN COMBINATION WITH ETOPOSIDE FOR THE FIRST-LINE TREATMENT OF PATIENTS WITH LARGE CELL NEUROENDOCRINE CARCINOMA OF THE LUNG

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Background. Large-cell neuroendocrine carcinoma (LCNEC), 1-3% of all lung cancers, at diagnosis is generally widespread. The prognosis is poor despite an aggressive approach with extensive surgical resection for low stages and multidisciplinary approach with chemotherapy and radiotherapy for advanced stages. In literature there is no optimal treatment for patients with LCNEC. A recent retrospective review (Sun JM et al., Lung Cancer, 77-2: 365-70) of 45 consecutive patients with advanced LCNEC assessed that the median PFS durations were 6.1 and 4.9 months ($p = 0.41$), and the median OS durations were 16.5 and 9.2 months ($p = 0.10$) depending on whether first-line chemotherapy used regimens designed for SCLC (N = 11) or for NSCLC (N = 34). Our aim is to evaluate the effectiveness of the doublet cisplatin-etoposide plus octreotide in LCNEC as a first-line therapy.

Patients and methods. We retrospective studied 33 patients with LCNEC from 2005 to 2013 who received cisplatin 90 mg/m^2 d 1q21, etoposide 100 mg/m^2 d 1-3q21 and octreotide LAR 30 mg every 28 days. Other eligibility criteria were performance status 0 or 1, any stage, no previous chemotherapy and a histologically documented LNEC. The Kaplan-Meier test was used in order to evaluate the progression-free survival (PFS) and overall survival (OS).

Results. Twenty-eight patients (84.8%) had a smoking history, median age was 66 (range 40-80), 60.6% men, 39.4% women. Patients received a median of 6 cycles (range 3-6). The median PFS was 12.5 months (95% CI 5.9-19.0) and the OS was 18.0 months (95% CI 11.3-24.7) respectively.

Conclusions. Results show that patients treated with cisplatin-etoposide and octreotide LAR have a poor prognosis similar to SCLC regardless of the stage of presentation, however our results, if compared to literature, support that cisplatin-etoposide plus octreotide based regimens may be effective against LCNEC.

H41 METRONOMIC VINORELBINE IN ELDERLY PATIENTS AFFECTED BY ADVANCED NSCLC

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Background. Average age of patients affected by advanced NSCLC is increasing due to aging of population. By now we have about 50% of patients aged 65 or more. In few years we are going to have 2/3 of patients over 70. Treatment of these patients is a challenge. In fact co-morbidities are the rule, PS is often low and use of platinum compounds may be of concern. Median OS is low (6 months) and PFS and symptom control are often poor. Vinorelbine iv is one of the most popular drugs in this setting of patients. ELVIM study demonstrated its efficacy and its low toxicity with less than 20% of G3 toxicity. We designed a phase II study vith oral vinorelbine administered with an innovative schedule.

Patients and methods. We have planned to enrol 100 chemonaïve patients affected by stage IIIB or IV NSCLC. Twenty patients (median age 75, 70-88) have been enrolled until now. Vinorelbine is administered at the fixed dose of 50 mg three times a week until unacceptable toxicity (G4 or 2 consecutive G3 toxicities) or progression. Dose escalation to 40 mg three times a week was planned in case of G3 toxicity. Primary endpoint is toxicity assessment (NCI-CTC). PFS, OS, RR are secondary endpoints. CT scans were performed every 6 weeks. If less than 20% patients will experience G3 toxicities at interim analysis (50 pts) or at the end, the study will be considered positive.

Results. Median duration of therapy was 7 weeks (2-18). Until now, we recorded only 2 G3 myeloid toxicities (neutropenia, recovered after 5 and 6 days). Both had dose escalation without

other toxicities. Other minor toxicities were recorded: 2 pts (10%) with G1 mucositis, 4 pts (20%) with G1 and 4 pts (20%) with G2 gastrointestinal toxicities, 2 pts (10%) with G1 anemia, 1 pt (5%) with G1 thrombocitopenia, 2 pts (10%) with oral mucositis. Median OS is 140 days with 5 patients (25%) still alive for more than 250 days. PFS is 70 days. Best response is PR in 2 pts (10%), SD in 9 pts (45%), PD in 9 pts (45%).

Conclusions. Our data are preliminary but promising. This regimen seems feasible, safe and effective. After full enrolment we will be able to confirm these conclusions.

H42 A STUDY ON THE PROGNOSTIC SIGNIFICANCE OF NEURON-SPECIFIC ENOLASE (NSE) PRETREATMENT BLOOD LEVELS AS POSSIBLE PREDICTOR OF CHEMOTHERAPY (CT) ACTIVITY IN METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC)

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The clinical and prognostic significance of NSE blood concentrations in NSCLC still remains to be established, since very few and controversial results have been reported in literature. In fact, both negative and positive prognostic significance has been attributed to NSE levels in patients with NSCLC. This retrospective study was performed in an attempt to obtain some preliminary data on the prognostic significance of NSE in NSCLC treated by chemotherapy (CT). Eligibility criteria were, as follows: histologically proven NSCLC, metastatic disease, measurable lesions, no previous CT for metastatic disease. The study included 40 consecutive patients, who had been hospitalized to receive CT from November 2010 to December 2011. According to the different tumor and clinical variables, patients were treated with cisplatin (CDDP) plus gemcitabine (GEM) (N = 8), carboplatin (CBDA) plus GEM (N = 9), CDDP plus pemetrexed (PTX) (N = 8), CBP plus PTX (N = 8), CDDP plus DOCETAXEL (N = 7). Normal values of NSE (95% confidence limits) were below 17.0 ng/mL. Abnormally high pre-treatment levels of NSE were observed in 26/40 (64%) patients, without significant differences between adenocarcinoma and other histotypes. Taken together, 12/40 (30%) patients achieved a partial response (PR). Moreover, irrespectively of the type of CT, the percentage of PR obtained in patients with normal pre-treatment values of NSE was significantly higher than that found in those with elevated NSE concentration prior to CT (9/14 (64%) vs 3/26 (12%), $p < 0.01$). The higher response rate in patients with normal pre-treatment values of NSE was also evident in relation to the single type of CT, even though the very low number of patients did not allow to reach a statistical significance. These findings seem to suggest that the evidence of abnormally high pre-treatment blood levels of NSE could predict a diminished efficacy of CT in metastatic NSCLC. Further prospective studies in equally treated patients are warranted in order to explore the predictivity value of NSE in metastatic NSCLC.

H43 A NOVEL RARE EGFR MUTATION IN EXON 18 SHOWED STABLE DISEASE AFTER TKI TREATMENT

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Background. The development of new targeted drugs for the treatment of non-small cell lung cancer in the last decade represents a promising approach to prolong the otherwise very poor prognosis of patients with advanced UICC stage. Specific activating mutations of epidermal growth factor receptor (EGFR) are eligible for the treatment with specific tyrosine kinase inhibitors like gefitinib or erlotinib. Beside typical deletions in exon 19 and point mutations in exons 18 and 21 with known clinical significance, there is a small group of uncommon heterogeneous EGFR mutations reported in small case numbers whose influences on the effectiveness of EGFR TKIs have not been fully elucidated.

Patients and methods. Here we report a case of 70-year-old woman diagnosed on a lymph node biopsy with an adenocarcinoma T4N3M1b (stage IV), grade II, with an IHC panel compatible with a primitive tumour of the right lung. Mutational analysis of the EGFR receptor (exons 18-21) was performed on DNA isolated from biopsy specimen by direct sequencing.

Results. The molecular analysis revealed a not previously reported EGFR mutation in exon 18 (I715T). Patient started treatment with gefitinib after poorly tolerated 1 cycle of cisplatinum + gemcitabine. Biological treatment resulted in a partial remission in 3 months that was maintained for 9 months, with an excellent improvement of her quality of life. The patient is at present under radiological evaluation.

Conclusions. The reported case confirms the heterogeneity of the clinical response to TKIs of rare EGFR mutations and highlights the importance to routinely conduct a full characterization of EGFR hotspots (exons 18-21) in order to not miss uncommon mutations and therefore to improve the personalized treatment of advanced non-small cell lung cancer in the future.

H44 TREATMENT WITH CISPLATIN-ETOPOSIDE IN THE HIGH-GRADE NEUROENDOCRINE TUMORS OF THE LUNG: IS HISTOLOGY IMPORTANT?

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Background. The optimal treatment for neuroendocrine tumors (NE) of the lung is still a matter of discussion. There is controversy regarding chemotherapy for large cell neuroendocrine carcinoma (LCNEC), in fact it is not clear if the optimal treatment for LCNEC is similar for small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). The aim of our study is to analyze the differences in demographic characteristics and survival between SCLC and LCNEC using the same therapeutic strategy in both histological types.

Patients and methods. Thirty-three and 24 patients with a diagnosis of LCNEC and SCLC respectively from 2005 to 2013 received cisplatin 90 mg/m^2 d1q21, etoposide 100 mg/m^2 d1q21 plus octreotide LAR 30 mg every 28 days. Other eligibility crite-

ria were performance status 0 or 1, any stage, no previous chemotherapy and a histologically documented LNEC. The Kaplan-Meier test was used in order to evaluate the progression-free survival (PFS) and overall survival (OS).

Results. In our single institution study we retrospective examined 57 patients of whom 50 (87.7%) with smoking history, median age of 64 (range 40-80), 63.2% male. Patients received a median of 6 cycles (range 3-6). For LCNEC the median progression-free survival (PFS) was 12.5 months (95% CI 5.9-19.0) and the overall survival (OS) was 18.0 months (95% CI 11.3-24.7). For the SCLC the PFS was 16.2 months (95% CI 7.9-24.6) and OS was 25.8 months (95% CI 16.8-34.9).

Conclusion. In our results LCNEC tumors treated with cisplatin and etoposide plus octreotide LAR have a lower PFS (12.5 vs 16.2 months) and OS (18.0 vs 25.8 months) than SCLC.

	PFS months	OS months
LCNEC	12.5 (CI 5.9-19.0)	18.0 (CI 11.3-24.7)
SCLC	16.2 (CI 7.9-24.6)	25.8 (CI 16.8-34.9)

H45 LONG TERM SURVIVAL OF FIVE PATIENTS WITH SMALL CELL LUNG CANCER

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Background. The small cell lung cancer (SCLC) is the most aggressive form and represents approximately 15-20% of all cases of lung tumors. It is characterized by specific biological behavior, chemoradiosensitivity, rapid relapse and easily metastasize at an early stage. Despite an initial sensitivity to chemotherapy, the majority of patients have disease recurrence. The prognosis for these patients is usually poor with survival time after recurrence of 2-4 months.

Materials and methods. We retrospectively reviewed all patients treated in our centre between 2002 and 2013 and initially classified as SCLC. Our report concerns five patients with histologically proven SCLC who showed a long term survival.

Results. Five cases with long term survival were selected, 3 women and 2 men, all hard smokers, median age was 59.6 (range 50-74). Patients histories are summarized in the Table below. Four of the patients are still alive, one without evidence of disease and three in stable disease.

Conclusions. Although the prognosis of SCLC in general remains poor, long-term survival is possible. Application of combined therapies, chemotherapy, thoracic radiotherapy and PCI probably prolongs survival in selected patients. It was also interesting to note that two of the five patients examined have developed an important degree of cognitive impairment after prophylactic brain radiation therapy: at present the correlation between the two phenomena is discussed.

H46 18F-FDG PET-CT METABOLIC TUMOR VOLUME (MTV) CORRELATES WITH EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) MUTATION STATUS IN PATIENTS WITH NSCLC: PRELIMINARY DATA

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Background and aim. Several molecular alterations have been identified in non-small cell lung cancer (NSCLC), with subsequent development of targeted therapies. In particular, EGFR-tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib showed efficacy in patients harboring EGFR mutations. Previous reports suggest a correlation between 18F-FDG PET maximum standardized uptake value (SUVmax) and EGFR mutation status in NSCLC. We evaluated whether the presence of EGFR mutations may correlate with 18F-FDG PET metabolic tumor volume (MTV) and standardized SUVmax.

Material and methods. We analyzed 18F-FDG PET-CT in 12 patients with EGFR mutations and a control group of 8 subjects with wild type EGFR. All patients underwent surgery resection for early-stage lung adenocarcinoma. 18F-FDG PET-CT was performed 3 ± 1 months before intervention and SUVmax as well as MTV (cm 3; 42% threshold) of lesions were computed on reconstructed images. SUVmax and MTV values were correlated to the presence of EGFR mutations.

Results. Mean SUVmax of lesions in patients presenting EGFR mutation was 7.1 ± 1 and it was 9.2 ± 3 in those who did not ($p = 0.8$). MTV(cm 3) of lesions was 47.8 ± 30 and 13.0 ± 3 ($p = 0.003$) in patients with and without EGFR mutation, respectively. A significant correlation ($r = 0.76$; $p = 0.008$) was found between MTV and the presence of EGFR mutations whereas SUVmax did not correlate with EGFR mutation status ($r = 0.04$; $p = 0.8$).

H45 - Table

Pts	Stage	Surgery	CHT	RT	PCI (months)	PFS	Other CHT	OS (months)
1	IB	R0 resection	adj EP	no	no	55	-	
2	IIIA	no	EP	mediastinal	yes	55	-	
3	IIIA	no	EP	mediastinal	yes	92	-	
4	IIIB	no	EP	no	no	18	- topotecan - carboplatin - EP	56
5	IV	no	EP	mediastinal	yes	62	-	

CHT-chemotherapy; RT-radiotherapy; PCI-prophylactic cranial irradiation; EP- etoposide and cisplatin.

Conclusions. Our preliminary data indicate that the quantitative assessment of 18F-FDG PET-CT MTV rather than SUVmax correlates with EGFR mutation expression; further studies are needed to better define the role of 18F-FDG PET-CT MTV in NSCLC patients harboring EGFR mutations.

H47 TREATMENT IN MALIGNANT PLEURAL MESOTHELIOMA AFTER THERAPY WITH CISPLATIN-PEMETREXED

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Background. The malignant pleural mesothelioma is a health problem of increasing incidence and severity.

The association cisplatin-pemetrexed (with supplementation of folinic acid and vitamin B) is the standard of care for advanced malignant pleural mesothelioma. The treatment rarely results in cure and should be considered palliative. For patients in progression with this approach there is no chemotherapeutic treatment of second-line that can be considered standard and the sick are generally aimed at a rapid deterioration of the general conditions and exitus, so you can ethically take only a pain therapy and/or support.

There are, however, some patients in such clinical conditions that it can be considered appropriate to continue a chemotherapy program, for the benefit of patients after standard treatment.

Patients and methods. We treated 9 patients: 7 men, 2 women, median age 65 years (range 55-71), PS <2, on progression after cisplatin-pemetrexed. We have adopted a chemotherapeutic regimen (acronym: BIG), including: bleomycin 15 Mu i.m. day 1, ifosfamide (with Mesna uroprotection) 2000 mg/m^2 e.v. day 1, gemcitabine 1000 mg/m^2 e.v. day 2. The treatment was repeated every 2 weeks, upon inspection of the bio-clinical parameters. The aim of our study is to evaluate efficacy and tolerability.

Results. After three months we carried out an instrumental revaluation of disease and found 3 objective responses (OR) and 1 stable disease, 2 PD; in the 4 patients (3 OR, 1 SD) therapy was continued for 3 months, noting 2 OR, 1 SD, 1 PD. The duration of response has been >6 months. In patients with response there has been a clear reduction of symptoms (pain, dyspnea, weight loss), with improvement of the clinical condition (reduction of the opioid analgesics, non-steroidal anti-inflammatory drugs, corticosteroids and anxiolytics). None of the patients required an interruption or hospitalization during the treatment period. The toxicities found: nausea and vomiting very low, moderate myelosuppression: in fact neutropenia, anaemia (I WHO) have not required the use of hematopoietic growth factors and/or erythropoietin and/or transfusion of blood products.

Conclusions. The results are encouraging for: the rate of the response, the moderate toxicity, the improvement of the quality of life. Therefore, the study stimulates to continue and try the same combination for a further valuation.

H48 MOTIVATING THE PATIENT TO WAIT FOR MOLECULAR TEST RESULTS IN NON-SMALL CELL LUNG CANCER (NSCLC): A PRACTICAL COMMUNICATIVE MODEL THROUGH KEY MESSAGES

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Background. The diagnostic workup of the patient who is suffering from NSCLC often takes longer than for other cancers. Given then the strong demand for immediate treatment, the communication of the need of further diagnostic steps for the definition of the appropriate therapeutic approach becomes critical. It is essential to provide adequate information to obtain consent for the execution of the molecular test, specifically for the determination of the activating mutation of EGFR.

Methods. We identified and selected a series of key messages to be highlighted in this type of clinical counselling. For the most, they are directed to underline the benefits which could be produced by the potential diagnosis of activating EGFR mutations and by therapeutic use of tyrosine kinase inhibitors such as gefitinib or erlotinib (TKI). The main messages that are specifically included in the communication item are:

- customer rating of an oral treatment compared to an intravenous treatment;
- limitation of occasions and times of access required the hospital;
- description of side effects expected with TKI and comparison with the effects of chemotherapy;
- high possibility of achieving tumor reduction (clinical response) compared to those of a chemotherapy treatment;
- ability to achieve a long lasting control of the disease (time to progression);
- ability to achieve a rapid symptom relief;
- careful monitoring by the attending physician of symptoms through the prescription of any therapy in the time frame;
- commitment of the structure to contain the technical time of the test within 10 days;
- ability to start premedication vitamin useful in the case of a negative result and the possible prediction of treatment with protocols containing pemetrexed.

Results. From the analysis of the very first cases approached with this method (11 pts), it was found an unanimous consent to molecular testing and acceptance of the proposed waiting time. This leads us to introduce, for subsequent cases, the evaluation of the patients anxiety in two groups at time of the proposal of molecular test (with or without our communication strategy) with a specific questionnaire, such as the Zung scale.

Conclusions. The presence of these key messages is emerging as an useful tool to ensure the achievement of adequate patient information goals, the optimal therapeutic choice, as well as the control of anxiety.

H49 A PRELIMINARY RETROSPECTIVE COST EFFECTIVENESS ANALISYS COMPARING PLATINUM-PEMETREXED VERSUS PLATINUM-GEMCITABINE THERAPY IN ADVANCED NON-SMALL CELL LUNG CANCER

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Background. The new treatments for lung cancer patients have significantly improved survival but the costs of therapy have dramatically increased over time. For instance, a phase III study comparing cisplatin-pemetrexed with cisplatin-gemcitabine has shown superiority of the former regimen among patients with adenocarcinoma and large-cell carcinoma (OS 10.9 vs 12.6 months), but at an increased cost. The purpose of this retrospective analysis was to evaluate the economic costs of therapy in 30 patients treated in our unit with cisplatin-gemcitabine or cisplatin pemetrexed.

Patients and methods. We evaluated the costs of chemotherapy for 30 patients with non-small-cell lung cancer with adenocarcinoma and large-cell carcinoma. A total of 15 patients (median age 56 years) were treated with cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 both on day 1 every 21 days, whereas 15 patients (median age 65) were treated with cisplatin 80 mg/m^2 on day 1 and gemcitabine 1250 mg/m^2 on day 1, 8 in a 21-day cycle. Both groups were treated for a maximum of six cycles. The median number of cycles was 5 in each group. Only direct medical costs related to chemotherapy were estimated.

Results. The global cost of cisplatin-pemetrexed therapy was 193,367 euro, with a mean of 2148 euro per cycle and 12,890 euro per patient. Two patients received only three cycles for early disease progression. The global cost of cisplatin-gemcitabine therapy was 7616 euro, 94 euro per cycle and 507 euro per patient. Five patients discontinued therapy after five cycles due to disease progression.

In both groups we observed a similar response rate and a similar toxicity (nausea, vomiting grade 2, asthenia, G3 neutropenia), but in the gemcitabine-group six patients switched to carboplatin for grade 2 creatinine increase. Median PFS was 8.3 months in the pemetrexed group and 9 months in gemcitabine group.

Conclusions. This preliminary report suggests that the greatly increased cost of the doblet cisplatin-pemetrexed is not justified by an increased benefit on PFS in adenocarcinoma and large cell lung cancer. Whereas our study is simply exploratory and clearly underpowered to draw firm conclusions, our findings raise the issue of increasing costs of palliative treatment which may not always be cost-effective.

H50 MULTIMODAL TREATMENT OF NEOPLASTIC TRACHEOBRONCHIAL OBSTRUCTION

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Background. Neoplastic bronchial obstruction is a medical emergency. Its treatment is almost always palliative and can be done with laser coagulation, endobronchial stent, endobronchial brachytherapy or external radiotherapy. We describe a case of primary tracheobronchial tumor obstructing the distal trachea and the main left bronchus, successfully treated with sequential Nd-YAG laser coagulation, chemoradiation and endobronchial brachytherapy.

Patients and method. A 71-years-old woman, 25 pack-years smoker, with history of pulmonary tuberculosis, was admitted in July 2012 to the Emergency Department of Ferrara Hospital for acute respiratory distress syndrome. Chest X-Ray showed complete opacity of the left hemithorax without air bronchograms. CT-scan showed vegetating lesion almost completely obstructing the trachea, total left pulmonary atelectasis, partial right pulmonary atelectasis. The patient underwent flexible bronchoscopy, that showed a vegetating lesion of the carina with complete obstruction of the left main bronchus and partial obstruction of the right main bronchus. A biopsy of the lesion revealed a lung squamous cell carcinoma. The mass was successfully resected by Nd-YAG laser coagulation during the endoschoscopic procedure, with progressive disappearance of dyspnea, and gaining of a good PS.

Results. The patient was referred to our multidisciplinary lung Unit (medical oncologist, thoracic surgical oncologist, radiation oncologist, pneumologist). After staging procedures (CT-scan, 18F-FDG PET, bone-scan) the patient was classified as locally advanced tracheobronchial squamous cell carcinoma (stage IIIA T4 NO MO, TNM 7th ed. 2010). In August 2012 external radiotherapy was performed with IMRT-SIB technique, delivering 50 Gy to the mediastinum and to the left main bronchus (2.0 Gy/fraction) with concurrent weekly carboplatin AUC 2. In September 2012 high dose rate endobronchial brachytherapy (HDR-EB) was performed, delivering 1500 cGy (500 cGy/fraction). CT-scan 1 month after brachytherapy showed a complete response of disease. Bronchoscopy with random biopsies did not reveal macroscopic and microscopic residual disease. At 1-year follow-up, the patient is still alive with good performance status (ECOG PS 0), without respiratory symptoms and signs of disease recurrence.

Conclusions. Multimodal approach of endobronchial obstruction should be performed by a multidisciplinary team, and can obtain significant effect in selected cases.

H51 SAFETY AND ANTITUMOR ACTIVITY OF CARBOPLATIN (CBDCA) PLUS PEMETREXED IN PATIENTS OLDER THAN OR EQUAL TO 75 YEARS WITH ADENOCARCINOMA OF THE LUNG: OUR EXPERIENCE

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Background. As the number of elderly patients diagnosed with non-small cell lung cancer (NSCLC) increases, the number of these patients receiving chemotherapy also increases. NSCLC chemotherapy decisions in patients ≥75 years old are complex because of toxicity, comorbidity and limited data exist regarding the use of chemotherapy in these patients. Platinum-based chemotherapy is considered to be a standard approach for advanced NSCLC. However, it is unclear whether elderly patients with a good performance status can tolerate platinum-doublet chemotherapy like younger patients. The purpose of this study was to evaluate the safety and antitumor activity of carboplatin plus pemetrexed in chemo-naïve elderly pts with advanced adenocarcinoma of the lung who were 75 years of age or older.

Material and methods. Between November 2010 and January 2013, 21 elderly pts (= 75 years) with metastatic adenocarcinoma of the lung were included in this retrospectively analysis. Patients baseline characteristics included: 15 pts were men, median age 77 (range 75-80), 16 pts stage IV and 5 stage IIIb, 13 pts ECOG 1 and 8 ECOG 2, all patients were EGFR wt. Regimen: carboplatin (CBDCA) AUC: 4 day 1 every 3 weeks and pemetrexed 500 mg/m^2 day 1 every 3 weeks. Therapy was continued for a maximum of six cycles in pts showing tumor response or stable disease.

Results. No pts experienced G 3-4 toxicities. Neutropenia G1-

2 was observed in 50% of the pts, anemia G1-2 in 40% of the pts and trombocytopenia G1-2 in 30 % of the patients. Non-hematological G1-2 toxicities were: fatigue (40%), nausea (20%), constipation (20%), mucositis (15%), anorexia (40%). No serious events requiring hospitalization were reported. No toxic related death was reported. The response was as follows: partial response 30%, stable disease 15%. PFS: 4.5 months.

Conclusions. Patients 75 years of age or older with advanced NSCLC may obtain clinical benefit from the administration of platinum-based doublet agent chemotherapy. Combination therapy using CBDCA with pemetrexed is tolerable and promising for elderly pts with adenocarcinoma of the lung.

Session L • Breast cancer

L1* FLUOROURACIL, EPIRUBICIN AND CYCLOPHOSPHAMIDE (FEC) VERSUS CONCURRENT EPIRUBICIN AND PACLITAXEL (EP) IN NODE-POSITIVE EARLY BREAST CANCER (BC) PATIENTS. FINAL RESULTS OF A PHASE III, RANDOMIZED STUDY OF GRUPPO ONCOLOGICO NORD-OVEST-MAMMELLA INTERGRUPPO (GONO-MIG5) GROUP

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Background. At the time the GONO-MIG5 trial was designed in 1996, paclitaxel was known to have efficacy in patients (pts) with advanced BC, but it was still to be established in the adjuvant setting. The study was designed to compare a standard FEC regimen to a new regimen combining both epirubicin and paclitaxel in high risk early BC patients.

Patients and methods. Node positive (≤9 positive nodes) stage I-III BC pts younger than 70 years were eligible and randomly assigned to receive either 6 courses of FEC (5-fluorouracil 600 mg/m^2, epirubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2, on day 1, q21) or 4 cycles of EP (epirubicin at 90 mg/m^2 and paclitaxel at 175 mg/m^2, 3-hour infusion on day 1, q21). The primary study endpoint was overall survival (OS). Secondary endpoints included toxicity and event-free survival (EFS). All analyses were conducted according to the intention-to-treat principle.

Results. From November 1996 to January 2001, 1055 pts were enrolled (520 in the FEC arm and 535 in the EP arm). More than 90% of pts completed the planned number of chemotherapy (CT) cycles both in FEC and EP arm. Patients treated with FEC experienced more frequently nausea and vomiting (85% in FEC arm and 76% in EP arm; p = .0001), stomatitis (46% vs 37%, p = .003) and leukopenia (52% vs 40%, p = .0002). Toxicities which occurred more frequently in EP arm were: anemia (17% vs 25% in FEC arm and EP arm, respectively, p = .006); fever (7% vs 15%, p = .0001); myalgias (1% vs 19%, p = .0001); neurotoxicity (6% vs 38%, p <.0001) and allergic reaction (1% vs 5%, p = .03). At a median follow-up of 12.8 years, 335 deaths have been recorded (172 in the FEC arm and 162 in the EP arm). Estimated actuarial 10-year survival was 73% (95% CI 69-77) in the FEC arm and 74% (95% CI 70-78) in the EP arm (p = 0.405). 422 events (ie, relapse, second malignancy, or death from any cause, whatever happens first) have been recorded (205 in the FEC arm and 217 in the EP arm). Actuarial 10-year event-free survival was 51% (95% CI 45-56) in the FEC arm and 49% (95% CI 44-55) in the EP arm (p = 0.572). In multivariate analysis no difference in the hazard of death was observed between EP an FEC treated pts (HR for EP = 0.85; 95% CI 0.68-1.06; p = 0.15). Pathological tumor size, nodal status (1-3 vs 4-9 positive nodes), and grading were independently associated with OS.

Conclusions. FEC for 6 cycles and EP for 4 cycles have similar efficacy but different toxicity profile in the adjuvant treatment of node positive early BC patients.

L2* HORMONAL INFERTILITY THERAPIES AND BREAST CANCER RISK: A SYSTEMIC REVIEW AND META-ANALYSIS OF POPULATION STUDIES

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Background. With the increasing practice of hormonal manipulations in infertile women, both for ovulation induction in anovulatory women and for ovarian hyperstimulation in assisted reproductive technologies, concerns have been raised about the long-term effects of such practice on the subsequent cancer risk. In the past years, a number of population-based studies have evaluated the possible relation between BC risk and fertility drugs, with inconsistent results. With these premises, we performed a systematic overview and pooled analysis of cohort studies on association between hormonal infertility treatments (HITs) and BC incidence, based on published data.

Methods. Cohort studies, evaluating the association between HITs and BC incidence were identified by MEDLINE search. Standardised incidence ratios (SIRs) were pooled across the studies by inverse variance weighting. Subgroup analyses were performed for the following covariates: length of follow-up (<10 yrs vs ≥10 yrs), type of hormonal therapy (clomiphene vs gonadotropins) and type of control group (population based or internal controls, ie infertile women). All statistical tests are two-sided.

Results. Seventeen eligible cohort studies, including 924,458 women, were identified and retrieved. All suitable studies report fertility treatments and BC incidence. Overall HITs were associated with a 11% increase in the incidence of BC as compared to untreated women (SIR 1.11; 95% CI 0.91-1.30). BC risk was significantly higher in clomiphene treated women (SIR 1.04; 95% CI 0.76-1.32) than in gonadotropins users (SIR 0.83; 95% CI 0.60-1.07). The increase in BC incidence seems to be dependent on follow-up duration (SIR 0.94; 95% CI 0.8-1.08 for <10 yrs vs 1.23; 95% CI 0.86-1.6 for ≥10 yrs, p for interaction <0.0001). Significantly higher risk of BC was seen in studies using population based estimates as controls than in studies with internal controls (SIR 1.13; 95% CI 0.86-1.41 for population vs RR 1.00, 95% CI 0.73-1.26 for internal, p for interaction <0.001).

Conclusions. Overall HITs do not appear to be consistently associated with an increase in BC incidence. Subset analyses suggest a possible increase in BC incidence with longer FU (>10 yrs) whereas, the use of gonadotropin might have a protective effect. Finally, analyses according to type of control suggest that the observed non-significant 11% increased risk may be attributable to the infertility condition itself.

L3* PHASE-III PREVENTION TRIAL OF LOW-DOSE TAMOXIFEN IN POSTMENOPAUSAL HORMONE REPLACEMENT THERAPY USERS: THE H.O.T. STUDY

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Background. Postmenopausal hormone replacement therapy (HRT) relieves menopausal symptoms and may decrease overall mortality in recently post-menopausal women, but increases breast cancer risk. A dose reduction of tamoxifen to 5 mg/day has shown retained activity in phase-II studies.

Material and methods. We conducted a phase-III trial in recently postmenopausal women on HRT for menopausal symptom relief. Between February 2002 and July 2007, 1884 women aged 53.3 ± 5.1 were randomized to either tamoxifen, 5 mg/day or placebo for 5 years. The primary outcome measure was breast cancer incidence.

Results. After 6.2 ± 1.9 years mean follow-up, there were 24 breast cancers on placebo and 9 on tamoxifen (RR 0.80; 95% CI 0.44-1.46). Tamoxifen showed favorable trends in luminal-A tumors (RR 0.32; 95% CI 0.12-0.86) and in HRT users <5 years (RR 0.35; 95% CI 0.15-0.82), but had no effect in the combined HRT subgroup (16 vs 16 events). In women completing 12 months of treatment and adjusting for non-adherence, there were 23 events on placebo and 10 on tamoxifen (RR 0.49; 95% CI 0.23-1.02). Serious adverse events did not differ between placebo and tamoxifen, including, respectively, coronary heart syndrome (6 versus 4), cerebrovascular events (2 versus 5), venous thromboembolic events (2 versus 5), and uterine cancers (3 versus 1). Vasomotor symptoms were 50% more frequent on tamoxifen.

Conclusions. Although an insufficient power prevents reliable conclusions, the combination of HRT and low-dose tamoxifen has the potential to retain some benefits while reducing risks of either agent in recently postmenopausal women. This hypothesis requires confirmation in a larger study.

L4* TREATMENT OF METASTATIC BREAST CANCER: IS PROGRESSION-FREE SURVIVAL AFTER FIRST-LINE PREDICTIVE OF BENEFIT FROM SECOND AND LATER LINES?

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Background. Despite the availability of several therapeutic options for metastatic breast cancer, treatments beyond first-line lack of predictive factors that could help clinical decision-making. Once first-line treatment has failed, the likelihood of benefit is estimated to decrease progressively but no clear data are available on the magnitude of this effect.

Aim. To assess the impact of benefit from first-line therapy on benefit from subsequent therapeutic lines.

Methods. We analyzed a consecutive series of 472 MBC patients treated with chemotherapy (CT) and/or endocrine therapy (ET) at the Department of Oncology of Udine, between 2004 and 2012. We evaluated progression-free survival at first- (PFS1), second- (PFS2), third- (PFS3) and fourth- (PFS4) line of treatment. Three distinct analyses were conducted: the first for CT lines only, the second for ET lines only and the third by counting both CT and ET lines. A PFS longer than 6 months was defined as "6-month benefit". The relative likelihood of a 6-month benefit was estimated through unconditional logistic regression.

Results. Median overall survival was 34 months and median PFS1 was 9 months. Median PFS1 in CT lines only was 7.1 months whereas median PFS1 in ET lines only was 9.5 months. Overall, 289 patients (63.5%) presented a "6-month benefit" at first-line, 128 (40.5%) at second, 76 (33.8%) at third and 34 (23.3%) at fourth. In the total series, not having a "6-month benefit" in PFS1 was associated with a lack of benefit both at second-line (OR = 0.48; 95% CI 0.29-0.77, p = 0.0026) and at any line beyond the first (OR = 0.39; 95% CI 0.24-0.62, p <0.0001). When CT only was considered, not having a "6-month benefit" significantly reduced by about 55% the probability of benefit both at second-line (OR = 0.45; 95% CI 0.25-0.81, p = 0.0072) and at any line beyond the first (OR = 0.43; 95% CI 0.2-0.7, p = 0.0026). A lack of benefit at the first ET line did not affect the outcome of second or any subsequent ET line. Stratification according to immunophenotype highlighted a statistical significance only among HER2-positive tumors (OR = 0.2; 95% CI 0.05-0.73, p = 0.0152 in second line and OR = 0.14; 95% CI 0.04-0.53, p = 0.0036 beyond first-line).

Conclusions. Our results suggest that the absence of at least a "6-month benefit" in PFS after first-line therapy predicts a lack of benefit from subsequent therapeutic lines, especially in HER2-positive disease.

L5* CHECKING OVERALL SURVIVAL IN METASTATIC BREAST CANCER PATIENTS: RESULTS OF A RETROSPECTIVE MULTICENTRE OBSERVATIONAL ITALIAN STUDY

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Background. Several studies suggest that new therapies can improve survival in metastatic breast cancer (MBC), but a different impact on overall survival (OS) is observed according to histology, stage and prognostic factors. The primary objective of this study was to determine whether the survival has improved from 2000 to 2008.

Methods. We retrospectively collected data from several Italian Medical Oncology Units (OUs); we registered all consecutive patients (pts) with breast cancer who developed metastases between 2000 and 2008. Demographic data, pathological characteristics, biological features and number of treatments administered were collected. OS was defined as the time from the diagnosis of MBC to death from any cause.

Results. A total of 2831 pts were analyzed from 20 OUs participated. Median age was 61.3 years (range 22.7-94.7 years). At first diagnosis of breast cancer 16% were metastatic and 84% was not. Molecular classification was: luminal A 69.8%, luminal B 19.2%, triple negative 7.1%, HER2+ like 3.9%. 64% and 57% of pts had been treated prior to recurrence with chemotherapy and endocrine-therapy, respectively. Only 4.2% were treated with trastuzumab as adjuvant therapy. Site of disease recurrence was: bone 23%, visceral 17.9%, soft tissue 14.7%, brain 5.2%, more than 1 site 39.2%. Patients received a median of 2 lines of chemotherapy (range 0-12) and 1 line of endocrine therapy (range 0-7); 21.5% received biological drugs. 11.7% of metastatic pts were enrolled in clinical trials. After a median follow-up of 6.5 years (range <0.1-12.9 years) 78.6% pts died and the median OS was 2.7 years (95% CI 2.6-2.8 years). Patients were divided into 3 groups according to recurrence date (2000-2002, 2003-2005, 2006-2008); median follow-up was respectively 10.3, 7.2, 4.8 years; we didn't observe any statistically significant trend in OS. A longer median OS was observed in luminal B (3.3 years; 95% CI 2.8-3.8 years) versus luminal A (2.6 years; 95% CI 2.5-2.8) and HER2+ like (2.7 years; 95% CI 1.6-3.2 years) and triple negative disease (1.8 years; 95%CI 1.5-2.1).

Conclusions. OS analysis shows statistically significant differences according to prognostic factors. We didn't observe the effect of recurrence year on overall survival although this comparison was affected by different follow-up length. OS data are superimposable to literature ones, showing a good transfer from clinical trials to clinical practice.

L6 THE PROMISE-GIM6 STUDY: LONG TERM ANALYSIS

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Background. The PROMISE-GIM6 (Prevention of Menopause Induced by Chemotherapy: A Study in Early Breast Cancer Patients-Gruppo Italiano Mammella 6) study showed that the use of triptorelin-induced temporary ovarian suppression during chemotherapy in premenopausal patients with early stage breast cancer reduced the occurrence of chemotherapy-induced early menopause. Twelve months after the last cycle of chemotherapy, the rate of early menopause was 25.9% in the chemotherapy-alone group and 8.9% in the chemotherapy plus triptorelin group, an absolute difference of -17% (95% CI -26% to -7.9%; p <.001) (Del Mastro L, JAMA, 2011). The present analysis evaluates long term outcomes.

Materials and methods. From October 2003 to January 2008, 281 premenopausal women with stage I through III breast cancer, who were candidates for adjuvant or neoadjuvant chemotherapy, were randomized to receive chemotherapy alone or combined with triptorelin. The primary study objective was to compare the incidence of chemotherapy-induced early menopause in patients treated with chemotherapy alone or combined with triptorelin. This analysis considers the planned secondary endpoints: pregnancies and recurrences.

Results. The median follow-up was 5.7 years (range 5.0-6.8). After the end of adjuvant treatments, 3 pregnancies (2.26%) occurred in the chemotherapy-alone group and 6 pregnancies (4.05%) occurred in the chemotherapy plus triptorelin group (p = 0.507). The recurrences rate was 17.29% (23 events) in the chemotherapy-alone group and 20.27% (30 events) in the chemotherapy plus triptorelin group (p = 0.462).

Conclusion. These results show that there is no statistically significant difference between the two groups in terms of number of pregnancies and recurrence rate. Further follow-up is needed to confirm the present data.

L7 ITALIAN ONCOLOGISTS PREFER LHRH-ANALOGS TO PRESERVE FERTILITY IN WOMEN WITH EARLY BREAST CANCER

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Background. Fertility preservation is an emerging issue among young women with breast cancer. A survey to evaluate the attitude of Italian Oncologists about this problem has been performed.

Methods. Between April and July 2011, an electronic questionnaire about the management of early breast cancer and the fertility preservation in premenopausal women has been completed by 611 Italian Oncologists (female 52%, age range 25-65, 81% from general hospital, 19% from research institutes). We compared the survey results on fertility (examined according to sex, age, working institution and geographic origin) with the recommendations available from guidelines of oncology and gynecology societies.

Results. The majority of Italian oncologists considered the administration of LHRH-analogs the treatment of choice to maintain fertility (independently from the hormone receptor status of the tumor in 83% of cases), being the monthly injection used in 2/3 of cases. A pregnancy test before starting chemotherapy however is considered mandatory only by 49.5% of oncologists, inde-

L7 - Table

	Eggs freezing	Embrio freezing	Ovarian tissue freezing	LHRH-analogs
ASCO (USA, 2006)	Investigational	Standard	Investigational	Investigational
CASA (Australia, 2012)	Standard	Standard	Investigational	Investigational
AIOM (Italy, 2012)	Standard	Not allowed by law	Special cases	Investigational
Present survey	24.8%	<1%	6%	68.2%

pendently from age and type of treatment. Comparison of survey results with guidelines recommendations is reported in the Table. Type of institution, geographic location (north, centre, south Italy), and physicians age were not related with the type of response.

Conclusions. The majority of Italian Oncologists would suggest LHRH-analog to preserve fertility in premenopausal women undergoing adjuvant chemotherapy for breast cancer. The limited number of specialized centres for oocyte freezing, and the lack of a multidisciplinary approach to the problem can represent potential barriers toward other accepted methods to maintain fertility.

L8 ACTIVITY AND DURATION OF SUBSEQUENT LINES OF CHEMOTHERAPY (CT) IN DIFFERENT BIOLOGIC SUBTYPE (BS) IN METASTATIC BREAST CANCER (MBC) PATIENTS

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Background. In MBC patients the benefit of CT after the first-line is slightly defined. We evaluated activity of subsequent lines of CT in different BS of MBC.

Methods. MBC patients treated in our center from 2007 to present with ER, PgR and HER2 on primary tumor and at least 1 line of CT for MBC were evaluated. Patients were classified as Luminal A (ER and/or PgR +, HER2 -, Ki67 ≤14%), Luminal B (ER and/or PgR +, HER2 -, Ki67 >14%), HER2+ (HER2+, any ER/PgR) and Triple-Negative (ER-, PgR- and HER2-). The objectives of our analysis were to estimate number of CT lines in different BS, to evaluate clinical benefit (CB) and overall survival (OS) by CT lines in every BS and to identify possible predictive factors for a greater number of CT lines. Time on CT was calculated from the start of the first-line to the end of the last line. Statistical analyses included Chi-square and Kruskal-Wallis tests, Kaplan-Meier curves and log-rank tests, and multivariate logistic regressions.

Results. 326 patients were identified, 50 were excluded because they did not receive any CT. Median follow-up was 32.3 months (mos). The median number (N) of CT lines was 2 (range 1-10). Number of CT lines and CB for every BS were reported in the Table. CB was inferior in TN pts as compared with the other ones in first- and in second-line (p = .027 and p = .093 respectively in first- and second-line). From third-line onward all pts showed the same CB independently from BS. Time on CT related to median survival (S) for every BS was almost the same. At multivariate analysis the characteristics independently associated with a greater probability of receiving more than 4 CT lines were HER2+ (p = .027) and less than 3 sites of metastasis (p = .05).

Conclusions. Our analysis showed that, despite the same time spent on CT, TN pts received less benefit from first- and second-line CT than other BS. On the other hand, HER2+ pts were more likely to receive multiple lines of CT with a significant impact on median S (p = .044).

	Luminal A	Luminal B	HER2+	TN
N patients	58	119	57	42
Median S, mos	60.5	50	69.2	32.3
Median CT lines	2	2	3	2
N CT lines (%)				
1	58 (100)	119 (100)	57 (100)	42 (100)
2	34(58)	71 (59)	41 (71)	29 (69)
3	24 (41)	41 (34)	30 (52)	18 (43)
4	13 (22)	19 (16)	21 (39)	7 (16)
5	8 (13)	9 (7.5)	14 (24)	5 (12)
>6	4 (7)	3 (2)	17 (29)	6 (14)
Median CT duration, mos	11	10	19	9.4
Time on CT related to median S, %	18	20	27	29
CB for CT lines (%)				
1	48 (87)	78 (80)	50 (97)	25 (69)
2	20 (64)	42 (69)	29 (73)	11 (46)
3	12 (57)	22 (61)	13 (48)	9 (64)
4	10 (83)	8 (53)	8 (42)	3 (60)
>5	3 (13)	5 (7.5)	11 (24)	3 (13)

L9 FERTILITY PRESERVATION IN BREAST CANCER PATIENTS: AN ITALIAN SURVEY

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Background. Given the rising trend to delay pregnancy later in life and the increasing number of breast cancer (BC) survivors below the age of 40, fertility preservation issues are becoming relevant. Young patients are more often enquiring feasible methods to reduce gonadal damage and the safety of pregnancy after BC. Although available data on the safety of pregnancy are encouraging, fertility preservation issues are not routinely offered in clinical practice. In the present study we explored attitudes on fertility preservation issues among Italian clinical oncologists dealing with BC.

Material and methods. 162 Italian clinical oncologists were anonymously expressing their opinion by a Delphi web-platform on 19 statements, regarding pregnancy related issues in BC. For each statement a consensus level was expressed (1 = strong disagreement, 2 = mild disagreement, 3 = agreement with reservation, 4 = agreement with minor reservation, 5 = strong agreement). The disagreement consensus was declared when 1 + 2

>66%, whilst the agreement occurred when 3 + 4 + 5 >66%.

Results. About 91% of panelists considered important discussing with their patients about fertility issues, but 81% was contrary to embryos cryopreservation. 83% believed that estrogens could stimulate the growth of hidden cancer cells during ovarian stimulation with gonadotrophins, mostly in ER positive tumors. 54% of oncologists declared that pregnancy does not affect oncologic prognosis and 60% that is safe for either mother and fetus. 91% agreed that breastfeeding in breast cancer patients was safe and feasible, and 70% considered it possible also from one breast only. 68% and 83% of panelists did not omit alkylating agents or shortened chemotherapy regimens and 76% did not shorten tamoxifen duration to favour a subsequent pregnancy. Using GnRHa during chemotherapy was considered the only medical means for ovarian preservation: 79% of panelists declared to use it regularly. 68% of panelists proposed GnRHa for 5 years in ER positive patients, particularly in women <40 years of age (79%) and at high risk of relapse (83%). 66% of panelists considered positively the occurrence of early menopause in ER positive women.

Conclusions. Italian clinical oncologists highly consider fertility issues in BC patients. Nonetheless, there are still misbelieve about the safety of pregnancy after BC and the role of estrogens during ovarian stimulation. GnRHa is the most widely used means of gonadal protection.

L10 RANDOMIZED, PLACEBO CONTROLLED, PHASE III TRIAL OF LOW DOSE TAMOXIFEN IN WOMEN WITH BREAST INTRAEPITHELIAL NEOPLASIA (STUDIO TAM-01). AN ONGOING STUDY

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Rationale. The annual risk of invasive disease in women with breast intraepithelial neoplasia (IEN) is 8-10 times higher the general population. Prior studies of tamoxifen in DCIS have shown conflicting results. Moreover, perceived risk of adverse events such as endometrial cancer and venous thromboembolism has limited tamoxifen broad. Recent trials from our group have shown that a dose of 5 mg/day does not increase endometrial proliferation and is associated with a decrease of estrogenic activity on IGF-I, SHBG and antithrombin-III. We have launched a phase III trial of low dose Tam in women with breast IEN.

Material and methods. This is a multicentric trial aimed at assessing the efficacy of Tam at the daily dose of 5 mg or placebo for 3 years to reduce breast cancer incidence in women with previous IEN (LIN 2-3 and ER-positive or unknown DIN 1b-3). Secondary endpoints are: incidence of other non-invasive breast disorders, endometrial cancer, clinical bone fractures, cardiovascular events, venous thromboembolic events, clinically manifest cataract. A pharmacogenetic sub-study is ongoing to assess whether CYP2D6 genotype can explain modulation of surrogate biomarkers of Tam efficacy and safety. We initially powered the study at 90% and 5% significance to detect 55 events with a hazard ratio of 0.6 (total number = 700 per arm).

Results. From 2008 to 30 April 2013, 18 centers have been activated with 362 women enrolled; 333 pts with DIN (92%) and 29 with LIN (8%), median age was 53.9 (30-74). After a median observation of 12 months, toxicity observed was: hot flashes N = 14 (3.87%); vaginal dryness N = 5 (1.38%); vaginal discharge N = 3 (0.82%); headache N = 3 (0.82%); endometrial polyps N = 3 (0.82%); metrorrhagia N = 2 (0.55%). Only 8 (2.20%) SAE were registered. No unexpected SUSAR were registered. So far, 7 patients (1.93%) have recurred.

Conclusions. The recruitment is ongoing with a very safe drug profile. Our aim is to recruit 500 subjects by September 2014 with a projected number of 15 breast events. By pooling these events with those of a prior study (IEO 007) in a similar population treated with the same dose of Tam, where a total number of events is predicted to be 75, we will have 80% power to detect as significant a 40% risk reduction in breast neoplastic events from both studies.

L11 PROGNOSTIC FACTORS ACROSS DIFFERENT LINES OF THERAPY FOR METASTATIC BREAST CANCER

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Background. The clinical decision making process in determining the most appropriate therapy of metastatic breast cancer (MBC) varies across different lines. Accordingly, prognostic factors that may help clinicians in the therapeutic choice are eagerly needed.

Methods. We evaluated a consecutive series of 472 MBC patients (pts) treated at University Hospital of Udine, between 2004 and 2012. The prognostic value of the following characteristics was tested: ER, PgR, HER2 and Ki-67 status, stage at diagnosis (advanced vs early), previous adjuvant therapy, visceral involvement, sites of metastasis (lung, brain, liver and "bone only" sites were analyzed distinctly), age, ECOG performance status. Prognosis was defined according to the following measures of outcome: overall survival (OS), progression-free survival (PFS) and

survival post progression (SPP). PFS and SPP were calculated at first (PFS1, SPP1) and subsequent (PFS2, PFS3, PFS4; SPP2, SPP3, SPP4) lines of therapy. Hazard ratio (HR) for OS, PFS and SPP was estimated through uni- and multi-variate Cox's Proportional Hazard Regression model.

Results. Median OS after diagnosis of MBC was 34.9 months. Median PFS1, PFS2, PFS3 and PFS4 was 9, 4.4, 4 and 3 months, respectively. Median SPP1, SPP2, SPP3 and SPP4 was 18.3, 12.2, 8.2 and 7 months, respectively. In multivariate analysis, the following factors showed independent prognostic value in terms of OS: ER status (ER+ vs ER-, HR 0.4, 95% CI 0.3-0.7), HER2 status (HER2+ vs HER2-, HR 0.3, 95% CI 0.2-0.5), liver metastasis (HR 2.2, 95% CI 1.4-3.4), lung metastasis (HR 1.8, 95% CI 1.2-2.8). ER+ disease was associated with longer PFS1 (HR 0.5, 95% CI 0.3-0.7). HER2+ disease was associated with longer PFS1 (HR 0.4, 95% CI 0.3-0.6) and PFS2 (HR 0.6, 95% CI 0.5-0.9). ECOG ≥2 was an unfavourable prognostic factor in terms of PFS2 (HR 1.9, 95% CI 1.3-2.9) and PFS3 (HR 2.1, 95% CI 1.3-3.2). Bone only disease (HR 0.6, 95% CI 0.3-0.9), liver metastasis (HR 1.7, 95% CI 1.1-2.8), lung metastasis (HR 2.1, 95% CI 1.3-3.4), and ECOG ≥2 (HR 2.4, 95% CI 1.4-4.2) were independently associated with SPP1. ECOG ≥2 was also predictive of SPP2, SPP3 and SPP4.

Conclusions. This study showed that, in MBC, biological and clinical characteristics may have different prognostic value across different lines of therapy. The potential implications of these findings are clinical and methodological (i.e. design and interpretation of clinical trials).

L12 POLYMORPHISMS INTERACTION ANALYSIS TO PREDICT BEVACIZUMAB (BV) EFFICACY IN METASTATIC BREAST CANCER (MBC) PATIENTS: AN EXPLORATORY RETROSPECTIVE STUDY

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Background. Pharmacogenetic studies have evaluated the role of VEGF single nucleotide polymorphisms (SNPs) to predict BV response for both PFS and OS in MBC pts with contrasting results (Schneider 2008, Grimaldi 2011, Lambrechts 2013, Miles 2013).

Methods. Based on these findings, we conducted a study to assess, in a population of MBC pts, the possible predictive role of SNPs in VEGF, VEGFR-2, IL-8, IL-6, HIF-1alfa, EPAS-1 and TSP-1 genes for bevacizumab response when combined with first-line paclitaxel (P) for both PFS and OS. Analyses were performed on germline DNA obtained from blood samples. Fourteen polymorphisms were investigated by real-time PCR technique. Furthermore, the multifactor dimensionality reduction (MDR) methodology was applied to investigate the value of an interaction between SNPs for predicting bevacizumab response, through the MDR programme (http://sourgeforge.net/projects/mdr/).

Results. The analyses were performed on blood samples of 113 pts, enrolled from 8 Oncology Units. Main pts characteristics are: median age 59 years (range 32-81), ECOG-PS 0/1 in 78%/22%, hormone receptor positive 83%, previous adjuvant chemotherapy 68%, disease-free interval (DFI) <12 months 27%. After a median follow-up of 25+ months (4.5-69.5+), mPFS was 11.6 months (95% CI 10.5-12.7) and mOS was 31.3 months (95% CI 23.7-38.9). None of SNPs were individually associated with PFS. Conversely, a genetic interaction profile consisting of carriers in rs11133360 of VEGFR-2 combined with carriers in rs4073 of IL-8 was significantly associated with PFS with a trend towards the OS. The mPFS was 14.1 months (95% CI 11.4-16.8) and 10.2 months (95% CI 8.8-11.5) for the favorable and the unfavorable genetic profile, respectively (HR = 0.44, 95% CI 0.29-0-66, p <0.0001). The mOS was 35.7 months (95% CI 26.8-44.5) and 24.3 months (95% CI 19.7-28.8) for the favorable and the unfavorable genetic profile, respectively (HR = 0.64, 95% CI 0.38-1.05, p = 0.081).

Conclusions. Genetic interaction between VEGFR-2 rs11133360 and IL-8 rs4073 polymorphisms may predict BV response for the PFS. Prospective study is planned to confirm these results.

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L13 THREE-WEEKLY TRASTUZUMAB PLUS INTRAVENOUS (IV) OR ORAL (OS) VINORELBINE (VNR) AS FIRST-LINE TREATMENT IN HER2+ METASTATIC BREAST CANCER (MBC): JOINT ANALYSIS OF TWO CONSECUTIVE PROSPECTIVE PHASE II TRIALS

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Background. Our Group has recently reported the results of activity, safety and quality of life (QoL) of intravenous (iv) or oral (os) VNR plus capecitabine as first-line chemotherapy (CT) in HER2- MBC through 2 subsequent prospective phase II trials (Clin Breast Cancer, 12: 30-9, 2012). Here we present the final results of the 'twin' study conducted over the same period of time in the HER2+ population.

Patients and methods. From April 2003 to February 2006, 95 consecutive pts were enrolled. Patients in Trial A (46) received trastuzumab (loading dose of 8 mg/kg day 1 of the first cycle, then 6 mg/kg for the subsequent 21-day cycles) combined with iv VNR 25 mg/m^2 on days 1 and 8. The following 49 pts enrolled in Trial B, performed when the oral (os) formulation of VNR became available at our Institution, received the same trastuzumab schedule combined with os VNR (60 mg/m^2 on days 1 and 8, every 3 weeks). Activity and toxicity were evaluated according to WHO criteria; QoL was measured at baseline and every 2 cycles using the EORTC QLQ-BR23 questionnaire.

Results. The response rate (RR) in Trial A was 86% (95% CI 64.4-81.2), including 18% complete responses (CRs). Clinical benefit (CB) was achieved in 88% of pts (95% CI 65.2-86.8). In Trial B overall RR was 84% (95% CI 63.0-78.0) with 17% CRs and CB of 86% (95% CI 65.48-87.2). All pts received a second-line trastuzumab-based CT; 45% of pts in trial A and 48% in trial B, respectively, had ≥3 further lines. In Trial A median progression-free survival (PFS) was 9.8 months (range 6-19+) and median overall survival (OS) was 38.4 months (range 19-44+). In Trial B median PFS and OS were 9.6 months (range 8-21+) and 37.3 months (17-39+), respectively. Treatment-related toxicity was manageable, with no grade 3-4 side effects. QoL assessment showed a statistically significant difference regarding body image ($p = 0.002$) and future perspectives ($p = 0.03$) in women receiving the hybrid iv/os regimen.

Conclusions. This joint analysis shows that both tested schedules produce high RR as first-line therapy of HER2+ MBC, with encouraging PFS and OS values. While toxicity profile did not significantly differ in the 2 groups, the suggested benefit on some aspects of QoL for the 'hybrid' schedule further supports a better patient compliance for oral CT.

L14 MEASURES OF OUTCOME VERSUS ENDPOINTS FOR DRUG DEVELOPMENT IN METASTATIC BREAST CANCER: HINTS FROM A SINGLE INSTITUTION ANALYSIS

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Background. In metastatic breast cancer (MBC), misalignment has been observed between endpoints used for drug developments and for the choice of treatment in real-life practice. In fact, it is questionable whether survival data derived from clinical trials are adequate to inform clinicians in their questions about individual patients (pts). Furthermore, information on post-trial therapy is seldom reported and differences on overall survival (OS) between treatments are often difficult to demonstrate because of statistical considerations. Analysis of survival post-progression (SPP) has been proposed as an instrument to understand how probable is to see OS gain in a clinical trial (i.e. longer SPP corresponds to lower likelihood to observe statistically significant differences in OS).

Aim. To analyse different measures of outcome across different lines of treatment and among different immunophenotypes in pts with MBC.

Methods. This is a retrospective analysis on 472 consecutive pts with MBC treated from 2004 to 2012 at the University Hospital of Udine. The study was conducted on 359 cases where information about immunophenotype was available. Time-to-event data [OS, progression-free survival (PFS) and SPP] were obtained for the first four lines of treatment.

Results. Eighty-eight pts (24.5%) had a luminal A (LA) disease, 138 (38.4%) a luminal B (LB) disease, 89 (24.8%) a HER2+ and 44 (12.3%) a triple negative (TN) phenotype. Median OS after diagnosis of MBC was 34 months. Median OS of LA, LB, HER2+ and TN was 45.3, 29.7, 43.5 and 10.2 months, respectively. After first-line of treatment, median PFS of LA, LB, HER2+ and TN was 15.1, 9.3, 10 and 3.9 months, respectively. After first progression, median SPP of LA, LB, HER2+ and TN was 24, 18.9, 19 and 6.1 months, respectively. Notably, in HER2+ group outcomes varied significantly on the basis of hormone receptor status. In addition, in TN group all outcomes after first-line were significantly lower than in the remaining population. For the total population, SPP1, SPP2, SPP3 and SPP4 were 18.3, 12.2, 8.2 and 7 months respectively.

Conclusions. After first-line treatment, median SPP of LA, LB and HER2+ groups was longer than 12 months. Accordingly, the choice of OS as a primary endpoint for clinical trials does not seem to be appropriate with these subtypes. On the contrary, OS could be adequately adopted when SPP is expected to be low (TN subtype after the first-line; other subtypes after the third-line).

L15 PHENOTYPIZATION WITH DEXTROMETHORPHAN SHOWED BETTER PREDICTION OF BLOOD ENDOXIFEN LEVELS COMPARED WITH CYP2D6 GENOTYPING IN BREAST CANCER PATIENTS TREATED WITH ADJUVANT TAMOXIFEN

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Background. Tamoxifen (TAM) activity is mainly due to its active metabolite endoxifen (END) prevalently produced by CYP2D6 hepatic enzyme; its metabolic status can be estimated by a phenotyping test using dextromethorphan (DM) as a drug probe and by CYP2D6 genotyping. Prediction of steady-state END plasma levels could help anti-estrogenic treatment personalization.

Methods. One hundred and twenty early breast cancer patients (pts) treated with TAM (20 mg/die) were the study population. The phenotypization test was executed before starting therapy: pts received DM 15 mg per os and collected urine for the following 8 hours. DM and its metabolite dextrorphane (DR) were measured by HPLC and the log transformed urinary metabolic ratio DM/DR (LUMR) was calculated. Leukocyte DNA was extracted and analyzed for CYP2D6 variant alleles with normal, null and reduced activity. After at least 4 months from treatment start, when pts were considered to be in steady-state (stable TAM and metabolites plasma levels), blood samples were withdrawn to determine END concentrations by HPLC. Patients were classified in the three different functional groups, separately using the predictive tests and direct END plasma levels, and correlations among them were evaluated.

Results. END plasma levels varied between 2.4 and 39.2 (median 8.7) ng/mL; their distribution appeared to create three classes of metabolizers: extensive, intermediate and poor. LUMR varied between -3.1 and +1.2 (median -1.6) and showed a three modal distribution, as well; there was a significant linear correlation between LURM and END blood concentrations ($r = -0.59$; $p < 0.0001$). CYP2D6 alleles with normal, null and reduced activity were found in 51.0, 26.8 and 22.2% of cases. There were 14 and 58 pts with both null alleles and at least one null or reduced activity allele, respectively; they had significantly lower END plasma levels compared to pts with normal genotypes (mean ± SD = 3.2 ± 1.1 vs 8.7 ± 5.2 vs 14.4 ± 8.1; $p < 0.0001$). A multiple regression analysis, carried out to identify which variable best predicts END plasma concentrations showed that only LUMR, but not CYP2D6 genotyping, was independently associated with TAM activation ($p = 0.001$).

Conclusions. Both dextromethorphan metabolism and CYP2D6 gene testing correlated with individual TAM activation, but only the ratio DM/DR appeared as an independent reliable predictor.

On behalf of Italian TAM group. Funded by Regione Veneto.

L16 HORMONAL RECEPTORS NEGATIVE EARLY STAGE BREAST CARCINOMAS WITH NEGATIVE HER2 STAINING (SCORE 0-1+ AT IMMUNOHISTOCHEMISTRY [IHC]): ARE THEY 'TRUE' TRIPLE NEGATIVE?

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Background. Triple negative breast cancer (TN-BC) represents a poor-prognosis molecular subtype of breast carcinoma characterized by the absence of expression of hormonal receptors (ER, PgR) and Her2. Fluorescence and silver *in situ* hybridization (FISH/SISH) analyses are currently performed only in presence of a Her2 IHC score 2+, although Her2 IHC score 0-1+ may occasionally hide gene amplification. This analysis aims to evaluate the incidence of Her2 gene amplification in the subset of early stage IHC-based TN-BC.

Materials and methods. ER-, PgR- and Her2 score 0-1+ breast cancer undergone surgery with curative intent were considered eligible in a retrospective fashion, and FISH and SISH analyses were performed. All cases harbouring Her2 gene amplification by using the SISH based system were also confirmed by using FISH analysis. Descriptive statistics was adopted, and confidence intervals (CI) were derived.

Results. One hundred and thirty-five patients (median age 62 years, range 29-97; node-positive: 43/135 (34%); grading G1-2/G3: 24 (18%)/111 (82%); Ki67 <20%/20-50%/>50%: 14%/17%/69%; histologies: 100 ductal, 16 apocrine, 7 metaplastic, 2 squamous and other minor histotype) were considered evaluable for the analysis; all 135 cases were ER and PgR negative with 78% and 22% of patients showing Her2 score 0 and 1+, respectively. Eight out of 100 (8%, 95% CI 2.6-13.3%) of the ductal triple negative breast carcinoma presented Her2/neu gene amplification, all of them with CK5 immunostaining; 2/35 (5.7%, 95% CI 0.1-13.4%) non-ductal TN-BC were amplified. Three cases showed a ratio of 2.5; one patient showed Her2/neu heterogeneous gene amplification. The other 6 showed from 7 to 8 absolute Her-2/neu gene copy number. Overall, 7.4% (95% CI 2.9-11.8%) of the originally defined TN-BC present Her2/neu gene amplification.

Conclusions. The currently adopted flow-charts for molecular diagnostics in clinical practice should not entirely rule out the possibility to screen for Her2 positivity Her2 IHC score 0-1+ in triple-negative breast cancers, in order to not deny an important therapeutic option such as anti Her2 targeted therapy.

L17 EFFICACY OF BIOLOGICAL AGENTS (BA) IN METASTATIC TRIPLE NEGATIVE BREAST CANCER (MTNBC)

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Background. Metastatic triple negative breast cancer (mTNBC) represents 15% of all invasive breast cancers, usually with a poor prognosis and without a specific target therapy. In this setting, biological agents (BA) in combination with chemotherapy (CT) may have a role, also based on the molecular characteristics of TNBC.

Materials and methods. To assess the role of BA in mTNBC we performed a systematic review of phase III randomized controlled trials (RCTs) published from January 2006 to February 2013, as well as presentations at ESMO, ASCO and SABCS congresses from 2010 to 2012. To collect as much data as possible, we consulted Pubmed and http://clinicaltrial.gov. Only studies comparing BA + CT versus CT alone in mTNBC, or in unspecified advanced breast cancer patients with specific data on TNBC subgroup were considered. The relevant statistical variables for the pooled analysis were the log of hazard ratio (HR) and relative variance for progression-free survival (PFS) and overall survival (OS).

Results. Out of 353 Pubmed publications and 229 studies registered on http://clinicaltrial.gov, 10 trials with these characteristics were selected. 5293 patients were analyzed: 1546 of them were mTNBC. BA studied were: 4 RCTs with bevacizumab, 2 RCTs with sunitinib and 1 RCT for each lapatinib, iniparib, sorafenib and cetuximab. In addition, a meta analysis of the 4 studies containing bevacizumab was performed and it showed a PFS improvement with a relative risk reduction of 35% (95% CI 25%-43%). No effect on OS was observed. No benefit on PFS and OS was detected with the other agents.

Conclusions. No improvement of PFS and OS was detected in pts treated with BA + CT vs CT alone, except for bevacizumab that demonstrated an improvement of PFS. No statistically significant effect on OS was observed, perhaps because of the long

median survival post-progression with the interference of subsequent lines of therapy. Finally the overall impact of these agents on patients survival is not as great as expected probably because this illness needs a better molecular classification to tailor the treatment.

L18 P53 AND BCL2 EXPRESSION ACROSS MOLECULAR SUBTYPES IN 1108 EARLY BREAST CANCER: CORRELATION WITH METASTATIC SITES AND OUTCOME OF DISEASE

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Background. The management of early breast cancer (BC) continues to be challenging because of the heterogeneity of the disease and a limited number of clinical/pathological factors are currently used to guide therapy and prognosis. Recently, p53, a tumor suppressor and BCL2, an antiapoptotic protein have been proposed as additional prognostic markers, although their relationship with conventional parameters and patient prognosis remain uncertain. In particular, there are few data concerning p53 and BCL2 distribution within the molecular BC subtypes, luminal A (LA), luminal B/HER2- (LB/HER2-), luminal B/HER2+ (LB/HER2+), HER2-like (H), and triple negative (TN).

Methods. We conducted a retrospective study using immunohistochemistry to evaluate p53 and BCL2 expression in 1108 early BC patients (median age 56 yrs [21-92], N+ 490 [44%]) surgically treated at our Institute between 2000 and 2006 with at least 5 yrs follow-up data. None of the HER2+ patients, included in our series, received trastuzumab because not yet available in the adjuvant setting. Associations among p53 and BCL2, T, N, G and molecular subtypes were analyzed by multiple correspondence analysis (MCA), while Kaplan-Meier method was applied to determine their impact on disease-free survival (DFS).

Results. p53 and BCL2 differently distribute within the 5 molecular subtypes (p value <0.0001). p53 is highly positive in LB-H+ (%), H (%) and TN (%), conversely, BCL2 is more frequently expressed in LA (%) and LB-H- (%) BC. The relationships among bio-pathological factors, analyzed by MCA, confirmed that p53 positive and BCL2 negative BC are located in the quadrant containing more aggressive conventional tumor phenotypes (H and TN subtypes, T3/T4, N+, G3 and presence of relapse). Kaplan-Meier curves identified BCL2 negativity as a significant discriminating factor for DFS (p = 0.024) while p53 does not discriminate BC patients independent of molecular subtypes. Focusing on the 351 BC who relapsed (135 visceral and 229 non-visceral metastases) we observed that visceral metastases are significantly less frequent in LA (30%), LB HER2- (37%) and TN (29%) BC as compared to H (52%) and LB-HER2+ (58%) BC (p = 0.003).

Conclusions. Our data indicated that lack of BCL2, in contrast to p53 positivity, appears to be a biomarker related to a more aggressive clinical course across BC molecular subtypes. Visceral metastases are more evident in H and LB-HER+ subtypes as compared to the other groups.

L19 BREAST CANCER MOLECULAR PROFILE ACCORDING TO BMI AND MENOPAUSAL STATUS

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Background. Several studies have shown a positive association between body mass index (BMI) and the development of estrogen receptor (ER)-positive breast cancer. However, correlation of BMI, menopausal status and molecular subtypes has not been established yet.

Material and methods. Overall 1,004 patients with early breast cancer (EBC) were recruited for this study. Clinical and tumor characteristics such as age, menopausal status, weight, height, tumor size (T), grading, ER, progesterone receptor (PgR), human epidermal growth factor receptor 2 (HER2) status, were prospectively collected. BMI was categorized into three groups (low ≤25; intermediate 26-30; high >30) and associations between BMI and clinicopathological variables were performed by $\chi 2$ test.

Results. Overall 615 (61.3%) pre-menopausal and 389 (38.7%) post-menopause women were enrolled. Of 615 premenopausal patients, 201 have a low BMI, 162 have an intermediate BMI and 227 have a high BMI. Among the 227 patients with a high BMI, 183 (80.6 %) were ER+ (p = .004), 186 (83.4%) were HER2- (p = .01) and 143 (64.4%) have a luminal A tumor subtype (p = .01). High BMI correlates with increased ER and lower HER2 expression and less aggressive tumor subtypes as luminal A. Furthermore, of 50 patients with a luminal B tumor subtype, 23 (46%) have a low BMI, 9 (18%) have an intermediate BMI and 18 (36%) have a high BMI (p = .01). Of 28 patients with a HER2 like, 14 (50%) have a low BMI, 2 (7.1%) have an intermediate BMI and 12 (42.8%) have a high BMI (p = .01). Of 74 women with a TN breast cancer 32 (43.2%) have a low BMI, 13 (17.6%) have an intermediate BMI and 29 (39.2%) have a high BMI (p = .01). These results show that premenopausal women with low BMI were more likely to develop a Luminal B, HER2 like or TN breast cancer.

Conclusions. Among premenopausal patient, high BMI is associated with less aggressive and more endocrine sensitive EBC. This is consistent with the hypothesis that higher estrogen exposure of breast tissue in women with higher BMI may drive growth of these cancers. If further confirmed, our data suggests that weight control in this subset of women may help to prevent cancer development.

L20 CHANGES IN THE KI-67 EXPRESSION BETWEEN PRIMARY BREAST CANCER AND PAIRED METASTASES: UNDERSTANDING THE PROGNOSTIC EFFECT OF DISCORDANCE

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Background. Many studies have been conducted to evaluate changes of biological markers between primary and recurrent breast cancer. However, little is known about the relationship between therapy, Ki-67 variation and prognosis.

Aim. To evaluate the prognostic impact of Ki-67 discordance between paired primaries and recurrences.

Patients and methods. We retrospectively analysed a series of 472 consecutive patients with metastatic breast cancer treated at the Department of Oncology of Udine, between January 2004 and July 2012. Information on Ki-67 expression in primary breast cancer and paired metastatic site was available for 81 patients. Variation of Ki-67 was defined as a categorical variable using the cut-off value of 14%. Variation in Ki-67 expression between primary site and recurrence was tested through McNemar test. Association between treatment and Ki-67 changes was investigated through logistic regression. To assess the prognostic role of Ki-67 in terms of overall survival, Cox regression was performed.

Results. Changes in Ki-67 expression between primary tumour and metastatic lesions were statistically significant ($p = 0.0004$). On univariate analysis, exposure to anthracycline-based regimens or taxanes lead to a higher probability in Ki-67 decrease (OR = 3.94, $p = 0.01$ and OR 2.94, $p = 0.04$, respectively). An inverse association was found after exposure to antiestrogen therapy (OR = 0.2, $p = 0.009$). On multivariate analysis, only previous treatment with anthracyclines or antiestrogens was significantly associated with Ki-67 changes (OR 3.89, $p = 0.04$ and OR 0.19, $p = 0.01$, respectively). The prognostic role of Ki-67 in terms of overall survival (OS) was noticed when a relative increase of Ki-67 was observed (44.51 months vs 23.11 months, HR = 0.52, $p = 0.02$).

Conclusions. Our results suggest that changes in Ki-67 expression between primary breast cancer and paired metastases may depend on previous treatment. It is tempting to hypothesize that different mechanisms of action of the therapeutic agents could have different effects on Ki-67 variation. Although counterintuitive, patients in which Ki-67 in metastatic lesion is higher than in the primary tumour experienced longer OS.

L21 IDENTIFICATION OF POLYMORPHIC VARIANTS CORRELATED TO TAXANES NEUROTOXICITY IN BREAST CANCER PATIENTS BY DMET MICROARRAY PLATFORM

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Background. Peripheral neuropathy is a disabling taxane-related adverse event. Genetic polymorphisms (GP) in drug transporters and drug-metabolizing enzymes (ADME) could be involved in taxane-associated neuropathy (TAN). We investigated the correlation between single nucleotide polymorphisms (SNPs) linked to ADME gene variants and ≥grade 3 (G3) TAN by the drug-metabolizing enzyme and transporter (DMET) microarray Affymetrix platform.

Patients and methods. Seventy-nine taxane-treated breast cancer patients were enrolled in a case control study: 27 experienced TAN (≥G3) while 52 were no-TAN matched controls. Peripheral blood cells DNA was genotyped by DMET Plus chip. The study primary endpoint was association between ADME-related SNPs and TAN; secondary endpoints were the association between TAN-related SNPs and treatment response or progression-free survival (PFS). Genotype association was analyzed by Fisher exact test and relevant SNPs were analyzed through log-rank test and Cox proportional hazards model.

Results. Nine SNPs significantly associated with TAN. After Bonferroni's correction only a SNP on NAT2 gene (rs1041983) remained significantly associated to TAN (= 0.003): the T/T genotype of the rs1041983 SNP showed the strongest association with = G3 neurotoxicity, being genotyped in 10/27 cases vs 4/51 control patients ($p = 0.003$, OR = 6.911, 95% CI 1.9114-24.9939). Polymorphic variants in rs3808607 (CYP7A1) and in rs2292954 (SPG7) SNPs were associated to treatment response. The genotype A/C of the rs3808607 SNP, was found in 5/17 patients with partial response (PR), in 5/5 patients with complete response (CR) and 0/13 patients with stable disease (SD)/progressive disease (PD) ($p = 0.003$) while the genotype A/G of rs2292954 SNP was found in 8/18 patients with PR, 4/5 with CR and 2/12 SD/PD ($p = 0.001$). TAN did not correlate with clinical outcome. The rs562 polymorphism (genotype C/C) mapping in the ABCC5 gene was correlated to prolonged PFS (median not reached). The G/G genotype only slightly correlated with TAN was not associated to response and showed an intermediate PFS (median 13.8 months). The C/G genotype was associated with a worse PFS (median 12.07 months).

Conclusions. A polymorphic variant of NAT2 gene was correlated to TAN, while polymorphic variant of CYP7A1, SPG7 and ABCC5 genes were correlated to treatment response and PFS. DMET can identify GP for personalized therapeutic strategies.

L22 EVALUATION OF ENDOXIFEN PLASMA LEVELS IN BREAST CANCER PATIENTS RECEIVING ADJUVANT TAMOXIFEN. AN ONGOING PROSPECTIVE STUDY

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Background. Tamoxifen (TAM) is a pro-drug undergoing conversion to endoxifen (E), a metabolite with higher anti-estrogenic activity. A prospective study is ongoing aimed at correlating individual TAM activation capability with disease recurrence in order to allow personalized approach in hormonal therapy.

Methods. Early breast cancer patients receiving adjuvant TAM are the study population. After at least 4 months from treatment start, 2 blood samples are withdrawn (3-6 months apart) and E plasma concentrations (Epc) are measured by HPLC. Clinical data are prospectively recorded and endocrine-therapy side effects are assessed by FACT-ES questionnaire. Reported treatment adherence is checked through direct patient interview.

Results. Data from 625 patients were available for a descriptive analysis. Median age was 51.3 yrs (range 26-91). Primary tumor stage was pT1 in 80%, 72.7% had node-negative disease and the most frequent tumor grading was G2 (52%). Median duration of TAM therapy was 16 months (range 0.2-50). Hot flashes were the most reported side effect (52.5% as mild-moderate and 25% as heavy) and showed a significant correlation with the other estrogen-related symptoms ($p < 0.0001$); they were significantly more frequent in younger pts ($p < 0.0001$), while no association was found with BMI or concomitant drugs. About 13% and 5% of pts declared to have missed only 1 or ≥2 TAM tablets, respectively, over the last month. A median of 2 samples/pt was analyzed (range 1-4). Epc varied of 20 folds among pts (median 8.6, range 2-42.5 ng/mL), and their frequency distribution appeared to identify at least 3 groups with different TAM activation capability: low, intermediate or high in 28.8, 40 and 31.2% of pts, corresponding to Epc<5, between 5 to 12 and >12 ng/mL, respectively. On the contrary, intra-individual fluctuations were very low, showing a mean coefficient of variation of 2.9 ± 27.9%. They were not influenced by age or menopausal status.

Conclusions. According to the large variability in metabolic enzyme activity, due to genetic and environmental factors, Epc were widely variable among pts treated with adjuvant TAM and could explain differential responses to anti-estrogen therapy. Self reported treatment adherence was good, according to the stable E concentrations found in pts blood over time.

On behalf of Italian TAM group. Funded by Regione Veneto.

L23 EVEROLIMUS IN COMBINATION WITH EXEMESTANE IN HORMONE RECEPTOR-POSITIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER PROGRESSED ON PRIOR ENDOCRINE THERAPY: THE ITALIAN EXPERIENCE WITHIN THE BALLET STUDY (CRAD001YIC04)

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Background. Breast cancer (BC) is the most common form of malignancy occurring in women, and approximately 40% of diagnosed patients will develop advanced/metastatic BC. Treatment for advanced BC (aBC) include endocrine therapy as the preferred option for hormone receptor positive disease, even in the presence of visceral disease, unless concern or proof of endocrine resistance or rapidly progressive disease. However, many patients do not respond to endocrine therapy, therefore treatment of these patients remains an area of unmet medical need. Additionally, hyperactivation of the mTOR pathway has been observed in patients progressing on endocrine therapy: this pathway is critical in cell proliferation, survival and angiogenesis. The BOLERO-2 trial reported improved progression-free survival in ER+ HER2-postmenopausal pretreated women in the advanced breast cancer setting by combining everolimus (an oral mTOR inhibitor) with exemestane.

Material and methods. This is an European, multi-center, open-label, single arm, phase IIIb study designed to make everolimus available to postmenopausal women in the above mentioned indication. Everolimus will be provided until locally reimbursed for this indication (or until 31 Jan 2014, whichever comes first). The objective of the study is to evaluate the safety of everolimus by using assessment of adverse events and laboratory data (hematology/chemistry), in particular grade 3 and 4. The study entails a screening phase, a treatment phase, and a follow-up 28 days after the intake of the last dose of study drug.

Results. Novartis Region Europe planned to enroll 2200 patients from up to 500 centers. The initial commitment for Italian sites was 600 patients, subsequently increased to 800 in 143 participating centers. In Italy, the trial started on 19 June 2012, and there are currently 120 sites actively enrolling with a total of 826 patients entered, 693 of which on treatment to date (28 May 2013). No formal interim analysis is planned.

Conclusions. There is a lack of evidence-based sequential endocrine therapy options for patients recurring or progressing during NSAI treatment for advanced disease. Treatment options for aBC should include agents that can delay disease progression while maintaining quality of life. The high rate of Italian patients recruited in the CRAD001YIC04 study probably reflects the unmet need of new therapies that may enhance and extend the benefit of current therapies in hormone receptor-positive aBC.

L24 PRE-TREATMENT NEUTROPHIL TO LYMPHOCYTE RATIO MAY BE AN USEFUL TOOL IN PREDICTING SURVIVAL IN EARLY TRIPLE NEGATIVE BREAST CANCER PATIENTS

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Background. There is a growing body of evidence that immune response plays a large role in cancer mortality. Prior studies have demonstrated an association between simple inflammatory markers and adverse outcomes with certain types of cancer (gastrointestinal tracts, renal, cervical, lung). The combined index, using neutrophil and lymphocyte counts in the form of a neutrophil to lymphocyte ratio (NLR), has been used as a cost-effective and simple parameter of systemic inflammation or stress. The purpose of this study was to investigate the association between pre-treatment NLR and disease-free survival (DFS) and overall survival (OS) of patients with early triple negative breast cancer (TNBC).

Patients and methods. We retrospectively reviewed the records of patients diagnosed with stage I-III TNBC at our Institution from January 2006 to December 2011. The optimal pre-treatment NLR cutoff value was 3. Patients were further divided into two groups, A (NLR <3) and B (NLR ≥3). The difference among variables was calculated by chi-square test. DFS and OS were estimated using Kaplan-Meier method. Cox analysis was performed to analyze clinical parameters for their prognostic relevance.

Results. A total of 90 patients were eligible for analysis; 19% of patients showed higher pre-treatment NLR (group B). Median age at diagnosis was 53 years (range 28-79). The median follow-up time was 53.8 months (13.1-195.2). There was no significant correlation among pre-treatment NLR and various clinicopathological factors, including age, menopausal status, tumour size, lymph nodes status, grading, Ki-67, necrosis, lympho-vascular invasion and androgen receptor expression. At univariate analysis patients with higher pre-treatment NLR (group B) showed significantly lower DFS (p <0.01; HR = 0.21, 95% CI 0.01-0.39) and OS (p <0.01; HR = 0.16, 95% CI 0.007-0.37). Multivariate analysis revealed that pre-treatment NLR was an independent prognostic factor influencing DFS (p = 0.006; HR = 5.12, 95% CI 1.6-16.38) and OS (p = 0.008; HR = 6.84, CI 1.6-28.5).

Conclusions. Our study suggests that pre-treatment NLR may be associated with DFS and OS of patients with early TNBC and can be easily introduced in clinical practice. Prospective studies are needed to determine the immunogenic mechanisms underlying NLR variations and to adequately assess the potential role of NLR in guiding treatment decisions, patient selection, and clinical trials design.

L25 USING ANDROGEN RECEPTOR EXPRESSION AS A NOVEL POTENTIAL BIOMARKER IN PREDICTING SURVIVAL OF WOMEN WITH METASTATIC TRIPLE NEGATIVE BREAST CANCER

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Background. The androgen receptor (AR) is a member of the steroid receptor subfamily with well known biological and therapeutic importance in prostate cancer. There is emerging evidence that the androgen signaling pathway also may play a critical role in normal and malignant breast tissue. Although it has been indicated that ARs are expressed in a significant number of early triple negative breast cancer (TNBC) and that they might play a role as a prognostic marker, to date we don't know if AR expression has a correlation with survival of patients with advanced TNBC. Therefore, in the present study we investigated the prognostic value of AR expression in metastatic TNBC.

Patients and methods. Patients diagnosed with stage IV TNBC (at diagnosis or with distant relapses after surgery) at our Institution from January 2006 to December 2012 were included in the analysis. Patients with poor performance status (ECOG >2) were excluded. Tumors with ≥10% nuclear-stained cells were considered to be positive for AR. The univariate and multivariate analyses were performed.

Results. Among 24 patients with advanced TNBC, 30% were AR positive. The median age at diagnosis was 62 years (range 30-81 years). All patients included in the study received a first-line chemotherapy for their disease. Median progression-free survival (mPFS) and overall survival (OS) were 3.4 (range 0.3-23.6) and 22.2 months (range 8.2-148.8), respectively. Univariate analysis showed that AR positive advanced TNBC had a significantly better PFS (7.9 vs 3.2 months; p = 0.02; HR = 2.57, 95% CI 1.15-10.53) and OS (47.4 vs 20.5 months; p = 0.01; HR = 2.88, 95% CI 1.32-9.43). Multivariate analysis confirms that AR expression was an independent prognostic factor of PFS (p = 0.04; HR = 0.15, 95% CI 0.02-0.91), while there was a borderline significance of OS (p = 0.05; HR = 0.21, 95% CI 0.04-1.05).

Conclusions. Our preliminary results suggested that AR expression is differently related to biological behaviour of advanced TNBC. In clinical practice this biomarker may be an useful tool to identify patients with poor prognosis and for whom benefits of first-line chemotherapy were relatively lower. Conversely, finding that about one third of metastatic TNBC expressed ARs may support novel potential treatment options for advanced TNBC.

L26 ANDROGEN RECEPTOR EXPRESSION IN EARLY TRIPLE-NEGATIVE BREAST CANCER: CLINICAL SIGNIFICANCE AND PROGNOSTIC ASSOCIATIONS

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Background. Triple-negative breast cancer (TNBC) consists of a group of tumours with poor prognosis, owing to aggressive tumour biology and lack of targeted therapy. The androgen receptor (AR) is one such newly emerging biomarker in TNBC. In recent years it has been showed that ARs play an important role in the genesis and the development of breast cancer, although their role as prognostic biomarkers is still unclear. In the present study, we investigated the expression of AR in early TNBC and explored its correlation with clinico-pathological features and prognosis of TNBC.

Patients and methods. Patients diagnosed with stage I-III triple negative breast cancer at our Institution from January 2006 to December 2011 were included in the analysis. Tumors with

≥10% nuclear-stained cells were considered to be positive for AR. We analyzed the relationship between AR and clinico-pathological parameters. The univariate and multivariate analyses were performed. The difference among variables was calculated by chi-square test.

Results. The study included 81 patients. Slides were stained immunohistochemically for estrogen and progesterone receptors, HER-2, CK5/6, Ki-67, ALDH1, e-cadherin and AR. Of the 81 TNBC samples, 18.5% showed positive immunostaining for AR, 22.2% had basal-like immunophenotype; 22.2% and 43.2% of patients were negative for e-cadherin and ALDH1, respectively. Positive AR immunostaining was inversely correlated with higher Ki-67 ($p < 0.0001$) and lympho-vascular invasion ($p = 0.01$). Univariate survival analysis revealed that AR expression was not associated with disease-free survival ($p = 0.72$) or overall survival ($p = 0.93$).

Conclusions. The expression of AR is related to biological features of TNBC, as Ki-67 and lympho-vascular invasion; however the prognostic significance of AR in TNBC remains relatively controversial. AR is expressed in a significant number of TNBC and this represents a potential opportunity for novel target treatment in this group of breast tumours for which therapeutic options are currently limited.

L27 MIRNA-10B AS PUTATIVE PREDICTIVE MARKER OF METASTASES DEVELOPMENT AND SURVIVAL FOR BREAST CANCER PATIENTS

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Background. miRNA-10b is a small non-coding RNA whose expression levels have been recently associated with poor prognosis in gastric and colorectal tumors, pancreatic cancer, renal and bladder tumors. It regulates tumor invasion and metastasis by targeting HOXD10, a negative regulator of cellular migration and extracellular modelling. The aim of this study is to evaluate the putative association between miR-10b expression and metastases development, DFS and OS in breast cancer patients.

Methods. We selected from our institutional fresh-frozen tissue bank 150 cases of surgically resected paired breast cancer and normal tissues. For each patient at least three years follow-up and clinico-pathological data were available. After ensuring a tumor cell content of at least 70% per sample by H/E stained-section evaluation, and RNA quality assessment, 101 cases were analyzed. A relative quantification method with standard curve was developed to determine miR-10b expression in tissues. Twelve paired tumor and normal mammary tissues were analyzed for HOXD10 by IHC.

Results. miR-10b relative expression in tumor to normal samples (RERs) was significantly higher in the subgroup of patients with metastases (median 0.25 IQR 0.11-1.02) as compared with patients without metastases (median 0.09 IQR 0.04-0.29) ($p = 0.023$, Mann Whitney Test). The association between miR-10b RERs and survival was evaluated in the group of patients without metastases at diagnosis (N = 90). In univariate Cox regression model, patients with high miR-10b RERs had a higher risk to develop metastases (HR 4.914, $p = 0.021$) and to die for the disease (HR 6.019; $p = 0.015$). In a multivariate Cox regression model adjusted for tumor size, lymph node metastases, grade, ER, PgR status, *HER2* amplification and Ki67 labeling index (N = 78), higher miR-10b RERs were still associated with increased risk to develop distant metastases (HR 18.843; $p < 0.001$) and disease related death (HR 15.394; $p = 0.003$). HOXD10 immunostaining shows a statistically significant inverse correlation among miR-10b expression levels and percentage of HOXD10 expressing cells (Spearman Rho -0.713 $p < 0.001$).

Conclusions. Both univariate and multivariate analyses show that miR-10b expression is associated with increased risk to develop distant metastases and worst overall survival in breast cancer patients. These results suggest that miR-10b expression could be used for individual patient's risk assessment and as potential therapeutic target.

L28 DOSE-DENSE NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CANCER. LONG TERM RESULTS OF AN ITALIAN MULTICENTER CO-OPERATIVE RETROSPECTIVE STUDY

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Background. Dose-dense chemotherapy results in better overall (OS) and disease-free survival (DFS) in women with hormone receptor-negative early breast cancer as shown with a systematic review and meta-analysis by Bonilla et al. (JNCI 2010). Aim of our study was to compare neoadjuvant dose-dense chemotherapy with standard dose schedule in T4 patients in terms of DFS and OS, according to hormone-receptor status.

Patients and methods. We analysed, retrospectively, 160 consecutive T4 patients, of median age 52 yrs (range 29-73) who received neoadjuvant anthra-based chemotherapy with and without taxanes, observed from 1989 to 2009; 74 patients (46%) received dose-dense schedule (q14) and 86 (54%) conventional dose (q21); 68 (42%) patients were ER-negative (32 q14; 36 q21) and 92 (58%) patients were ER-positive (42 q14; 50 q21). No trastuzumab was allowed during neoadjuvant treatment.

Results. At a median follow-up of 130 months (range 8-241 months), overall, 10 yrs DFS was 41.9% and 30.2% on q14 and q21 schedules, respectively ($p = 0.085$); 10 yrs OS was 48.6% on q14 and 44.2% on q21 schedule, ($p = 0.343$). ER-negative patients who received q14 schedule had better DFS (46.9%) than those on q21 schedule (16.7%), ($p = 0.007$) (relative risk 0.63 and odds ratio 0.22) and better OS (50%) than those on q21 schedule (30.6%) ($p = 0.083$) (relative risk 0.61 and odds ratio 0.44). DFS and OS did not differ on q14 and q21 schedules in ER- positive patients.

Conclusions. Our findings are consistent with published data and suggest that there is no appreciable survival benefit from increasing dose density among T4 ER-positive patients. Dose-dense neoadjuvant chemotherapy may be justified in LABC patients with T4 ER-negative tumors.

	DFS			OS		
	q14	q21	p	q14	q21	p
ER-	46.9%	16.7%	0.007	50%	30.6%	0.083
ER+	38.1%	40%	0.512	47.6%	54%	0.344

L29 CARDIAC SAFETY ASSESSMENT OF ADJUVANT NON-PEGYLATED LIPOSOMAL DOXORUBICIN (MYOCET®) (NPLD) PLUS CYCLOPHOSPHAMIDE (C) FOLLOWED BY PACLITAXEL (P) IN ELDERLY BREAST CANCER (EBC) WOMEN

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Background. Doxorubicin is effective in early breast cancer but concerns about higher incidence of cardiac toxicity due to anthracyclines in older patients (pts) (Swain SM, Cancer, 2003), contributed to limit its use in this setting. NPLD is active in advanced disease and has much less cardiotoxicity than doxorubicin.

Methods. With the aim to assess the feasibility of adjuvant NPLD in terms of cardiac safety, we are conducting a phase II pilot study in high risk EBC pts older than 65 years with NPLD 60 mg/m^2 day 1 plus C 600 mg/m^2 day 1 q 21 for 3 cycles followed by P 80 mg/m^2 weekly for 9 weeks. Hormonal therapy and radiotherapy post chemotherapy when indicated. Cardiac safety is evaluated by comparison between the baseline left ventricular ejection fraction (LVEF) assessed with echocardiogram (ECHO) and LVEF at the end of NPLD + C, after P and every 6 months for 2 years. Cardiac events were defined as appearance of congestive heart failure and/or grade 3-4 LVEF decline, asymptomatic LVEF decline below 50% or an absolute drop >15%.

Results. Up today 31 pts have been enrolled. Main pts characteristics were: median age 74 (range 67-83), ECOG-PS 0/1 = 23/8, baseline LVEF >50% in all pts and no relevant cardiac comorbidities. Baseline median LVEF was 61% (range 55%-75%). 81 cycles of NPLD + C have been administered. After NPLD + C the median LVEF is unchanged with a value of 61% (range 56%-70%). No pts had cardiac events as above defined. One patient discontinued NPLD + C after the first cycle for an episode of asymptomatic arrhythmia. Toxicities ≥3 were not observed.

Conclusions. These preliminary data suggest the feasibility of adjuvant NPLD + C followed by P in EBC pts. The study is ongoing and a total of 42 pts are planned to better define early and late cardiac events.

L30 INVASIVE LOBULAR (ILC) VS INVASIVE DUCTAL (IDC) BREAST CANCER (BC): CLINICO-PATHOLOGICAL FEATURES AND CLINICAL OUTCOMES IN MONO-INSTITUTIONAL SERIES

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Background. ILC is less common than IDC and is usually diagnosed at a later stage.

Aim. The aim of our study was to investigate different clinico-biological behavior associated to ILC compared to IDC and to evaluate implications on survival outcomes.

Methods. We analyzed data from 3749 consecutive cases of IBC treated from 1995 to 2008 and classified as ILC, IDC and mixed/other. Relationships with clinico-pathological variables and the impact of ILC/IDC types on event-free survival (EFS), overall survival (OS) and post-progression survival (PPS) were analyzed.

Results. We have identified 445 ILC (12%), 3021 IDC (80.5%), 149 mixed (3.9%) and 134 other histotypes (3.6%). The median age of pts with ILC and IDC was 62 and 60 years, respectively. ILC presented a larger tumor size (T >2: 46.9 vs 33.7%) and more frequent axilla involvement (43 vs 37%) vs IDC. Poorly differentiated tumors were less frequent in ILCs than in IDCs (G3: 12.9 vs 34.8%), whereas HR+ tumors were consistently higher in ILC than IDCs both for ER (95.5 vs 82.6%) and PR (77.3 vs 69.4%). HR level was higher in ILC than IDC (88.6 vs 75.4%). ILC were also more likely to be HER-2 negative compared to IDC (93.1 vs 82.6%) and to show a low proliferation index (ki67 <15%: ILC 51.9 vs IDC 35.3%). Mastectomy was more frequently required for ILC (45%) than IDC (37%). Adjuvant hormonal (± previous chemo) therapy was more frequently given (77 vs 64%) to ILC pts due to higher ER expression than IDC. At a median follow-up of 77 (0-272) months (mos), there were not significant differences in EFS (81.4 vs 82.1%; p = 0.7) and OS (82.8 vs 84.6%; p = 0.19) between ILC vs IDC. Local and distant relapses were 15 (3.3%) and 50 (11.2%) in ILC vs 179 (5.9%) and 225 (7.4%) in IDC; the site of first distant relapses was preferentially bone for ILC pts, (52 vs 43%), while visceral involvement was more frequent in IDC (ILC 46 vs IDC 57%). Contralateral and second tumors were 9 (2%) and 22 (5%) in ILC vs 84 (2.8%) and 174 (5.7%) in IDC. Median time to first event was 38.3 mos in ILC vs 35.23 in IDC. PPS was 16.5 mos in ILC vs 22.2 in IDC. ILC showed worse prognosis in term of OS than IDC within luminal A (86.9 vs 93.5%; p = 0.003), HER2 luminal (70.4 vs 88.5%; p = 0.028) and triple negative (50 vs 72%; p = 0.021). There were no differences in EFS and OS between ILC and IDC considering age, size, HER2 and HR status.

Conclusions. ILC pts did not show in our series a better outcome than IDC pts, despite a quite favorable biological pattern.

L31 ACTIVITY AND SAFETY OF PACLITAXEL ALBUMIN (NAB-PACLITAXEL) IN SECOND AND FURTHER LINES OF CHEMOTHERAPY (CT) FOR METASTATIC BREAST CANCER (MBC) PATIENTS: A TWO-YEAR MULTICENTER ITALIAN EXPERIENCE

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Background. Nab-paclitaxel (nab-P) has been shown to improve outcome of MBC pts when compared to conventional taxanes in randomized trials. Clinical evidence is available for the registered 3-weekly (q3w) regimen at 260 mg/m^2 and for alternative weekly schedules. We sought to describe patterns of treatment and outcome of women receiving nab-P for their MBC at 6 italian Institutions during the first two years of use.

Patients and methods. Ninety-three MBC pts treated with nab-P from February 2011 to March 2013 were evaluated: median age 54 years (range 36-76), visceral dominant disease 61%, ≥3 metastatic sites 72%; previous anthracycline- and/or taxane-based CT in all pts; the cut-off data analysis was May 2013.

Results. The q3w schedule was used in 75 pts (41 in second-line, 16 in third and 18 in ≥fourth) and the 125 mg/m^2 weekly regimen in 18 pts (14 in second-, 4 in ≥fourth-line); median number of administered cycles was 8 (range 3-18). Objective response rate (ORR) in the whole population was 49% (4 complete and 42 partial responses, 36 stable diseases >6 weeks), for an overall CB rate of 86%. Median progression-free survival (PFS) was 6.8 months (range 3-16+). Major toxicities were expected and manageable: G3-4 neutropenia in 19%-7% of pts, G1-2 fatigue 38%-27% of pts; G3 sensory neuropathy occurred in 12% of pts, with a median time to G2 improvement of 19 days (range 13-28). No need for premedication and short infusion duration allowed good treatment compliance in the outpatient setting. A subgroup analysis showed no significant differences in activity and safety parameters according to disease site, previous CT, or nab-P schedule, while a trend toward better ORR and median PFS values was observed in women treated in second-line CT compared to those given 3 lines (61% vs 38% and 9.6 vs 4.8 months, respectively). Analysis of QoL, available for 34 pts included in a second-line prospective single-center phase II trial, showed no worsening of the evaluated items over a long-term treatment.

Conclusions. Our data, consistent with published efficacy results, confirm that nab-P is highly active with favorable toxicity profile in MBC, also in heavily pretreated disease and in advanced lines of treatment. In clinical practice, the chance of a flexible schedule of administration allows a better targeted therapeutic approach to each individual woman at different points of her history, basing on both disease-related factors and patient attitudes.

L32 ALTERATION OF P53 CENTROSOMAL LOCALIZATION IS STRICTLY ASSOCIATED WITH SEVERE NEUROTOXICITY INDUCED BY TAXANE-TREATMENT

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Background. In mitosis, the tumor suppressor p53 localizes at the centrosomes in an ATM- and microtubule-dependent manner. We capitalized on this p53 behavior and developed a rapid, straight-forward, inexpensive, non invasive, and reliable test to identify mutant *ATM* zygosity by measuring the percentage of mitotic cells with p53 localized at the centrosomes (p53-MCL). In a preliminary study, our test confirmed that *ATM* is a breast cancer (BC)-susceptibility gene (Prodosmo et al., J Clin Invest, 2013). Further analyses of wild-type *ATM* carriers showed that alterations of p53-MCL are significantly enriched in taxane-treated BC patients that will suffer severe neurotoxicity.

Materials and methods. Peripheral blood mononuclear cells (PBMCs) from a total of 80 BC patients were evaluated for p53-MCL by our new test; 100 healthy donors were analyzed as control. Seven of 80 (8.75%) BC patients showed a p53-MCL compatible with a heterozygous germ line mutation of the *ATM* gene (ATM-htz) that was confirmed by direct sequencing. This result is in agreement with the expected BC increase in ATM-htz compared with the general population (8.75% vs 1.69%-3.43%; i.e., the theoretical frequency of ATM-htz in the Italian population). In the present study, these patients were excluded from the following analyses. Of the remaining 73 BC patients, 34% were treated with taxanes while the other followed other protocols free from antimitotic drugs that target microtubule dynamics.

Results. We observed that 32% of the taxane-treated patients developed a grade G3 neurotoxicity and among them, 87.5% have alterations in p53-MCL in their PBMCs. In contrast, in the patients with less sever neurotoxicity (G2), only 20% showed p53-MCL alterations. Of relevance, no p53-MCL alterations were observed in the patients that were treated with protocols free from taxanes.

Conclusions. Our preliminary results suggest that alterations of p53-MCL in the PBMCs of BC patients treated with taxanes might correlate with severe neurotoxicity opening the possibility of predicting this adverse effect. A larger-scale screening is required to verify this hypothesis.

L33 ITALIAN ONCOLOGIST HABIT APPROACH IN ADJUVANT HORMONAL THERAPY IN PREMENOPAUSAL BREAST CANCER

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Background. The increasing age of first pregnancy among Italian women and the number of available therapies in premenopausal patients make adjuvant hormonal therapies a hot topic justifying a survey on the habit of therapeutical approach of italian oncologists to breast cancer. A post-hoc comparison with 2013 St. Gallen Consensus is also interesting to evaluate adhesion of Italy to these recommendations.

Material and methods. From April to July 2012 a 11 items electronic questionnaire was submitted to Italian oncologists and 611 filled questionnaires were collected: 48.1% M and 51.9% F; age range 25-65; 34.5% from north Italy, 28.3% from centre and 37.2% from south; 81% from general hospitals, 19% from re-

search institutes. The results were examined globally and according to these categories: sex, age, working institution and geographical place of work of the oncologists.

Results. 97.7% of patients aged less than 40 years needing only hormonal therapy would receive both tamoxifen (TAM) and LHRH analog (LHRHa); 2.3% TAM or LHRHa alone. 93.6% of patients aged over 40 years would receive the combination; TAM or LHRHa alone would be offered to more women (6.4%). When LHRHa would be added to TAM the treatment length would be: 5 years in 60% and 44%, 3 years in 20.8% and 26.4%, 2 years in 19.2% and 29.6%, in patients aged under and over 40 respectively. In patients aged under 40 with chemotherapy induced amenorrhea, the oncologists would prescribe: TAM in 22.4%, TAM and LHRHa in 68.1% (LHRHa for 5 years in 55.3%, for 3 years in 22.1%, for 2 years in 22.6%), aromatase inhibitor (AI) ± LHRHa in 6.6%, LHRHa alone in 2.9%. A greater number of patients would be treated with AI among women aged over 40 (11%). The reasons to add LHRHa to TAM and the length of treatment would be: higher efficacy of the combination: 45.5%; patient's age: 30.1%; risk of recurrence: 20.8%; and side effects: 3.6%. No difference was noted in questionnaire responses as regards sex, age, geographical place of work and working institutes of the oncologists.

Conclusions. A high concordance between the Italian oncologists attitude and the 2013 St. Gallen recommendations is confirmed by this large survey. However we note a wide preference for a TAM/LHRHa combination in premenopausal patients (97.7% and 93.6% in patients aged under and over 40 respectively) that is twofold respect St. Gallen Consensus (combination therapy in 40.9% of under 40 aged women).

L34 FISH IN TRIPLE NEGATIVE BREAST CANCER MAY BE USEFUL?

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Background. Triple-negative breast cancer (TNBC) represents around 15% of all breast cancers. TNBC consists of tumors that do not express estrogen (ER) and progesterone (PR) receptors and do not overexpress human epidermal growth factor receptor 2 (HER2). TNBC is associated with poor prognosis and a high risk of distant recurrence and death within the first 3-5 years of follow-up. Chemotherapy is the only approved treatment for this subgroup of patients. A better understanding of phenotypic heterogeneity may allow improvements in individualized treatments for this disease. Then a possible strategy may be represented by reexamination of samples with negative (0 or 1+) HER2 immunoistochemistry (ICH), with fluorescent *in situ* hybridisation (FISH) as suggested by recent literature.

Material and methods. The study includes 22 consecutive patients affected by TNBC (ER, PR and HER2 negative) undergone breast surgery from January 2012 until April 2013. All patients required chemotherapy, 21 adjuvant treatment and one first-line treatment. All these cases had negative HER2 ICH status and were retested with FISH in our molecular biology laboratory from January 2012 until April 2013.

Results. Our interim analysis showed positive FISH in 5 of 22 cases (22.7%). In this subgroup of patients, we could add monoclonal antibody trastuzumab to standard chemotherapy with antracycline and taxanes. Our preliminary data agree with recent literature, despite of the small size of population in study.

Conclusions. Percentage of discrepancies between ICH e FISH (intralaboratory) is around 7-18%. It is very important to identify discordant cases because patients with negative ICH and positive FISH can benefit from the addition of anti-HER2 agents. In this way patients, previously misclassified as TNBC, can receive the best medical treatment available. The addition of anti-HER2 agents in this subgroup of patients is associated with an important prognosis improvement. In conclusion, the reexamination of sample with FISH in 1+ or negative HER2 ICH allows to obtain data which can determine significant changes in clinical practice. We hope that this procedure may become shortly a standard and may be extended also to patients affected by breast cancer ER and PR positive.

L35 ASSOCIATION OF ENOS POLYMORPHISMS WITH CLINICAL OUTCOME IN BEVACIZUMAB TREATED BREAST CANCER PATIENTS

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Background. Vascular endothelial growth factor (VEGF) production is enhanced in many tumors. VEGF up-regulates the endothelial nitric oxide (NO) synthase (eNOS) and the resultant overproduction of NO may be associated with disruption of endothelial barrier, edema and impaired drug delivery within tumors. Functional polymorphisms in the eNOS gene, including -786T>C and 894G>T, have been associated with reduced production of NO and higher incidence of hypertension (HT). Since suppression of VEGF-eNOS axis by antiangiogenic drugs may restore interstitial pressure and drug distribution in tumors, but may induce HT in patients, the purpose of this study was to examine the association between the major eNOS variants -786C>T and 894G>T with treatment outcome and risk of HT in metastatic breast cancer (MBC) patients given bevacizumab.

Methods. Forty-one MBC patients given bevacizumab as per approved label were enrolled. Main characteristics were: mean age 49.5 years (range 29-73) at first diagnosis, 53 years (range 34-74) at metastatic progression and PS 0-1. Four subjects with HT and 1 patient with compensated cardiovascular disease were also included. Twenty-six subjects had received neoadjuvant or adjuvant chemotherapy based on anthracycline and taxane. First-line chemotherapy for metastatic disease was paclitaxel plus bevacizumab for all patients; 14 subjects received hormone-therapy for metastatic disease. Germline DNA was extracted from peripheral blood and used to screen patients for eNOS -786T>C and 894G>T variants by Real Time PCR and automatic sequencing. The study was approved by local Ethics Committee.

Results. Genotype frequencies are reported in Table 1. The presence of -786CC genotype was associated with longer PFS compared with the other genotypes (median PFS 95% CI, CC = 24.5 vs TT/TC = 15 months, p = 0.0421), but not with any grade

of HT. None of the other genotypes was significantly associated with PFS or HT.

Conclusion. Patients bearing deficient eNOS variant were not at risk of developing HT with respect to the wild-type allele but enjoied a longer PFS.

L33 - Table 1

SNP	Genotype frequencies %		
-786T>C	TT	TC	CC
	31.70%	46.30%	21.90%
894G>T	GG	GT	TT
	29.30%	63.40%	7.30%

L36 PROGESTERONE RECEPTOR (PGR) STATUS AND CLINICAL OUTCOME IN BREAST CANCER (BC) PATIENTS WITH ESTROGEN RECEPTOR POSITIVE (ER+) LOCO-REGIONAL RECURRENCE (LLR)

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Background. The aim of this retrospective multicentric study was to evaluate the impact of PgR loss on LLR in patients with ER+ BC and ER+ recurrence.

Patients and methods. We retrospectively collected data on patients with diagnosis of ER+ BC between 1990 and 2009, who experienced ER+ LLR. Eight Italian oncology centres participated in this study. No central pathology review was carried out for this analysis. In each centre, ER, PgR and Ki67 values were obtained by IHC; HER-2 status by IHC or FISH/ SISH. ER and PgR status was considered positive if there were at least 1% positive tumor nuclei in the sample (ASCO-CAP guidelines 2010). HER-2 status was considered positive if 3+ by IHC (strong, complete staining in >10% or 30% of cells) or amplified by FISH/SISH (HER-2/chromosome 17 ratio ≥2.0).

LLR was defined as recurrence of BC in the ipsilateral breast, after initial breast conservative surgery, or in the skin of the chest wall, after previous mastectomy, and/or in the regional lymph nodes. Both primary tumors and LLRs were ER-positive. PgR status of recurrent disease was compared with that of primary BC.

According to concordance or not between primary tumor and LLR of PgR status, we obtained three groups: 1) PgR^{pos} group: PgR positivity persistence in LLR compared to primary tumor; 2) PgR^{neg} group: PgR negativity persistence in LLR compared to primary tumor; 3) PgR^{loss} group: PgR positivity loss in LLR compared to PgR positivity in primary tumor.

To evaluate the clinical impact of PgR status in ER+ LLR compared to primary tumor, we assessed the distant metastasis-free survival (MFS), defined as elapsed months from the LLR to the first distant metastasis in these three groups of patients.

Results. Data were available for 265 patients who experienced a breast cancer from 1990 to 2009. Median MFS was 111 months in PgR-positive both primary tumor and LLR (PgR^{pos}), 38 months in PgR-negative both primary tumor and LLR (PgR^{neg}), and 63 months in PgR-positive primary tumor and PgR-negative LLR (PgR^{loss}). In multivariate analysis, PgR status was independently associated with the MFS, with a HR of 2.84 (95% CI 1.34-6.00) for PgR^{neg} compared to PgR^{pos}, and 2.93 (95% CI: 1.51-5.70) for PgR^{loss} compared to PgR^{pos}.

Conclusions. PgR absence was found to be a negative prognostic factor in ER-positive loco-regional recurrence. Thus, PgR status could be a biological marker in ER-positive relapsing BC.

L37 WHEN LESS IS BETTER: THE SAFETY AND EFFICACY OF COMBINATION OF TRASTUZUMAB AND CONTINUOUS LOW ORAL DOSE CHEMOTHERAPY (HEX) AS FIRST-LINE THERAPY FOR HER2 POSITIVE ADVANCED BREAST CANCER (ABC): RESULTS FROM A PHASE II MULTICENTRIC TRIAL ON BEHALF OF GRUPPO ONCOLOGICO ITALIA MERIDIONALE (GOIM)

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Background. Clinical activity of combination of chemotherapy plus trastuzumab in HER2+ metastatic breast cancer has been well documented. We report results in terms of activity and safety of the combination of trastuzumab plus metronomic capecitabine and cyclophosphamide as first-line therapy in HER-2 positive ABC.

Methods. Patients at first relapse or with synchronous metastasis, were treated with trastuzumab (4 mg/kg, loading dose 6 mg/kg) plus oral capecitabine (1500 mg/daily) and cyclophosphamide (50 mg/daily). Primary endpoint was overall response rate (ORR), secondary endpoint time to progression (TTP), clinical benefit rate (CBR; PR+ CR + prolonged SD for ≥24 weeks) and tolerability. The optimal two-stage design was applied.

Results. A total of 31 patients with histologically confirmed, measurable ABC, tumors scored as +3 positive for HER-2 or FISH +, no pretreated with chemotherapy or trastuzumab for advanced disease have been enrolled, 28 actually valuable for response and toxicity. Median age was 59 years (range 42-87), visceral metastases were present in most patients (61%). Median number of cycles was 12 (range 1-37+). The ORR was 61% (95% CI, 41-78%), with 1 CR (3.6%) and 16 PR (57.1%). Nine patients had prolonged SD (32%). The CBR was 82.1% (95% CI, 63%-94%). Five progressions were observed (18%). Median TTP was 7 months (range 2- 19+ months). Worst toxicities were grade 2 hand-foot syndrome in 4 pts, grade 2 anemia in 4 pts, grade 2 nausea in 2 pts and diarrhea grade 3 in 1 patient. Cardiac toxicity grade 2 in 1 patient. Alopecia was not reported.

Conclusions. Combination of trastuzumab and low dose metronomic oral chemotherapy in HER-2 positive breast cancer has shown clinical activity. The tolerability was excellent and allowed the prolonged delivery of the combination. Thus, the patients accrual is ongoing to the pre-set target of 66 patients.

L38 TREFOIL FACTOR 1: A PREDICTIVE FACTOR OF BONE RELAPSE IN BREAST CANCER PATIENTS

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Background. Patients with breast cancer frequently develop bone metastases, which are responsible for high morbidity and reduced quality of life. The early detection of patients with a high probability of relapsing in this site could be used to select candidates for tailored therapy with bone-specific drugs such as bisphosphonates or RANK-L inhibitors. We aimed to identify a pattern of tissue markers in primary breast cancer that could predict bone metastatization.

Methods. Expression of different markers was retrospectively analyzed in frozen breast cancer tissue samples from 90 patients comprising 30 cases with no evidence of disease (NEDP), 30 with bone metastases (BMP), and 30 with visceral metastases (VMP). Eight transcripts were analyzed by quantitative real time PCR: trefoil factor 1 (TFF1), bone sialoprotein (IBSP), heparanase (HPSE), SPARC, connective tissue growth factor (CTGF), B2 microglobulin (B2M) and receptor activator of Nf-kB (RANK). Immunohistochemistry of TFF1 was performed on a part of the case series.

Results. Marker expression analysis in the 3 different subgroups showed at least twofold higher median values of all markers in the NEDP or VMP subgroups than in the BMP and TFF1, B2M and CXCR4 levels showed statistically significant values. In particular, median TFF1 value in BMP patients was 430.64 compared to 115.83 and 32.79 in VMP and NEDP, respectively ($p = 0.0043$). Considering markers as dichotomous variables, TFF1 expression in BMP reached 59 per cent compared to 21 per cent and 23 per cent in NEDP and VMP, respectively ($p = 0.0022$). Univariate analysis confirmed that TFF1 predicted the relapse and also the site of relapse. Immunohistochemistry data on TFF1 revealed that this protein was expressed only by cancer cells. Furthermore, the accuracy of the marker did not change at RNA or protein level, with the exception of a post transcriptional control of the RNA.

Conclusions. In this study we identified a gene expression pattern in primary breast cancer that can identify patients destined to relapse to the bone. In particular, TFF1 would seem to be a suitable marker for bone metastatization and a possible target for the development of new drugs.

L39 A NEW TWIST ON AN OLD STORY: SIGNIFICANT ACTIVITY OF TESTOSTERONE IN HEAVILY PRE-TREATED METASTATIC BREAST CANCER PATIENTS

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Background. The role of hormone receptors as prognostic and therapeutic tools is pivotal in the management of breast cancer. In the past, testosterone was the most common endocrine additive therapy in metastatic disease; its use, however, has almost completely been discontinued and has been replaced by several other active agents in the last 40 years. Based on past experience, we started to treat with testosterone hormone responsive patients that become refractory to all hormonal lines, with unexpectedly favorable results.

Patients and methods. From September 2007 to November 2010, 53 patients with ER/PgR positive metastatic breast cancer, in progression after several lines of endocrine therapy and chemotherapy, were treated in our unit with 250 mg intramuscular (i.m.) testosterone propionate once every two weeks, then once every four weeks, until progression or toxicity. We retrospectively analyzed treatment-related toxicities, clinical response, progression-free survival (PFS), and overall survival (OS).

Results. The ORR was 17% (CR 2%, PR 15%), with 42% of stable disease (22 patients).The estimated median OS was 12 months from the beginning of testosterone treatment. With regard to tolerability and safety, androgen typical related side effects, mainly hirsutism and dysphonia, were seldom noted.

Conclusions. Testosterone showed considerable activity in heavily pre-treated metastatic breast cancer patients, with a favourable toxicity profile. These results may reinstate it as a treatment for patients with hormone-sensitive metastatic breast cancer.

L40 ON-AND-OFF METRONOMIC ORAL VINORELBINE IN ELDERLY WOMEN WITH ADVANCED BREAST CANCER

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Background. Elderly patients with metastatic breast cancer (MBC) are less likely to receive chemotherapy than younger patients, especially for the presence of multiple comorbidities, adverse drug events, and functional decline. Low-doses oral administration of cytotoxic agents with no drug-free intervals represents the most appropriate approach for this setting, maintaining drug efficacy (antiangiogenic proprieties), tolerability and low toxic effects. Vinorelbine is a semi-synthetic vinca alkaloid that interferes with microtubule assembly leading to arrest of cell division and tumor growth. Furthermore, oral administration of vinorelbine is usually well tolerated.

Patients and methods. From February 2010 to March 2013, 20 patients (N = 20) with MBC: median age 74 years (range 65-

83) were treated with oral vinorelbine 30 mg (total dose), one day on and one day off, until disease progression or unacceptable toxicity levels were reported. Eight patients received vinorelbine as first-line treatment, five patients as second-line and seven patients as third-line. Four patients were luminal A, three were luminal B, five were HER2-like and eight were basal-like. Toxicity and quality of life were evaluated.

Results. Toxicity was minimal in all patients and no grade (G) 3-4 adverse events were observed. In details: granulocytopenia G2, N = 8, G1, N = 12; anemia G1, N = 13; non-hematologic toxicity G1 and G2 were the following: asthenia G1, N = 5; diarrhea G1, N = 2; constipation, N = 6. Six patients died for tumor progression. The average duration of the treatment was six months. Descriptive statistics was used to determine the overall quality of life for patients at baseline and 6 months. Matched t tests were conducted to discern whether baseline and 6 months differed on the quality-of-life indicator ($p < 0.05$ was considered significant). Statistical analysis was performed using Graph Pad Prism 5.0 (GraphPad Software Inc., San Diego, CA, USA).

Conclusions. On-and-off metronomic vinorelbine oral administration appears to have a manageable tolerability and safe profile in our selected elderly population, and improved patient adherence to therapy. The present study demonstrated that metronomic vinorelbine might be a potential treatment in elderly patients by reducing adverse effects and increasing the quality of life, setting the stage for future extensive clinical trials.

L41 COCULTURE SYSTEM FOR THE STUDY OF THE VICIOUS CYCLE OF BONE METASTASES: THE EFFECT OF GEFITINIB ON OSTEOBLASTS AND BREAST CANCER CELLS INTERACTIONS

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Background. Highly bone metastatic breast cancer cells often overexpress metalloproteinases which can release EGF-like growth factors from tumor and stromal cell membranes. Activation of the EGFR pathway on osteoblasts enhances differentiation and activity of osteoclasts, promoting bone resorption and release of growth factors from bone matrix, favoring tumor growth. Despite failure in improving patients survival, EGFR tyrosine kinase inhibitors (EGFR-TKi) proved effective in reducing bone pain, opening a potential therapeutic window for treatment of bone metastases. The aim of the present study is to evaluate the effect of the EGFR-TKi gefitinib on osteoblasts, both in monocultures and in a coculture system with breast cancer cells.

Material and methods. Osteoblasts were obtained culturing bone marrow-derived mesenchymal stromal cells (MSC) with differentiation medium. Cocultures with breast cancer cells were performed culturing 14-day osteoblasts with MDA-MB-231 conditioned medium. Gefitinib was added both to cell monocultures and to cocultures for 72h at 1, 10, 100, 500 or 1000 ng/mL. Cytotoxic activity was detected by SRB assay. Apoptosis was detected by flow cytometry with TUNEL assay and Annexin-V assay. Protein expression was evaluated by ELISA and western blotting. EGFR mutation status was detected by Pyrosequencing.

Results. All cells were EGFR wild type. OPG secretion increases during MSC osteogenic differentiation. Conditioned medium from MDA-MB-231 enhances OPG secretion at 14 and 18 days of differentiation. EGF and RANKL are not detectable in osteoblasts culture media, neither with MDA-MB-231 conditioning. MDA-MB-231 are resistant to gefitinib at all tested concentrations. In osteoblasts monocultures, gefitinib induces a 10% increase in OPG secretion, at all drug concentrations tested. OPG secretion by MSCs is not affected by treatment with gefitinib. In cocultures with breast cancer cells, gefitinib induces a 10% and a 60% decrease of OPG secretion in osteoblasts and MSCs respectively.

Conclusions. We developed an *in vitro* osteogenesis model and observed the modulation of OPG during MSC osteogenic differentiation and in breast cancer cocultures. The OPG modulation induced by gefitinib could depend on the blockade of EGFR pathway by the drug. EGF was not detected in osteoblasts media, neither in monocultures nor in cocultures with breast cancer cells, suggesting that other EGFR ligands may be involved in the vicious cycle.

L42 HER-2/NEU GENE AMPLIFICATION IN THE CONTEXT OF A SCREENING-DETECTED POPULATION OF 54,472 WOMEN ENROLLED IN THE 'BREAST CANCER SCREENING PROGRAM IN VERONA'

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Background. Although the incidence of Her2 positive breast cancer (BC) has been extensively documented for clinically detected early stage and advanced disease, accounting for 18-20% and 20-25%, respectively, few data with regard to its incidence in the context of the population of screening-detected BC are reported. Given the potential 'positive' impact of anti-Her2 targeted therapies upon the natural disease history (regardless of the stage) and the 'negative' effect of such intervention with regard to costs, a sizeable measurement of Her2 positivity in screening programs is warranted.

Materials and methods. Patients accrued in the 'Breast Cancer Screening Program in Verona' from July 1999 to June 2004 were retrospectively gathered. Of them, available paraffin blocks from invasive BC were analysed for Her2 overexpression, by immunophenotypical (IHC) and fluorescence in situ hybridization (FISH, whereas required). Descriptive statistics was adopted, and confidence intervals (CI) were derived; concordance between IHC and FISH was analyzed according to K-statistics.

Results. Overall, 54,472 women were screened and 323 (0.6%) were found to be invasive cancers. Paraffin blocks were available for 153 patients (47.4% of invasive BC), with a median age of 58 years (range 50-70) (attrition rate = 52.6%). Of them, 118 (77%) and 23 (15%) were ductal and lobular; tumor grading was G1, G2 and G3 for 77 (50%), 54 (35%) and 13 (8.5%) patients, respectively. T-size was pT1, pT2, pT3 and pT4b for 135 (88%), 10 (6.5%), 5 (3%) and 3 (2%) patients. Ki67 was >15%

and <15% in 13 (9%) and 140 (91%) patients, respectively. Her2 IHC positivity displayed as follows: 3+ in 16 (10.4%, 95% CI 5.6-15.3%), 2+ in 12 (7.8%, 95% CI 3.5-12.1%), 1+ in 29 (18.9%, 95% CI 12.7-25.1%) and 0 in 96 (61.7%, 95% CI 55.1-70.4%) of 153 cases. All 3+ Her2-positive and 2/12 2+ cases showed Her2/neu gene amplification (mean ratio 3.2, range 2.8-4.3). All 2+ and 3+ cases were ductal breast carcinomas. Cromosome-17 polysomy was found in 3/12 (25%, 95% CI 0-49.4%), 2/29 (6.9%, 95% CI 0-16.1%) and 3/96 (3.1%, 95% CI 0-6.6%) of the 2+, 1+ and 0 patients. Concordance between IHC and FISH was high (K = 0.80).

Conclusions. Although the significant attrition (52.6%), in contrast to the higher incidence reported regardless of the stage, only 10% and 11% of the screening-detected breast cancers displayed Her2 overexpression or Her2/neu gene amplification, respectively.

L43 COCULTURE SYSTEMS OF BREAST CANCER AND BONE CELLS TO TEST THE ACTIVITY OF BONE TARGETED DRUGS

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Background. Metastatic bone disease has a major impact on morbidity and mortality of breast cancer patients. The studies on the bone metastasis biology have led to the development of the most widely used drugs for bone metastatic patients: zoledronate (Zol) and denosumab (Den). Dissecting the complex crosstalk that occurs between breast cancer and the bone environment is a promising strategy for the identification of critical pathways and for the design of targeted drugs. The aim of the present study was to develop a coculture system of breast cancer and bone cells to test the activity of bone targeted molecules.

Material and methods. The study was performed with a breast cancer cell line MDA-MB-231 and with human osteoclasts obtained from the differentiation of peripheral blood monocytes of a voluntary healthy donor. Cocultures were performed through conditionated media. Osteclastogenesis was detected by TRAP assay at 7, 14 and 21 days of differentiation with MCSF and RANKL and with 10% MDA-MB-231 conditionated media. Den (0.5, 1 and 5 μg/mL), and Zol (0.1, 1 and 10 μM) were administrated for 7 days after 7 days of osteoclasts differentiation. Osteoclastogenesis was detected after treatment. Protein expression was evaluated by ELISA assay and western blotting. Apoptosis was detected by TUNEL assay.

Results. MDA-MB-231 was found to secrete MCSF especially at confluent growth. Conditionated media from MDA-MB-231 double the differentiation of monocytes into osteoclasts. NFk-B was activated in osteoclasts and absent in undifferentiated monocytes. Induced osteoclasts were sensitive to bone targeted drugs. Den blocks osteoclasts differentiation and survival, Zol induced osteoclasts apoptosis. Osteoclasts induced by breast cancer were less sensitive to Zol respect to osteoclasts induced by differentiation factors whether the sensitivity to Den was similar. A significant increase of MCSF was observed in osteoclasts media after treatment with the highest concentration of Den.

Conclusions. We developed an *in vitro* model to reproduce the interactions between breast cancer cells and the bone environment. Our model represents a valid system for preclinical trials of bone targeted drugs and for the study of molecular mechanisms beyond breast cancer interplay with bone cells. The entire model will include the role of osteoblasts and drugs combination tests, in particular with antibodies against MCSF seeing the increment of MCFS levels after Den treatments.

L44 FIRST-LINE THERAPY IN HER2-POSITIVE METASTATIC BREAST CANCER PATIENTS RELAPSING AFTER ADJUVANT TRASTUZUMAB: A RETROSPECTIVE OBSERVATIONAL TRIAL

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Background. There are few clinical data available that assessed the benefit of a retreatment with trastuzumab (T) in patients relapsed after adjuvant chemotherapy plus T. Since T is nowadays a standard adjuvant therapy, it is important to assess the benefit of re-exposing patients with metastatic breast cancer (MBC) to T. We retrospectively evaluated the patterns of care and outcomes of MBC patients re-exposed to T after adjuvant therapies.

Materials and methods. HER2-positive MBC patients who received T or lapatinib (L) as first-line therapy were evaluated; patients who did not receive any anti-HER2 therapy or who underwent pertuzumab or TDM1 as first-line therapy were excluded from the analysis. Analyses were carried out according to pretreatment (yes/no) with adjuvant T, and type of anti-HER2 agents (T vs L) administered as first-line therapy. Statistical analyses were performed with IBM SPSS statistics 20.0; progression-free survival (PFS) was compared by cohort using Kaplan-Meier method.

Results. A total of 76 patients with a median age of 57 years (range 32-90) were identified. A total of 47 patients (62%) had hormone receptor positive disease. The first site of relapse was: soft tissue in 15 patients (20%), bone in 17 (22%), lung/liver in 35 (46%), and brain in 9 (12%). Among the 76 patients who received T or L as first-line therapy, 16 had received prior adjuvant T. In the 60 patients who did not receive prior T and in the 16 patients pre-treated with T, we observed the following outcomes, respectively: PFS, 22 months (range 3.5-96.3) vs 11.2 (range 3.0-63.1); complete response (CR), 28 patients (46.7%) vs 3 patients (18.8%); clinical benefit rate (CBR: CR + partial response + stable disease), 56 patients (93.3%) vs 15 patients (93.8%).

Among the 16 patients who received adjuvant T, 11 patients received T (median interval since the completion of adjuvant T: 11.7 months [range 0-65.4]) and 5 patients received L (median interval since the completion of adjuvant T: 29.6 months [range 10.5-40.1]) as first-line therapy. The observed PFS in patients treated with T vs patients treated with L, was 10.9 months (range 3.0-56.2) and 11.5 months (range 7.5-63.1), respectively.

Conclusions. This analysis suggests that T is an effective first-line therapy for MBC patients who relapsed following adjuvant T, but these patients showed a worse prognosis with a shorter PFS and a lower rate of response to first-line therapy.

L45 CARDIAC SAFETY OF TRASTUZUMAB (T) CONCURRENT WITH PACLITAXEL (P) AND ANTHRACYCLINES (A) AS NEOADJUVANT TREATMENT OF LOCALLY ADVANCED (LA), HER-2 POSITIVE, BREAST CANCER

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Background. T-based regimens are used as neoadjuvant treatment in Her-2 positive LA breast cancer. Phase III clinical trials have shown a limited and controllable cardiac toxicity regarding the use of concomitant T and A based regimen. We retrospectively evaluate the cardiac safety of the combination of T with P and A in the neoadjuvant setting.

Methods. Twenty-three patients, with proven pathological HER-2 3+ or HER-2 2+ and FISH-amplified locally advanced breast cancer, were treated with the following regimen: P 80 mg/m^2/weekly for 12 weeks followed by FEC (epirubicin 75 mg/m^2 [one pt received 90 mg/m^2], 5-FU 500 mg/m^2 and cyclophosphamide 500 mg/m^2) for 4 cycles. T (4 mg/kg loading dose followed by 2 mg/kg/weekly) was administered for 24 weeks from the start of treatment (Buzdar A: J Clin Oncol, 23: 3676-3785, 2005). Main patients characteristics were: median age 52 years (27-73), postmenopausal/premenopausal 15/9, axyllary node involvement: 19 pts, HER-2 3+: 18 pts, Her-2 2+ FISH amplified: 5 patients. Hormone receptors positive: 15 pts, median Ki67: 30% (range 10-80%). To monitor the ejection fraction (EF) echocardiography was performed at baseline, at the end of concomitant treatment with P and T, after the first and the fourth cycle of AC + T, then during adjuvant T.

Results. Twenty-two pts were evaluable for analysis of cardiac safety. The median baseline EF was 65% (range 50-75%). Transient asymptomatic reduction of EF ≥10 points was observed in 4 pts (18%). In 3 pts it was observed after the first cycle of A + T, whereas in one patient it was observed 4 weeks after the end of P + T treatment. Further EF reductions were not observed after the fourth cycle of concomitant therapy nor during T treatment. No grade 3/4 cardiac toxicities were observed.

Conclusions. In the large phase III trial NOAH (Lancet, 30: 375, 2010) T was well tolerated and only two patients (2%), treated with concomitant doxorubicin, developed symptomatic cardiac failure. On the basis of NOAH trial the European Medicines Agency extended the indications of T in combination with neoadjuvant chemotherapy followed by adjuvant T. In our experience the cardiac safety of concurrent administration of T and P followed by A-based chemotherapy is confirmed and does not differ from that observed in clinical trials. Whereas some patients have a decrease in their ejection fraction these decreases have not progressed. Left ventricular ejection fraction should be adequately monitored during A and T concomitant treatment.

L46 FATIGUE AND CUTANEOUS ERYTHEMA IN EARLY STAGE BREAST CANCER PATIENTS RECEIVING ADJUVANT RADIATION THERAPY

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Purpose. We investigated the hypothesis that patients developing high-grade erythema of the breast skin during radiation treatment are likely to present increased levels of serum pro-inflammatory cytokines which may, in turn, lead to associated fatigue symptoms.

Patients and methods. Between 2007 and 2010, 40 women with early stage breast cancer who received adjuvant irradiation after breast conserving surgery were studied. Fatigue symptoms, erythema and cytokine levels (IL-1α, IL-1β, IL-2, IL-4, IL6, IL-8, IL10, vascular endothelial growth factor-VEGF, epidermal growth factor-EGF, tumor necrosis factor α-TNF-α, interferon γ-IFN-γ and monocyte chemoattractant protein 1-MCP-1) were registered at baseline, during treatment and after radiotherapy completion. The Heckman two-step approach was adopted to account for the correlation of skin erythema with pro-inflammatory marker levels and fatigue and to avoid endogeneity problems.

Results. Seven (17.5%) patients presented fatigue symptoms without associated depression/anxiety. Grade 2 erythema was observed in 5 of these 7 patients. Interleukin 1β, IL-2, IL-6 and TNFα were statistically increased after radiotherapy. After the Heckman two-step analysis a statistically significant increase in pro-inflammatory markers ($p = 0.00001$) was recorded with respect to skin erythema; in the second step, these blood markers have been found to have a significant impact on fatigue symptoms ($p = 0.026$). A seemingly increase in fatigue, erythema and pro-inflammatory markers was observed between the fourth and the fifth week of treatment followed by a decrease after RT completion. There were no significant effects of hormone therapy, breast volume and anemia on fatigue.

Conclusions. Our study seems to suggest that fatigue is related to high-grade breast skin erythema during radiation therapy through the subsequent increase of cytokine levels.

L47 RESPONSE RATE BY MOLECULAR SUBTYPES AND P53 EXPRESSION IN NEOADJUVANT THERAPY FOR BREAST CANCER WITH TAC REGIMEN: A SINGLE-CENTRE EXPERIENCE

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Aims and background. Pathologic complete response (pCR) is a proven surrogate for survival, although its value seems to be restricted to specific subtypes of breast cancer (BC). Aims of our study were to determine the response rate (RR) and pCR according to commonly accepted BC subtypes and p53 expression in neoadjuvant setting.

Methods. This single-centre retrospective study analyzes a series of consecutive patients (pts) treated with TAC regimen (docetaxel 75 mg/m^2, doxorubicin 50 mg/m^2, cyclophophamide 500 mg/m^2, d1q21) for locally advanced BC between 2004 and 2012. RR >50 and pCR (defined as no evidence of residual cancer or residual *in situ* component only in the primary tumour and lymph nodes) were compared to St. Gallen 2011 molecular sub-

types and p53 expression, categorized as positive with a nuclear staining >50%.

Results. Forty-nine pts, median age 51yrs (24-78), were classified as follows: luminal A 0% (0/49), luminal B-HER2-ve 36.7% (18/49), luminal B-HER2+ve 14.3% (7/49), HER2+ve 8.2% (4/49), triple negative 40.8% (20/49). All pts received 6 cycles of TAC regimen before surgery that was breast conservative in 22 cases (44.9%) or modified radical mastectomy in the others. RR was 75.5% (37/49), overall pCR 20.4% (10/49) and pCR rate by molecular subtypes was: luminal B-HER2-ve 5.5% (1/18), luminal B-HER2+ve 14.3% (1/7), HER+ve 25%(1/4), triple negative 35% (7/20). RR was 77.8% (16/22) in p53+ve tumours and 72.7% (21/27) in p53-ve, pCR was 50% (5/10) in both p53+ve a d p53-ve. At a median follow-up of 55.5 months (15-104), 44 pts are still alive and 39 of these are disease-free while all pts that achieved pCR are in a disease-free status at a median follow-up of 63 months (24-102).

Conclusions. Our data for RR and pCR agree with the literature for all molecular subtypes and show that p53 expression was not an independent predictor for response. This study confirms our previous report that TAC regimen is highly effective in neoadjuvant setting and shows that it is especially active in HER2+ve and triple negative BC.

L48 METABOLIC AND ANTHROPOMETRIC CHANGES IN EARLY BREAST CANCER PATIENTS RECEIVING ADJUVANT THERAPY

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Background. Weight gain and metabolic changes are common during the first year after breast cancer diagnosis. In this study, we examined clinical factors associated with body size at diagnosis and weight gain during the subsequent year.

Material and methods. An inception cohort of 465 women with newly diagnosed early breast cancer (EBC) underwent anthropometric [BMI (kg/m^2), weight (kg), waist and hip circumferences (cm), waist-to-hip ratio] and metabolic [insulin level (mU/mL), glucose level (mg/dL), H1Ac (%), total cholesterol level (mg/dL), HDL cholesterol level (mg/dL), LDL cholesterol level (mg/dL), triglycerides level (mg/dL), HOMA score] parameters measurements at baseline and 1 year post diagnosis. Information on tumor- and adjuvant treatment-related variables was collected. All women received adjuvant therapy.

Results. Fifty-seven% of women were postmenopausal, 37% were premenopausal and 7% were unknown. The mean ages were 43.2 ± 5.8 and 61.9 ± 7.7 years among premenopausal and postmenopausal women respectively. Overall, mean weight, waist and hip circumferences, BMI, total cholesterol level, triglycerides level, significantly increased among premenopausal women: +2.1 kg (95% CI 1.2-3.0), +2.3 cm (95% CI 1.1-3.6), +1.5 cm (95% CI 0.3-2.7), +0.8 kg/m^2 (95% CI 0.5-1.2), +10.1 mg/dL (95% CI 3.8-16.4), +29.0 mg/dL (95% CI 16.9- 41.1) respectively. Most of the changes were observed in women receiving hormonal therapy with or without chemotherapy. Among postmenopausal women, mean triglycerides level increase: +24.0 mg/dL (95% CI 11.6-36.3) and a significant decrease of H1Ac, HDL and LDL cholesterol levels: -0.2 (95% CI -0.43 to -0.03], -5.9 mg/dL (95% CI -11.4 to -0.5), -9.6 mg/dL [95% CI -18.4 to -0.8] respectively were the only significant metabolic changes. Adjuvant therapies do not seem to affect glucose, insulin and HOMA score levels in our dataset.

Conclusions. Profound metabolic changes and weight body distribution occur in patients receiving adjuvant therapies after EBC diagnosis. These changes are more relevant in premenopausal women. Use of adjuvant chemotherapy and the onset iatrogenic induced amenorrhea (either with chemotherapy or hormonal treatment) may play a major role. Further follow-up is needed to correlate such changes with patient prognosis.

L49 ERIBULIN IN BREAST CANCER SKIN METASTASES: CLINICAL ACTIVITY AND SYMPTOMS CONTROL

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Background. Skin metastases (SM) occur in 20% of metastatic breast cancers (mBC). In literature few trials report clinical outcome and description about them, even if they affect quality of life and determine great impairment in self perception of the disease. Eribulin (E) is a new drug, approved in mBC, after at least 2 lines of chemotherapy. The aim of this survey was to evaluate outcome of breast cancer SM treated with E, and to compare systemic and skin response to treatment. Cutaneous symptoms (pain, infiltration, bleeding, smell and ulceration) were also evaluated.

Materials and methods. This study was conducted from November 2012 to January 2013 in 14 Italian Cancer Centers. Oncologists completed a database with patient (pts), tumor and treatment characteristics. Skin lesions were assessed with RECIST criteria; cutaneous symptoms were evaluated with a present/absent criteria. Descriptive summary statistics were applied. Progression-free survival (PFS) and OS were calculated according to Kaplan-Meier method.

Results. Of 109 pts with mBC on E treatment 23 (21%) with SM were identified and analyzed. Basal Karnofsky performance status was 90 (50-100). Only two patients had exclusively skin disease, 21/23 pts had other metastatic sites. Infiltration was present in 78%, ulceration in 70%, pain in 43%, bleeding in 43% and smell in 17% of cases. After E, 43% of patients obtained a partial response (PR), 35% stable disease (SD), 22% progressive disease (PD). We evaluated skin response independently and found that 26% obtained a complete response (CR); 22% PR,

39% SD, 13% PD. Skin responses were in complete accordance with overall response in 16/23 (70%) pts, in partial accordance in 4 pts (skin CR, with an overall PR) and were discordant in 3 pts (1 skin SD despite overall PR, and 2 cutaneous CR despite overall PD). An improvement in SM symptoms was observed: pain control, smell and bleeding were gained in 50% of patients. Infiltration disappeared in 17%, while ulceration improved in 44% of patients. With a median follow-up of 6 months, 21 (91%) pts had PD, median PFS was 4.3 months (95% CI 2.9-6) and median OS was 9.1 months (95% CI 7.0-n.a.).

Conclusions. During E, the response rate of SM was coherent with systemic responses, in the majority of cases. The good clinical response reflects symptoms improvement, an issue difficult to assess, but of great significance for the patient. Interestingly, a fairly good Karnofsky PS was maintained during the treatment period.

L50 TRASTUZUMAB-BASED ADJUVANT CHEMOTHERAPY FOR BREAST CANCER: EARLY MYOCARDIAL DYSFUNCTION DETECTED BY SPECKLE TRACKING ECHOCARDIOGRAPHY (STE)

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Background. Trastuzumab (TZB), an anti HER-2 receptor monoclonal antibody, was shown to be effective in breast cancer patients over-expressing HER-2 in the neo-adjuvant, adjuvant and metastatic setting. Careful cardiac monitoring is required when administered in combination with anthracyclines (ANT) which can increase its toxicity. Myocardial deformation indexes associated with STE myocardial imaging were shown to be very sensitive in identifying left ventricular (LV) dysfunction.

Patients and methods. A phase IV, prospective, non-randomized study was designed to assess by STE technique the amount, timing and type of TZB-induced pre-clinical cardiac dysfunction when administered after epirubicin (EPI) in patients with HER-2 positive breast cancer. The schedule of TZB treatment was 6 mg/kg q3w for 1 year following EPI. Inclusion criteria: 18-70 yrs, histologically confirmed HER-2 positive breast cancer, LVEF ≥55%; ECOG PS score 0-2, no history of cardiac disease. ECOG PS score, conventional echocardiography and 2D STE parameters (circumferential and longitudinal S and SR, LV torsion), were assessed at baseline, after EPI treatment and one week after each TZB administration up to the 8th TZB administration.

Results. Thirty-eight patients (mean ± SD age 51 ± 10 yrs) were enrolled from May 2012. A significant reduction in SR longitudinal peak ($p < 0.05$) and a significant increase in circumferential function ($p < 0.01$) were observed after EPI treatment. From the third TZB dose a marked reduction in circumferential function ($p < 0.01$) and LV rotation ($p < 0.001$) and no further reduction in longitudinal function were detected. A slight but significant reduction of the LVEF occurred soon after the fourth dose of TZB.

Conclusions. We showed that after treatment with EPI longitudinal function was impaired while a compensatory increase in LV circumferential function and LV torsion was observed. TZB treatment had a negative impact on mid and sub-epicardial fibres function, responsible mainly for circumferential function and left ventricle torsion. These effects could be attributed to the higher toxicity of TZB on hyperactive myocardial fibres after EPI treatment. The study is in progress and longer follow-up will show if this mid and sub-epicardial myocardial impairment persists over time and eventually results in an overt clinical cardiac dysfunction.

L51 A RETROSPECTIVE STUDY FOR THE EVALUATION OF BONE MINERAL DENSITY AND FRACTURE RISK WITH FRAX SYSTEM IN WOMEN WITH BREAST CANCER TREATED WITH AROMATASE INHIBITORS

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Background. Breast cancer patients treated with aromatase inhibitors (AIs) are at risk of developing skeletal fractures. The FRAX (Fracture Risk Assessment) is an useful tool for the assessment of this risk. To date there are few data on the application of this instrument in breast cancer patients treated with AIs.

Materials and methods. The aim of this study was to evaluate bone mineral density (BMD) and fracture risk in a cohort of women with breast cancer treated with AIs. Patients were evaluated by rheumatologist for determination of densitometry by DXA (Lunar Prodigy, GE, USA) and for the identification of risk factors for fracture. All patients were subjected to blood sampling for the determination of 25-idrossivitaminaD [(25 (OH) D3]. Normal value of 25 (OH) D3 was considered >30 ng/mL. BMD results were expressed in g/cm^2 and the diagnosis of osteoporosis was defined according to WHO as a T-score <-2.5. For each patient was calculated using the FRAX algorithm the percentage of risk fracture considering therapy with AIs a risk factor for secondary osteoporosis. We evaluated 60 consecutive breast cancer patients (mean age 62.3 ± 9.4 years) in adjuvant therapy with AIs for an average of 31.18 ± 20.7 months and we compared them with 48 healthy controls matched for age (mean age 61 ± 5 years).

Results. Thirty-eight patients (60.3%) had reduced levels of bone mass and in particular 33.3% revealed osteoporosis and 27% osteopenia. BMD was significantly lower in women treated with AIs compared to the control group (L1-L4 BMD = 0.891 g/cm^2 vs 1.039 ± 0:12 ± 0:18 g/cm^2, $p < 0.001$, entire femur BMD = 0.767 g/cm^2 vs 0.903 ± 00:09 00:11 g/cm^2, $p < 0.001$). 30% of patients were smoker, 19% had previous fractures (wrist 3%, 6% column, femur 3%), 12% had a family history of fractures, 46% received prior chemotherapy and 71% radiotherapy. Mean values of 25(OH) D3 were 18.6 ± 9.6 ng/mL and only 3% of patients resulted in the normal range. Fracture risk at 10 years calculated using the FRAX integrated with the bone mineral density was 7.8% for non-femoral fractures and 1.7% for femoral fractures.

Conclusions. Patients treated with AIs generally have reduced BMD and insufficient levels of vitamin D. FRAX algorithm could be a useful and simple tool for assessing the risk of fracture in this clinical setting allowing you to diversify, depending to the risk level, a corrective therapy.

L52 MANAGEMENT OF PRIMARY AND METASTATIC BREAST CANCER: ATTITUDE AND PRACTICE OF ITALIAN MEDICAL ONCOLOGISTS

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Background. Heterogeneity of choices represents a major problem in medicine for patients and stakeholders. It reflects different attitudes of doctors in terms of risk evaluation and management and it is particularly relevant in the clinical situations for which many options are available. Guide-lines may mitigate this heterogeneity but many situations remain in a gray zone where the evidence is poor and the opinion of experts is more relevant.

Material and methods. Some clinical scenarios have been shown to a group of 175 Italian medical oncologists during a session of a meeting organized by Accademia Nazionale di Medicina, Genova. They concerned common clinical problems in the treatment of early and advanced breast cancer. Specifically: 1) 39-years-old, ductal, pT1c N1a ER 90% PgR 85% G2 Ki67 18% HER2-0; 2) 40-years-old, adenoid cystic, pT1c N0 ER0% PgR 0% G3 Ki67 10% HER2-0; 3) 55-years-old, ductal, pT1c N2 ER 0% PgR 0% Ki67 60% HER2-3+, 4 months after the term of adjuvant therapy (FEC-docetaxel + trastuzumab) liver relapse; 4) 56-years-old, ductal, pT2 N0 ER 80% PgR 0% Ki67 55% HER2-0, 2 years after the term of adjuvant chemotherapy (CT) (FEC-paclitaxel), during letrozole, symptomatic relapse (liver, lung, nodes); 5) 60-years-old, ductal, pT1c N0, ER 90% PgR 50% Ki67 20% HER2-0, during adjuvant anastrozole, asymptomatic liver relapse. For each of them a panel of four or more responses was shown; participants had the possibility to vote by an electronical device and results of votation were registered.

Results. For scenarios 2, 3, 5 the most voted response did not reach 50%; the most voted response was >70% only for scenario 4 (in favour of bevacizumab plus CT vs poli vs monoCT, 72.8% vs 22.2% vs 8.6%) and for scenario 1 (in favour of adding CT to endocrine therapy, 78.3% vs 21.5%). Major divergences regarded the scenarios 2 (40% no adjuvant treatment, 32.9% anthracycline-taxane based CT, 13.8% CMF) and 3 (35.6% capecitabine and lapatinib and 46.1% CT plus dual anti-Her2 blockade). Regarding scenario 5 the majority voted in favour of endocrine therapy but did not agree on type (48.5% fulvestrant, 20.5% exemestane plus mtor inhibitor, 9.1% fulvestrant plus anastrozole).

Conclusions. These data reflect the controversies existing in the clinical practice of early and advanced breast cancer in our country. It is important to be aware of the current limitations of available evidence and improve patients communication and empowerment.

L53 DISCRIMINATING CLINICAL OUTCOME OF HER2-POSITIVE BREAST CANCER (BC) PATIENTS AFTER FAILURE TO ADJUVANT TRASTUZUMAB (ADJT): THE POTENTIAL OF TIME TO RELAPSE (TTR)

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Background. Clinical trials for HER2-positive recurrent BC pts excluded prior AdjT and/or relapse within 1 year (yr) from the end of AdjT. Therefore, we planned a cross-sectional study in pts progressing on AdjT to analyze: a) the clinical presentation; b) the use of anti-HER2 therapy; c) the anti-tumor activity as a function of TTR.

Methods. We reviewed the medical charts of BC pts relapsing on AdjT and admitted at the National Cancer Institute of Milan in the 2013 first quarter. Fisher's exact test was used for contingency tables, log-rank test for survival distribution; $p < 0.05$ was considered statistically significant.

Results. Forty pts were identified. Median age at diagnosis was 47.4 (22.1-76.3) yrs; 27 (67.5%) pts had stage III; anthracycline ± taxane were offered as neo/adj therapy to 93% and hormonotherapy to 55% of patients. Median age at relapse was 48.7 (26.0-79.9) years. Median TTR was 23.5 (5.2-108.5) months (mos). Relapse occurred during (early) or after (late) AdjT in 12 (30%) and 28 (70%) patients. Early and late relapses shared a similar distribution of hormone receptor positive and negative status (35% vs 25%, $p = 0.73$). Early relapses were less likely to report lung (8% vs 36%, $p = 0.12$), bone (25% vs 36%, $p = 0.72$) and multiple (8% vs 36%, $p = 0.12$) metastases; liver was affected by 42% and 29% of early and late relapses ($p = 0.48$). All patients but 2 had anti-HER2 as first-line. Of 12 pts with early relapse, 8 (67%) received T and 3 (33%) tyrosine kinase inhibitors (TKIs); only 2 (7%) pts with late relapse had first-line TKIs. After a median follow-up of 21.3 (0.6-98.6) mos, 29 (72.5%) pts had progressed; 4 and 18 pts had complete (CR) and partial response (PR), for an overall response rate (ORR) of 61%. Median time to progression (TTP) was 12.7 mos (95% CI 9.0-15.3). Of note, pts with early relapse to AdjT had a worse TTP than pts with late relapse, 9.2 (95% CI 3.9-13.3) vs 15 mos (95% CI 9.1-27.9), $p = 0.048$. Second-line was T and TKIs in 65.5% and 24% of pts, ORR was 50% (4 CR, 9 PR).

Conclusions. T was the choice in both first- and second-line. Anti-tumor activity was consistent with literature, but data should be interpreted with caution, as the cross-sectional design may have favored the inclusion of pts at good prognosis. Notwithstanding the above, we observed pts with early relapse to AdjT showing a worse outcome. Further investigation to tailor therapy for these pts is recommended. Patients data collection continues and an update will be presented at the meeting.

L54 ANTHRACYCLINE-BASED REGIMENS AND TRASTUZUMAB RELATED CARDIOTOXICITY AFTER ADJUVANT THERAPY IN EARLY BREAST CANCER: A SINGLE CENTER EXPERIENCE

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Background. Quality of life of patients who survive breast cancer can be compromised by cardiotoxicity related to anthracycline-based regimens (ABR) and trastuzumab (T). The aim of our retrospective study was to evaluate left ventricular systolic and diastolic function performance in women with early breast cancer (EBC) treated with ABR associated or not to trastuzumab.

Material and methods. One hundred and thirteen women, median age 51 (range 25-79), without basal alteration of left ventricular ejection fraction (LVEF) and diastolic function were con-

sidered. Forty-four patients received 6 cycles of FAC (N = 19) or 6 cycles of FEC_{100} (N = 25). Forty-four patients received 4 cycles of EC plus 4 cycles of docetaxel (D). Twenty-five patients with Her2-positive EBC received 4EC + 4D + T up to 1 year. Management of cardiac function was assessed with Doppler echocardiogram at baseline (T0), during chemotherapy (T1) and 5-year follow-up (T2). Cardiac toxicity was defined according to CTCAE-NCI-2.0 and NYHA class.

Results. No cardiac heart failure (CHF) event was determinate after treatment with 4EC + 4D or 4EC + 4D + T for 1 year. Two CHF events occurred in patients treated with FAC and FEC_{100}, 5 years after the end of the FAC treatment (LVEF: 35%) and 2 years after the end of the FEC_{100} treatment (LVEF: 40%), respectively. In the group of patients receiving ABR, the incidence of grade 1 diastolic dysfunction was 37% and 50% at T1 and T2, respectively. In Her2 positive EBC patients treated with trastuzumab, the incidence of diastolic dysfunction was 23% at T1 and it was increased to 27.7% at T2.

Conclusions. Our data show that 4EC + 4D regimen has a good cardiac safety related to low cumulative dose of epirubicin (400 mg/m^2). Cardiotoxicity incidence (1.76%), observed in patients treated with FAC/ FEC_{100} regimens, agrees with other studies. Trastuzumab addiction in HER2+ patients has not caused systolic dysfunction. Data on incidence of grade 1 diastolic dysfunction, compared between the two groups, at T1 and T2, were no statistically significant. Therefore, trastuzumab treatment does not increase the risk of occurrence of diastolic dysfunction.

L55 PROGNOSTIC VALUE OF BODY MASS INDEX IN METASTATIC BREAST CANCER

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Background. Several studies have investigated the body mass index (BMI) in women with breast cancer (BC). Data suggest an association between BMI and tumor characteristics, menopausal status and clinical outcome in patients with BC.

Methods. We retrospectively evaluated 472 consecutive patients with diagnosis of metastatic BC (MBC) treated at the Department of Oncology of the University Hospital of Udine from 2004 to 2012. Patients were grouped according to BMI categories: normal (BMI <25kg/m^2), overweight (BMI 25.1-29.9 kg/m^2) and obese (BMI ≥30 kg/m^2). We analyzed association of BMI and different histological subtypes, menopausal status and outcome. We performed univariate analyses (X^2-test and Wilcoxon two-sample test) and survival analysis (Cox regression and Kaplan Meier test).

Results. BMI >25 was associated with histological luminal B subtype whereas BMI ≤25 was associated with histological luminal A subtype (p = 0.03). Patients with BMI >25 were more likely to be older and postmenopausal. In particular, the median age of BC diagnosis was 62.5 (range 30.3-91.9) and 54.3 (range 27.8-88.4) for patients with BMI >25 and BMI ≤25, respectively (p <0.0001). The menopausal status was found in 46.77% and in 38.53% patients with BMI >25 and BMI ≤25 respectively (p = 0.0026). Patients with BMI >30 did not differ in terms of menopausal status. No association was observed in overweight and obese patients (BMI >25) compared to normal-weight patients (BMI ≤25) in terms of PFS and OS. In addition, efficacy of endocrine therapy with aromatase inhibitors in postmenopausal patients did not vary among BMI subgroups.

Conclusions. The study confirmed previous observations of a higher incidence of histological luminal B subtype and postmenopausal status in patients with BMI >25. According to this analysis, in MBC, BMI did not result of prognostic value overall and in the subgroup of postmenopausal patients treated with aromatase inhibitors.

L56 ER STRESS PROTECTION BY TRAP1 INDUCES RESISTANCE TO PACLITAXEL IN BREAST CARCINOMA CELLS

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Background. TRAP1 is a chaperone up-regulated in human malignancies and responsible for survival responses throughout the regulation of the mitochondrial apoptotic pathway. Recent evidences suggest that TRAP1 is involved in the crosstalk between mitochondria and endoplasmic reticulum (ER) and ER stress protection of tumor cells.

Materials and methods. Based on the mechanistic link between ER stress, protection from apoptosis and drug resistance, we questioned whether this novel role of TRAP1 is relevant for its antiapoptotic function and may favor resistance to paclitaxel, a microtubule stabilizing/ER stress inducer agent widely used in breast carcinoma (BC) therapy.

Results. We observed that: 1) TRAP1 expression is increased in about 50% of human BCs, and 2) the ER stress protecting activity of TRAP1 is conserved in human tumors since TRAP1 is co-upregulated with the ER stress marker, BiP/Grp78. Notably, ER-associated TRAP1 modulates mitochondrial apoptosis by exerting a quality control on 18kDa Sorcin, a TRAP1 mitochondrial client protein involved in TRAP1 cytoprotective pathway. Furthermore, this TRAP1 function is relevant in favoring resistance to paclitaxel: indeed, the transfection of a TRAP1 deletion mutant, whose localization is restricted to the ER, in shTRAP1 cells enhances the expression of mitochondrial Sorcin and protects from apoptosis induced by ER stress agents and paclitaxel. Furthermore, BC cells adapted to paclitaxel or ER stress inducers share common resistance mechanisms: both cell models exhibit cross-resistance to single agents and the inhibition of TRAP1 by siRNAs or gamitrinib, a mitochondria-directed HSP90 family inhibitor, in paclitaxel-resistant cells rescues the sensitivity to paclitaxel.

Conclusions. These results support the hypothesis that ER-associated TRAP1 is responsible for an extramitochondrial control of apoptosis and, therefore, an interference of ER stress adapta-

tion through TRAP1 inhibition outside of mitochondria may be considered a further compartment-specific molecular approach to rescue drug-resistance.

L57 PREVALENCE OF BRCA1/2 MUTATIONS AND TRIPLE-NEGATIVE RECEPTOR STATUS IN BREAST CANCER CASES FROM SARDINIA

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Background. Germline mutations in BRCA1/2 genes have been demonstrated to increase the risk of developing breast cancer (BC). The disease stage and the receptor status play a crucial role as prognostic factors in BC patients. Triple-negative breast cancer (TNBC) constitutes a disease subgroup that is negative for oestrogen, progesterone, and HER2 receptor expression, presenting a worse prognosis.

Methods. During the period from January 1998 to December 2006, 726 consecutively collected patients with histologically proven diagnosis of malignant breast cancer and ascertained Sardinian origin were enrolled. Genomic DNA was isolated from peripheral blood and screened for germline mutations in BRCA1 and BRCA2 genes through a sequential combination of denaturing high-performance liquid chromatography (DHPLC) analysis and automated sequencing approach.

Results. Overall, patients carrying a germline mutation in BRCA1 or BRCA2 genes were 21/726 (3%). The TNBC phenotype was significantly associated with the BRCA1 mutations ($p < 0.001$), whereas no association was found with the BRCA2 mutations ($p = 0.837$). Considering the patients origin within the Sardinia island, a significant inverse distribution of mutations was found: BRCA1 and BRCA2 mutations represented the 86% and 93% of the mutated cases in South and Middle-North Sardinia, respectively ($p < 0.001$). Patients from the geographical area with BRCA1 mutation prevalence presented a TNBC incidence much higher than that observed in cases from the area with BRCA2 mutation prevalence (12% vs 4%, respectively; $p = 0.037$).

Conclusions. Our findings further confirmed that occurrence of TNBC was significantly associated with the BRCA1 mutation carrier status as well as that different "genetic background" may have a phenotypic impact in the onset of breast cancer.

L58 POPULATION-BASED EVALUATION OF THE ECONOMIC IMPACT OF TRASTUZUMAB PRESCRIPTION IN PIEDMONT

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Background. Health economic assessment based on cost-effectiveness analyses was only marginally used by decision makers. The main limitation of studies was their lack of budgetary impact in a real population setting. The main objective of the present study is to provide population based estimates of the treatment costs of HER2+ breast cancer patients in Piedmont that will help local decision makers in resource planning and health care management.

Patients and methods. We estimated the number of patients at early stage eligible for trastuzumab treatment from the Piedmont Cancer Registry incidence data, while number of patients with metastatic breast cancer was estimated from prevalence data, using, as a proxy, those patients who were prone to fail in a mixture cure model. Treatment patterns, disease stage and clinical characteristics were measured in five of the 24 breast reference centres (GIC) of Piedmont on a sample of 345 patients admitted in 2010 and 2011. From expenditure administrative data of the current and previous two years in Piedmont we measured costs by drug dose, associated cost and cost for other treatments. Model parameters and their distributions were then applied in a Bayesian empirical model for probabilistic sensitivity analysis (PSA) that allowed investigating the impact of different strategies and policies on total expenditures.

Results. Each year, in Piedmont about 685 women with a HER2+ breast cancer undergo chemo-treatment with trastuzumab, mainly adjuvant or neoadjuvant (74%). Early stages (*in situ* and 1a or b stage) represented about 28% of patients, while advanced stages and metastases were 31%. "Shorter" experimental protocol was administered in 16% cases, with an average 2223 mg of total dose: differences in the protocol adoption was found among the breast units. About 8% of patients suspended treatment because of toxicity. In Piedmont, total expenditure for trastuzumab was about € 11.5 million in 2010. Furthermore, it was estimated that other costs including the other associated chemotherapies and general care totalled other € 12 million.

Conclusions. Costs for HER2+ breast cancer was mostly influenced by the different adoption of treatment protocols. PSA showed that the duration of treatment, especially off-label prolongation of treatment in metastatic patients, is the principal component of the increase in the total expenditure for trastuzumab in a real setting using population-based data.

L59 INCREASE IN MEAN CORPUSCOLAR VOLUME (MCV) IN ADVANCED BREAST CANCER (BC) PATIENTS TREATED WITH THE METRONOMIC SCHEDULE OF VINORELBINE (VNB) AND CAPECITABINE (CAPE) IS CORRELATED WITH DISEASE PROGRESSION. RESULTS OF THE VICTOR STUDY

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Background. The metronomic schedule of VNB 40 mg thrice a week and CAPE 500 mg thrice a day, continuously, was demonstrated to be effective and well tolerated in advanced pretreated BC pts (Cazzaniga ME, 2010). A possible antiangiogenic effect was also hypothesized for metronomic treatments (Dellapasqua, 2008) and the same Author (Dellapasqua, 2012) demonstrated that the development of macrocytosis, not sustained by a fall in haemoglobin levels, in those pts treated with metronomic cyclophosphamide and capecitabine was correlated to a poorer prognosis. Aim of the present analysis is the evaluation of MCV and its correlation with tumor response in a population of advanced BC pts enrolled in the phase I-II part of the VICTOR study.

Patients and methods. From October 2009 to April 2011, 34 pts entered the trial. Biological characteristics of the pts were: HR+ 88%, HER2- 74%; 21 pts (62%) had received 1 or more treatments for the metastatic disease. The vast majority of the pts (79%) had ≥2 metastatic sites. ECOG PS was 0-1 in 76% of the pts. We retrospectively collected the MCV levels of the enrolled pts, together with haemoglobin and platelets counts at baseline and after 3 and 6 cycles of metronomic therapy, at the time intervals planned for disease restaging.

Results. In our laboratory, MCV normal range is 80.0-99.0 fL. All the data needed for the present analysis were available in 24 out of 34 pts enrolled. Mean MCV before starting therapy was 82.51 fL (78.40-96.80) and no pt presented macrocytosis. At the first disease restaging, after 3 cycles of therapy, mean MCV was 87.5 fL (79.0-101.5) and was 92.4, 91.4 and 91.3 in PR, SD and PD pts, respectively, without any significant difference among the 3 groups. One SD pt developed macrocytosis. At the second restaging, after 6 cycles of metronomic therapy, 17/24 pts were available for the analysis: mean MCV was 99.14 fL (86.1-107.2); according to disease evaluation, mean MCV was 93.3 in 2 PR pts, 98.2 in 8 SD pts and 101.8 in the 7 PD ones. In addition, 9/17 (52.9%) pts showed an increase in MCV above the normal range, distributed as follows when analyzed according to disease response: 6/7 PD (85.7%), 3/8 SD (37.5%). No responder pt showed increase in MCV.

Conclusions. Macrocytosis is inversely correlated to the risk of disease progression and could be used as an early marker of response to metronomic treatment with VNB and CAPE. Further data are warranted to confirm these findings.

L60 SELECTIVE TARGETING OF MTOR PATHWAY BY RAD001 MODULATES THE *IN VITRO* BREAST CANCER-INDUCED OSTEOCLASTOGENESIS

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Background. Osteolytic bone metastases are common features in patients with advanced breast cancer (BC) and BC cells are known to produce soluble osteoclastogenic factors that enhance osteoclast (OC) formation and function *in vivo*. mTOR pathway is involved in OC differentiation, but it is suspected that its interconnection with NFkB pathway drives the release of OC-stimulating mediators by BC. We tested this hypothesis and explored the efficacy of RAD001, a selective mTOR inhibitor, to restrain the paracrine osteoclastogenic activity of BC.

Methods. MDA-MB231 and MCF7 BC cell lines were treated with subtoxic doses of RAD001. Both treated and untreated cells, and relative culture media (CM) were assessed by both RT-PCR and ELISA for major osteoclastogenic factors. CM were evaluated for the capacity to influence the OC differentiation by PBMCs. Multinucleated TRAcP$^+$ OC-like cells were counted by optical microscopy and assessed for the expression of OC genes as well as for the resorbing activity on experimental bone substrates. The activation of mTOR/NFkB axis was investigated by western blot (WB) in both treated and untreated BC cells.

Results. PBMCs incubated with CM from BC cells generated higher number of giant TRAcP$^+$ OC-like cells than those stimulated with CM from RAD001-treated cells. These OC-like cells overexpressed both TRAcP and c-fms, and produced higher number of erosive pits than those stimulated with CM from RAD001-treated BC cells. Tumor cell lines expressed detectable mRNA levels of MCSF, IL1b, TNFa and MMP13 while RAD001 significantly lowered the expression of MCSF and IL1b in MDA-MB231 and MCF7 cells, respectively. This was also confirmed by ELISA in relative CM. WB analysis suggested that RAD001 concurrently down-regulated the kinases included in both mTOR and NFkB pathways in each tumor cell line.

Conclusions. Our data suggest that mTOR signalling is interconnected with NFkB pathway in regulating the intrinsic capacity of BC cells to produce osteoclastogenic factors such as MCSF and IL1b. The selective inhibition of mTOR by RAD001 impairs the osteoclastogenic activity of BC cells, although each tumor cell line shows a proper pattern of drug response in terms of variability of the secreted soluble factors. Further investigation is thus needed to identify the precise mechanisms regulating this effect and to define the therapeutic role of RAD001 for BC-induced bone metastases.

L61 SAFETY PROFILE AND TOLERABILITY OF TRABECTEDIN AND INDOLE-3-CARBINOL COMBINATION IN REFRACTORY ADVANCED BREAST CANCER. PRELIMINARY RESULTS OF A PHASE 1 CLINICAL STUDY

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Background. Trabectedin (T) is a tetrahydroisoquinoline indicated in the treatment of metastatic ovarian cancer and sarcoma and it's under evaluation in a variety of solid tumors, including advanced breast cancer (aBC). The principal dose-limiting side effects of T are represented by myelosuppression and hepatotoxicity. It has been shown that high dose dexametasone (HD-Dex) protects from T-induced hepatotoxicity. However, the potential use of HD-Dex might be confounded by adverse effects. Indole-3-Carbinol (I3C) is a microcostituent of cruciferous vegetables and it acts as a potent inducer of CYP450, able to mitigate the T-related hepatotoxicity. From above, we aimed to explore a novel I3C-based antidotal strategy in aBC receiving T in the context of a phase1 clinical trial. Primary objective was to determine the feasibility and tolerability of the I3C-T combo in refractory aBC. Secondary objective was to correlate PK parameters of T with the safety profile of the combo.

Methods. Overall, 12 heavily pretreated, refractory aBCs

were enrolled. Patients were divided in 3 cohorts, receiving dose-escalation of I3C (200, 400 and 600 mg/daily p.o) without HD Dex pre-medication and T at a fixed dose of 1.3 mg/m^2 (q.4wks, in 3hrs i.v.). In a double blind with placebo scheme, pts were randomized to receive or not I3C either during the first or the second T cycle. Patients hematology and liver function were serially tested while on treatment.

Results. Currently, 8/12 pts were evaluable for hematological and liver toxicity of T-I3C combo and for PK parameters. In spite of a mild neutropenia (G2) reported at day 15, we observed in all pts a rapid, dramatic and a selective effect on monocytes, with a decrease of more than 70% from baseline at 96 hrs. No differences b/w I3C vs placebo were observed. The liver function findings confirmed an universal transaminitis (G3-4) in the 4 pts enrolled in the first I3C 200 mg cohort, while a trend in hepatoprotection was reported in the 4 pts receiving higher doses of I3C (400 and 600 mg).

Conclusions. For the first time, these results figured out that T determines an early and selective cytotoxic effect on monocytes in all evaluable patients. This unique effect was not anticipated in literature and might represent a specific activity of T that deserves further investigations. The hepatoprotectant activity of I3C is slightly evident only at the higher doses of the drug. Our preliminary observations need to be confirmed in an extended cohort of patients.

L62 BREAST CANCER PROGNOSIS IN BRCA 1/2 MUTATION CARRIERS: A CASE-CONTROL STUDY

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Background. Overall 5-10% of primary breast cancers (BC) are inherited. About 84% of hereditary BCs derive from BRCA1/2 mutations: prognosis in this setting is still not well defined. The aim of the present study is to evaluate the tumor features and prognostic effects of germline BRCA1/2 mutations in early BC compared with sporadic BC (SpBC).

Patients and methods. Twenty-four BRCA-positive (BRCA+) BC pts with germline BRCA1/2 mutations and 94 wildtype (WT) BC pts were selected from our database and matched (1:20) with 2959 SpBC controls for stage, histologic subtype, age and year of diagnosis. Clinical characteristics, recurrence pattern, disease-free survival (DFS) and overall survival (OS) were analyzed.

Results. Compared with WT and SpBC, BRCA+ pts were less likely to express the estrogen receptor (ER) (71.1% vs 80.2% vs 48.1% respectively; p <.0001) and progesterone receptor (PgR) (73% vs 70.7% vs 52% respectively; p <.04). Compared with WT and SpBC, BRCA+ pts were more likely treated by radical mastectomy (41.5% vs 35.0% vs 41.5% respectively; p <.0001). Pattern of events was also different. Compared with WT and SpBC, BRCA+ developed more second primary tumors (2.1% vs 2.0% vs 2.9% respectively; p <.0001) and less local or distant recurrences (1.1% vs 0.3% vs 0% respectively; p <.0001). Contralateral BC was more frequent in WT compared to the BRCA+ and SpBC pts (14.9% vs 0.3% vs 11.8% respectively; p <.0001). At a median follow-up of 88 months, at univariate analysis, BRCA+ but not WT pts had worse OS compared to SpBC (p = .0001). A better DFS was observed for BRCA+ when compared to WT and with SpBC patients. At multivariate analysis, after adjustment for age, stage, grade, nodal status, hormone receptors, adjuvant therapy and year of diagnosis, BRCA+ pts continued to have and increased risk of death compared to SpBC.

Conclusions. Confirming previous findings, BRCA+ BCs seem to have a different natural history compared to SpBC. In our dataset, despite decreased incidence of local or distant recurrences, BRCA+ pts more likely die compared to SpBC. Development of second cancers may account for these findings.

L63 ERIBULIN IN ADVANCED BREAST CANCER. RESULTS OF A RETROSPECTIVE REVIEW OF MULTIPLE CENTERS

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Background. Eribulin is an anticancer drug approved by FDA and EMA to treat patients with metastatic breast cancer (ABC) who have received at least two prior chemotherapy regimens for late-stage disease, including both anthracycline- and taxane-based. Treatment with eribulin demonstrated to improve overall survival of heavily pretreated ABC although did not demonstrate to be superior to capecitabine in anthra-taxane pretreated patients (pts).

Methods. An observational, retrospective analysis was proposed to South Italy oncologic centers by eribulin use, with at least 3 candidate patients who had/could have received ≥3 cycles of treatment by 03/2012. Patient and disease characteristics, as well as efficacy and safety parameters, were collected until March 2013. Patients with measurable/evaluable disease were enrolled after signing an informed consent.

Results. Out of 58 screened ABC pts in 4 participating hospitals, 54 were enrolled and 50 evaluable. Median age was 58 years and 65% were post-menopausal. Visceral disease occurred in 32/50 (64%) patients. ECOG status was ≤1 in 80% of patients. Estrogen receptor expression was found in 65% of tumors; 18% overexpressed HER2. 70% of pts received 2-4 treatment lines for ABC before eribulin, and 30% more than 5 lines. Mean eribulin treatment duration was 3 months (5 cycles). Disease control rate was 50% (5% CR, 15% PR, 30% SD). By 03/2012, 55% of pts were still alive and median PFS was 102 days (95% CI 75-145). 75% of pts reported ≥1 adverse events, being asthenia, neutropenia, anemia, alopecia, nausea, and mucositis the most frequent ones (≥10%). Grade ≥3 adverse events occurred in ≤5% of patients. In particular, G-CSF given as primary or secondary prevention of grade IV neutropenia was given to 10/50 (20%) of patients.

Conclusions. The favorable efficacy and safety profile of eribulin observed in this study is consistent with the previous phase III studies (EMBRACE and 301 study) and confirms the activity of this drug in the treatment of ABC. A confirmatory national observational study (ESEMPIO) is planned.

L64 RETROSPECTIVE ANALYSIS OF SAFETY AND ACTIVITY OF ORAL ETOPOSIDE IN HEAVILY PRETREATED BREAST CANCER

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Background. Metastatic breast cancer (MBC) patients may derive benefit from several lines of treatment with chemotherapy. Oral etoposide (VP-16), a semi-synthetic derivative of podophyllotoxin, was found to be clinically active in MBC patients in phase II trials conducted in the past. With the availability of other active drugs, strongly supported, VP-16 use declined. Moreover, its toxicity was probably overestimated. We were therefore interested in evaluating oral VP-16 in a population of MBC patients who had failed most of the current therapies to treat this disease.

Patients and methods. Study population: 66 patients affected by MBC. The median number of previous treatments for metastatic disease was 8 (range 2-13) and most of the patients were exposed to taxanes, anthracyclines, capecitabine, vinorelbine and gemcitabine. The patients received VP-16 (50 mg/day in cycles of 20 days with 1-week rest) at our Institution between 2003 and 2012. All patients were evaluated for clinical benefit rate (CBR, complete responses, partial responses and disease stabilization >24 weeks), progression-free survival (PFS), overall survival (OS) and toxicities.

Results. Median PFS was 4 months, CBR was 18% (RR 4%), median OS from VP-16 start was 11 months. Very few relevant toxicities were observed. No patients had to withdraw from the treatment due to VP-16 induced toxicity.

Conclusions. Our findings and the low cost of the drug suggest that VP-16 is an attractive option for the treatment of heavily pretreated MBC.

L65 BONE HEALTH IN BREAST CANCER PATIENTS: EXPERIENCE OF OSTEONCOLOGY CENTER (CDO) AT CANCER INSTITUTE OF ROMAGNA

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Introduction. Treatment for cancer may cause gonadal dysfunction and bone loss (cancer treatment-induced bone loss: CTIBL). Especially, endocrine therapies for breast cancer determine a significant CTIBL risk. Therapy-induced premature menopause in premenopausal breast cancer patients (pts) and the use of aromatase inhibitors in postmenopausal breast cancer patients increase bone loss and fracture risk. In this subset of patients the prevention of bone loss can have a role not only in the prevention of fractures but also on the delay of systemic disease relapse.

Methods. In January 2011 we proposed to patients treated radically and presenting gonadal disfunction a specific clinical path for the maintenance of bone health (BH). Here we report a retrospective analysis on 215 pts with breast cancer in adjuvant setting which refer at our service from March 2012 to March 2013 in treatment with endocrine therapy. We evaluated bone loss risk factors according to 2012 AIOM guidelines: Body Mass Index (BMI <20 kg/m^2), smoking, corticosteroid therapy (more than 5 mg/PN eq. for more than three months) and family history of osteoporotic fractures. We also analyzed the presence of morphometric vertebral fractures, the basal value of 25OHD, and the values of T-scores at the femur.

Results. Seventy-three patients (34% premenopausal status) were under treatment with tamoxifen and LHRH analogs and 142 pts (66% postmenopausal status) with aromatase inhibitors. Twenty pts (9%) with BMI <20, 39 pts (18%) smokers, 24 pts (11%) with previous corticosteroid therapy and 37 pts (17%) showed a family history of osteoporosis fractures. The T-score value recorded at the femoral bone densitometry were <-1 on 95 pts, <-2 on 66 pts and <-3 in 25 patients. Radiological vertebral assessment was done on the entire case series revealed on 25 (12%) asymptomatic fractures at dorsal tract and 5 (6%) fractures at lumbar tract. On 190 pts, the 25OHD level showed a deficiency on 39 pts (20%), failure status on 41 pts (22%) and sufficiency status on 110 pts (58%).

Conclusions. During cancer treatment with gonadal dysfunction, our preliminary data confirm the need of specific clinic paths for the maintenance of bone health. This approach could prevent osteoporotic fractures with, consequently, an increase in life quality, a decrease of health expenses, and probably a survival increase due to the impact on the natural history of the tumor of this new therapeutic strategy.

L66 UNBRANDED DOCETAXEL (UD) IN BREAST CANCER: A SAFETY ANALYSIS

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Background. D is one of the most effective drugs used in a wide variety of cancers, expecially in breast cancers (BC), in neo or adjuvant and in metastatic setting, demonstrating a safe profile.

Aim. To assess toxicity due to the use of UD, recently introduced into clinical practice, we made a comparison with historical data of referential trials (Roché H: JCO, 2006; Valero V: JCO, 1995).

Patients and methods. From late 2012 to date we treated 33 BC pts, median age 51 years (range 32-76), with UD 100 mg/m^2 d1, q 21 for 6 cycles in monotherapy in advanced tumors (3/33 pts: 9.1%) or for 3 cycles, following 3 cycles of FEC schedule (5-fluorouracil, epidoxorubicin, cyclofosfamide), in neo (8/33 pts: 24.2%) and adjuvant (22/33 pts: 66.7%) setting.

Results. Comparing with usual toxicities according with NCI criteria we detected: neutropenia G3-4: 2/33 pts (6%) vs 11.2% despite prophylatic use of G-CSF or peg-filgrastim in all pts, infections G3-G4: 1/33 pts (3%) vs 1.6%, stomatitis G3-4: 1/33 pts (3%) vs 5.9%, skin G3-4: 4/33 pts (12.1%) vs 0%, moderate or severe nail disorders: 7/33 pts (21.2%) vs 10.3%, moderate or se-

vere arthralgia: 7/33 pts (21.2%) vs 0%, moderate or severe fluid retention 3/33 pts (9.1%) vs 4.8%, moderate or severe conjunctivitis: 1/33pts (3%) vs 8%. Due to side effects, 12/33 pts (33.4%) needed a change of CT-treatment (3/12 pts (25%): dose reduction of 25% and 9/12 (75%) cross to paclitaxel weekly).

Conclusions. In our department the use of UD was associated with increased toxicity, expecially severe neutropenia, arthralgia, skin and nail disorders, fluid retention. Possible reasons could be: variable concentration of drug in vials, residual refuses that could compromise preparation stability and pH of the solution, as yet reported in literature (Vial J: Curr Med Res Opin, 2008). Therefore the UD use needs more attention regarding evaluation of onset of side effects.

L67 ERIBULIN (E) IN METASTATIC BREAST CANCER (MBC) PATIENTS: A MULTICENTER RETROSPECTIVE ANALYSIS OF TOXICITY AND ACTIVITY ACCORDING TO THE LINE OF TREATMENT

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Introduction. A randomized phase III study demonstrated overall survival superiority of E over a real-life treatment of physician's choice, in women with heavily pretreated MBC (Cortes J et al.: Lancet, 2011). E is widely used in Italy in pts who progress after anthra and taxanes and at least 2 CT lines for MBC. On this basis a retrospective study was undertaken in MBC pts pretreated with chemotherapy (CT) for advanced disease, in order to evaluate toxicity and activity of E, in a real life condition according to the line of treatment.

Materials and methods. Ninety-nine MBC pts, treated in 10 different oncologic centers in Italy, with a median of 9 (2-21) pts/center. Median age 62 yrs (30-79), median PS (ECOG) 1 (0-2), median number of CT lines for MBC before E 3 (1-10). Dominant metastatic sites were: viscera 75 pts (75.8%), bone only 6 pts (6.0%), soft tissues 18 pts (18.2%).

Results. Median age 63 yrs (32-77) vs 62 yrs (30-79), mPS 1 (0-2) and dominant metastatic sites (viscera 79.5% vs 72.7%, bone 1% vs 5% and soft tissues 8% vs 10%) were well balanced in pts less pretreated vs more respectively. Activity and main toxicities (NCI-CTCAE) are depicted in the following Tables.

Conclusions. Our preliminary results suggest that an early use of E (after second line CT) is to be preferred in order to obtain the best results in terms of activity. The probability of adverse events seems to be similar in the two groups of pts according to the good tolerability of E. Definitive results will be presented.

L68 MYOCARDIAL PERFORMANCE IN BREAST CANCER SURVIVORS

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Background. The upper limbs edema in breast cancer survivors is a frequent side effect, often controlled with sport activity as Dragon Boat. Few information are available on the cardiovascular performance when this sport is regularly practiced. The study aims to evaluate, in a group of survivors breast cancer women (BC), the effects of Dragon Boat sport on the myocardial performance during 4 years of follow-up.

Methods. Since 2006 to 2010, one year after the diagnosis of breast cancer, a group of 55 women, previously treated with adjuvant therapy without evidence of metastases, has been consecutively enrolled in a Dragon Boat competitive team. They were yearly submitted to an ergometric test, and to an 2D echocardiographic exam (MayLab 50-ESAOTE) to evaluate the hemodynamic, morphological and functional cardiac parameters. All data have been matched with a control group of 36 healthy women (HW) who practiced competitive sport activity.

Results. Both groups have maintained a normal systolic function during all the period, despite the CMi and BMI and EF values were higher in HW. At the onset of the study, the diastolic function of the BC group turned out to be compatible with an ini-

L67 Table 1

Previous CT lines	RP N pts (%)	SD N pts (%)	PD N pts (%)	Too early or not evaluable pts	mPFS (mos)
2 (37 pts evaluable)	11 (30)	13 (35)	13 (35)	7	5.0 (4.0-6.0)
>2 (43 pts evaluable)	5 (11)	17 (39)	21 (48)	12	4.0 (3.0-5.0)
Total	16 (20)	30 (38)	34 (42)	19	4.2 (3.9-4.5)

L67 Table 2

Previous CT lines	Asthenia % G1-2	Alopecia % G1-2	Peripheral neuropathy % G1-2	Neutropenia % G3-4	Use of G-CSF % cycles	Dose reduction % pts
2	51	28	31	12.8	29	29.5
>2	43	18	18	22.5	20	21.8
Total	47	23	25	17.7	24	25.3

tial diastolic dysfunction, if compared with the HW group. After 4 years of sport Dragon Boat activity, the diastolic parameters resulted to be improved in all women and specially in BC group (A peak: from 68.5 ± 15.1 cm/sec to 50 ± 14.1 cm/sec with $p < 0.05$; E': from 9.3 ± 2 cm/sec to 11.89 ± 1.7 cm/sc with $p < 0.001$). The data obtained from the ergometric test showed in both normal values despite in HW group the data were significantly higher than in BC (Double Product 23870 ± 3190 in HW vs BC 22785.8 ± 276 with $p < 0.005$).

Conclusions. The results obtained demonstrate significant improvement of the diastolic function in BC survivors after four years of Dragon Boat sport training with an excellent effort of tolerance. Competitive sport activity does not seem to have any negative impact on the myocardial performance in patients previously treated with chemotherapy.

L69 TEMOZOLOMIDE AND HERCEPTIN COMBINATION IN BRAIN METASTASES FROM HER2-POSITIVE BREAST CANCER: A SINGLE INSTITUTION EXPERIENCE

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Background. Brain metastases (BM) are diagnosed in one third of patients (pts) treated with trastuzumab (Herceptin-H) for HER2+ metastatic breast cancer (mBC). H beyond progression is a common strategy for mBC even after BM development. Temozolamide (T) is a drug that demonstrated efficacy and safety in high-grade glioma and BM from solid tumors. Our aim was to evaluate the feasibility of H plus T combination in pre-treated mBC with BM.

Patients and methods. From 2009 to 2012 we observed and treated 6 consecutive HER2+ mBC pre-treated with H-based chemotherapy. Patients characteristics: median age 44 years (range 31-57), median ECOG-PS 1 (range 1-2), 5/6 pts with central nervous system (CNS) progression after a median period of 24 months from visceral recurrence, 1/6 pts relapsed with a single BM. Three pts progressed after stereotactic radiosurgery (SRS) and whole brain radiotherapy (WBRT). Three out of six pts presented with neurologic symptoms at BM diagnosis. Schedule of treatment: H 6 mg/kg (day 1 every 21 days) plus oral T 150 mg/m^2/day (days 1-5 every 28 days). We assessed CNS response with brain CT scan and/or brain MR performed in median every 8 weeks (range 4-12) using Response Evaluation Criteria in Solid Tumors (Recist 1.1).

Results. The H-T combination was administered in median as a second-line of therapy (range 1-3) after CNS progression. CNS responses (Recist 1.1): 1 CR, 1 PR, 4 SD. Median time to progression (TTP) was 7 months (range 3-15). Characteristics of two best CNS responders: one pt, with a single asymptomatic 30 mm (longest diameter) BM, recurrent after three years from initial BC diagnosis, received surgical partial eradication followed by WBRT (30 Gy) concurrent with H-T, obtaining a CR with TTP of 15 months; another pt, after 10 years from initial BC diagnosis, relapsed with visceral extra-CNS disease and symptomatic multiple BM treated with SRS and WBRT. After radiotherapy progression she received H-T combination obtaining a PR with TTP of 5 months. The other 4 pts achieved a SD with TTP of 3, 4, 9 and 12 months respectively. Toxicity data are available for all pts: most common adverse events were fatigue (grade 2, 3/6 pts) and thrombocytopenia (grade 2, 1/6 pts).

Conclusions. The H-T combination achieved disease control in 6/6 pts with median TTP of 7 months. To our knowledge, this is the first reported experience of H-T in heavily pretreated HER2+ mBC with BM. These observed results warrant further evaluation of the H-T regimen.

L70 MANAGEMENT OF NEUTROPENIA: EFFICACY AND SAFETY OF LENOGASTRIM (L) AND PEGFILGRASTIM (P) IN NON-METASTATIC BREAST CANCER PATIENTS TREATED WITH FEC 100 PLUS DOCETAXEL

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Background and aims. Neutropenia (N) is a common adverse event in patients undergoing chemotherapy for non-metastatic breast cancer. Moreover, in literature a higher incidence of G3/G4-N was reported in first chemotherapy cycle respect last doses. This retrospective analysis compared the efficacy and safety of L (263 μg), administrated from day 5 to 9, and P (6 mg) in single injection on day 2, for primary prophylaxis of N in chemotherapy-naïve pts undergone adjuvant chemotherapy with 5-fluorouracil, epirubicin, cyclophosphamide (FEC 100) plus docetaxel (D).

Patients and methods. Eighteen women (median age 55 years) underwent 3 cycles of FEC 100 plus 3 cycles of D. At every cycle, 12 pts received daily subcutaneous L injection from day 5 to 9 (5 total injections), while 6 pts received one dose of P on day 2. We evaluated absolute neutrophil count, incidence of N, febrile neutropenia (FN) and bone pain (Numerical Rate Scale >7).

Results. In overall population incidence of N was 83.3%, while G3/G4-N was 72.2%. Regarding pts treated with P, G3/G4-N was 50% and 83.3% in those receiving L. No case of FN occurred in both groups. During the first cycle of chemotherapy the incidence of G3/G4-N was 0% in patients who received P and 50% in patients treated with L; during the last cycle of chemotherapy no one had G3/G4-N in the P group while it occurred in two pts of L group. 33.3% and 50% of pts experienced bone pain in P and L group, respectively. Chemotherapy dose reduction was performed in 55.5% of cases, in particular 3 out of 6 patients in P group and 7 out of 12 patients in L group.

Conclusions. In our experience, a single injection of P was more effective than 5 daily administrations of L to control N. During first chemotherapy cycle G3/G4-N events were more frequent than in last cycle, according to literature data. The safety profiles of P and L were similar with the same incidence of bone pain in both groups. No differences were observed about chemotherapy dose reduction.

L71 ROLE OF ANDROGEN RECEPTOR (AR), KI 67 AND E-CADHERIN AS PROGNOSTIC MARKERS IN TRIPLE NEGATIVE BREAST CANCER (TNBC)

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Background. TNBC is an aggressive subset of breast cancer associated with poor outcome, earlier relapse and higher rates of recurrence in visceral organs and central nervous system. It is the only subtype with no specific target therapy.

Methods. In our observational and retrospective study we analyzed 45 cases of TNBC to evaluate the expression of some molecular determinants such as the AR, E-cadherin and Ki-67 in relation to the histological type, time to relapse and overall survival. The molecular determinations were carried out on formalin-fixed paraffin-embedded tumor samples by immunohistochemistry (IHC). Patients (pts) were defined as TNBC if ER and PgR 0% and HER2 IHC score 0/1 or FISH not amplified.

Results. Median age was 58.8 years (range 39-77). Histological type: ductal in 35 pts (77.7%), lobular in 7 (15.5%), medullary in 3 (6.6%). Histolgical grade: G2 in 16 pts (35%) and G3 in 29 pts (64.4%). Tumor stage: I 6/45 (13.3%), IIA 21/45 (46.6%), IIIA 11/45 (24.4%), IIIB 3/45 (6.6%) and IV 4/45 (8.8%). All patients received treatments; the most frequently used regimens were anthracycline and taxane. The androgen receptor was positive (IHC >10%) in 12/45 (26.6%). E-cadherin expression was semi-quantitatively analyzed according to the percentage of cells showing membrane positivity: 0 (0-10%); 1+ (10-30%); 2+ (30-70%); 3+ (>70%). E-cadherin expression was considered positive if the score was ≥2, and negative when score was ≤1; this latter event appeared in 24/45 (53.3%) cases. The Ki-67 index was ≥25% in 17/45 (37.7%). The statistical analysis showed that patients with AR negative and Ki-67 positive expression have a significant correlation with the ductal histotype and G3 tumors ($p < 0.001$). Univariate analyses showed that AR, E-cadherin and Ki67 are significantly associated with overall survival. Multivariate analysis showed that AR and Ki-67 expression are independent variables associated with overall survival.

Conclusions. Our data suggest that combination of AR and E-cadherin expression are a favorable prognostic factor while the high Ki 67 was associated with more aggressive clinical features. Hence these molecular determinants might be useful to classify subgroups of TNBC.

L72 INCREASED LONG-TERM SURVIVAL IN ELDERLY WOMEN WITH METASTATIC BREAST CANCER, CHEMOTHERAPY NAÏVE, TREATED WITH THREE LINES OF SEQUENTIAL CHEMOTHERAPY (PRE-PLANNED)

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Aim. To evaluate feasibility in terms of response rate and tolerability of sequential single agent pre-planned chemotherapy, in elderly, chemotherapy-naïve women (>70 years old), with advanced breast cancer.

Program. Elderly women with advanced HER2-negative breast cancer, who received no prior chemotherapy, regardless of hormone receptors status, were treated with a sequential chemotherapy program consisting of three drugs prescribed for a minimum of 6 cycles or until clinical progression; the schedules included 6 cycles of epirubicin 60 mg/m^2; 6 cycles of weekly paclitaxel 60 mg/m^2 and 6 cycles of gemcitabine 1000 mg total on day 1 and 15 every 4 weeks.

Methods. We treated fifteen elderly patients (range 70-78 years), with ECOG PS 1-2. Sites of metastasis were: liver (8 patients), liver and lung (4 patients) and lung (3 patients). All patients underwent baseline cardiac funtional evaluation, with Doppler ultrasonography, and all had EF >60%. Imaging staging was not scheduled until the end of treatment or until clinical progression.

Toxicity. Six patients had mild paresthesias after the treatment with taxanes, 5 patients had G2 NCI thrombocytopenia during gemcitabine administration, requiring a treatment delay of two weeks; two patients with clinical progression had a documented radiologic disease progression before the end of the program, and discontinued planned treatment.

Conclusions. The pre-planned sequence of treatment has been completed by almost all patients (except two patients with documented radiologic progression), without relevant problems. This sequence was well tolerated; at the end of the program 9 patients had SD and 4 patients had disease progression. We assessed patients quality of life parameters, with an internal survey carried out by our team of psychologists, and there we didn't find data showing any significant worsening during the sequential treatment, with the exception of the two patients who experimented both clinical and radiological disease progression. Such a pre-planned, single-agent sequential approach can be a viable tool and strategy for the treatment of metastatic breast cancer, allowing good control of disease, increasing long-term survival and improving quality of life

L73 ERIBULIN MESYLATE IN THE TREATMENT OF HEAVILY PRETREATED ADVANCED BREAST CANCER PATIENTS

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Introduction. Patients with advanced breast cancer previously treated with anthracyclines and taxanes usually have a poor prognosis. Therefore new drugs or new combinations of drugs are needed. An approach has been to focus on the type of chemotherapy with low toxicity that preserves quality of life during treatment.

Materials and methods. We have studied 20 heavily pretreated breast cancer patients (mean previous chemotherapy lines 4 with a range of 3-6) treated with eribulin mesylate 1.23 mg/m^2 day 1 and 8 q 21. The main characteristics of patients were as

follows: male 1 pt (5%), female 16 pts (95%), PS (ECOG) 1-2, median age 54 years, ER/PgR positive (100%), 19 patients were HER2 negative and 1 HER2 positive. The main sites of metastatic disease were: liver (100%), breast (11%), bone (80%), nodes (75%), skin (5%), lung (40%). All patients were pretreated with anthracyclines, taxanes, capecitabine, gemcitabine and vinorelbine. The patient HER2+ received previously trastuzumab and lapatinib.

Results. Seventeen evaluable patients (85%) received a mean of 3 cycles (range 2-7), 3 patients (15%) were not evaluable for efficacy because of only one cycle, but all 20 patients (100%) were evaluable for toxicity. A dose reduction was necessary in 3 (15%) patients. Anemia and neutropenia were the main toxicities (20%). One patient (5%) experienced headache and one patient (5%) experienced fever. In 13 patients (65%) we didn't register any toxicity. In the 17 evaluable patients, we registered 5 partial response (29%) and 3 stable disease (17%) with a mean TTP of 3 months (range 2-5 months) and 4 months (range 3-6), respectively. To date 16 of 20 included patients are alive (80%).

Conclusions. Erbulin mesylate is a new drug that is widely placed in the treatment of breast cancer pretreated with anthracyclines and taxanes. In our experience, all patients were pretreated with at least 3 lines of chemotherapy and this may justify the results recorded. In contrast, the modest toxicity in this setting of patients confirms the good tolerability of the drug.

L74 GEMCITABINE AND OXALIPLATIN COMBINATION CHEMOTHERAPY IN HEAVILY PRETREATED ADVANCED BREAST CANCER (ABC): PRELIMINARY RESULTS

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Background. Gemcitabine plus oxaliplatin combination chemotherapy showed, in some phase II studies, moderate activity and mild toxicity in anthracycline and taxanes heavily pretreated ABC patients (pts).

Material and methods. We collected retrospective data from October 2009 to May 2013 to evaluate combination chemotherapy with gemcitabine and oxaliplatin (GEMOX) in ABC pts.

Results. We identified 12 pts treated with GEMOX (gemcitabine 1000 mg/m^2 day 1 and oxaliplatin 100 mg/m^2 day 2 every 14 days) for ABC. Median age was 63 years (range 45-73); 11 pts were ER/PgR positive, 4 pts were HER2 positive, 1 patient (pt) was triple negative. Eight pts had liver metastases, 6 lung metastases, 5 bone involvement; 3 pts were metastatic at the beginning and 4 pts had 3 or more metastatic sites. The median number of previous chemotherapy regimens was 4; 12 (100%) pts were pretreated with anthracycline and taxane, 11 (92%) with vinorelbine, 10 (83%) with capecitabine and 2 (17%) with gemcitabine. GEMOX was administered for a median of 6 cycles (range 1-8). Nine (75%) pts had a stable disease (SD), 1 (8%) pt had a partial response (PR) and 2 (17%) a progressive disease (PD) for a DCR of 83%. Up to May 2013, 4 pts are alive and 2 pts are still on treatment with GEMOX. The median progression-free survival (PFS) was 5.6+ months (range 1.6-8.4), while the median overall survival (OS) was 9.6+ months (range 2.7-20). Main toxicities were: grade 3 liver toxicity (1 pt), grade 2 nausea (4 pts) and grade 2 thrombocytopenia (3 pts); no one had grade 3-4 hematological toxicity or peripheral neuropathy.

Conclusions. Our experience seems to confirm the activity and good tolerability of gemcitabine and oxaliplatin combination therapy in patients with heavily pretreated ABC.

L75 QUALITY OF LIFE AND SYMPTOMS EVALUATION IN METASTATIC BREAST CANCER PATIENTS TREATED WITH ERIBULIN: PRELIMINARY RESULTS OF A PROSPECTIVE OBSERVATIONAL STUDY

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Background. Eribulin (E) is a non taxane microtubule inhibitor currently indicated for third-line chemotherapy (CHT) of MBC. To evaluate its tolerability and impact on quality of life (QoL) and symptoms improvement in metastatic breast cancer (MBC) patients (pts), since April 2012 we conducted a prospective observational study.

Methods. Patients pretreated with anthracyclines (A) and taxanes (T) who had received 2 CHT lines for MBC, scheduled to be treated with E, were considered eligible. Patients completed the Edmonton Symptoms Assessment Scale (ESAS) at each cycle and the Functional Assessment of Cancer Therapy-Breast (FACT-B) every 2 cycles. Outcome of QoL included the FACT-B total score, FACT General (FACT-G) score and the Trial Outcome Index (TOI) score. Groups of data were analyzed using ANOVA and the Friedman test. Kaplan-Meier method was used for survival calculation. Overall survival was calculated by the Kaplan-Meier product-limit method.

Results. Thirty-one consecutive MBC pts entered the study. Median age 65 (range 31-77), 97% of pts had PS (ECOG) 0-1, 26% had triple-negative MBC, 71% ER/PgR positive and 7% HER2 positive. All pts were pretreated with A and T, 19 (61%) also with capecitabine. Median cycles administered 6 (range 3-14), 33% of pts received more than 6 cycles. Ten pts are too early for symptoms evaluation and quality of life. Main toxicities were: G1 alopecia 58% and G2 42%, G2 asthenia 38%, G2 peripheral neuropathy 33%, G2 neutropenia 9% and G3-G4 5%. At a median follow-up of 6 months (mos) (range 2-11), 16% of pts achieved partial response (PR), 53% stable disease (SD) and 31% progressive disease; disease control rate (PR + SD = 6 mos) occurred in 32% of patients. Median PFS is 5 mos (95% CI 4-6); currently 63% of pts are alive. Data of ESAS and QoL are reported in the Table.

L75 - Table

	Basal median score (range)	Final score (range)	p value
ESAS	21 (3-59)	19 (0-52)	0.03
FACT-B	82 (5-113)	79 (61-108)	0.93
FACT-G	58 (44-88)	62 (46-81)	0.55
TOI	52 (35-74)	52 (33-71)	0.75

Conclusions. Our preliminary results show that treatment with E is associated with a significant improvement of ESAS scores (p = 0.03) and with a good maintenance of QoL with expected and manageable toxicities. Data collection is ongoing and update results will be presented.

L76 PROGNOSTIC SIGNIFICANCE OF ESTROGEN-RECEPTOR, PROGESTERONE RECEPTOR, KI-67 AND HER-2 VARIATIONS IN LOCALLY ADVANCED BREAST CANCERS TREATED WITH NEO-ADJUVANT CHEMOTHERAPY: A SINGLE INSTITUTIONAL EXPERIENCE

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Background. Neoadjuvant chemotherapy (NAC) is the standard of care for locally advanced breast cancers to downstaging tumors prior to surgery. Furthermore, few studies to date have investigated the effect of NAC on the molecular profile with somewhat controversial results. The purpose of our analysis was to compare immunohistochemical (IHC) setting of primary breast cancer before and after NAC and to investigate the prognostic role of these variations.

Patients and methods. Primary breast carcinomas, after needle core biopsies or fine needle aspiration undergoing NAC with anthracycline and taxane based regimens at our Institution between 2007 and 2010, were included. Histologic data (grade, tumor size, lymph node status, ER, PgR, HER2 and Ki-67) was collected for each case. The difference among variables was calculated by chi-square test. The univariate and multivariate analyses were performed.

Results. Fifty-four patients were included. The median age was 50 years (range 30-75 years), 57.4% of patients were premenopausal. Pathologic complete response (pCR) rate was 14.8%. ER-negative and tumor size were found to be significantly related with pCR (p = 0.03). IHC studies showed 74.3% positivity for ER pre-NAC and 51.4% positivity post-treatment (p = 0.01); 47.2% were positive for PgR pre-treatment and 33.3% post-treatment (p = 0.1). HER2 was positive in 16.2% pre-NAC and in 13.5% post-treatment (p = 0.02). Ki-67 status changed significantly when compared to initial biopsies (64.7% and 38.2% expressed a high Ki-67 index in pre- and post-treatment, respectively; 5.9% and 32.4% expressed a low Ki-67 index in pre- and post-treatment, respectively; p = 0.02).

At univariate analysis a better relapse-free survival (RFS) was related to variations in HER2 status (p = 0.03) and in Ki-67 index (p <0.001). Besides, a better overall survival (OS) was related to changes in Ki-67 index (p = 0.005). Multivariate analysis confirmed that variations in Ki-67 after NAC were an independent prognostic factor influencing RFS (p = 0.01; HR = 0.28, 95 CI 0.1-0.8) and OS (p = 0.01; HR = 0.2, 95% CI 0.05-0.69).

Conclusions. Our study suggests the biological markers variations of ER, HER-2 and Ki-67, from the same primary breast cancer material after NAC. Among these biological markers, variations of Ki-67 proliferation index may have a prognostic role. Further evaluations are requested to assess if this data may affect treatment decision.

L77 CLINICAL BENEFIT OF FULVESTRANT IN POSTMENOPAUSAL WOMEN WITH ADVANCED BREAST CANCER ACCORDING TO PRIOR THERAPY

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Background. Hormone therapy (HT) is limited by the onset of resistance. Preclinical studies suggest that complete blockade of the estrogen receptor (ER) with the ER antagonist fulvestrant (F) can overcome this resistance. The aim of this study was to evaluate the efficacy and tolerability of F in postmenopausal women with hormone-responsive (HR) metastatic breast cancer (MBC) previously treated with tamoxifen (T) or aromatase inhibitors (AI).

Patients and methods. From May 2006 to July 2008, 83 patients with HR MBC progressing after T or AI for adjuvant or metastatic disease receiving F 250 mg/month were identified. Median time to progression (TTP), overall survival (OS), clinical benefit rate (CBR) defined as the proportion of partial or complete responses (CR, PR) or stable disease (SD) lasting at least 6 months were analyzed.

Results. Six, 32, 33 and 12 patients received F as first-, second-, third- and fourth-line of HT for MBC, respectively. Fulvestrant resulted in an overall CBR of 38.6% (32/83) with 0% CR, 9% PR, 30% SD, 56% PD. Disease was not evaluable in 4.8% of cases. Median TTP to F was 4.9 months (4-5.8 95% CI) and OS was 20.1 months (15.8-24.4 95% CI). Patients with visceral metastases and with more advanced lines of overall therapy had worse outcome (OR 3.13, 1.17-8.37 95% CI; p = 0.023 and OR 0.72, 0.54-0.96, 95% CI; p = 0.025, respectively). However, fulvestrant showed activity up to the fourth line of endocrine therapy regardless of number of metastatic sites and previous AI or T therapy. Overall treatment was well tolerated. Arthralgia, swelling, and myalgia were the most common adverse events, all were grade 1 or 2. No injection-related adverse events were reported.

Conclusions. Fulvestrant is an active treatment in HR MBC previously challenged with HT. Safety profile is optimal and it may be a suitable option in extensively pre-treated patients. Further exploration of its use in this patient population is warranted.

L78 ROLE OF PEGFILGRASTIM (P) AND LENOGRASTIM (L) IN PATIENTS WITH NON-METASTATIC BREAST CANCER RECEIVING ADJUVANT FEC 100 CHEMOTHERAPY

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Background and aims. Neutropenia (N) is common in pts receiving myelosuppressive chemotherapy. Moreover, in literature a higher incidence of G3/G4 N was reported in the first chemotherapy cycle respect last doses. We, retrospectively, evaluated efficacy and safety of a single injection of P (6 mg) compared with daily L (263 μg), in primary prophylaxis of N, in non-metastatic breast cancer, chemotherapy-naïve pts receiving adjuvant FEC 100.

Patients and methods. Twenty-eight women (median age 53 years) underwent 6 cycles of chemotherapy. At every cycle, 15 pts received daily L from day 5 to 9 (5 total injections), while 13 pts received one dose of P on day 2. Absolute neutrophil count, incidence of N, febrile neutropenia (FN) and bone pain (Numerical Rate Scale >7) were evaluated.

Results. In overall population incidence of N was 60.7%, while G3/G4 N was 46.4%. Regarding pts treated with P, G3/G4 N was 38.5% and 53.3% in those receiving L. Only one case of FN occurred in the group of P. During the first cycle of chemotherapy, the incidence of G3/G4 N was 23% in patients who received P and 33.3% in patients treated with L; instead nobody had G3/G4 N during the last cycle of chemotherapy. Incidence of bone pain was 15.3% and 13.3% in P and L group, respectively. We reduced chemotherapy doses in 11 pts, in 38.4% of pts in P group and 40% in L group.

Conclusions. In our experience, a single injection of P was more effective than 5 daily administrations of L to control N. No difference was reported between P and L in G3/G4 N incidence during the first cycle. The safety profiles of P and L were similar, with the same incidence of bone pain in both groups. No differences were observed about chemotherapy dose reduction.

L79 PACLITAXEL AND BEVACIZUMAB IN FIRST-LINE TREATMENT FOR HER-2 NEGATIVE ADVANCED BREAST CANCER PATIENTS: WHO COULD BENEFIT?

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Background. Angiogenesis is essential for tumor growth and development of metastases in human breast cancer. Randomized studies have shown that bevacizumab (inhibitor of VEGF) combined with taxane-based regimens increases response rates and prolongs progression-free survival (PFS) of patients with metastatic breast cancer (MBC). However predictive or prognostic markers that identify the appropriate target population, thus improving the cost-effectiveness ratio of this treatment, are still needed. In this retrospective analysis, we investigated the impact of traditional clinical and pathological features in order to identify the subgroups of patients who derive the greatest benefit from antiangiogenic-agents.

Patients and methods. Retrospectively, we included consecutive patients treated with bevacizumab (10 mg/kg on days 1 and 15) and paclitaxel (90 mg/m^2, on days 1, 8 and 15) as first-line treatment for HER2-negative MBC at our Institution between June 2007 and December 2012.

Results. Thirty-three patients were included. Median age was 50 years (31-68). 78.8%, 12.1% and 9.1% of patients had luminal B, triple negative and luminal A breast cancer, respectively. 66.6% of patients had visceral disease. The overall response rate was 31.2%. Median PFS and overall survival (OS) were 7.7 months (range 1.9-14 months) and 95.2 months (range 11.6-205.8 months), respectively. Univariate analysis highlighted a statistically significant relationship between PFS to the first-line and the following factors: relapse-free survival (RFS ≤12 months vs >12 months; p <0.001), disease control rate (p = 0.001), Ca15.3 reduction of more than 50% from baseline (p = 0.03), reduction of LDH from baseline (p = 0.02). No significant relationship resulted between PFS and the biological characterization of neoplasia, age, receptor status, Ki-67, nodal status at diagnosis, having carried out a previous (neo)adjuvant chemotherapy (with or without taxane), having visceral disease at time of relapse, the histological evidence of lymph-vascular invasion. At multivariate analysis, RFS was the only confirmed independent prognostic factor (p = 0.01; HR = 0.18; 95% CI 0.04-0.73).

Conclusions. Our results confirmed the efficacy and the acceptable toxicity profile of bevacizumab plus paclitaxel as first-line regimen for MBC. RFS may be an useful tool in the clinical practice to select HER-2 negative MBC which may obtain a better prognosis administering this particular regimen.

L80 ROLE OF KI 67 AND HORMONAL STATUS AS A PREDICTOR OF EARLY RELAPSE IN PATIENTS AFTER ADJUVANT BREAST CANCER TREATMENT IN REGIONAL SOUTHERN ITALY EXPERIENCE (RETRAST)

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Background. Trastuzumab (T) improves survival in the adj treatment of HER-2+ breast cancer and is the standard of care for pts both in early and in metastatic disease. Since trastuzumab is widely used in the adj setting, it is important to evaluate the benefit of retreatment in first-line in pts who relapsed after early-stage treatment with T. T seems to be the best therapeutic choice in the rare pts who relapse (15%) after adj therapy. In this work we want to investigate the predictive role of the factors that can influence relapse.

Material and methods. From June 2006 to December 2011, data (RETRAST) were collected from 10 departments in Sicily. Sixty-two HER2+ pts, relapsed following adj therapy containing T, were re-treated with T in metastatic first-line therapy. We have analyzed pts characteristics to identify those who had a greater risk of relapse.

Results. We report data from 47 on the 62 pts evaluable in this analysis. HER2 status was assessed by IHC in 51 pts and by FISH in 11 patients. Patients had a median age of 53 years at diagnosis (29-79 years). ER/PgR-cases were 16 (34%). Ki67 was >20% in 34 pts (74%). Thirty-one pts (64%) had 3 nodes involved. All the pts received adj therapy with anthra ± txn. 88.8% of pts relapsed on visceral site and 11.2% had local breast recurrence. 55% of pts had 2 metastatic sites. Median time from last dose of T to relapse was 10 months (range 2-35 months). Thirty-three pts experienced an early (<12 months) progression and 14 pts a late (12 months) progression after adj T. First-line therapy was T in combination with mono (42 pts-89.3%) or polychemotherapy (5 pts-10.6%). To 17 pts (36.1%) was administered NVB, to 19 (40.4%) pts TXN in monotherapy and to 11 pts (23.4%) different drugs including polychemotherapy. Twenty-seven pts (57.4%) had objective responses (CR 5, PR 22) and 7 pts (14.8%) stable disease. Thirteen pts (27.6%) have already progressed to T containing first-line therapy, with a median TTP of 4 months (range 2-7 months). Five pts (38.4%) were ER/PgR- and 8 pts (61.5%) ER/PgR+, with no statistical difference in median TTP between the two groups (3.7 months and 4.8 months, respectively; p = 0.4). Nine (69.2%) of 13 pts had a Ki67 >20%.

Conclusions. RETRAST data show that hormonal receptor does not affect the response and suggests that pts with KI 67 >20% relapse earlier. Patients who relapsed very early, probably, did not benefit from treatment with T. Probably, patients with HER2+, Ki67 and high presence of multiple nodes need to receive a more personalized therapy.

L81 THE OBSTETRIC (MIDWIFE) IN THE OUTPATIENTS DEPARTMENT OF BREAST CANCER

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Background. "The Obstetric recognizes centrality of the women, of the couple, of the newborn baby, of the child, of the family and of the community and carries out interventions adequate to the needs of health, in the execution of her duties for the prevention, the care, the safeguard and the rehabilitation of the individual and the common health". Aim of this study was to evaluate the potential role of the obstetric in the prevention of breast cancer and its recurrences, specially acting among younger women, who are not subjected to screening mammography.

Methods. An anonymous survey was distributed to the patients (pts) at the Department of Medical Oncology of Università Politecnica Marche. The questionnaire focused on women's perspective on the potential role of the midwife for breast cancer prevention and was distributed to pts who were performing a follow-up for breast cancer, after undergoing surgery. The pts completed the survey immediately after the examination performed by the oncologist and the obstetric.

Results. Forty-eight out of the 50 pts receiving the questionnaire, fulfilled the survey (96%). Among them, 85.4% (41 pts) declared that they had a previous contact with a midwife for different reasons and 66.6% (32/48 pts) of them believed that the midwife's role could include competences in the field of breast screening (including implementing palpation, teaching self-examination, affecting lifestyle). The data highlight that an obstetric performed a clinical breast examination only to 6.25% of the pts. Again 16 out of the 48 pts knew about self-examination at the time of cancer diagnosis. Despite the high percentage of pts who did not know the method of self-examination and despite adherence to current screening programs, 24 of 48 pts were directly responsible of the detection of a suspicious breast lump. Finally, our study showed that 58.33% (28 pts) of these pts believed that a clinical breast examination by a health professional (including midwives) would certainly have a positive impact in their history of illness.

Conclusions. Despite the limitation of this study, the results confirm that the intervention of a midwife could be useful for breast cancer prevention. The collaboration of professionals including midwives could be particularly relevant in the young age that is not included within the screening programs, helping in the secondary prevention, teaching self-examination and performing breast examination.

L82 FULVESTRANT 500 MG AFTER FAILURE OF ANTIAROMATASE THERAPY IN METASTATIC BREAST CARCINOMA. PRELIMINARY DATA FROM OUR EXPERIENCE

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Background. Fulvestrant is a selective estrogen receptor antagonist that was approved for the treatment of postmenopausal women with advanced ER+ breast cancer who have progressed or recurred on prior tamoxifen or antiaromatase therapy.

Patients and methods. From November 2011 to March 2013 we treated 29 postmenopausal women with advanced ER+ breast cancer with fulvestrant 500 mg on days 0, 14, 28 and every 28 days thereafter. Median age was 68 years (range 46-80) and all patients (pts) had ECOG 0-2. We analysed the following endpoints: progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR) and toxicity profile. One patient stopped the therapy after 3 cycles for acute left leg deep venous thrombosis and was not evaluable for efficacy.

Results. The efficacy for the 28 evaluable patients was: 2 complete response (7%), 9 partial response (32%), 12 stable disease (43%) and 5 progression disease (18%); the DCR achieved was 82%. The sites of metastases were: visceral plus node/bone in 11 pts (39%), node plus bone in 5 pts (18%), only bone in 10 pts (36%), only node in 1 patient (3.5%) and only skin in 1 patient (3.5%). Median PFS for the evaluable pts was 7 months (range 3-21+); twenty pts (71%) are ongoing. Six, ten and seven pts received fulvestrant as first-, second- and third-line respectively; for the remaining five pts fulvestrant was administered as fourth-line therapy. The possibility of obtaining a benefit from fulvestrant did not seem to correlate to the line of treatment nor to the presence of visceral metastases. The treatment was well tolerated and no serious adverse event was reported in the 28 evaluable pts for response.

Conclusions. Our retrospective study in unselected patients showed that fulvestrant is active in treating metastatic breast carcinoma and has good toxicity profile. Also patients with visceral metastases and heavily pretreated seem benefit from fulvestrant

therapy. The favourable toxicity profile and efficacy data suggest that fulvestrant may be an appropriate first-line option also for chemonaïve pts without life-threatening visceral metastases.

L83 PROGNOSTIC VALUE OF CIRCULATING TUMOR CELLS IN PATIENTS WITH METASTATIC BREAST CANCER AND METASTATIC PROSTATE CANCER

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Introduction. Metastatic breast cancer (MBC) and metastatic prostate cancer (MPC) are two of the most common and fatal neoplasms. In this study we investigated whether the presence of a value of circulating tumor cells (CTCs) ≥5 predicts the prognosis in patients with newly diagnosed MBC and MPC who were about to start first-line therapy.

Patients and methods. Between January 2011 and September 2012, 18 patients with MBC and 13 patients with MPC were evaluated for the presence of CTCs. Patients with MBC (1 male and 17 female) had a median age of 61.3 years (range 40-76 yrs). Patients with MPC had a median age of 68.9 years (range 48-82 yrs). Enumeration of CTCs in 7.5 mL of blood was carried out with the FDA-cleared Cell Search system. CTCs count was performed before the start of first-line of chemotherapy.

Results. In patients with MBC a value of CTCs <5 was detected in 12 patients (66.7%, median age 58.3 yrs, range 40-74 yrs); while 6 patients (33.3%, median age 64.3 yrs, range 42-76 yrs) had a value of CTCs ≥5. In patients with MPC a value of CTCs <5 was detected in 8 patients (61.5%, median age 73.5 yrs, range 69-82 yrs); 5 patients (38.5%, median age 64.4 yrs, range 48-76 yrs) had a value of CTCs ≥5. The median follow-up was respectively 13 months for MBC and 18 months for MPC. In MBC the median PFS was 4.3 months for patients with a value of CTCs ≥5 and 9.6 months for patients with a value of CTCs <5 ($p = 0.075$). In MPC the median PFS was 5 months for patients with a value of CTCs ≥5 and 15 months for patients with a value of CTCs <5 ($p = 0.028$).

To date we have not yet reached an adequate follow-up in order to calculate the median overall survival (OS).

Conclusions. Despite the small number of patients in both tumors our data confirms the literature knowledge. The detection of a value of CTCs ≥5 before initiation of therapy is significantly predictive of poor prognosis in patients with MPC. Although the correlation between CTCs value and PFS in MBC patients was not statistically significant, a negative trend was observed for patients with CTCs ≥5.

L84 INCIDENCE OF ANTRACYCLINE CARDIOTOXICITY IN BREAST CANCER WOMEN: A RETROSPECTIVE ANALYSIS OF 6 YEARS CLINICAL PRACTICE

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Background. Anthracyclines are important drugs in treatment of breast cancer (BC). Despite their efficacy, these agents cause important cardiological manifestations. In particular, asymptomatic or symptomatic left ventricular dysfunction, myocardial damage, congestive heart failure and cardiac dead have been reported. The increased cardiovascular morbidity is correlated with several defined risk factors such as cumulative lifetime anthracycline dose, concomitant radiation therapy, comorbidity, age and genetic predispositions. We reported the incidence of left ventricular ejection fraction (LVFE %) reduction occurred in BC women treated with antracyclines and correlation between cardiac function variation and patients age.

Material and methods. From January 2007 to January 2013, we analyzed retrospectively 52 women affected by BC who received antracycline-based chemotherapy. Median age population was 56 years (range 34-79). Patients (pts) are affected by metastatic disease or underwent adjuvant treatment. Chemotherapy regimens used were fluorouracil-epirubicin-cyclophosphamide (FEC), epirubicin-cyclophosphamide (EC), doxorubicin-cyclophosphamide (AC). We considered LVFE % variation as the values difference registered at baseline and at the end of chemotherapy by echocardiography.

Results. Overall population received an average antracycline total dose of 430 mg. In 35 out of 52 (67.3%) pts there was a LVFE % reduction. The median LVFE reduction was 8%: 66% of pts had LVFE reduction ≤8% while 34% of pts had LVFE reduction >8%. We registered 4 cardiotoxicity events (7.7%); in particular 3 pts were hospitalized due to heart failure and one pt experienced atrial fibrillation. We divided patients into three groups according to age: <50 years, 50-60 years, >60 years. In <50 years group all women (11 pts) had LVFE reduction ≤8%, 7 pts in 50-60 years group had LVFE reduction ≤8% vs 2 pts >8%, while in ≥60 years group 5 pts had LVFE reduction ≤8% vs 10 pts >8% ($p = 0.0013$).

Conclusions. In literature, the incidence of antracycline cardiotoxicity is about 1.5-2.5%. In our experience, we reported cardiotoxicity events of 7.7%. Most of the pts had LVFE% reduction ≤8% and pts with LVFE >8% are older than pts with LVFE ≤8%. For this reason a more accurate monitoring of cardiac function is recommended in BC women aged over 60 years.

L85 TOC SCHEDULE PURPOSE (TOTAL ORAL CHEMOTHERAPY) CAPECITABINE (CAP) AND ORAL VINORELBINE(O-VIN) FIRST EVALUATION OF SAFETY AND EFFICACY VS CLASSICAL CMF IN VERY OLD WOMEN (VOW) WITH BREAST CANCER

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Background. Due to the extension of mankind's life, incidence and mortality for cancer have dramatically grown in elderly people. Need of specific and safety schedules particularly devoted to elderly's cancer treatment is a common feeling between oncologists today. Breast cancer expecially affects in equal mode adult and elderly women but the principal obstacle to chemotherapy is the condition of frailty and the particularly vulnerability of this condition.

Aim. Under these considerations a TOC pilot schedule with CAP followed by O-Vin in treatment of BC in VOW was performed in order to evaluate overall toxicity, QoL and CB vs classical CMF.

Methods. Twenty-three pts, median age 79 (range 72-89) with hystologically confirmed and written consensus acquired BC with PS (ECOG) 0-1, were evaluated with comprehensive geriatric assessment (CGA) and comorbidity (Carlson's Score); further pts were evaluated for I-II-III groups frailty, according to Balducci, Extermann in order to enrole them in this study (chemotherapy could be supported only by I-II group of Balducci's classification). VES scale ((vulnerability elderly score) was also performed. The schedule was as follows: CAP 1000 mg twice daily 'flat dose' day 1-14 followed by O-Vin 60 mg/m^2 at day 21 and 28. Recycle after one week rescue.

Results. Twenty-one pts were evaluated. Two pts experienced hand-foot syndrome grade 3-4 and withdraw treatment. All other pts received the scheduled drugs in due time without significant delay. No one pt experienced haematological toxicities grade 3/4. Pheripheral neuropathy grade 3 was noted in 5 patients. Fatigue in 8 pts (out of 21). QoL and CB improved in all evaluable patients. Historically, pts unsuitable for other treatment, treated with CMF, experienced grade 3-4 haematological toxicity, N and V grade 2-3 severe asthenia and fatigue. OS was longer with TOC rather than CMF, HFS was more common with TOC.

Conclusions. TOC improved OS, CB, and QoL more than classical CMF in VOW with breast cancer, total oral schedule was well tolerated with low overall toxicities. This schedule seems to be safe and efficient and is specifically designed for elderly people. A larger number of pts must be enrolled to confirm the first encouraging outcomes.

Session M • Sarcomas

M1* SUPERFICIAL EWING SARCOMA. A RETROSPECTIVE ANALYSIS OF 20 PATIENTS

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Background. A retrospective review of patients with superficial Ewing sarcoma (ES) was conducted to report on epidemiology, treatment and outcome.

Patients and methods. Between 1994 and 2008, 20 patients with superficial ES were treated at the Royal Marsden Hospital and University College of London Hospital.

Results. The median age was 31 years (range 16-82), M/F was 1:3. Primary sites included extremity in 13 patients (65%), trunk in 7 (25%), and head and neck in 2 (10%). The median size of the lesion was 4 cm (range 2-8). No patients had metastatic disease at presentation. All patients underwent surgery, margins were microscopically involved or <1 mm (R1) in 9 patients (45%), >1 mm (R0) in 10 (55%), indeterminate for 1. R1 patients received re-excision (1), postoperative radiotherapy (5) or both (3). All patients received chemotherapy (1 preoperative, 14 postoperative, 5 both) with a median number of 6 cycles (range 4-9). Regimens included EVAIA (1), VIDE (4), IVAD (8), VAC (3) and VID (4). Most common G3-4 toxicities were neutropenia (12, 60%), thrombocytopenia (3, 15%) and oral mucositis (3, 15%). Nine patients (45%) required dose reduction. All patients treated with etoposide developed G4 neutropenia, 4 (80%) required dose reduction and 2 discontinued etoposide. No treatment related sequelae were recorded. Follow-up was available for 19 patients. At a median follow-up of 8 years (95% CI 5-11), 17 patients are disease-free, with a 5 years disease-free rate of 89% (95% CI 88.4%-88.6%). One patient relapsed locally, one developed metastatic progression 2 years after surgery. Both had microscopically involved margins at the time of surgery. Mean DFS was 7 years (range 1-14). In patients who underwent R0 resection mean DFS was 8 years (range 2-12) compared with 5 years in R1 patients (range 1-14; $p = 0.08$). Conversely, DFS did not vary according to number of chemotherapy cycles (< or = 6, $p = 0.43$) and use of etoposide ($p = 0.44$).

Conclusions. Superficial ES mainly occurs in young female patients and tends to have a favourable outcome. Adequate local control is essential. The contribution of chemotherapy to overall outcome is uncertain and requires further evaluation. In this small series, etoposide significantly increased toxicity and its use in this setting should be discouraged.

M2* BONE METASTASES (BM) IN SOFT TISSUE AND BONE SARCOMAS: INCIDENCE AND NATURAL HISTORY

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Introduction. BM represent an important clinical problem in advanced soft tissue and bone sarcomas, that can deeply affect patients performance status and quality of life. This monoinstitutional retrospective analysis aimed to explore the impact of bone involvement in sarcoma patients (pts).

Patients and methods. Among 1,017 bone and soft tissue sarcoma pts treated at Humanitas Cancer Center from January 2003 to March 2013, we observed 54 pts with BM. Data on clinicopathology, characteristics of BM, skeletal-related events (SREs) and bone-directed therapies were recorded.

Results. The incidence of BM was 5.3%. Male/Female ratio 30/24. Median age 47 years (range 18-79). The histological subtypes were: leiomyosarcoma (13 pts), Ewing/pPNET (7 pts), vascular sarcomas (7 pts), liposarcoma (5 pts), bone sarcomas (6 pts), synovial sarcomas (5 pts), others (11 pts). The histological grade was G1 in 9%, G2 in 18%, G3 in 63% of pts, unknown 10%. The primary tumor sites were the extremities and trunk wall in 38% of pts, retroperitoneum in 20%, other sites in 42%. In 26% of cases, BM were observed at diagnosis, while the median time to BM development was 21.7 months. Eight pts had a single bone lesion. The most common site of bone involvement was axial skeleton (74%), followed by hip/pelvis and long bones (48% and 28%, respectively). BM were lytic in 92% of cases. Forty-eight pts developed at one least SRE, among these 21 pts had 1 SRE, 18 pts had 2 SREs, 9 pts had 3 or more SREs. Median number of SREs/pt was 1.8. The most common SREs were radiotherapy (72%) and neurosurgery for cord compression (16%). Median time from the BM diagnosis to the first SRE was 3.7 months. Bisphosphonates were administered in 19 pts: in 8 pts before the first SRE, in 7 pts after, while in 4 pts no SRE were observed. Zoledronic acid was used in 18 patients.

Conclusions. Our data suggest a low incidence of bone metastases in this setting. However, they represent a significant clinical problem in the natural history of sarcoma pts, expecially in peculiar histologies, such as leiomyosarcoma, vascular sarcomas and Ewing/pPNET. High histological grade and primary tumors of the extremities and trunk wall were more frequently associated to BM. An integrated and standardized treatment of BM in sarcoma pts focused on pain control, quality of life and prevention of SREs is encouraged.

M3 BIOLOGICAL FEATURES, PROGNOSTIC FACTORS AND OUTCOME OF 114 PATIENTS WITH GISTs: A SINGLE INSTITUTION EXPERIENCE

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Background. To retrospectively analyze the distribution of biological features and their impact on clinical outcome in a cohort of 114 patients with gastrointestinal stromal tumour (GIST) treated at the GIST Unit of Palermo University between 2000 and 2012.

Methods. We retrospectively analyzed 114 patients with GIST treated at the GIST Unit of Palermo University during the past 12

years. Patients with localized disease were stratified according to Fletcher and Miettinen criteria. Patients were treated according to NCCN guidelines. Biological features on tumor specimens, treatment and clinical outcome were recorded and compared with published data.

Results. Among 114 patients, 88 had resectable disease, 26 had metastases at diagnosis. Ninety GISTs were examined for mutational analysis of KIT or PDGFRα, resulting KIT exon 11 mutation in 59%, KIT exon 9 mutation in 16%, PDGFRα mutation in 11% while 14% were wild type. Median 5-year recurrence-free survival of 88 patients with localized disease undergoing radical resection was 60 months. Adjuvant imatinib 400 mg daily was delivered in 21 cases; 5 patients recurred and received standard treatment for advanced disease while 16 are still free of disease. Clinical outcomes were significantly poorer for 19 patients with exon 11 delection. Miettinen criteria better predicted the risk of recurrence than Fletcher criteria ($p = 0.0046$ vs $p = 0.1$). In patients with metastatic disease undergoing standard first- and second-line therapy with imatinib and sunitinib ($N = 29$ and $N = 18$) median progression-free survival was respectively 36 and 6 months. Six patients progressing prior to treatment with TKI were enrolled in a randomized multicenter phase III trial of regorafenib, experiencing 7 months mPFS. This result was comparable to data from the phase II trial of regorafenib (mPFS = 10 months).

Conclusions. All data from our retrospective analysis reproduced those from published literature. Mutational analysis allows risk stratification, predicts response to TKI and should be routinely performed at diagnosis. Our experience demonstrates that GIST Unit guarantees a high standard for diagnosis, biological assessment for risk stratification, staging and treatment delivery, providing clinical outcomes that are comparable to published data. Therefore it is essential for patients with rare tumours to be addressed to highly specialized multidisciplinary centers.

M4 TRABECTEDIN-RELATED LIVER TOXICITY IN SOFT TISSUE SARCOMA PATIENTS: ALWAYS A GOOD REASON TO DISCONTINUE THE TREATMENT?

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Background. A transient increase in liver enzymes is a well described side effect developed by almost 40% of soft tissue sarcoma (STS) patients treated with trabectedin, often leading to treatment delays or discontinuation. We retrospectively analysed the correlation between trabectedin-related liver toxicity and treatment outcome.

Patients and methods. Data from a total of 83 patients receiving trabectedin administered at the dose of 1.5 mg/m^2 iv 24 hours in 3 reference centers were evaluated. This exploratory analysis was performed to assess the impact of liver toxicity (grade 3-4 AST and ALT increases) on the trabectedin efficacy and outcome in STS patients. All the patients included had metastatic disease or locally advanced inoperable and received at least one previous line of treatment containing anthracycline. All patients received standard steroids premedication.

Results. Median age was 54 years (range 27-79 yrs) and male/female ratio was 49/34. STS histologies were: liposarcoma 21 cases, leiomiosarcoma 19, pleomorphic sarcoma 15, synovial sarcoma 9, 19 other histologies. For 39 patients a G3-4 ALT increase in the first two cycles was reported while for 44 was not. Calculations show that hazard ratios for PFS and OS are not statistically significant (HR = 1.103, p = 0.860 and HR = 0.947, p = 0.920, respectively). Furthermore, the analysis was repeated dividing the population between patients with G3-4 ALT elevation during treatment vs patients without such elevation. Again, hazard ratios for PFS and OS are not statistically significant (HR = 0.810, p = 0.371 and HR = 0.958, p = 0.930, respectively). Finally, the analyses were repeated, splitting the population in patients with peak ≥15 ULN vs patients with peak <15 ULN and once again no statistical significant differences were identified neither in terms of PFS (HR = 0.840, p = 0.302) neither in terms of OS (HR = 0.830, p = 0.241).

Conclusions. Liver toxicity is a common event during treatment with trabectedin and does not affect outcome. These results should discourage the premature discontinuation of the drug due to the increase in liver enzymes.

M5 TRABECTEDIN: REVIEWING SAFETY AND DRUG-DRUG INTERACTIONS OF TRABECTEDIN

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Background. Trabectedin (Ecteinascidin 743, ET-743, Yondelis®) is a potent antitumor drug possessing high activity against sarcoma, and different soft tissue sarcoma subtypes. It is used as monotherapy or in combined treatment; its safety profile is still under evaluation and more importantly, since it is metabolized by cytochrome P450 (CYP) 3A4, several drug-drug interactions have already been identified and more might appear.

Methods. Studies or articles were identified using predefined search criteria in PubMed and Cochrane Library as databases. The included studies were clinical trials and peer-reviewed articles published between January 2006 and February 2013. Terms used were: trabectedin, sarcoma, interactions and safety.

Results. A total of 30 articles were considered. The safety and tolerability profile of trabectedin is based on evaluation of patients in two important clinical trials: STS-201 (2009) and OVA-301 (2010). Trabectedin, as monotherapy or in combination with doxorubicin, shows none of the toxicities often associated with other common chemotherapeutic agents and has no cardiac, pulmonary or renal toxicity or ototoxicity. Transient neutropenia and increased transaminases, the most common hematological changes, have a low incidence of clinical consequences. It must be not administered in patients with severe hepatic impairment. When administered before trabectedin, doxorubicin or pegylated liposomal doxorubicin, carboplatin, gemcitabine or paclitaxel do not seem to influence its pharmacokinetics. Trabectedin is a substrate of P-glycoprotein (P-gp), therefore a concomitant administration of P-

gp inhibitors (e.g. cyclosporine) are expected to alter its distribution and/or elimination. Since trabectedin might cause rhabdomyolysis (CPK increases in association with rhabdomyolysis were reported in less than 1% of patients), co-administration with other drugs causing rhabdomyolysis (e.g. statins) requires caution.

Conclusions. Overall, trabectedin has a good efficacy/risk profile. The main adverse reactions are hematological and hepatic, similarly to other antitumoral drugs. Serious adverse events are infrequent. Fatal adverse reactions are often due to a combination of clinical conditions such as pancytopenia, febrile neutropenia, hepatic impairment and rhabdomyolysis. However, favourable pharmacokinetics and safety profile of trabectedin contribute to its tolerability, particularly in pre-treated cancer patients.

M6 METRONOMIC CONTINUOUS ORAL CYCLOPHOSPHAMIDE AS SECOND AND FURTHER LINE IN SOFT TISSUE SARCOMAS (STS) OF THE ADULT

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Background. In STS third-line treatment is poorly defined. However many patients (pts), after aggressive therapy as first- and second-line progress in their disease and ask to be treated. Oral cyclophosphamide (CPM) was already used in breast cancer, prostate cancer and in elderly pts with STS with favourable results. Aim of our study was to define the feasibility, tolerability and activity of oral CPM as third-line and further line chemotherapy.

Patients and methods. Forty-five pts (19 M; 26 F) with advanced or metastatic STS heavily pretreated were included. Oral CPM was given daily at total dose of 50 mg/day without interruption excepted for toxicity or progressive disease.

Results. Median age was 60 (32-81), histological subtypes were: leiomyosarcoma 12, liposarcoma 10, condrosarcoma 5, sinovial sarcoma 4, sarcoma NOS 4, other 10. Primary sites were: extremities 21, retroperitoneum 19, trunk 5. Forty-one pts were metastatic, 4 locally advanced. Forty-one pts were pretreated with chemotherapy (15 were in second-line, 17 in third-line, 7 in fourth-line, 2 in fifth-line). Median PS (ECOG) was 2. Median duration of therapy was 4 months (1-38). Progression-free survival (PFS) ranged from 0 to 42+ months (median 4 months). Treatment was well tolerated, we registered only one episode of leucopenia G2 and one of asthenia G2. No complete responses were seen. Only 3 minimal responses and 18 stable disease were seen.

Conclusions. Oral CPM showed a mild activity and good tolerability in advanced soft tissue and metastatic STS. It could be an appropriate solution as second-line and further therapy and in unfit or elderly patients.

M7 SOFT TISSUES SARCOMAS (STS): WHY SO OFTEN WE HAVE A DELAYED DIAGNOSIS AND THERAPHY? A NETWORK PIEDMONTESE ONCOLOGY OBSERVATIONAL STUDY

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Background. STS are 1% of malignant tumors in adults. Rarity, heterogeneity in presentation, low expertise in primary care physicians (PCP) or in general hospitals, organisation problems in specialized centres may cause a delay in both diagnosis and treatment. Aim of this study is to acknowledge the barriers to optimal care and the consequences of the delay on prognosis.

Patients and methods. Patients with STS of the extremities, trunk, retroperitoneum treated and followed from 1999 to 2011 by the same multidisciplinary group were included. Time and pattern of symptoms onset, anatomic site, tumor volume, patients age, gender and home, interval between diagnosis and surgical treatment or neoadjuvant chemotherapy, time to start adjuvant RT or CT were considered in a univariate-multivariate analysis.

Results. 449 adult patients (53% F, 47% M, median age 55 years) were followed for a median time of 116.38 months. 65.7% of STS were at the extremities, 17.6% retroperitoneal, 16.7% at the trunk wall. Median volume at diagnosis was 8 cm for trunk and extremities; 15 cm for retroperitoneum. Commonest histologies: liposarcoma. 18.2%; leiomyo 16.8%; mixofibro 13.6%. Increasing mass, pain and abdominal discomfort were the main revealing signs of diseases. Median time of delay was: from onset of symptoms to first medical visit 68 days for trunk and extremities, 82 for retroperitoneum; 104 days from symptoms to histological diagnosis; 129 days from symptoms to start of therapy. Time to surgery after definitive diagnosis was 12 days in extremities and 21 in abdomen. Adjuvant CT started 22 days after surgery for extremities, 25 in trunk, 35 in retroperitoneum. RT initiated after 78 days. Longer delay in treatment leads to worse prognosis: MS 89.95 months if delay is >3 months; 190.40 months if wait is <3 months ($p = 0.007$).

Conclusions. Low self consciousness of the patient; misdiagnosis or inadequate approach in general hospitals; late referral to specialized centres are 75% of the causes of wasted time. Organization problems at the referral Centre concur for 25% of delays. Guidelines implementation and educational programme among general population and PCP are necessary.

M8 SECOND-LINE CHEMOTHERAPY WITH TRABECTEDIN IN SOFT-TISSUE SARCOMAS AFTER FAILURE OF ANTHRACYCLINE TREATMENT

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Background. Soft-tissue sarcomas (STS) are rare tumours, accounting for approximately 1% of all cancers worldwide each year. The treatment of STS is often palliative, although a subset of patients may be cured or have a prolonged disease-free interval. Trabectedin is a novel marine-derived antineoplastic agent that appears to bind to the minor groove of a DNA strand and probably inhibits DNA transcriptional activation, although the mechanism is complex. It is licensed as standard second-line therapy for STS.

Materials and methods. From February 2010 to March 2013 we treated eight patients with metastatic STS (all males, mean age 62 years [40-71 years], 3 with liposarcoma, 2 fibrosarcoma, 2 leiomyosarcoma, and 1 synovial sarcoma). Seven were treated with trabectedin as second-line therapy after failure of anthracycline-based first-line therapy, and one received first-line trabectedin due to impaired cardiac function. The dosage was 1.5 mg/m^2 every 21 days for a total of 49 cycles (mean 6.1, range 3-12). CT scanning of target lesions was performed at baseline and after four treatment cycles to evaluate treatment response using Response Evaluation Criteria in Solid Tumors (RECIST) criteria.

Results. The maximum RECIST responses achieved were: partial response (PR) = 2 patients, stable disease (SD) = 4 patients, and progressive disease = 1 patient. The overall response rate (PR+SD) was 85%. The median overall survival was 10 months and median progression-free survival was 6 months (range 3-9). Two patients are still receiving treatment. Overall, trabectedin was well tolerated; the most common grade 4 side effect reported was thrombocytopenia.

Conclusions. Trabectedin therapy resulted in a PR or SD in 7 of the 8 patients (ORR 88%) and was well tolerated.

M9 COMBINED TREATMENT OF CARDIAC ANGIOSARCOMA WITH WEEKLY LOW DOSE DOCETAXEL AND CONFORMATIONAL RADIOTHERAPY

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Introduction. Cardiac tumors are a rare cancer event and may originate from each of the various tissues of the heart. Angiosarcoma is the most common cardiac malignancy which mostly arises sessile, or intra-cavity within right atrium, often involving pericardium. Symptoms may be initially not specific while, in advanced stages, fatigue, fever, dyspnea, arrhythmias or cardiac tamponade can eventually occur.

Methods. A medline search has been performed for the treatment of cardiac angiosarcoma, that is usually based on surgical resection with or without chemotherapy and/or radiation, but no randomized clinical trials have been reported. Chemotherapeutic regimens were mostly based on the use of taxanes, anthracyclines and cyclophosphamide and in some cases the addition of biological agent such as IL-2 is described. The combination strategies including chemo/radiotherapy plus surgery have reported survival between 5 and 53 months as compared to chemo/radiotherapy alone (survival 3-12 months). In our clinical case, a 62-year-old man was admitted to our medical oncology unit for the presence of an approximately 5 cm right intra-atrial lesion, occupying three-quarters of the atrial cavity, extending also outside of the atrium with a total maximum diameter of 9 cm, at CT scan. The ECG showed also P-wave atriogram abnormalities with increased amplitude.

Results. The right neoplasm adherent to the atrium roof was removed by minithoracotomy. The residual tumor portion outside atrium (90 mm x 37 mm) was not resectable. The patient underwent conformational fractionated adjuvant radiotherapy targeted on right atrium associated to docetaxel 20 mg/m^2 weekly as radiosensitizer drug (for 4 weeks). After this initial treatment, we extended the weekly low dose of docetaxel therapy for further 4 weeks. The combination therapy was well tolerated and the CT scan performed at the end of treatment showed tumor regression of the neoplasm (size: 72 mm x 24 mm). The disease was stable even at 10 months after the diagnosis.

Conclusions. The treatment of cardiac angiosarcoma is a challenge, due to the dynamics of the heart and the potential relevant toxic effects. There are few reports about treatment of cardiac angiosarcoma with taxanes, because standard chemotherapy is represented by doxorubicin, dacarbazine, methotrexate, cyclophosphamide or vincristine. Our experience demonstrates the efficacy and safety of docetaxel as radiosensitizer treatment in this particular setting.

M10 TWO YEARS DISEASE STABILIZATION WITH THIRD-LINE TRABECTEDIN IN A PATIENT WITH METASTATIC DUODENAL LEYOMIOSARCOMA: A CASE REPORT

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Background. Soft tissue sarcomas (STS) are a group of rare tumors originating from mesenchimal tissue. Systemic chemotherapy is the main treatment for metastatic disease, but prognosis remains ominous. First-line standard treatment is anthracycline/ifosfamide based. Trabectedin is an alkaloid isolated from a marine tunicate, now produced by chemical synthesis. Interacting with DNA transcription and repair factors, it has proved activity in phase II trials in advanced STS refractory to anthracyclines.

Material and methods. A 63-years-old female patient presented in April 2007 after surgical resection of a duodenal mass, with hepatic ilum involvement and distal tract of portal vein invasion. Histology was leiomyosarcoma with pleomorphic aspects. Tumor size was 7 cm. After surgery, CT and US revealed a liver lesion suspected to be metastatic. Patient received ADM+IFO 4 cycles with no CT evidence of residual disease after treatment. On April 2009 CT and NMR scans revealed liver progression. Second-line treatment with 6 cycles docetaxel/gemcitabine was performed.

Results. CT scan on January 2010 revealed lung and abdominal progression with main liver lesion of 10 cm. Therefore we started third-line treatment with trabectedin 1.5 mg/m^2 conventional dose. Patient received 20 cycles up to July 2012. On February 2011 CT scan displayed disease stabilization with vascular enhancement of liver metastasis central area, as for pseudoaneurismatic evolution. As of toxicity, after first cycle patient displayed G4 neutropenia, G3 thrombocytopenia and G2 transaminase elevation (CTCAE 4). Hospitalization was required, due to *E. Coli* sepsis. Anemia G3 required transfusions and erythropoietin. Further cycles were delayed and dose was reduced to 1.2 and then to 1 mg/m^2. Reduced and tolerable toxicity was therefore attained. Further septic episodes linked to CVC infections were appropriately treated. April 2012 CT scan confirmed disease stabilization at 110 mm diameter of main liver lesion. Since then patient, due to severe depressive status, has decided to stop treatment. Out of fatigue, all toxicities proved to be reversible. CT scan performed on May 2013 displayed main le-

sion increased up to 16.5 cm; patient is at home receiving best supportive care.

Conclusions. This case contributes to determine a positive role of trabectedin for heavily pretreated STS, supported by observation of a two years disease stabilization. Tumor control, rather than disease shrinkage appeared to be a reasonable goal in this refractory disease.

M11 MULTIDISCIPLINARY MANAGEMENT OF RARE TUMORS. POSSIBILITY OR NECESSITY?

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Background. The radio-induced angiosarcoma after breast cancer and conservative surgery is the most frequent breast "second malignancy". Often, this second tumor is very resistant to standard treatments and is highly disabling for the patient.

Patient. We report the rare case of a 52-years-old woman with an angiosarcoma grade 2 arising 8 years after the first mammary adenocarcinoma. We managed this case in collaboration with the Italian rare tumors network (Rete Tumori Rari = RTR).

In 1999 the patient performed quadrantectomy for breast adenocarcinoma and subsequently chemotherapy and radiotherapy on residual breast. In 2007, for the appearance of nodules near the scar, has undergone radical mastectomy. Histology was 'angiosarcoma infiltrating the skin and the subcutaneous adipose tissue'. New relapses, always treated only surgically, occurred in 2009 and 2010.

Results. In June 2010, following further local recurrence and hyper-specialist consultation, the patient comes to our observation and begins chemotherapy with weekly taxol. In September 2010, after a disease progression, the patient started a new weekly chemotherapy with gemcitabine. In January 2011 for further progression was started third-line chemotherapy with epirubicin/ifosfamide q21. Despite the progression, the disease still always remained localized to the chest wall and caused no pain. PS ECOG was 0/1.

In April 2011 for further progression, we proposed to the patient further off label treatment with Nexavar. The patient, although we do not recommend other surgical approaches, decides to undergo equally surgery at another hospital. The patient returned to our observation after two months, under the advice of the emergency room. Presented fever, and showed healed scar on the chest wall from which drained necrotic/purulent material; was present ipsilateral pleural effusion positive for neoplastic cells. PS was 4 and she died in a few weeks.

Conclusions. The management of these rare and complex diseases need a multidisciplinary assessment directed by oncologists. The RTR aims to help the individual practitioner precisely in cases like the one just described.

Session N • Lymphomas and myeloma

N1 ANTI-MYELOMA ACTIVITY OF MIR-34A ENCAPSULATED INTO SNALPS: *IN VITRO* AND *IN VIVO* EVIDENCE

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Background. MicroRNAs (miRNA) are small molecules regulators of gene expression that target mRNAs and trigger either translation repression or degradation. At the present, miRNAs are attractive targets for therapeutic intervention. Aberrantly expressed miRNAs may play key roles in cancer and correcting these miRNA defects by either antagonizing or restoring miRNA function may produce a therapeutic benefit. Among human malignancies, multiple myeloma (MM) is characterized by deregulated expression of miRNAs. A promising strategy to target the miRNA network is to enforce the expression of downregulated miRNAs that act as tumor suppressor genes, such as miR-34a, a critical modulator of the p53 pathway. We recently investigated the therapeutic potential of miR-34a mimics, encapsulated in nanocarriers specific for delivery of oligonucleotides, called Stable Nucleic Acid Lipid Particles (SNALPs) against human MM cells *in vitro* and *in vivo*. SNALPs, which are composed of ionizable phospholipids, have high encapsulation efficiency and plasma stability.

Methods. SNALPs formulations were prepared by modified ethanol injection method and then the mean diameter and size distribution were determinated by photon correlation spectroscopy (PCS). For *in vitro* study, SKMM1 cells were treated with formulated SNALP-miR-34a or scrambled oligonucleotide (miR-NC) for cell viability assay after 24, 48 and 72 hours. For *in vivo* study, male CB-17 severe combined immunodeficient (SCID) mice were inoculated (sc) with 5 x 10^6MM cells in 100 μL RPMI-1640 medium. After detection of palpable tumors, mice were randomized into 5 groups and systemically treated, viatail vein, with 1 mg/kg miR-34a or miR-NC encapsulated in SNALPs.

Results. *In vitro* study confirmed the efficacy of miR-34a formulated in SNALP compared to naked SNALPs, after 24 and 48 hour treatment ($p = 0.0089$ and 0.02, respectively). *In vivo* we evaluated the antitumor effects induced by systemic delivery of SNALP-miR34a including transferrin-SNALP coupled nanovectors. Following 5 injections (3 days apart), significant anti-tumor effect of SNALP-miR-34a versus naked SNALP and SNALP-NC-miR was demonstrated as well as for tranferrin-coupled-SNALP-miR-34a ($p < 0.05$).

Conclusions. Our data provide evidence that SNALPs are efficient carriers to deliver miRNAs in tumors. The activity of tranferrin-coupled-SNALP-miR-34a is also demonstrated . We provide a rationale and a framework for clinical development of this miRNA-delivery system in MM.

N2 FUNCTIONAL OC-LIKE DIFFERENTIATION OF MYELOMA CELLS BY VITD

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Introduction. Recent evidences support the hypothesis that malignant plasma cells (MPCs) may acquire a functional osteoclast (OC)-like phenotype and directly participate to myeloma bone disease (MBD). Since OCs derive from monocyte-macrophages, the MPC OC-like transdifferentiation implies morphological and functional overlaps between lymphoid and myeloid lineages. To this regard, B lymphoma myc5 cells acquire *in vitro* a myeloid phenotype by silencing PAX 5, a lineage specific gene also known as B cell identity guardian. Moreover, MPCs morphologically become monocyte-like cells if treated with 1.25(OH)2VitaminD3 (VitD) and the CCAAT/enhancer binding protein a (CEBPa). VitD is involved in differentiation of a number of cells including OCs, since peripheral blood mononuclear cells stimulated with VitD and MCSF generate OCs. Here, we investigated the OC-like transdifferentiation of MPCs in MBD using factors involved in osteoclastogenesis such as vitD, MSCF and RANK-L.

Materials and methods. VitD IC20 was administered to RPMI8226 and U266 multiple myeloma (MM) cells to measure CEBPa and PU.1 mRNAs by real-time PCR, while CD33 as myeloid marker was assessed by flow cytometry. Immunofluorescence with both DAPI and phalloidin was completed to verify morphological changes and anti-paxillin staining was used to characterize cytoskeleton rearrangements. The expression of avß3integrins, v-ATPase and MCSFR as markers of OC differentiation was assessed by real time PCR and flow cytometry. Finally, MPCs were cultivated on calcium phosphate discs to evaluate number and size of the erosion pits.

Results. VitD induced a shape elongation on MPCs as well as formation of paxillin-rich adhesion in a fashion similar to activated OC, together with the increased expression of CD33 and both CEBPa and PU.1 mRNAs. Incubation of MPCs with VitD triggered the transcription of several functional markers of OCs as av-ß3integrin, v-ATPase and MCSFR. In addition, VitD pretreatment of MPCs cultured on bone substrates in the presence of MCSF and RANKL resulted in significantly higher resorption activity as compared with control.

Conclusions. Our results show the capability of VitD to prime the lymphoid-myeloid transdifferentiation of MPCs, thus favouring their OC-like phenotype. The significance of this study may be translated to clinical observation in patients with MM whose treatment with exogenous VitD may ultimately contribute to the functional OC-like differentiation of MPCs.

N3 ROLE OF NON-HOMOLOGOUS END JOINING IN MULTIPLE MYELOMA GENOMIC INSTABILITY AND AS POTENTIAL PROGNOSTIC MARKER

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Background. The underlying molecular basis of multiple myeloma (MM) genomic instability is largely unknown. Since non-homologous end joining (NHEJ) is one of the most important mechanisms involved in repair of double-strand breaks (DSBs), we have investigated its possible alteration in MM.

Materials and methods. Difference in NHEJ activity among normal and MM cells was assessed by a dual gene plasmid based assay using both *intact cells* and *free cell extracts*. The first one is a chemiluminescent assay while the second is based on qPCR. The plasmid contains both test gene (Luciferase-LUC) measuring end joining as well as reporter gene (Alkaline Phosphatase-SEAP) to control for transfection efficiency. Ku86 binding activity of nuclear proteins was analyzed using the ELISA Ku70/86 DNA Repair kit (Active Motif). Basal DNA damage was quantified by an immune-fluorescent based assay for DSBs. The IFM dataset was used to perform globaltest analysis on 28 genes of the NHEJ pathway and OS or CNV.

Results. We first evaluated the NHEJ activity in MM cells by directly measuring LUC and SEAP in the supernatant of the cells 24h after electroporation with the plasmid. A significant increase in EJ was observed in all 6 MM cell lines used compared to peripheral blood mononuclear cells and bone marrow stromal cells from healthy donors. We next validated these results in 4 out of 5 MM cell lines using *free cell extracts* with an assay based on qPCR. Moreover, the same screening on 10 patient MM cells from different disease stage showed a significantly elevated EJ in primary cells. To confirm this anomalous activation on a genomic level, we showed an augmented binding-activity of ku86, a key protein of such pathway, in nuclear extracts of 9 MM cell lines respect to controls. Most importantly, we noticed a direct correlation between that and the basal level of DSBs. Finally, the Globaltest analysis on 170 patients showed a significant correlation between expression of NHEJ pathway-related genes and OS in MM. The same method confirmed greater significance of this signature in the low risk subgroup. Moreover, virtual karyotyping using SNP data revealed very strong correlation with CNV and NHEJ signature. Ongoing experiments with ku86 shRNA KO are assessing the role of NHEJ in MM chromosomal abnormalities.

Conclusions. In conclusion, our data suggest that an aberrant NHEJ might contribute to MM genomic instability, likely suggesting its role in progression and prognosis.

Session P • Primary and secondary brain tumours

P1* A MIRNA SIGNATURE FOR DEFINING AGGRESSIVE PHENOTYPE AND PROGNOSIS IN GLIOMAS

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Background. Gliomas account for approximately 80% of all primary malignant brain tumors and, despite improvements in clinical care, they remain still associated with poor prognosis. They are currently classified by the WHO system in low grade gliomas (LGGs, WHO I, II) and high grade gliomas (HGGs, WHO grade III, IV) based on histological features such as nuclear atypia, mitotic figures, microvascular proliferation and necrosis. LGGs and HGGs share several morphological traits and pathways abnormalities but have a different clinical behaviour. miRNAs have emerged as key regulators of many biological processes mediating genesis and dissemination of cancer. Molecular analyses based on miRNAs measurements have shown to be able to better stratify and discriminate the two tumor types. We hypothesize the comparison of miRNA profile between LGGs and HGGs may lead to the identification of miRNAs associated with the most aggressive form, that is GBM (WHO IV).

Methods. miRNA expression profiling was performed in 8 LGGs, 24 HGGs, and 4 normal brain tissues (NBT) by using the Affymetrix GeneChip® miRNA Array 1.0. Data analysis was performed by Partek Genomic Suite software, setting a significative p value = 0.01 and a fold change cutoff of 2. A relative quantification method (qRT-PCR) with standard curve was used to validate the 22 miRNA signature resulted by array analysis. The prognostic performance of the 13 validated miRNAs was estimated by using the Tumor Cancer Genome Atlas (TCGA) dataset.

Results. miRNA profiling identified 80 miRNAs differentially expressed in LGGs vs NBT and 71 in HGGs vs NBT. A panel of 22 miRNAs clearly differentiated HGGs and LGGs. qRT-PCR assay confirmed differential expression for 13 out of the 22 miRNAs in LGG vs HGG. In addition, 6 among our 13-miRNA signature (miR-21, miR-210, miR-22, miR-155, miR-223, miR-219-2-3p) were found to be significantly associated with GBM molecular subtypes when compared on TCGA dataset. Moreover miR-21 and miR-210 show correlation with worse overall survival in both univariate and multivariate Cox Regression analysis (HR 1.19, 95% CI 1.008-1.406, p = 0.04; and 1.183, 95%, CI 1.018-1.375, p = 0.03).

Conclusions. We show that the comparison of LGGs and HGGs profiles is able to identify miRNAs associated with invasive phenotype. Our results also support a direct involvement of miR-21 and miR-210 in glioma progression, suggesting they may represent promising targets for new therapeutic approaches in gliomas.

P2* BEVACIZUMAB PLUS FOTEMUSTINE COMBINATION: ACTIVITY AND SAFETY IN RECURRENT MALIGNANT GLIOMAS

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Background. Recurrent malignant gliomas (RMGs) have a dismal prognosis with a median survival of 4-6 months. Although bevacizumab (BV) has been showed to provide encouraging tumor responses and prolonged survival in the treatment of RMGs, no clearly established chemotherapy (CT) regimens do exist. We conducted an observational prospective study to evaluate the activity and the toxicity of BV in combination with fotemustine (FTM) in adults with RMGs.

Methods. Enrolled patients received BV intravenously (iv) at the dose of 10 mg/kg every 2 weeks (induction phase) and then at the dose of 15 mg/kg every three weeks in the maintenance phase. FTM was administered iv weekly for 3 consecutive cycles at 60 mg/m^2 (induction phase) followed by triweekly cycles at 75 mg/m^2 (maintenance phase) given after 5-week rest period. MGMT gene promoter methylation status was evaluated.

Results. Twenty-six pts [17 M, 9 F, 13 GBM, median age 38 yrs (23-68), median KPS 80 (70-100)] were enrolled. Eighty-five percent of patients had received only one previous line of CT, namely temozolomide in association with radiotherapy; 11% of pts were treated with two prior lines of CT. Response rate was achieved in 8 (31%) pts (all partial responses [PR]), and disease stabilization (SD) in 16 (61.5%) pts (disease control rate: 62%); 10 (38%) pts had clinical benefit. Responses were observed in all histotypes. Median PFS and OS were 4 months (95% CI 3.0-4.9) and 6 months (95% CI 4.2-7.8), respectively. OS differed with regard to response: 10 months (95% CI 3.8-16.2) for pts with PR; 7 months (95% CI 4.5-9.5) for SD; 4 months (95% CI 2.0-6.4) for pts with progressive disease. MGMT status was evaluated in 19 (73%) patients. We observed 10 (38%) and 9 (35%) pts without and with MGMT methylation, respectively. Patients with MGMT methylation achieved 33% of response while non-methylated MGMT pts had 10% of response. The most common toxicities (all grades) were neutropenia (23%), thrombocytopenia (15%), hypertransaminasemia (11%). Grade 4 adverse events (AEs) were neutropenia (4%) and lymphocytopenia (4%). AEs related to BV included venous thromboembolism (8%), asymptomatic central nervous system hemorrhage (4%), proteinuria (2%) and a grade 2 gastro-intestinal (2%) perforation.

Conclusions. The combination of BV and FTM in RMGs revealed a good activity in pts previously treated with CT. Treatment was well tolerated. Final results will be presented at the meeting.

P3* CONDITIONAL SURVIVAL OF PATIENTS TREATED WITH RADIOTHERAPY PLUS CONCOMITANT AND ADJUVANT TEMOZOLOMIDE FOR GLIOBLASTOMA

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Background. Glioblastoma polymorphous (GBM) is the most common brain tumor and has the worst prognosis. We assessed the use of conditional survival, a measure that accounts for elapsed time since treatment initiation, for prognostication in patients with GBM treated with radiotherapy (RT) plus concomitant and adjuvant temozolomide (TMZ).

Patients and methods. We obtained data for patients with GBM who were treated with radiotherapy plus concomitant and adjuvant TMZ for GBM between January 2003 and April 2013. Data were collected from 6 Italian centers involved in the treatment of GBM. The primary outcome was 2-year conditional survival, defined as the probability of surviving an additional 2 years from a given time-point since the start of RT chemotherapy (CT). Secondary analyses included conditional survival based on length of time on therapy. Overall survival (OS) and progression-free survival (PFS) were estimated with the Kaplan-Meyer method with 95% CI.

Results. A total of 229 pts were enrolled in this analysis. The median age was 64 yrs (range 30-78) and 137 pts (59.8%) were male. Median OS was 17.7 months (IQR 10.9-26.3). We observed an increase in the 2-year conditional survival probability from 34.1% (95% CI 28.0-40.2) at 0 months to 48.4% (95% CI 42.0-54.8) at 12 months from diagnosis. At the start of RT, 2-year conditional survival probability was 26.2% (95% CI 20.5-31.9). The median PFS of adjuvant TMZ was 4.6 months (IQR 2.6-8.2). When conditioned on time on TMZ from 0 to 6 months, 2-year conditional survival probability improved from 18.8% (95% CI 13.7-23.9) to 38.2% (95% CI 31.9-44.3). Among the 105 pts who received a second-line CT, median PFS was 3.3 months (IQR 1.8-6.2). Thirty-two pts were treated with alternative TMZ schedules, 68 pts with fotemustine and 5 with bevacizumab. In these pts, 2-year conditional survival probability from time 0 to 6 months increased from 12.4% (95% CI 6.2-18.6) to 37.3% (95% CI 28.1-46.5).

Conclusions. Based on survival since treatment initiation or therapy duration, conditional survival represents a relevant prediction measure to adjust the prognosis of glioblastoma pts, especially in the adjuvant and second-line settings.

P4 PERFUSION IMAGING (CT AND MRI) IN PATIENTS WITH HIGH-GRADE MALIGNANT GLIOMAS TREATED WITH BEVACIZUMAB

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Background. To determine whether early monitoring of the effects of bevacizumab in patients with recurrent high-grade gliomas, by perfusion CT or MR imaging, may be predictor of the response to treatment in patients with recurrent high-grade brain tumor.

Materials and methods. Twenty patients with high-grade brain tumor were enrolled in the study. For each patient two perfusion examinations, before and after the first dose of bevacizumab, were acquired. Sixteen patients underwent a perfusion CT (PCT) exam by using a 128-section CT scanner and four patients a dynamic contrast enhancement (DCE) MR exam on 1.5-T system. The areas of abnormal cerebral blood volume (CBV) have been outlined on the two studies, using contrast-enhanced T1-weighted images as a guide to the tumor identification. Normalized CBV (nCBV) maps were obtained dividing the original CBV maps by the mean CBV value inside a healthy region in the hemisphere contralateral with respect to the lesion. Specific hypo- and hyper-perfused sub-volumes were calculated, as absolute voxel counts within the region of interest in which nCBV values were less or greater than fixed thresholds, respectively. The correlations between the early changes in perfusion and volume changes at the first follow-up were investigated.

Results. The changes of nCBV maps indicated an effective normalizing effect of the drug on the areas of abnormal vascularity, even if initial nCBV values >3 suggested a reduced activity of the anti-angiogenic agent, as if the normalization effect was less efficient. The reductions of mean, median and standard deviation of the nCBV after the first dose were statistically significant ($p \leq 0.0001$). An improvement in hypoxia after a single dose of bevacizumab was a predictor of a greater reduction in T1-weighted contrast-enhanced volumes at first follow-up.

Conclusions. These preliminary results show that a quantification of changes in necrotic intra-tumoral regions could be proposed as a potential imaging biomarker of tumor response to anti-VEGF therapies.

P5 RADIOTHERAPY PLUS CONCOMITANT AND ADJUVANT TEMOZOLOMIDE TOXICITY PROFILE FOR HIGH GRADE GLIOMA IN ELDERLY PATIENTS: A SINGLE INSTITUTION EXPERIENCE

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Background. Patients (pts) aged 65 years or older represent half of all pts with high grade glioma (HGG). The standard treatment for pts <70 years old is cytoreductive surgery followed by chemotherapy with temozolomide (TMZ) plus concomitant radiotherapy (RT) and subsequent 6 cycles of adjuvant TMZ. The optimal treatment for elderly pts (>70 years old) remains controversial. We report our experience about the toxicities observed in a group of elderly pts treated with RT+TMZ, followed by adjuvant TMZ.

Materials and methods. We treated 65 pts for HGG in our Institution from November 2011 to May 2013. Twenty (31%; 13 males, 7 females) pts were 70 years old (median age 76 years, range 70-82); ECOG Performance Status (PS) 0/1/2 was reported among 1/11/8 pts. The histology was multiform glioblastoma in 14 pts (70%), oligodendroglioma in 2 (10%), oligoastrocytoma in 4 (20%). Patients were treated with RT (daily fractions of 2 Gy, total of 60 Gy) plus concomitant TMZ (75 mg/m^2/die) followed by 6 cycles of adjuvant TMZ (150-200 mg/m^2 for 5 days every 28). Two patients received hypofractionated RT (46 Gy) due to PS 2 or early deterioration and/or disease progression. We retrospectively evaluated toxicities for these 20 elderly patients.

Results. Toxicity reports of 16 pts were evaluated (4 pts were excluded because RT+TMZ is ongoing). No G3-G4 hematologic toxicities were observed during RT+TMZ. Four pts (25%) experienced G1-G2 thrombocytopenia (3 G1, 1 G2), 2 pts (12.5%)

showed anemia G1. Thirteen pts (81.25%) received adjuvant treatment (median number of cycles 6; range 2-21), 6 of them (46.2%) received chemotherapy at the dose of 150 mg/m^2/die (75%) due to hematologic toxicity registered during RT+TMZ or ECOG PS 2. Four of the pts who received adjuvant TMZ (30.77%) experienced thrombocytopenia G1 (1 pt taking TMZ at 200 mg/m^2), 3 (23.08%) presented anemia (2 G1, with 1 pt taking TMZ at 200 mg/m^2), 1 pt referred nausea G1.

Conclusions. Our experience, even if with a small number of pts, demonstrates that RT plus concomitant and adjuvant TMZ is feasible and well tolerated for elderly pts with newly diagnosed HGG. In particular, RT+TMZ was associated with mild hematologic toxicity, while adjuvant TMZ did not determine any additional toxicities. The administration of TMZ at a reduced dose may represent an effective strategy to prevent the worsening of previously occurred adverse events or deterioration of the PS of frail or potentially frail patients.

P6 GENETIC POLYMORPHISMS OF EGF 5'-UTR IN PATIENTS WITH GLIOMA: A POSSIBLE PREDICTIVE MARKER OF OUTCOME

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Background. Epidermal growth factor (EGF) plays an important role in carcinogenesis. An adenine (A) to guanine (G) single nucleotide polymorphism at position 61 in the 5'-untranslated region (5'-UTR) of the EGF gene has been found to be associated with levels of EGF production and contribute to the risk of glioma. However, published data are contradictory. EGF +61G/A polymorphism may contribute to the risk of glioma in different ethnic groups. Patients with glioma and GG genotype have been reported to have a risk of poorer outcome than patients with AA genotype. Purpose of this study is to investigate the potential role of this polymorphism in cancer progression and its role as predictive marker of outcome in glioma Caucasian patients.

Material and methods. The significant SNP rs4444903, EGF 61A/G, was analyzed in glioma patients and was determined by means of polymerase chain reaction and direct sequencing method from blood samples. Association of this genetic polymorphism with clinical and pathological data of patients was evaluated.

Results. We investigated EGF +61G/A polymorphism in 28 glioma patients. EGF +61G allele has been found in 68% of glioma patients (22% G/G genotype and 46% A/G genotype). In astrocytomas, EGF +61G allele represents a 83% frequency; in glioblastomas and in oligodendrogliomas, EGF +61G allele frequency represents respectively 73% and 54%. In WHO IV gliomas, the EGF +61G allele represents a 72% frequency (27% G/G and 45% A/G), in WHO III gliomas a 81% frequency (54% G/G and 27% A/G) and in WHO II gliomas a 33% frequency (80% A/G). Median PFS of glioblastoma patients was 9 months. 79% of glioblastoma patients with a relapsing disease showed the G/G and A/G genotype. No difference was detected in the others histotypes.

Conclusions. Our data confirm previous studies which reported G allele as a risk factor for glioma in Caucasian. G/A and G/G genotypes seem to be more representative in high grade gliomas. Despite limited number of patients, our study supports the predictive role of EGF 61 A/G polymorphism in GBM. Additional large studies are warranted to confirm the role of EGF polymorphism as independent prognostic factor in glioma.

P7 A RANDOMIZED PHASE II TRIAL OF HYDROXYUREA ± IMATINIB IN THE TREATMENT OF RECURRENT OR PROGRESSIVE MENINGIOMAS

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Background. Hydroxyurea (HU) is amongst the most widely used salvage therapies in progressive meningiomas after surgery, radiosurgery and radiotherapy. Platelet-derived growth factor receptors (PDGF-R) are expressed in virtually all meningiomas. Imatinib sensitizes transformed cells to the cytotoxic effects of chemotherapeutic agents that interfere with DNA metabolism. The combination of HU with imatinib yielded intriguing results in recurrent malignant glioma. The current trial addressed the activity of this association against meningioma.

Methods. Patients with recurrent or progressive WHO grade I-III meningioma, without therapeutic indication for surgery, radiotherapy or stereotactic radiosurgery, aged 18-75 years, ECOG performance status (PS) 0-2 and not on enzyme-inducing antiepileptic drugs (EIAED) were randomized to receive HU 500 mg BID ± imatinib 400 mg QD. Treatment was administered until progression, unacceptable toxicity, or patient's refusal. The primary endpoint was progression-free survival rate at 6 months (PFS-6).

Results. Between September 2009 and June 2011, 15 eligible patients were randomized to receive, HU + imatinib (N = 7; Arm A) or HU alone (N = 8; Arm B). Afterwards the trial was prematurely closed due to slow enrolment. Patients' characteristics were (A/B): median age 68/68, median PS 1/1, grade 1: 1/1; grade 2: 4/5, grade 3: 1/0, unknown: 1/2, second surgery: 6/6, three or more surgeries: 4/1, biopsy: 1/0; radiotherapy: 6/5, radiosurgery: 1/3. All arm A patients progressed within 6 months while 4/8 are currently progression-free in arm B. PFS-6 and median PFS (A/B) was 0%/75% and 4/15.4 months. Two arm A and 4 arm B patients are alive. Median and 2-yr OS (A/B) were: 6.5/21.8 months; 14.3%/62.5%. No objective response was observed; 4 arm A and 8 arm B patients had stable disease. Median number of cycles (A/B) was 4 (range 2-7) and 11 (range 4-14). Main G3-4 toxicities were: G3 neutropenia in 1/0, G4 headache in 1/1 and G3 vomiting in 1/0.

Conclusions. This study confirmed that HU is an active and well tolerated agent in recurrent meningioma. Conversely, the addition of imatinib may have a detrimental effect. However due to the small number of patients included in this study, no firm conclusion can be drawn.

Session Q • Gastrointestinal tumours (colorectal excluded)

Q1* REGARD: A PHASE 3, RANDOMIZED, DOUBLE-BLIND TRIAL OF RAMUCIRUMAB AND BEST SUPPORTIVE CARE (BSC) VERSUS PLACEBO AND BSC IN THE TREATMENT OF METASTATIC GASTRIC OR GASTROESOPHAGEAL JUNCTION (GEJ) ADENOCARCINOMA FOLLOWING DISEASE PROGRESSION (PD) ON FIRST-LINE PLATINUM- OR FLUOROPYRIMIDINE-CONTAINING COMBINATION THERAPY IMCL CP12-0715

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Background. VEGF and VEGFR-2 mediated angiogenic signaling contributes to gastric cancer pathogenesis. Ramucirumab (RAM; IMC-1121B) is a human IgG1 monoclonal receptor targeted antibody for VEGF-receptor 2. We conducted a placebo-controlled, double-blind, phase III trial to evaluate the safety and efficacy of RAM in patients with metastatic gastric or GEJ adenocarcinoma who demonstrated PD on first-line platinum- or fluoropyrimidine-based combination therapy.

Methods. Patients were randomized 2:1 to receive RAM (8 mg/kg IV) plus BSC or placebo (PL) plus BSC every 2 weeks until PD, unacceptable toxicity, or death. Eligible patients had PD during or <4 months (mos) after first-line therapy or <6 mos after adjuvant therapy. The primary endpoint was overall survival (OS). Secondary endpoints included progression-free survival (PFS), 12-week PFS rate, overall response rate (ORR) and safety.

Results. 355 pts were randomized (RAM: 238; PL: 117). Baseline characteristics were balanced between arms. The Hazard Ratio (HR) for OS was 0.776 (95% CI 0.603-0.998; p = 0.0473). Median OS was 5.2 m for RAM and 3.8 m for PL. The HR for PFS was 0.483 (95% CI 0.376-0.620; p <0.0001). 12-week PFS was 40% for RAM and 16% for PL. The OS and PFS benefit for RAM was noted across groups including stratification and other disease-related factors including extent of metastases and prior therapy. ORR was 3.4% for RAM and 2.6% for PL. Disease control rate was 49% for RAM and 23% for PL (p <0.0001). Grade ≥3 adverse events (AEs) occurring in >5% of patients on RAM were: hypertension (7.6% RAM; 2.6% PL), anemia (6.4% RAM; 7.8% PL), abdominal pain (5.9% RAM; 2.6% PL), and fatigue (6.4% RAM; 9.6% PL).

Conclusions. Statistically significant benefit in OS and PFS was observed for RAM vs PL in gastric or GEJ cancer after progression on first-line therapy. No grade ≥3 AE was observed in ≥10% of patients.

Q2* MOLECULAR CHARACTERIZATION WITH NEXT GENERATION SEQUENCING (NGS) OF RESECTED GASTRIC CANCER (RGC) ACCORDING TO A PROGNOSTIC CLINICAL BIOLOGICAL RISK STRATIFICATION MODEL TAKING INTO ACCOUNT FHIT, APC AND HER-2 OVEREXPRESSION

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Background. We recently proposed (and internally validated) that FHIT, APC and HER-2 may powerful complement clinical parameters to accurately predict individual patient risk for RGC (Bria et al., Ann Oncol, 2013). NGS multigene analysis may help to concurrent screen for potential genetic abnormalities deputed to drive cancer prognosis or therapeutic opportunities.

Methods. According to the developed risk model, tumor blocks from 114 intestinal-histology patients (out of the original 208) at Good (2-yr cancer specific survival 89.7% and overall survival 84.8%) and poor prognosis (CSS 7.3% and OS <1%) were analyzed for mutations in 50 cancer-associated genes using multiplex PCR amplification of DNA from microdissected paraffin samples and the Ion AmpliSeq Cancer Panel (Life Technologies).

Results. Forty-two patients displayed to be Good and Poor prognostic performers at both CSS and OS; 30 patients (71.4%) were evaluable for NGS analysis. Patients characteristics: Good (N = 13, median FU: 70.8; male/female: 3/7; grading 1/2/3: 1/5/7; MLH1/MSH2/MSH6: 10/13/1; B-catenin/E-caderin: 11/9); Poor (N = 17, median FU: 10.8; male/female: 13/4; grading 1/2/3: 2/8/7; MLH1/MSH2/MSH6: 13/17/6; B-catenin/E-caderin: 9/15). Sixteen RGC contained multiple gene alterations and 7 a single gene mutation. The remaining 7 did not show any muta-

Q2 - Table

	APC	ATM	CDKN2A	EGFR	ERBB2	EZH2	FBXW7	FGFR3	FLT3	IDH1
Good	1	0	0	1	2	0	1	1	1	0
Poor	1	2	1	0	1	1	1	1	0	1
	JAK3	**KIT**	**KRAS**	**NOTCH1**	**NRAS**	**PI3KCA**	**SMAD4**	**SMARCB1**	**STK11**	**TP53**
Good	1	1	3	1	1	3	1	0	2	5
Poor	0	0	3	1	0	4	2	2	1	2

tion among the 50 investigated genes. The most frequently mutated genes were KRAS (N 6), PIK3CA (N 7), and TP53 (N 7). KRAS and PIK3CA mutations were confirmed at Sanger sequencing and TP53 mutations by immunohistochemistry. The genes mutated at lower frequency were APC, ATM, CDKN2A, EGFR, ERBB2, EZH2, FBXW7, FGFR3, FLT3, IDH1, JAK3, KIT, NOTCH1, NRAS, SMAD4, SMARCB1, and STK11. No significant association was found between mutational profiles and either clinico-pathological characteristics or the presence of microsatellite instability. Details according to prognosis are shown in the Table.

Conclusions. NGS technologies with formalin-fixed and paraffin embedded tissues may potentially represent a strong driver for future customized management of RGC and should be investigated in larger samples to complement clinical parameters to accurately predict individual patient risk.

Q3 CANCER STEM CELLS (CSCS) MARKERS EXPRESSION AND SURVIVAL IN RESECTED PANCREATIC CANCER PATIENTS

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Background. Emerging evidences suggest that cancer stem cells (CSCs), characterized by the capacity to both self-renew and produce differentiated progeny, may play critical roles in drug resistance, invasion and metastasis in pancreatic cancer (PC). It has been demonstrated by *in vivo* studies that pancreatic CSCs, identified by expression of markers such as CD44, CD24 and CD133, have higher tumorigenic potential compared to other cancer cells. In our analysis we compared the overall survival (OS) of resected PC patients according to expression of CD44, CD24 and CD133.

Patients and methods. Gene expression tests were performed on tumour samples from patients with resected pancreatic cancer to assess the expression of CD44, CD24 and CD133 genes. To assess the relationship between CSCs markers expression and survival we compared OS of patients with overexpression of the three markers (Group A) versus pts with overexpression of one or two markers (Group B) versus pts without CSCs markers overexpression (Group C).

Results. A total of 124 resected PC patients were included in our analysis. The majority of patients (88 patients, 69.4%) presented overexpression of one or two CSCs markers (Group B). Group A included 22 patients (17.7%) while Group C included 16 patients (12.9%). The three groups of patients resulted comparable for baseline characteristics of clinical relevance. Patients in Group A, with overexpression of CD44, CD24 and CD133, showed the shortest OS (median OS = 8.3 months), when compared to patients in Group B (median OS = 16.2 months) and patients in Group C (median OS = 30.8 months; p = 0.004).

Conclusions. Our analysis suggests that CSCs markers overexpression may be related to a worse OS in resected PC patients. These results are in line with pre-clinical findings showing a higher proliferative capacity for pancreatic cancer cells with CSCs phenotype. Further studies are warranted to validate the prognostic role of CSCs markers and to improve our knowledge of signalling pathways leading to acquisition of CSCs phenotype in PC.

Q4 NEOADJUVANT FOLFIRINOX FOR LOCALLY ADVANCED PANCREATIC CANCER (LA-PDAC) PATIENTS IN ROUTINE CLINICAL PRACTICE: A FEASIBILITY ANALYSIS

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Background. The combination of oxaliplatin, CPT-11 and 5-fluorouracil (FOLFIRINOX) represents an important step forward for the therapeutic strategies of the treatment of advanced PDAC. Given its improvement in terms of activity in the advanced disease, the adoption of such regimen for LA-PDAC, whereas the achievement of response may open surgical approaches, seems reasonable in routine clinical practice.

Methods. Clinical charts of 35 LA-PDAC pts receiving neoadjuvant FOLFIRINOX at 2 different institutions were gathered and analyzed for activity [objective response rate (ORR); disease control rate (DCR): ORR plus stable disease] and toxicity; descriptive statistics was adopted and 95% confidence intervals (CI) were derived for the intention-to-treat (ITT) and the evaluable population.

Results. Thirty-five pts (M/F: 16/19; median age 57 yrs, range 37-70; stage II/III: 4/31; ECOG PS 0/1: 31/4; smokers yes/no: 20/15; site head/body/tail: 22/10/3; T2/T3/T4: 1/12/22; N0/N+: 9/26; vascular invasion yes/no: 32/3; endoprotesis yes/no: 11/24) and 245 cycles were analysed (median 6, range 2-12); 33 pts were evaluable for activity. ORR occurred in 16 pts (ITT 45.7%, 95% CI 29.2-63.2%, evaluable 48.5%, 95% CI 31.4-65.5%), with 1 complete response, and DCR in 17 pts (ITT 77.1%, 95% CI 63.2-91.1%, evaluable 81.8%, 95% CI 68.6-95.0%). At a median follow-up of 11 months (range 2-23), median/mean PFS was 9 months (95% CI 7-12) and 12 months (95% CI 9-15), respectively; 6- and 12-month PFS rate was 77.9% and 35.8%, respectively. With 71.4% of pts still alive, mean OS was 18 months (95% CI 15-21.1; median not reached); 12-month OS rate was 72.6%. The median duration of response was 10 months (95% CI 8-13). Eleven (31.1%) and 6 (17.7%) pts underwent radical and derivative surgery, respectively. Toxicity was mild with G3/4 AE in <1% of cycles, except for neutropenia (G3/4: 8.6%), thrombocytopenia (G4: 2.9%), anemia, diarrhea, mucositis, nausea and vomiting (G3: 2.9%). These results satisfy the following post-hoc statistical hypothesis: p0: 30%, p1: 55%, a: 5%, 1-b: 90%, according to A'Hern exact single stage phase II design.

Conclusions. FOLFIRINOX may be considered a reasonable treatment option for LA-PDAC pts, in order to increase the chance to undergo radical surgery. These data support further randomized trials according to the available strategies in routine clinical practice (i.e. radiotherapy, RFTA, etc.) in this challenging disease setting.

Q5 TARGETING THE CANCER-STROMA INTERACTIONS: COULD KRAS MUTATION STATE HAVE A POTENTIAL CLINICAL APPLICATION IN PANCREATIC CANCER TREATMENT?

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Background. Pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal human cancers. A hallmark of PDAC is the presence of a complex desmoplastic response (DR) which supports tumor growth, promotes metastasis and is an established impediment to delivery of chemotherapy. This dense DR consists mainly of pancreatic stellate cells (PSCs) and fibroblasts that synthesize and secrete SPARC (secreted protein acidic and rich in cysteine), whose stromal expression has been associated with poor survival. A number of pathways including Sonic hedgehog, Notch, Wnt- β-catenin and TGF β signaling are involved in mediating cross-talk between the tumor and its associated stroma. The aim of our study is to investigate the relationship and the potential prognostic role of the biomarkers of these interactions in association of KRAS mutation status.

Material and methods. In 170 histological samples of pancreatic ductal adenocarcinoma were performed immunohistochemical evaluations of tumoral and stromal IL6 expression and molecular biology assessment of KRAS, SPARC expression, NOTCH1, SMAD4, Lgr5 and SHH.

Results. Preliminary analysis demonstrated that KRAS wild type (WT) (46%) patients showed higher expression of SMAD4 (66% vs 37%; p = 0.0003) and of NOTCH1 (p = 0.0147) compared to mutants (MT) (54%). In addition, our analysis showed a strict correlation between KRAS mutation and high levels of SHH (p = 0.0048) and Lgr5 (p = 0.0102). Furthermore a correlation between stromal IL-6 expression and high levels of SHH (p = 0.0039) and SPARC (p = 0.0043) was found. No correlation was found between tumoral IL-6 expression and others biomarkers.

Conclusions. Our data indicate that KRAS status can differentiate two prognostic categories of PDAC: one (KRAS MT) probably more aggressive and characterized by early metastasization, more intense inflammation associated to pronounced desmoplastic reaction (higher SPARC) due to two important pathways: SHH and Wnt- β-catenin; the other (KRAS WT) with a more favourable behavior, correlated with a local invasiveness, with lower inflammatory profile and lower desmoplasia regulated by NOTCH pathway. We can speculate that patients with an aggressive profile defined by KRAS mutation would be the best potential candidates for treatment with Hedgehog and Wnt inhibitors and nab-paclitaxel whilst KRAS WT patients would be evaluated for treatment with NOTCH inhibitors.

Q6 SECOND-LINE TREATMENT IN EXON 11 MUTATED GIST PATIENTS: IMATINIB DOSE ESCALATION OR SUNITINIB? RETROSPECTIVE ANALYSIS OF A MULTI-INSTITUTIONAL EXPERIENCE

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Background. We retrospectively analysed data from metastatic GIST patients harbouring an exon 11 KIT mutation who received a second-line treatment with sunitinib or dose escalated imatinib to compare the outcome.

Patients and methods. 75 exon 11 KIT mutated metastatic GIST patients treated in three Italian reference centres were included in the present analysis. After progression on imatinib 400 mg/die the patients received, on discretion of physician, a second-line treatment with either imatinib 800 mg/die or sunitinib (50 mg/die 4 weeks on/2 weeks off or 37.5 mg/day continuous daily dose). The type of exon 11 KIT mutation was recorded (deletion versus others).

Results. Among the patients included, 53/75 (70.7%) received a second-line treatment with imatinib while 22/75 (29.3%) received sunitinib. For 56 patients the exact mutation was available. Among them exon 11 KIT mutation was represented by a deletion in 24/56 cases (42.9%), by other gene aberrations in 32/56 (57.1%). Median follow-up was 58 months. The median time to progression (TTP) in the population receiving sunitinib as a second-line treatment was 10 months (95% CI 8.6-11.3) compared with 5 months (95% CI 4.4-6.5) in those who received imatinib 800 mg/ie (p = 0.02). Conversely, no significant difference was found in term of overall survival (OS) (58 versus 62 respectively, p = 0.6). Interestingly, sunitinib was found to be more effective in the subgroup of patients harbouring an exon 11 KIT deletion than in those characterised by a different KIT 11 mutation (p = 0.01) while no difference was found in patients treated with imatinib 800 mg/die (p = 0.86), even if this result is biased by the low number of patients included in this analysis.

Conclusions. In exon KIT 11 mutated GIST patients progressing on a first-line treatment with imatinib 400 mg/die, a second-line treatment with sunitinib is associated with an improvement in TTP. It might be a valuable option for those patients harbouring an exon 11 KIT deletion. No impact on survival was observed probably because of the influence of subsequent treatments received.

Q7 CLINICAL SIGNIFICANCE OF PREOPERATIVE SERUM VEGF-C LEVELS IN PATIENTS WITH RESECTABLE GASTRIC CANCER

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Background. Vascular endothelial growth factor C (VEGF-C), also known as vascular endothelial growth factor related protein (VRP) is a VEGF growth factor family member playing a key-role in lymphangiogenesis. It is overexpressed in 30-60% of gastric cancer patients (pts), showing a strong correlation with an advanced stage and a poor survival. Based on this background we

investigated the meaning of serum levels of VEGF-C in 161 gastric cancer pts suitable for surgery.

Methods. Preoperative VEGF-C serum levels were determined by enzyme-linked immunoadsorbent assay (ELISA) in 161 pts with gastric carcinoma and 51 healthy subjects (control group).

Results. Preoperative VEGF-C serum levels were significantly higher in gastric cancer pts (mean 295 pg/mL; range 55-865 pg/mL) if compared with the control group (mean 30 pg/mL; range 11.8-60.2 pg/mL; p <0.001). High VEGF-C serum levels correlated with nodal diffusion: in fact, node positive pts showed significantly higher levels (mean 339 pg/mL, 95% CI 307.4-370.6; p <0.001) when compared to node negative pts (mean 93 pg/mL, 95% CI 72- 114; p <0.001). Moreover, preoperative VEGF-C serum levels were significantly lower in pts who underwent curative surgery (248.7 pg/mL, range 54.9-865.2 pg/mL) compared with pts who underwent palliative surgery (mean 461.1 pg/mL, range 120.5-805.8; p <0.001).

Pearson correlation analysis demonstrated a significant negative correlation between preoperative VEGF-C serum levels and OS (Pearson correlation -0.281; Sig.(2 code) 0.001). Finally at multivariate analysis elevated serum VEGF-C levels were an independent prognostic factor in patients with gastric cancer.

Conclusions. Our data suggest that increased serum VEGF-C levels appear as poor prognostic factor correlating with a nodal involvement and a worse OS.

Q8 PROGNOSTIC RELEVANCE OF OBJECTIVE RESPONSE ACCORDING TO EASL AND MRECIST CRITERIA IN HCC PATIENTS TREATED WITH LOCO-REGIONAL THERAPIES: A LITERATURE BASED META-ANALYSIS

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Background. The European Association for the Study of the Liver (EASL) criteria and the modified Response Evaluation Criteria in Solid Tumors (mRECIST) are currently adopted in the evaluation of radiological response in patients affected by HCC. Available comparative data cannot discriminate which method best correlate with survival. Aim of this meta-analysis is to compare mRECIST and EASL criteria and evaluate their correlation with survival in HCC patients treated with loco-regional therapies.

Material and methods. A comprehensive research of the literature was performed in electronic databases PubMed, EMBASE, MEDLINE, COCHRANE LIBRARY, ASCO conferences and EASL conferences up to April 8, 2013. Key words were HCC, mRECIST, and EASL. Loco-regional procedures included transarterial embolization (TAE), transarterial chemoembolization (TACE) and cryoablation. Studies were eligible if patients undergoing loco-regional treatments were evaluated by both mRECIST and EASL criteria. Each identified trial was evaluated for eligibility and quality, and then the data were abstracted and analyzed (RevMan 5). Inter-method agreement between EASL and mRECIST was assessed using the kappa coefficient. Hazard ratio (HR) for overall survival was collected, considering responders (complete or partial response) versus non responders patients. To account for the heterogeneity of studies, a random-effects model was applied.

Results. Of 13 titles identified in the original search, 6 reports including 989 patients were considered eligible. Five studies were published as full-text articles, one as abstract meeting. All reports were conducted retrospectively. Proportion of responders according to mRECIST and EASL criteria was 70.7% and 71.4%, respectively. Kappa statistics (available in 5 studies) showed very high concordance (k value >0.8) between responses assessed by using EASL and mRECIST criteria. HR for overall survival (responders vs non responders) according to mRECIST and EASL was 0.36 (95% CI 0.24-0.55, p <0.00001) and 0.37 (95% CI 0.25-0.55, p <0.00001), respectively.

Conclusions. In this literature based meta-analysis, mRECIST and EASL criteria show very good concordance in HCC patients undergoing loco-regional treatment. Objective response according to both criteria confirms a strong prognostic value in terms of overall survival. This prognostic value appears to be very similar between the two criteria.

Q9 HER2 OVEREXPRESSION IN GASTRIC CANCER (GC): A RETROSPECTIVE ANALYSIS

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Background. HER2 overexpression in GC is reported in 20% of cases; it is considered a negative prognostic factor with a positive predictive value of response to trastuzumab. We reviewed our case records analyzing their clinical significance.

Methods. We retrospectively collected the data for patients (pts) with histologically confirmed GC and tumor specimens.

Results. From January 2011 to December 2012 we analyzed HER2 status in 76 pts (M/F 50/26, median age 64 years, ECOG performance status 0/1/2 = 59/12/5) with GC (adenocarcinoma, AC: 93.4%; G1/G2/G3 = 6.6%/22.4%/71%). In 36.8% of pts gastric body was the primary tumor site. 15.8% of pts had a IIIA-B stage at diagnosis, while 54.5% presented a metastatic disease. HER-2 overexpression was observed in 17.1% of patients. In HER2-positive group (N = 13, M/F = 10/3, median age 63 years), all the pts presented a gastric AC (75% intestinal and 25% diffuse Lauren's histotype; G1/G2/G3 = 15.4%/30.8%/53.8%) and 46.1% had a metastatic disease. T3-T4 tumors and N+ disease were observed in 46.1% respectively. The primary tumor site was: proximal 30.8%, middle 30.8%, distal 30.8%, gastro-esophageal junction, GEJ 7.6%). 46.1% of pts received an adjuvant chemotherapy (CT) with a median disease-free survival (mDFS) of 10 months (range 3-19) and 46.1% a first-line CT with a median progression-free survival (mPFS) of 5 months (range 3-7) and a median overall survival (mOS) of 9 months (range 3-23). In HER2-negative group, (N = 63, M/F = 40/23, median age 64 years), 92.1% of pts had a gastric AC (45.5% in-

testinal and 54.5% diffuse Lauren's histotype; G1/G2/G3 = 4.8%/20.6%/74.6%) and 55.5% a metastatic disease. T3-T4 tumors were assessed in 65.1% of pts and N+ disease in 61.9%. The primary tumor location was: proximal 31.8%, middle 38.1%, distal 23.8%, GEJ 6.3%. 41.3% of pts received an adjuvant CT with a mDFS of 14 months (range 2-29) and 57.1% a first-line CT with a mPFS of 5.5 months (range 2-30) and a mOS of 10 months (range 2-67). No statistically significant differences for mPFS (p = 0.08) and mOS (p = 0.06) were observed between HER2 positive and HER2 negative metastatic patients.

Conclusions. According to our results, HER2 overexpression doesn't seem a negative prognostic factor. In particular, it is not correlated with a worse histology and higher stage at diagnosis. Furthermore, no differences in terms of mPFS and mOS were observed between HER2 positive and HER2 negative metastatic patients.

Q10 CORRELATION BETWEEN VEGF AND VEGF-R POLYMORPHISMS, TOXICITY AND CLINICAL OUTCOME IN HCC PATIENTS RECEIVING SORAFENIB

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Background. The introduction of sorafenib for the treatment of advanced HCC radically changed patients clinical outcome. However, response to treatment as well as toxicity are still largely unpredictable in the single patient. We previously reported that VEGF and VEGFR polymorphisms may have a predictive and prognostic role in this setting, but little is known about the possible correlation with toxicity. The aim of our study was to evaluate whether VEGF and VEGFR genotyping was able to correlate with toxicity in HCC patients receiving sorafenib.

Material and methods. Seventy-three histological samples of HCC patients receiving sorafenib were tested for VEGF-A, VEGF-C and VEGFR-1,2,3 single nucleotide polymorphisms (SNPs). Patients time to progression (TTP), overall survival (OS) and toxicities were analysed.

Results. VEGF-A rs833061 T>C, rs699947 C>A and rs2010963 C>G polymorphisms were significantly associated with any grade global (respectively: p = 0.031; p = 0.018; p = 0.003) and cutaneous toxicities (respectively: p = 0.043; p = 0.019; p = 0.025). Furthermore patients with any grade global and cutaneous toxicities showed a better progression-free survival and overall survival (global toxicity PFS 7.0 vs 5.0 months, p = 0.016; OS 26.8 vs 13.0 months, p = 0.023) (cutaneous toxicity PFS 7.6 vs 5.1 months, p = 0.033; OS 22.7 vs 13.3 months, p = 0.014).

Conclusions. In our analysis patients with polymorphism T at rs833061, C at rs699947 and C at rs2010963 showed a higher rate of toxicities and, accordingly to our previous report, this correlates with a better PFS and OS. Analysis of VEGF and its receptor genes polymorphisms represents a clinical tool to identify patients with favourable response to sorafenib presumably related to a more efficient control of tumour growth. The occurrence of toxicity could be an interesting clinical surrogate during sorafenib treatment and may help clinicians in a more cautious and aware management of HCC patients.

Q11 EFFECT OF ENZASTAURIN, A PKCa/ß AND GSK3ß INHIBITOR, IN HUMAN HEPATOCELLULAR CARCINOMA CELLS

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Background. Enzastaurin is a dual inhibitor of PKCα/β and GSK3β. Although several preclinical data showed a significant role of the GSKβ/β-tubulin in the regulation of growth/survival of hepatocellular carcinoma (HCC) cells, no studies are currently available regarding the use of enzastaurin in this human neoplasm. For such reasons, we investigated the effect of enzastaurin, alone and in combination with sorafenib, a targeted agent routinely used for the treatment of patients with HCC, on human HCC cell lines, both *in vitro* and *in vivo*.

Materials and methods. We first tested the sensitivity of different human HCC cell lines, including SKHEP, PLC/PRF, HEP3B and HEPG2 cells, to enzastaurin, sorafenib or their combination, both *in vitro*, through MTT assays, and *in vivo*, using nude mice orthotopically xenografted with HEPG2 cells. We then analyzed, through western blotting analysis, the expression of VEGFR1, VEGFR2, pMet, pPKCα/β, pGSK3β, pMAPK, pAKT and pp70S6K after treatment with sorafenib, enzastaurin or the combination. We also investigated invasion and migration perturbation induced by the treatment with sorafenib, enzastaurin or the combination, by using wound healing, Boyden chambers and fibroblast assays.

Results. We found that all the used cell lines were sensitive to enzastaurin (with IC_{50} of 1 μM for HEP3B and HEPG2, and 2.5 μM for SKHEP and PLC/PRF). The combination of sorafenib and enzastaurin synergistically inhibited growth and migration of all cancer cell lines analyzed, both *in vitro* and *in vivo*. In addition, enzastaurin treatment, alone and in combination with sorafenib, was able to strongly reduce activation of GSK3β, Akt, p70S6K and MAPK, while no change in the total amount of VEGFR1 and VEGFR2 was observed.

Conclusions. Our data suggest that enzastaurin, alone and in combination with sorafenib, could be clinically investigated as an effective therapeutic option for patients with HCC.

Q12 ROLE OF POLYMORPHISMS OF PRO-ANGIOGENIC FACTORS AND OUTCOME OF FIRST-LINE CHEMOTHERAPY IN METASTATIC GASTRIC CANCER PATIENTS

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Background. Platinum chemotherapy doublets are standard first-line therapeutic options for metastatic gastric cancer patients. Preclinical and clinical data suggest a potential interaction between VEGF-A and response to platinum compounds. We conducted an analysis on metastatic gastric cancer patients treated with standard chemotherapy doublets and assessed if outcome could be linked to various polymorphisms of genes implied to have a role in VEGF pathway.

Patients and methods. We conducted a retrospective analysis on metastatic gastric cancer patients treated in the 2007-2012 period with chemotherapy doublets (either 5FU/capecitabine + oxaliplatin/cisplatin) in first-line setting. We assessed the relationship between different polymorphisms of VEGF-A, VEGF-C, FLT1, KDR, FLT4 and overall survival, progression-free survival and response rate. Stratification criteria were sex, age, performance status, metastatic sites, chemotherapy backbone, prior gastrectomy, second-line treatment received if any. Survival analysis was conducted by Kaplan-Meier method whereas differences in response rates were evaluated by Chi-square test.

Results. Ninety-four patients were eligible for analysis. Thirty-six (38%) partial responses, 29 (31%) stable disease and 29 (31%) progressions were seen. Median overall survival was 9.1 months and median progression-free survival was 5.9 months. A significant impact in terms of different progression-free survival was seen for 72 (76%) patients harbouring VEGF-A rs25648 CC genotype vs 22 (24%) TT or C/T genotype patients: respectively 6.8 months vs 4.0 months (HR 0.30, 95% CI 0.03-0.44, p <0.0001). The same association was found for overall survival (9.4 vs 5.9 months, HR 0.43, 95% CI 0.12-0.78, p <0.0003) and for response rate (44% vs 18%, p = 0.04).

Conclusions. Our analysis seems to suggest that VEGF-A rs25648 could have a potential role as indicator of worse prognosis in particular for metastatic gastric cancer patients treated in first-line with chemotherapy doublet containing platinum compounds and oral/ev fluoropyrimidines. It is thus suggested that different chemotherapy options (for example use of taxanes or irinotecan) should be tested in this group of patients to identify drugs that may have a better profile of activity.

Q13 EFFICACY AND SAFETY OF DOSE-DENSE MODIFIED TCF REGIMEN (TCF-DD) IN METASTATIC OR LOCALLY ADVANCED GASTROESOPHAGEAL CANCER (GEC): UPDATE ON A LARGE COHORT OF PATIENTS

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Background. TCF is a standard first-line option for GEC. The Norton-Simon hypothesis suggests that chemotherapy efficacy can be enhanced by decreasing intervals between cycles. We previously reported on the high activity of TCF-dd in GEC (Tomasello, 2010). The aim of this study is to investigate the efficacy and safety of this intensified dose-dense regimen in a single-center large cohort of patients (pts).

Methods. 150 pts with measurable or evaluable GEC, PS 0-2, with adequate organ function, treated in our center from 2004 to 2012 received TCF-dd: docetaxel (60-85 mg/m^2 d 1), cisplatin (50-75 mg/m^2 d 1), l-folinic acid (100 mg/m^2 d 1-2), 5-FU (400 mg/m^2 bolus d 1-2, and 600 mg/m^2 as a 22 h continuous infusion d 1-2), plus pegfilgrastim 6 mg d 3, every 14 days. Patients aged ≥65 years received the same schedule with a dose reduction by 30%. Analysis was based on the intention to treat population.

Results. At a median follow-up of 44 months, 128 pts were evaluable for response, all for survival. Median age 65 (range 31-81), M:F 112:38. Seventeen pts (11%) with locally advanced inoperable GEC, 133 pts (89%) with metastatic GEC. Metastatic sites: liver 40%, peritoneum 31%, bone 14%, lung 12%. A median of 4 cycles (range 1-7) per patient was administered. 33% required a dose reduction. 33% were treated without any delay. 10 CR, 74 PR, 24 SD and 20 PD were observed, for an ORR of 66% (95% CI 57-74). Median OS was 13 months (95% CI 9.7-14.2). Most frequent grade 3/4 toxicities: neutropenia (34%), asthenia (28%), thrombocytopenia (17%), hypokalemia (16%), diarrhea (11%), febrile neutropenia (10%), anemia (9%), and stomatitis (4%). Eleven pts (7%) (7 metastatic, 4 locally advanced) became operable after TCF-dd and underwent surgery. We identified 12 metastatic pts (8%) with overall survival >3 years and 7 (5%) still maintaining a long lasting CR at the time of the current analysis.

Conclusions. TCF-dd in GEC is very active and may be an option for conversion therapy. Toxicity can be relevant and requires a careful monitoring.

Q14 COX-2, STROMAL AND TUMORAL IL-6 EXPRESSION AND UPREGULATION OF VEGF AND PDGFR IN PANCREATIC CANCER PATIENTS

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Background. Inflammatory mediators have been indicated to be involved in pancreatic cancer (PC) progression and in stroma-tumour interactions. IL-6 has been reported to be overexpressed in PC patients (pts) and high serum levels of IL-6 have been associated with a worse outcome in these patients. In this analysis we assessed the relationship between stromal and tumoral IL-6 and COX-2 expression and expression of VEGFA, PDGFR-beta and SPARC in PC.

Patients and methods. Stromal and tumoral IL-6 expression and COX-2 expression was assessed by immuhistochemistry (IHC) on resected PC samples. Gene expression tests were performed to evaluate the expression of VEGFA, PDGFR-beta and SPARC.

Results. A total of 120 resected PC pts were included in our analysis. Stromal and tumoral IL-6 was found to be overexpressed, in association with COX-2, at IHC in 62 pts (51.7%). A significant correlation between inflammatory mediators (IL-6 and COX-2) and VEGFA expression was showed (p = 0.0066) and a similar correlation was found with PDGFR-beta (p = 0.002) while no significant correlation was demonstrated between IL-6 and COX-2 and SPARC expression.

Conclusions. Our study confirms the preclinical findings

showing that IL-6 and COX-2 may upregulate VEGF and PDGFR expression in PC. Induction of VEGF and PDGFR seems to be a way by which inflammation promotes tumour progression in PC patients. Treatment strategies directed against VEGF and PDGFR may be useful in a subset of PC patients and deserve further evaluation.

Q15 PROGNOSTIC MODEL FOR PATIENTS WITH ADVANCED BILIARY TRACT CANCER (ABTC) RECEIVING SECOND-LINE CHEMOTHERAPY (CT)

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Background. Prognosis of patients with aBTC remains poor and the role of second-line CT has not been definitively established. We aimed to devise a prognostic model by assessing several baseline factors predicting overall survival (OS) of aBTC patients undergoing second-line CT.

Patients and methods. Consecutive aBTC patients treated with second-line CT at 9 Italian Institutions between 2004 and 2013 were identified. Clinical, laboratory and pathological data were collected and their association with OS was investigated by log-rank test: to account for multiple testing, a two-sided p value of <0.005 was considered significant at univariate analysis. Multivariate analysis was then carried out using stepwise Cox proportional hazards regression modeling, stratifying for second-line CT regimens received and setting statistical significance at p <0.05.

Results. 300 patients were identified. Baseline characteristics were the following: male/female, 45%/55%; median age, 64 years (range 28-85); ECOG performance status (PS) 0/1/2, 58%/32%/10%; disease site, intrahepatic 52%/extrahepatic 21%/gallbladder 18%/ampullary 9%; sites of metastases 1/>1, 41%/59%; previous surgery on primary tumour, 56%; previous adjuvant CT, 20%; first-line gemcitabine plus platinum derivative, 64%; second-line monotherapy/combination, 37%/63%. At multivariate level, favourable prognostic factors were previous surgery on primary tumour [p = 0.0270; hazard ratio (HR) 0.609; 95% CI 0.392-0.945], median progression-free survival after first-line CT >6 months (p = 0.0267; HR 0.633; 95% CI 0.422-0.949), CA19.9 <152 U/mL (p = 0.013; HR 0.574; 95% CI 0.370-0.891), and an ECOG PS of 0 (p <0.001; HR 0.348; 95% CI 0.215-0.562). Of 249 patients with complete data for these four variables, 98 patients were categorized as good-risk group (0 to 1 factors), 73 patients as intermediate-risk group (2 factors), and 78 patients as poor-risk group (3 to 4 factors). Median OS for good, intermediate, and poor-risk groups were 13.1 months, 6.6 months, and 3.7 months, respectively (p <0.001).

Conclusions. Prognosis of patients with aBTC undergoing second-line CT widely varies according to several, easily available clinical and laboratory factors. This simple model allows individual patient risk stratification and thus may help in treatment decision and trial design after the failure of first-line CT.

Q16 CHARACTERIZATION OF PANCREATIC DUCTAL ADENOCARCINOMA PATIENTS USING WHOLE-TRANSCRIPTOME SEQUENCING

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Pancreatic cancer (PDAC) is the most lethal malignancy and new treatments are needed. Our challenge is to implement a whole transcriptome massively parallel sequencing (RNASeq) study to better understand the PDAC biology. We collected 17 PDAC samples by ultrasound-guided biopsy or by surgical specimen for DNA and RNA extraction. Fourteen samples were analyzed by high resolution copy number analysis (CNA) on Affymetrix SNP array 6.0 and analyzed with segmentation algorithm against a reference of 270 Ceu HapMap individuals (Partek Genomic Suite). All the samples were analyzed by RNASeq, performed at 75x2 bp on a HiScanSQ Illumina platform. Single nucleotide variants (SNVs) were detected with SNVMix2 and filtered on dbSNP, 1000genomes, Cosmic. Non-synonymous SNVs were analyzed with SNPs&GO and PROVEAN. The relative presence of tumor cells in the sample was evaluated based on the presence of KRAS mutation. Nine patients out of 14 showed both macroscopic and cryptic cytogenetic alterations with a mean of 10 CNA/patient. Gains were observed in 18q11.2 involving GATA6 (3/14) and 19q13 targeting AKT2 (3/14) while hotspot deletions were found on 18q21 (7/14), 17p13 (6/14), 9p21.3 (6/14), 15q (5/14) and 1q35 (4/14). RNAseq results in a mean of 145 (range 61-240) non-synonymous SNVs. We highlighted the major oncogenic hits of PDAC, confirming KRAS mutations and CDKN2A (mutated in 3 cases and deleted in 5 cases, in hetero- or homozygosity), SMAD4 (altered by point mutations or gene deletion in 5/17), and TP53 (lost in 6/14 and mutated in 5/17). Furthermore ten patients carried multiple rearrangements leading to new genes fusions, although no recurrent translocations were found. Most rearrangements were inter-chromosomal (66%) and did not change the reading-frame (51%). Genes involved in the rearrangements belong to specific pathways, as DNA damage, cell migration, TGFbeta signaling, apoptosis and cell proliferation. In particular the majority of translocations affected chromosomes 17 and 18, that carry other recurrent genetic hits in PDAC as those involving TP53 and SMAD4. PDAC carries defects in the driver genes, KRAS, CDKN2A, p53 and SMAD4 belong to the classical pathways involved in the PDAC development. However not all tumors show alterations of these signaling, and key mutations appeared to differ from one cancer to another. PDAC still represents a challenge and innovative approaches are needed to eradicate the disease.

Q17 PHASE II STUDY OF NEOADJUVANT CHEMOTHERAPY WITH FOLFOXIRI IN BORDERLINE RESECTABLE PANCREATIC CANCER

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Background. The combination of 5-fluorouracil/folinic acid, oxaliplatin and irinotecan (FOLFIRINOX) has shown higher activity and efficacy than gemcitabine in metastatic pancreatic cancer (PC). Considering its activity, the regimen could be of interest also for inoperable locally advanced disease. Our group has developed a similar schedule with the combination of the same drugs named FOLFOXIRI containing no bolus 5-fluorouracil and a slight lower dose of irinotecan with good activity in colorectal cancer. Therefore, we have decided to perform a phase II trial to prospectively evaluate the activity of FOLFOXIRI in borderline resectable (BR) PC.

Patients and methods. The study enrolled patients with diagnosis of PC, stage III BR disease (according to AHPBA/SSO/SSAT Consensus Conference), cM0, ECOG performance status (PS) 0 or 1, age 18-75. The primary endpoint of the study was the percent of radical surgical resection after chemotherapy; the trial was designed with a p0 = 30% and a p1 = 50%. Patients have been treated with FOLFOXIRI: oxaliplatin 85 mg/m^2, irinotecan 150-165 mg/m^2 and folinic acid 200 mg/m^2 on day 1, plus infusional 5-fluorouracil 2800-3200 mg/m^2 administered in 48 hours on days 1 to 3, every 14 days.

Results. Thirty-two patients have been enrolled; M/F = 12/20; PS 0/1 = 16/16. Median age was 60 years (range 44-75). A total of 233 cycles of FOLFOXIRI have been administered; median number of cycles was 7 (range 2-14). Grade 3-4 toxicities was experienced by 20 patients requiring dose reduction in 12 patients, delays of chemotherapy in 16 patients and use of G-CSF in 7 cases. Twelve partial responses (38%) and 18 stable diseases (56%) have been observed; 2 patients had progressive disease (6%). After chemotherapy 23 patients received a local treatment: 17 (53%) radical surgical resection and 6 concomitant chemo-radiotherapy. In 4 cases occult metastases have been found at explorative laparotomy. In 1 case surgery is planned while 4 patients progressed during chemotherapy or during the planning of radiotherapy. Median progression-free survival is 14.0 months for all patients and 17.8 months for the resected ones; median overall survival is 24.2 months with a two-year survival rate of 54%.

Conclusions. Treatment with FOLFOXIRI resulted active in BR PC and may allow to obtain a downstaging of disease leading to achieve a curative surgical resection in some patients. Longer follow-up is needed to better evaluate long-term outcome of this strategy.

Q18 FEASIBILITY STUDY OF PREOPERATIVE OR PERIOPERATIVE CHEMOTHERAPY WITH DOCETAXEL, OXALIPLATIN, CAPECITABINE (DOC) IN LOCALLY ADVANCED RESECTABLE GASTRIC CANCER PATIENTS

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Background. Two randomized trials on perioperative chemotherapy, one conducted in the UK and the other in France, showed an absolute improvement in survival of about 13%. In actual fact, only the preoperative part of the therapeutic program was completed, while in the postoperative part, only about 50% of the patients completed the program. Therefore, there is a strong suspicion that the preoperative part was responsible for the positive results. The first objective of the study was to assess the feasibility of preoperative or perioperative chemotherapy with docetaxel (D) 35 mg/m^2 day 1 and 8, oxaliplatin (O) 80 mg/m^2 day 1 and capecitabine (C) 750 mg/m^2 x 2 daily for 2 weeks every 3 weeks in locally advanced resectable gastric cancer patients.

Methods. Randomized phase II study on behalf of GIRCG (Gruppo Italiano Ricerca Cancro Gastrico). After hystologically confirmed diagnosis of gastric cancer, the staging system considered CT/PET, chest and abdominal CT scan, laparoscopy with peritoneal cytology. Arm A: 2 cycles of DOC, restaging, 2 cycles of DOC, restaging and then surgery. Arm B: 2 cycles of DOC, restaging, surgery and then 2 cycles of DOC.

Results. Between September 2010 and December 2012, 25 patients started the treatment. Actually only 16 patients completed the trial and are evaluable: 9 patients in arm A and 7 in arm B. Seven patients in arm A and 3 in arm B completed the treatment. There were 4 serious adverse events (SAE), these patients discontinued the chemotherapy due to asthenia G2 (SAE), allergic reaction to docetaxel (SAE) in arm A; diarrhea G4 (SAE), dehiscence of the duodenal stump (SAE) in arm B. Globally, the number of completed cycles was 34 (94%) and 21 (75%) in arm A and B respectively. All 16 patients were radically resected and only one patient progressed on peritoneum during the treatment. Every SAE is solved.

Conclusions. Chemotherapy seems manageable, even if it takes a lot of care and multidisciplinary collaboration.

Q19 FEASIBILITY OF THE FOLFIRINOX REGIMEN FOR PANCREATIC CANCER (PC): THE MILAN NATIONAL CANCER INSTITUTE EXPERIENCE

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Background. FOLFIRINOX resulted in significant survival benefit compared with gemcitabine in patients with metastatic

PC (MPC) (Conroy et al., N Engl J Med, 364: 1817, 2011). However, FOLFIRINOX should be used with caution owing to its increased toxicity. To assess the clinical feasibility of the regimen, we reviewed our experience with FOLFIRINOX.

Methods. All patients who received FOLFIRINOX at Milan Cancer Institute were included in this retrospective series. The doses were identical to the Conroy's trial; dose attenuations were at the discretion of the treating oncologist. Patients were treated until progression, unacceptable toxicity, or surgical resection. Primary endpoint was tolerability (CTCAE criteria, v. 4.03). Secondary endpoint was tumor response.

Results. Between 9/2011 and 04/2013, 25 patients with unresectable locally advanced PC (LAPC; N = 12) or MPC (N = 13) were treated. The median age was 57 years (range 40-70), 17 were male, and all had ECOG PS of 0 or 1. All but three patient were chemo-naïve; 12 (48%) patients had primary tumor in the pancreatic head and 6 of them required the implantation of biliary stent. The median number of cycles per patient was 4 (range 1-10). The majority of patients (68%) received full doses of all drugs with cycle 1 whereas 8 patients received dose attenuation of FOLFIRINOX in cycle 1 to assess tolerability. Twelve (48%) patients had a dose reduction due to toxic effects. Dose reductions occurred in 57 of the 106 cycles administered: irinotecan 55 cycles, oxaliplatin 25 cycles, bolus fluorouracil 18 cycles, infusional fluorouracil 21 cycles. Bolus fluorouracil was omitted in 33 cycles. Ten patients received prophylactic pegfilgrastim after cycle 1. Grade 3/4 chemotherapy-related toxicities were neutropenia (40%), febrile neutropenia (4%), fatigue (8%), diarrhea (4%), and infection (12%). Only one patient discontinued treatment due to severe toxicity occurring in cycle 1. Four patients are still on treatment before response assessment (4 cycles). Among 21 evaluable patients, 5 (20%) achieved PR. Stabilization occurred in 8 (32%) patients. Four patients with LAPC underwent resection.

Conclusions. In our experience, FOLFIRINOX is a feasible option with manageable toxicities in fit patients treated in a good supportive-care environment. The regimen or its dose-attenuated modification should be not only prospectively evaluated in the neoadjuvant setting but also explored as a backbone for innovative combination regimens.

Q20 IS THERE A CENTRAL NERVOUS SYSTEM RECURRENCE SUSCEPTIBILITY IN PATIENTS WITH HER-2 POSITIVE GASTRIC CANCER?

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Background. Brain metastasis from cancers of the gastrointestinal tract is uncommon; brain metastasis from gastric cancer is rare and its incidence is low. The purpose of this study was to review our experience with gastric cancer metastatic to the brain and to assess whether patients with brain metastases are also HER2 positive.

Patients and methods. Between 2007 and 2011, a total of 3847 patients were seen for first time evaluation of malignant tumour at Ospedale Guglielmo da Saliceto, Piacenza. Of these patients, 200 (5.2%) had a diagnosis of gastric cancer; however, only 6 of these patients were found to have brain metastasis on imaging studies. We performed a retrospective review of these 6 patients to evaluate whether patients with brain metastases are also HER2 positive.

Results. Patients were considered to have HER-2 positive disease if the primary or metastatic lesion had strong overexpression (3+) on IHC or had gene amplification (ratio of HER-2 to chromosome17 copy number >2) by fluorescence in situ hybridization (FISH). Patients were considered to have HER-2 negative disease if they had either negative expression by IHC (0 or 1 and plus) or did not have gene amplification by FISH. Five out of six patients with gastric cancer metastatic to the brain had HER-2 positive disease. These patients tended also to have a higher initial disease stage and a more aggressive phenotype.

Conclusions. Despite the small number of patients known and retrospective data, our results suggest that there is a CNS recurrence susceptibility in patients with HER-2 positive gastric cancer. We are now evaluating prospectively all our patients with gastric cancer to confirm these preliminary data.

Q21 A SINGLE CENTER EXPERIENCE WITH WEEKLY NAB-PACLITAXEL AND GEMCITABINE IN METASTATIC PANCREATIC CANCER (MPC)

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Background. MPC is a deadly disease with a very poor prognosis. A new option of treatment is offered by nab-paclitaxel plus gemcitabine (J Clin Oncol, 30: 34; abstr LBA148, 2012). The MPACT study showed an overall survival (OS), a progression-free survival (PFS) and a response rate (RR) advantage of this new combination regimen over standard gemcitabine alone.

Material and methods. We performed a retrospective data collection of MPC patients (pts) treated at our Oncology Department with nab-paclitaxel plus gemcitabine.

Results. From September 2011 to May 2013, we identified 19 evaluable MPC pts treated with nab-paclitaxel 125 mg/m^2 plus gemcitabine 1000 mg/m^2 on day 1, 8 and 15 every 28 days, for at least 1 cycle. Median age was 61 years (range 37-71), male/female ratio was 74%/26% and median PS (ECOG) was 1 (range 0-2). Six pts had 3 or more metastatic sites, 11 had liver metastasis, 7 lung metastasis and 6 peritoneal metastasis. 79% of pts were heavily pretreated with gemcitabine (5 pts), gemox (9 pts) and folfirinox (4 pts); nab-paclitaxel plus gemcitabine was administered as first-line treatment in 4 (21%) pts, however all of them were pretreated with gemcitabine or gemox in a neoadjuvant/adjuvant setting. The median number of administered cycles for each patient was 4+ (range 1-10). Four (31%) pts had a progressive disease (PD), 6 (46%) pts had a partial response (PR) and 3 (23%) pts had a stable disease (SD) for a DCR of 69%; 8 pts (5 PR and 3 SD) had a biochemical response with a ≥50% decrease in CA19.9 levels. Six pts have not yet been assessed for response. Notably, 2 out of 4 pts refractory to folfirinox achieved a PR. In our series, the median PFS was 5.3+ months, while the median OS was 4.4+ months. Up to May 2013, 12 pts are alive, and 11 of them are still on treatment. Most common grade ≥3 adverse events were thrombocytopenia (3 pts) and neutropenia (1 patient). No grade 3 or 4 neuropathy was observed whereas grade 2 neuropathy was experienced by 3 patients.

Conclusions. Our single center experience with nab-paclitaxel plus gemcitabine combination seems to confirm both the efficacy and the good tolerability profile of this regimen even in pretreated MPC patients.

Q22 EC-GEMCAP REGIMEN TO PATIENTS WITH ADVANCED PANCREATIC ADENOCARCINOMA FAILING FIRST-LINE FOLFIRINOX

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Background. FOLFIRINOX is considered the most active first-line regimen in advanced pancreatic cancer patients (pts) with good performance status (PS). No data are available regarding second-line treatment. Aim of the study was to evaluate the activity and the tolerability of the combined systemic and intra-arterial EC-GEMCAP regimen as second-line approach after FOLFIRINOX.

Patients and methods. Patients with locally advanced or metastatic pancreatic adenocarcinoma who progressed after first-line chemotherapy (CT) with FOLFIRINOX regimen and who had measurable disease conform with RECIST criteria were eligible for this study. The combined systemic and loco-regional EC-GEMCAP regimen consisted on epirubicin 35 mg/m^2 and cisplatin 42 mg/m^2 given through celiac axis by bolus infusion on day 1, gemcitabine 1000 mg/m^2 by 30 minutes systemic infusion on day 2, capecitabine 650 mg/m^2 twice a day orally, from day 2 to day 15. Cycles were repeated every 28 days. The primary endpoint was survival.

Results. From September 2011 to March 2013, 23 pts entered the study. There were 13 males and 10 females; median age was 56 years (range 44-71). ECOG PS was 0 in 11 pts, 1 in 6 and 2 in 6. Median time to progression to first-line CT was 6.3 months. Eight pts had locally advanced pancreatic cancer and 15 pts had metastatic disease. Grade III and IV neutropenia were observed in 26% and 17%, respectively; 17% experienced a grade III and 8% a grade IV thrombocytopenia. Among the 19 evaluable pts, we observed 1 partial response (5%) and 8 stable diseases (42%), for a disease control rate of 9/19 (47%). Median overall survival of the entire series, from the diagnosis and from the start of EC-GEMCAP treatment, was 16.8 and 5.2 months, respectively. The 15 pts with metastatic disease had an overall survival of 13.5 months, while the overall survival of the 8 pts with locally advanced disease was 24.2 months.

Conclusions. The combination of four new drugs both intra-arterially and systemically EC-GEMCAP is well tolerated and active after failure of FOLFIRINOX in pts with locally advanced or metastatic pancreatic cancer.

Q23 POSTOPERATIVE CHEMORADIATION FOR R1 RESECTED GASTRIC CANCER: A RETROSPECTIVE MONO-INSTITUTIONAL STUDY

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Background. Improved disease-free and overall survival (DFS, OS) were seen in curatively resected patients with gastric and gastroesophageal adenocarcinoma treated with the Intergroup 0116 protocol of postoperative adjuvant chemoradiotherapy compared to surgery alone. However, there are very limited data about the efficacy of this approach in patients with microscopic positive margins (R1 resection). To evaluate the efficacy of a combined chemoradiation regimen in this setting, we reviewed our case records from 43 consecutive patients with R1 resection treated between May 2008 and July 2012.

Methods. Forty-three patients with histologically confirmed gastric adenocarcinoma received combined adjuvant chemotherapy with FOLFOX-4 for 8 cycles and concomitant radiotherapy (45 Gy in 25 daily fractions over 5 weeks). Radiotherapy was begun after 2 cycles of FOLFOX-4, (reduced by 20% during the period of concomitant radiotherapy). Patients were required to have an ECOG PS ≤2 and an adequate organ and bone marrow function. Patients were followed at 3-month intervals for 2 years, at 6-month intervals for the next 3 years and yearly thereafter.

Results. The median age was 62 years (range 22-74) and the majority of patients (76.7%) were males. Tumor location was equally distributed in the stomach. Most of the patients had locally advanced disease: 93% had T3-4 tumors and 74.4% had lymph node involvement. There was no treatment related death. Gastrointestinal grade 3 toxicity was observed in 11.6% of patients, while haematologic grade 3 and 4 toxicity was observed in 9.3%. Experienced toxicities led to chemotherapy dose reductions in 9 patients and dose delay in 11 patients; 7 patients had a delay in radiotherapy. With a median follow-up of 36 months (range 2-49) for the 43 R1 patients, 74.4% died of gastric cancer, 11.6% are alive with no evidence of recurrence and 13.9% are alive with disease. 66.6% of the relapses in this group occurred at distant sites and 33.3% were locoregional The estimated 3-year OS was 19%. The median DFS was 14.5 months and the median OS was 16 months.

Conclusions. These results seem to imply at least some benefit for the postoperative treatment, as nearly 19% of the R1 patients in our study remained free of recurrence at 3 years from surgery. In the absence of phase III data and consequently lack of clear guidelines in this setting, our results support the common practice of adding postoperative chemoradiation after R1 gastrectomy.

Q24 A PHASE II TRIAL OF FOLFOX AND RADIATION THERAPY AS PREOPERATIVE TREATMENT IN LOCALLY ADVANCED ESOPHAGEAL CANCER: PRELIMINARY RESULTS

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Background. Preoperative chemo-radiotherapy followed by surgery (trimodality treatment) represents the recommended strategy for the management of locally advanced esophageal carcinoma (LAEC).

Methods. We report our experience in 32 patients with LAEC treated with neoadjuvant chemotherapy with FOLFOX-4 and concurrent radiotherapy for a total dose of 50.4 Gy followed by surgery.

Results. From January 2011 to April 2013 we treated 32 patients (M/F: 26/6, ECOG performance status 0/1: 25/7) with histological diagnosis of LAEC, with neoadjuvant FOLFOX-4 in association to radiation therapy (50.4 Gy in daily fractions of 1.8 Gy, five days per week). Median age was 57.8 years (range 39-72). 50% of the patients had an adenocarcinoma and 50% a squamous-cell carcinoma. After a mean number of 4.4 cycles administered, all the patients underwent a total esofagectomy. Eighteen patients (56.2%) received a R0 resection; a complete tumor regression (TRG1, according to Mandard criteria) was observed in 9 patients, while the remaining 9 patients obtained a partial tumor regression (TRG2, TRG3, TRG4). Six patients progressed at the end of therapy and 6 are at present in treatment. No surgery-related death was observed. The median follow-up for the entire group was 10.5 months (range 2-34). Of 32 patients analyzed, 19 are actually alive. The 3-year median overall survival was 31.6%.

Conclusions. Our preliminary results confirm that FOLFOX-4 and concurrent radiotherapy (50.4 Gy) as neoadjuvant treatment represents a valid option for patients with LAEC and PS 0-1 increasing the complete resection and survival rates.

Q25 A MULTICENTER SURVEY ON SECOND-LINE CHEMOTHERAPY FOR ADVANCED BILIARY TRACT CANCER

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Background. There is no established standard chemotherapy for second-line treatment in patients with advanced biliary tract cancer (BTC). However, many patients remain in good clinical conditions and maintain a normal liver function after progression to first-line chemotherapy and therefore are suitable for second-line chemotherapy.

Material and methods. We retrospectively reviewed data of consecutive patients who received second-line chemotherapy for BTC at 9 Italian institutions from 2004. We report data on characteristics of patients and on the outcome of second-line treatment.

Results. A total of 300 evaluable patients were identified. Patients characteristics are reported in Table 1.

Q25 - Table 1

	N	%
Total number of patients	300	100
Sex		
Male	164	55
Female	136	45
Median age (range)	64 years (28-85)	
ECOG PS		
0	175	58
1	96	32
2	29	10
Site of primary tumor		
Intrahepatic	157	52
Extrahepatic	64	21
Gallbladder	53	18
Ampullary	26	9
Median number of metastatic sites (range)	2 (1-5)	
Previous surgery on primary tumor	167	56
Platinum-gemcitabine combination in first-line	192	64
Partial response in first-line	57	19
Median progression-free survival in first-line	6 months	-
Second-line chemotherapy		
Platinum-based	96	32
Fluoropyrimidines	74	25
Gemcitabine	22	7
Fluoropyrimidines plus gemcitabine	44	15
Taxanes-containing regimens	11	4
Irinotecan-containing regimens	22	7
Other regimens	31	10

With second-line treatment, 12 partial responses (5%) and 88 stable diseases (31%) have been observed with a disease control rate of 34%; 7 patients have not been evaluable for response. Median progression-free survival (PFS) was 3.2 months (95% CI 2.92-3.48) and median overall survival from the beginning of second-line was 7.2 months (95% CI 6.04-8.36). At multivariate analysis, the following parameters resulted associated with longer second-line PFS: CA19.9 lower than median ($p = 0.028$); normal white blood cells count ($p = 0.029$), ECOG PS 0 ($p = 0.030$), first-line PFS longer than 6 months ($p = 0.04$). The use of combination regimen vs monotherapy in second-line seemed associated with slightly higher disease control rate (39% vs 26%, $p = 0.03$) and longer PFS (3.4 vs 3.0 months, $p = 0.002$).

Conclusions. Second-line chemotherapy could be active for a group of patients with advanced BTC progressed to first-line chemotherapy. However, considering the moderate benefit of treatment, the analysis of prognostic and predictive factors is needed and prospective randomized trials are necessary.

Q26 IMPACT OF PRIOR CHEMOTHERAPY (CT) AND SOMATOSTATIN ANALOGUES (SSAS) ON CLINICAL OUTCOME IN WELL DIFFERENTIATED PANCREATIC NEUROENDOCRINE TUMORS (PWDNETS) BEFORE TREATMENT WITH EVEROLIMUS (EV)

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Background. Everolimus (EV) has been investigated in advanced pWDNETs patients (pts) within a large phase III trial (RADIANT-3), showing a significant improvement of progression-free survival (PFS) of 6.4 months compared with placebo. This effect was long lasting (35% stable at 18 months) but tumor

remissions were rare (5%). The most frequent adverse events included stomatitis (64%), rash (49%), diarrhea (34%), fatigue (31%), infections (23%) and pulmonary infiltrates (17%). Based on such results, EV was approved for the treatment of advanced pWDNETs by both FDA and EMA. The ESMO Clinical Practice Guidelines 2012, for diagnosis, treatment and follow-up, recommended the use of EV in advanced pWDNETs G1/G2 patients. Aim of this study was to evaluate the disease control rate (DCR) at first radiologic assessment (12 weeks) defined as the proportion of the best radiological response achieved in pts with complete response (CR), partial response (PR) or stable disease (SD), as a measure of antitumor effect of EV on either pWDNETs naïve pts or pts progressing after CT and/or SSAs.

Patients and methods. We retrospectively analyzed 32 pWDNETs pts treated with EV, between 2010 to April 2013 at our institution.

Results. Median age was 55.5 years, male/female = 22/10. Overall, 22/32 pts received prior SSAs or CT (group A), and 10/32 were treatment naïve (group B) before commencing EV. DCR was documented in both groups 12 weeks after EV treatment as follows: 90% (group A) and 70% (group B) respectively. Four out of 32 pts (2 pts in group A and 3 pts in group B) showed disease progression at first evaluation. Although 13 pts are still on EV treatment, overall SD was achieved in 80% of pts, with a median duration of response of 10 and 13 mos for pretreated and naïve patients respectively.

Conclusions. Despite median SD of EV is better in responder naïve pts, the overall DCR at 12 weeks is worse when compared to pretreated patients. RADIANT III showed the benefit of EV in terms of PFS, but the therapeutic sequencing for advanced pWDNET remains still unclear. A comparative study is warranted to assess the best sequence strategy for EV in order to evaluate its role up front or following SSAs+/-CT in pWDNETs.

Q27 RETROSPECTIVE ANALYSIS ON THE MANAGEMENT OF METASTATIC GASTRIC CANCER (MGC) PATIENTS. A MONO-INSTITUTIONAL EXPERIENCE. WHAT HAPPENS IN CLINICAL PRACTICE?

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IRST, IRCCS, Meldola

Background. Few studies show what happens outside of randomized clinical trials (RCTs). The purpose of this study was to describe the clinical management of mGC patients resident in Forlì area from 2000 to 2009.

Material and methods. 270 mGC patients at diagnosis or relapse were considered. Data from medical records were analysed, survival probabilities were calculated using the Kaplan-Meier method.

Results. 115 patients received best supportive care (BSC), 155 at least one line of chemotherapy. 119 patients (76.7%) in chemotherapy group received first-line chemotherapy with at least two drugs. Seventy-one patients (45.8%) underwent second-line chemotherapy, 49 patients (31.6%) required a drug dose reduction during the first cycle of first-line. Twelve patients (7.7%) died within 15 days from finishing the last chemotherapy. Eleven out of 28 patients who died within 1 month of their last chemotherapy started chemotherapy with low dose of the drug/s: 5 patients had a mono-chemotherapy, 6 patients had a poly-chemotherapy. Factors associated with the choice of mono or poly-chemotherapy were: age at diagnosis ($p = 0.0004$), comorbidity ($p = 0.0208$) and performance status ($p = 0.0385$). Median overall survival (OS) with BSC or with chemotherapy was 3 months (95% CI 2-4) and 11 months (95% CI 9-12) ($p < 0.0001$), respectively.

Conclusions. About 20-30% of patients were treated with single-agent and or low doses of medication and they are not represented in RCTs. Second-line therapy was common. Chemotherapy given towards the end of life was similar to other experiences. Median OS was similar to RCTs.

Q28 SECOND-LINE TREATMENT FOR ADVANCED GASTRIC CANCER (AGC): A RETROSPECTIVE ANALYSIS

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Background. Although no standard second-line chemotherapy (CT) is actually defined for patients (pts) with AGC after first-line chemotherapy progression, two small randomized phase III trials have recently suggested a survival benefit for docetaxel and irinotecan as salvage CT compared to best supportive care alone. We report our experience in this setting of pts with poor outcome.

Methods. We retrospectively collected the data for pts with AGC progressing from a first-line fluoropyrimidines-based CT.

Results. From January 2008 to January 2013 we evaluated 144 pts, 42 of whom received a second-line CT for AGC (M/F 28/14, ECOG performance status 0/1/2 = 18/16/8). Median age was 60 years (range 44-80). The primary localization of tumor was: gastro-esophageal junction: 4 (9.5%), proximal: 14 (33.3%), middle: 16 (38.1%), distal: 8 (19.1%). All pts received a first-line treatment with fluoropyrimidines (both oral and intravenous) alone (14.3%) or in association with platinum compounds (52.4%), cisplatin and epirubicine (28.6%), cisplatin and docetaxel (4.7%). Patients with HER2-positive disease received cisplatin, 5-fluorouracil and trastuzumab. The schedules of CT used as second-line treatment were docetaxel at dose of 75 mg per square meter every 3 weeks (30 pts, 71.4%) and FOLFIRI (12 pts, 28.6%). The mean number of cycles administered was 7 (range 1-16). The median progression-free survival (mPFS) was 4 months (range 1-9), the median overall survival (mOS) from the start of second-line was 6 months (range 1-12). The estimated 3-year OS was 14.3%. In particular, within docetaxel treated group the mPFS was 3 months (range 1-7) with a mOS of 5 months (range 3-10). G3-G4 toxicities occurred in 35.3% and the most frequent were neutropenia (30.8%) and anemia (7.7%). Seven pts (23.3%) delayed treatment and 5 needed a dose reduction (16.6%). In FOLFIRI-treated group, the mPFS was 3 months (range 1-10) with a mOS of 7 months (range 3-13). G3-G4 toxicities occurred in 28.3% of pts and the most frequent were diar-

rhea (25.3%), neutropenia (26.4%), asthenia (26.0%), and anemia (14.5%). Four pts (33.3%) delayed treatment and 2 (16.6%) needed a dose reduction.

Conclusions. Our data support the evidence that second-line CT for pts with AGC and ECOG performance status 0-2 seems to be a valid option. In particular, the use of single agent docetaxel and FOLFIRI resulted in a survival improvement with a quite good compliance to therapy.

Q29 A NOVEL SOMATIC ALTERATION INVOLVING THE HMGCR GENE IN A PATIENT AFFECTED BY LOCALLY ADVANCED PANCREATIC CANCER

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We analyzed the clinical history of a patient newly diagnosed of locally advanced pancreatic cancer (LAPC), merged with data obtained from a whole transcriptome massively parallel sequencing (RNASeq). A 56-year-old man was diagnosed of LAPC involving the AMS and VMS, with an histological confirmation of pancreatic adenocarcinoma. After signed agreement we collected a fragment of the tissue sample to perform the RNASeq. The analysis was performed at 75x2 bp on a HiScanSQ Illumina platform. After mapping to the HG19 reference genome, single nucleotide variants (SNVs) were detected with SNVMix2 and filtered on dbSNP, 1000genomes, Cosmic. Non-synonymous SNVs were analyzed with SNPs&GO and PROVEAN. Patient received gemcitabine and oxaliplatin (GEMOX) for 6 cycles followed by chemoradiotherapy with concurrent gemcitabine as radiosensitizer for six weeks. The CT-scan showed a reduction of the mass with a persistent involvement of the vascular axis. The patient received further GEMOX for 12 cycles, with an increased radiological response. Currently the radiological response persists after 17 months. For the biological analysis the relative presence of tumor cells in the sample was estimated at 40% based on the presence of KRAS mutation. We confirmed the p.G12R KRAS mutations and CDKN2A and SMAD4 deletions. RNASeq showed the SNV p.H672D involving the catalytic domain of hydroxymethylglutaryl coenzyme A reductase (HMGCR), the rate-limiting enzyme in the mevalonate pathway. This SNV was not previously reported neither in the COSMIC nor in the ICGC databases. New genomic rearrangements leading to new fusion genes emerged: two in frame gene fusions regulating RAS-MAPK and apoptotic pathways (the intrachromosomal ANKRD44-GULP1 on chromosome 2 and the interchromosomal ATXN10-TMEM49 involving chromosome 22 and 17) and two out of frame fusions [t(15;3) and t(19;22)] leading to SMAD3-KIAA1143 and LTBP4-SPATS2L, both disrupting genes of the TGFbeta pathway. We found a novel somatic alteration involving HMGCR, in a patient affected by LAPC with a negative anamnesis for hypercholesterolemia. Due to the key role of HMG-CoA reductase in cellular transformation we hypothesize a potential of mutations of this gene in the development and prognosis of pancreatic cancer. Further investigations are required to verify the meaning of this SNV in pancreatic cancer and to identify new therapeutic strategies for LAPC, whose optimal treatment remains to be elucidated.

Q30 EVEROLIMUS (EV) TREATMENT IN PRETREATED METASTATIC WELL DIFFERENTIATED GASTROINTESTINAL (GNET) AND PANCREATIC NEUROENDOCRINE TUMORS (PNET): SINGLE INSTITUTION EXPERIENCE

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Background. Everolimus has been approved for advanced well differentiated G1-G2 PNET and has been studied in GNET. The aim of this study was to evaluate Ev efficacy in metastatic G1-G2 P- and G-NET with progressive disease after previous treatments, analyzing our single center experience.

Material and methods. Between September 2006 and February 2013, 29 patients (pts) were treated with Ev, administered at 10 mg/die, for advanced disease: we treated 14 GNET pts, primary site was: small bowel tract (9 pts), colon (1 pt), stomach (1 pt) and 15 PNET patients. All pts experienced disease progression after somatostatine analogs (SSA), or successive line of therapy (5 pts received Ev in second-line, 8 pts in third-line, 3 pts in >third-line), including chemotherapy (CT), peptide receptor radionuclide therapy (PRRT) or interferon (IFN). All patients received SSA during Ev treatment.

Results. In the GNET group, disease control (CR+PR+SD) was reached in 7 pts, 2 pts, 3 pts, 1 pt in first, second, third, >third-line of treatment respectively. In the PNET group disease control was reached in 5 pts, 3 pts, 5 pts, 1 pt in first, second,

Q30 - Table

Treatment line	Pathology	N pts (pts ongoing)	Median PFS (months)	Objective response RC	RP	SD	PD
First-line	PNEt	5 (3 ongoing)	19.9	\	1	4	\
	GNET	8 (1 ongoing)	18.48	\	1	6	1
Second-line	PNET	3	23.00	\	1	2	\
	GNET	2 (1 ongoing)	15.35	\	\	2	\
Third-line	PNET	5 (1 ongoing)	10.17	\	\	5	\
	GNET	3	9.90	\	\	3	\
>Third-line	PNET	2	8.43	\	\	1	1
	GNET	1	3.37	\	\	1	\
Total pts	PNET	15	15.7	0	2	12	1
	GNET	14	18.27	0	1	12	1

third, >third-line of treatment respectively. Treatment period was 14.18 months (1.93-31.83+) in the GNET group, 9.56 months (1.17-66.5+) in the PNET group. Median PFS was 14.93 months (2.13-67.9+) in all pts, 18.27 months (2.21-66.5+) in the GNET group, 15.7 months (2.13-67.9+) in the PNET group. In the GNET group median PFS was 18.48, 15.35, 9.9, 3.37 months in first, second, third, >third-line of treatment respectively. In the PNET group median PFS was 19.9, 23.00, 10.17, 8.43 months in first, second, third, >third-line of treatment respectively (see Table). Grade 3-4 adverse events observed were mucositis (10%), asthenia (10%), pneumonia (6%), thrombocytopenia (3%).

Conclusions. Ev treatment demonstrated comparable efficacy in terms of response rate and PFS both in GNET and PNET after SSA failure and successive lines of treatment with manageable toxicities.

Q31 K-RAS STATUS IN BILIARY TRACT CANCER (BTC): A SINGLE CENTER EXPERIENCE

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Background. Poor knowledge about genetic alterations and clinicopathological associations is available in BTC. We tried to assess the prevalence and the prognostic significance of *KRAS* status in a patient population affected by BTC treated at our Institute.

Material and methods. Forty-eight patients (pts) diagnosed with advanced or resected biliary tract adenocarcinoma between 2009 and 2013 were assessed for *KRAS* mutations at G12-G13 codons by both direct sequencing and pyrosequencing analyses after tumor tissue macrodissection. The observed results were correlated with histopathological variables and patients survival.

Results. Main pts characteristics were: 21 (44%) intrahepatic disease (IHCC), 13 (27%) extrahepatic biliary cancer (EHCC), 14 (29%) gallbladder cancer (GALLB); 24 (50%) with histological grade 2 differentiation, 11 (23%) with grade 3 and 1 (2%) with grade 1. For 12 pts (25%), the grading was not available. Median age was 66 (range 41-75) years, 30 female (62%), median KPS 100 (range 70-100). A *KRAS* mutation was detected in 6 of 48 (12%) BTC pts: 2 with EHCC, 2 with IHCC and 2 with GALLB. The *KRAS* mutation occurred at codon 12 in all 6 pts: 4 were transition (3 G12D and 1 G12S) and 2 transversion (2 G12V). Patients characteristics were (*KRAS* mutation/wild type): median age 70/66 yrs; stage IV 50%/36%; median basal CA19.9 1122/65. 67% of pts were resected in both groups and median disease-free survival was 3.1 versus 6.5 months. Chemotherapy for advanced/metastatic disease was administered to 4/31 pts and consisted of gemcitabine-platinum agent combinations in all cases except 1: a partial response was observed in 25%/35%; stable disease in 0%/39%; progressive disease in 75%/26%, median PFS was 3.1/5.4 months, median OS 6 and 8.5 months.

Conclusions. Differently from pancreas cancer, a high prevalence of *KRAS* wild type status seems to be present in BTC thus confirming a biological different cancer entity. The low number of pts with *KRAS* mutations and the heterogeneity of this sample size do not allow to draw definitive conclusions on the predictive and prognostic role of *KRAS*. However, pts with *KRAS* mutation seem to have a more aggressive and less chemoresponsive disease. Again, the high prevalence of *KRAS* wild type status seems to justify the investigation on anti-epidermal growth factor receptor (EGFR) therapy. Ongoing trials with anti-EGFR therapy will soon clarify the role of this treatment in this disease.

Q32 BIOMOLECULAR ASSESSMENT IN RADICALLY RESECTED BILIARY TRACT CANCER

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Background. Biliary tract cancers are generally grouped and evaluated together due to their anatomic localization, without a molecular stratification. Currently, the role of specific tumor mutations or protein expression is unclear in this disease, and their prevalence is discussed.

Material and methods. We conducted a retrospective research of tumor mutations and protein expression of candidate genes and proteins in radically resected biliary tract cancers. In particular, we investigated mutations on BRAF (codon: 600), KRAS (codons: 12, 13, 61) and EGFR (codons: 18, 19, 20, 21) genes by direct sequencing and HER-2 protein expression by immunohistochemistry.

Results. Radically resected tumors from 44 patients were analyzed (median patients age was 67, range 32-84). Of these, the primary tumor site was intrahepatic cholangiocarcinoma (IHCC) in 12 patients, peri-hilar biliary tract cancer (KLAT) in 4, gallbladder cancer (GC) in 5, distal common bile duct (DIST) in 9, and ampullary (AMP) in 14 patients. Twenty-four tumors had positive nodes (54.5%). No BRAF or EGFR mutations were found. KRAS mutations were detected in 9 (20.5%) patients (IHCC: 3, GALL: 1, DIST: 3, AMP: 2). Mutations were heterogeneous and localized on different codons (6, 1, and 2 respectively on codons 12, 13 and 61). Immunohistochemical analysis of the expression of HER-2 protein showed absent expression (0) in 20 (45.5%) patients, mild expression (1+) in 11 (25%) patients, intermediate expression (2+) in 9 (20.5%) patients (IHCC: 1, KLAT: 2, DIST: 3, AMP: 3), and high expression (3+) in 4 (9.1%) patients (IHCC: 1, DIST: 2, AMP: 1). No statistically significant associations were demonstrated between the molecular alterations described and positive lymph nodes (N), extension (T) or site of primary tumor. HER-2 expression was associated with disease-free survival (DFS); in particular, patients with high HER-2 expression (3+) showed shorter DFS compared to other patients (9.3 versus 64.8 months; $p = 0.02$). KRAS mutations had no impact on patients DFS.

Conclusions. The molecular study of biliary tract cancers should be implemented. In our series, HER-2 expression seems an interesting molecular alteration in terms of prevalence and role and it could also become a therapeutic target in a selected population. Further prospective data should explore this hypothesis.

Q33 NEUTROPHIL-LYMPHOCYTE RATIO IN PANCREATIC CANCER PATIENTS TREATED WITH GEMCITABINE

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Background. High neutrophil/lymphocyte ratio (N/L), as a measure of enhanced inflammatory response, has been negatively associated with prognosis in patients with localized pancreatic cancer (PC) undergoing pancreasectomy. In the present study, we aimed at confirming for the first time the prognostic value of N/L in metastatic PC patients treated with standard first-line gemcitabine-based regimen.

Methods. Consecutive PC patients (N = 103, male:female = 53:50) treated with either gemcitabine alone (N = 45) or gemcitabine + oxaliplatin (N = 58) as first-line regimen between April 2005 and October 2012 at our institution were included. Exclusion criteria were treatment with steroids and active infection. Histologically or cytologically confirmed diagnosis of adenocarcinoma was required. Neutrophil and lymphocyte counts and their ratio were routinely assessed before treatment commencement and correlated with outcome together with sex, age, platelet count (PLT), Hb concentration, monocyte, CEA, CA19.9, body mass index (BMI), Karnofsky performance status (KPS).

Results. At the univariate analysis, the following variables were found to be significantly associated with overall survival (OS): CA 19.9 (Exp(b) = 2.0573, 95% CI 1.2860-3.2912, p = 0.0028), lymphocyte count (Exp(b) = 0.6797, 95% CI 0.4719-0.9790, p = 0.0390), neutrophil count (Exp(b) = 1.0781, 95% CI 1.0023-1.1596, p = 0.0443), N/L (Exp(b) = 1.1105, 95% CI 1.0409-1.1849, p = 0.0016) and age (Exp(b)=1.0244, 95% CI 0.9998-1.0496, p = 0.0534). Gem/Oxa was associated with longer OS, but this was not statistically significant (median OS 8 vs 6 months, HR 0.7719, 95% CI 0.4782-1.2459, p = 0.2488). At the multivariate Cox regression analysis only CA19.9 and N/L were found to be independent prognosticator for OS with a near two-fold increase in the risk of death for CA19.9 >400 UI/mL (Exp(b) = 1.9926, 95% CI 1.2398-3.2027, p = 0.0046) and a 10% death risk increase for 1-unit increase in N/L (Exp(b) = 1.1030, 95% CI 1.0339-1.1766, p = 0.0031). N/L change during treatment was not associated with prognosis (median OS 8 months for both increasing and decreasing N/L after one month of therapy, p = 0.602).

Conclusions. We were able to confirm the independent prognostic value of baseline N/L for metastatic PC patients approaching a gemcitabine-based first-line chemotherapy. N/L and CA19.9 may help to identify a subgroup of patients for whom a particularly poor prognosis might justify more intensive, yet less tolerable, regimens (e.g. FOLFIRINOX).

Q34 RAMUCIRUMAB FOR GASTROINTESTINAL MALIGNANCIES: A BRIEF OVERVIEW OF ONGOING CLINICAL TRIALS

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Background. Vascular endothelial growth factor (VEGF) and VEGF receptor-2 mediated signalling and angiogenesis contribute to the pathogenesis and progression of different gastrointestinal malignancies. Ramucirumab (IMC-2111B, ImClone Systems Inc) is an intravenously administered, fully human IgG1 monoclonal antibody, that blocks VEGFR-2 and prevents ligand binding and receptor-mediated pathway activation in endothelial cells. Aim of this literature search was to merge available information on this new compound, with a focus on phase II and III ongoing clinical trials.

Materials and methods. To evaluate the available data, a comprehensive web-based literature search was performed, including online information sources such as Pubmed, Embase, Clinicaltrials.gov, EudraCT, controlled-trials.com, clinicaltrialsregister.eu, and Google Scholar. Abstracts presented in the last 3 years at major general or gastrointestinal-focused international congress venues were also retrieved and reviewed.

Results. More than 30 phase I, II and III trials testing ramucirumab were found. Specifically focusing on gastric and gastroesophageal junction adenocarcinomas, ramucirumab (8 mg/kg every 2 weeks) produced survival benefit compared to best supportive care alone when used in 355 pretreated patients (REGARD trial, median survival gain of approximately 1.5 months, HR 0.77), and the accrual of the RAINBOW trial that compared in second-line paclitaxel plus or minus ramucirumab has been completed. Also, the antiangiogenic is being tested in combination with chemotherapy in patients with advanced colorectal cancer both in first- and second-line settings. Moreover, the REACH trial, that compared the drug against placebo in liver cancer patients who had previously failed sorafenib, has recently completed the accrual and preliminary results are soon expected.

Conclusions. Waiting for final results of many ongoing clinical trials and the full publication of the phase III REGARD study, the antiangiogenic compound ramucirumab seems to be an interesting new drug for patients with gastrointestinal malignancies and may further broaden the landscape of the antiangiogenic strategy beyond bevacizumab, aflibercept, and regorafenib.

Q35 SERUM CA19.9 AS A MARKER OF SURVIVAL IN PATIENTS WITH BORDERLINE RESECTABLE PANCREATIC CANCER TREATED WITH NEOADJUVANT FOLFOXIRI

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Background. The carbohydrate antigen (CA) 19.9 is frequently increased in patients with pancreatic cancer and its baseline level or its change with treatment have been studied as a prognostic marker both during adjuvant treatment for resected patients and during first-line chemotherapy for metastatic disease. However, data on its role in locally advanced not metastatic disease are very limited and no other valid marker has been proposed as surrogate of efficacy in this setting in which also radiographic evaluation of response may be difficult in some cases.

Patients and methods. The aim of our analysis was to evaluate the role of CA19.9 values in patients with borderline resectable pancreatic cancer treated with neoadjuvant FOLFOXIRI in a phase 2 trial and to correlate its basal and post-chemotherapy levels with therapeutic response, radical surgical resection, and

survival. CA19.9 was centrally determined baseline before the beginning of neoadjuvant chemotherapy and after 2 and 4 months of treatment. Associations were evaluated by Chi-square test, Kaplan-Meier curve and log-rank analysis.

Results. A total of 25 patients with evaluable of both basal and post-treatment CA19.9 values have been identified, 15 women and 10 men. Median age was 60 years (range 44-75). Eight patients had a partial response to chemotherapy, 15 a stable disease and 2 progressed. Thirteen patients underwent radical surgical resection after chemotherapy. Median progression-free and overall survival were 13.9 and 20.1 months, respectively. The median value of basal CA19.9 was 425 U/mL. Ten patients had a decrease of CA19.9 after chemotherapy higher than 50% and 7 patients higher than 90% of basal level. A post-treatment reduction of CA19.9 higher than 50% of basal value was associated with partial response to chemotherapy (70% versus 7%; p = 0.0017) and with the probability of radical surgical resection (80% versus 33%; p = 0.02) while a reduction of CA19.9 higher than 90% correlated with a longer progression-free survival (23.2 versus 13.7 months; p = 0.01) and overall survival (31.2 versus 15.2 months; p = 0.02). No associations have been found according to the basal value of CA19.9.

Conclusions. Baseline CA19.9 level showed no prognostic role in our experience but the post-chemotherapy CA19.9 decrease resulted associated with survival in patients with borderline resectable pancreatic cancer and could be taken into account in the choice of local treatment for these patients.

Q36 NAB-PACLITAXEL (NabP) AND GEMCITABINE (G) AS A FIRST-LINE TREATMENT IN ADVANCED PANCREATIC CANCER (APC)

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Background. APC represents a strongly aggressive disease with an extremely poor prognosis. G has represented the backbone of chemotherapy regimens both as single agent and in combination since 1997. NabP, an innovative molecule, has shown a promising activity and efficacy in combination with G in treatment of APC in a phase I/II trial and data of a randomised phase III trial comparing G + NabP combination vs G alone have shown the superiority of combination over G alone.

Methods. Patients (pts) with APC treated with association of G 1000 mg/m^2 + NabP 125 mg/m^2 days 1, 8 and 15 every 4 weeks as first-line chemotherapy were included in our analysis.

Results. From November 2011 to December 2012 a group of 16 pts (M/F:5/11) with median age of 67 (range 40-77), ECOG PS 0-1 (81.3%) or 2 (18.7%) received G + NabP m^2 as first-line treatment for APC. Histological diagnosis was ductal pancreatic adenocarcinoma located in the head (46.1%), body (38.5%) or tail (15.4%). 18.7% of pts received prior surgery and adjuvant treatment with G. 30.8% of pts had 2 or more metastatic sites. Two pts had unresectable locally advanced measurable disease; 14 pts had measurable metastatic disease located to liver (46%), lung (23%), lymph nodes (15.4%), peritoneum (15.4%) and bone (6.7%). Median CA19.9 level at baseline was 87.2 U/mL (range 17.6-789.3). A median number of 6 cycles was performed (range 2-12) and G + NabP schedule was well tolerated with no grade 4 toxicities. Grade 3 neutropenia was recorded in 4 pts (25%) on day 15 of their first cycle and prophylactic use of G-CSF was started. No dose reduction was needed during the treatment period. Partial responses (PR) were detected in 6 pts (37.5%) with stable disease in 7 pts (43.8%) and progression disease in 3 pts (18.7%), with a disease control rate (DCR) defined as PR + SD of 81.3%. A patient with locally advanced disease became resectable after 6 cycles of G + NabP. Median PFS among evaluable pts was 6.5 months (range 1.5-11). Definitive survival data will be presented during the meeting.

Conclusions. Targeting the stroma seems to be an effective way to treat APC. NabP has a peculiar mechanism of action closely linked to its molecular structure and it seems to enhance G activity in combination regimens. Our experience confirms that the combination of G + NabP is effective both in terms of DCR and PFS, with a good safety profile.

Q37 NUTRITIONAL PARAMETERS AS PROGNOSTIC FACTORS IN PATIENTS WITH PANCREATIC CANCER: A SINGLE INSTITUTION EXPERIENCE

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Background. Very few studies have evaluated the relationship between prognosis of patients with advanced pancreatic cancer (APC) and nutritional factors. Patient nutritional status might play a role in determining compliance to treatments and in modifying clinical outcomes. Most recognized nutritional prognostic indicators of poor outcome are: weight loss, malnutrition and wasting. In addition, significant weight loss at the time of diagnosis has been associated with decreased survival and reduced response to surgery, radiation therapy and chemotherapy. Aim of this study is to investigate a possible correlation between a large set of nutritional factors and survival.

Patients and methods. Patients with APC underwent the following nutritional measurements: body mass index, weight loss in the last six months, malnutrition universal screening tool, phase angle, serum albumin, prealbumin, transferrin, C-reactive protein. Data were collected at the start of chemotherapy, after three and six months. Statistical analysis was carried on including also clinical parameters (Ca 19-9 and stage).

Results. Between September 2012 and May 2013 sixty (60) patients with APC were admitted at our Institution. About nutritional parameters, we have observed, at the present time with a median follow-up of only 4.4 months, that weight loss in the last six months is resulted a significant prognostic factor for survival; both Ca 19-9 and stage resulted statistically significant for survival.

Conclusions. The present study demonstrates that weight loss is a strong prognostic indicator of survival in APC. The main limit of this study is related to the short median follow-up. At the congress we'll be able to have an adequate follow-up and so results might be more conclusive to introduce the evaluation of nutritional parameters in the early assessment of patients with APC.

Q38 BONES METASTASES (BM) IN GASTRIC CANCER PATIENTS: A SINGLE CENTER RETROSPECTIVE ANALYSIS

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Background. Bone metastases (BM) are a common occurrence in advanced breast, lung, prostate, kidney and thyroid cancers. In gastric cancer BM occur rarely and are known to have a very poor prognosis.

Methods. We analysed 563 pts with gastric cancer admitted at the Medical Oncology Department of S. Chiara Hospital, Trento, between January 2000 and December 2012. The aim of this retrospective study is to evaluate the radiological, clinical and therapeutic aspects in gastric cancer with BM.

Results. In a total of 563 pts analyzed, BM were detected in 24 pts (4%). The mean age at the time of diagnosis of gastric cancer was 58 years (range 31-82 years). BM were synchronous to gastric cancer in 5 pts and in 19 pts occurred from 1 to 84 months after primary tumor diagnosis (mean 17 months). Undifferentiated and poorly differentiated histology was predominant (84% of cases). Positive nodal status was found in 16 cases (67%). BM were associated with nodal metastases in 17 cases (71%), liver metastases in 6 cases (25%), peritoneal dissemination in 6 cases (25%) and lung metastases in 4 cases (17%). Five pts (21%) had only BM. Diagnosis of BM was achieved by computed tomography in 13 pts (54%), by bone scintigraphy in 6 pts (25%) and by PET in 5 pts (24%). All pts had symptoms related to BM: bone pain in 13 pts (54%), spinal cord compression in 1 pt (4%). Eleven pts (46%) developed thrombocytopenia. Thirteen pts were treated with analgesic drugs, 11 pts (46%) with palliative chemotherapy, 8 pts(33%) with bisphosphonates and 4 pts (16%) with radiotherapy. The median survival from diagnosis of BM was 5 months (1-25 months). In the pts with thrombocytopenia the median survival was even shorter (1-150 days).

Conclusions. Our data confirmed the low incidence of BM in the gastric cancer. The prognosis of pts with gastric cancer and BM is poor. In this population, the development of thrombocytopenia is associated with a lower survival. Related to the quick clinical deterioration of pts with BM, an early diagnosis and multidisciplinary approaches may be important in the management of these patients.

Q39 MOLECULAR BIOLOGY AND OUTCOME IN PATIENTS TREATED WITH EVEROLIMUS (RAD001) FOR GASTROENTEROPANCREATIC NEUROENDOCRINE TUMORS

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Background. Neuroendocrine gastroenteropancreatic tumors (GEP NETs) constitute a group of tumors with their origin in neuroendocrine cells of the embryological gut. The incidence is estimated to be 5.25/100,000/year. The prevalence is 35/100,000/year. Recently mTOT inhibitor everolimus (RAD001) has been approved by FDA and EMA in progressing well-moderately differentiated pancreatic NET. Tumors exhibiting constitutively activated phosphatidylinositol-3-kinase-AKT-mTOR pathway are potentially susceptible to mTOT inhibitor. Nevertheless, no specific biological factors have been studied to be used for predicting the response or efficacy of everolimus. Our aim is to determine the expression of some factors of the pathway of p-m TOR in patients treated with everolimus and to evaluate the possible correlations with clinicasl outcomes.

Methods. Thirty-seven patients treated with everolimus affected by GEP NETs were included in our analysis. We evaluated several molecular factors involved in mTOR pathway (p-mTOR, pS6, p70S6, p4EB1, p-AKT and PI3K) and we correlated them to time to progression (TTP). Cut-off to determine the resistance or sensitiveness to everolimus was 6 months. Immunoistochemistry was used for all parameters, except PI3K mutation that was assessed by molecular analysis. Scoring of p-mTOR was based on distribution and intensity of staining in neoplastic cells. Samples were classified as high expression when score was >3. Ki67 was classified as <10% and >10%. Statistical analysis was performed by Fisher exact test and t-test.

Results. We present data about p-mTOR and KI67 and their correlation with TTP. Analysis of other biological factors is ongoing. Median TTP was 8 months. Eleven patients progressed before 6 months. Among all patients, 14 (37%) presented high expression of p-mTOR. Ki67 was >10% in 18 patients. No statistical correlation was found between Ki67 percentage and TTP ($p = 0.457$), pmTOR and TTP ($p = 0.161$) and between p-mTOR and KI67 ($p = 0.234$).

Conclusions. Our data are preliminary but showed no significant correlation between p-mTOR and Ki67 and between pmTOR- Ki67 and outcome disease. We are waiting data from evaluation of remaining biologic parameters and more mature data on survival.

Q40 COMBINED PERCUTANEOUS MICROWAVE ABLATION (MWA) AND TRANSARTERIAL CHEMOEMBOLIZATION (TACE) FOR HEPATOCELLULAR CARCINOMA

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Background. Locoregional therapies are useful for the treatment of unresectable hepatocellular carcinoma (HCC). Radiofrequency thermal ablation (RFA) is considered the standard of care for patients with lesions smaller than 3 cm in diameter not suitable for surgery. However the likelihood of complete ablation using RFA declines rapidly as tumor diameter is greater than 3 cm. The combination of RFA and transarterial chemoembolization (TACE) has resulted in higher percentage of complete necrosis of the HCCs over 3 cm. Microwaves ablation (MWA) has recently emerged as a new technique promising larger and faster ablation areas without some of the RFA limitations. There is only one report in literature regarding the use of MWA in association with TACE in the treatment of liver lesions; herein we report our preliminary results on feasibility and effectiveness of the combination of thermal ablation with a new 2.45-MHz generator of microwaves and TACE in unresectable HCCs larger than 3 cm.

Material and methods. Thirty-six nodules (size 3-11 cm, mean 4.78 cm, DS = 2.09) of HCC were treated with a combination of percutaneous US-guided MWA and TACE (one treatment of ablation and one session of TACE for each lesion). Abdominal contrast enhanced CT scan was carried out 1 month after treatments, and then every three months to assess efficacy. "Technique effectiveness" was defined as complete absence of contrast enhancement with homogeneous hypodensity in the treated area.

Results. Technique effectiveness was achieved in 83.3% of the lesions; intermediate-sized HCCs obtained 100% of complete necrosis. Local tumor progressions were found in 3 treated lesions (8%) a median of 9 months after the procedures (range 7-19). Treatments were followed by few adverse effects (AEs), without G4 AEs, according to CTCAE 4.0; particularly, we found hypertransaminasemia G3 in two cases (5%), without any worsening of liver function according to Child-Pugh score. No deaths, or other major complications occurred.

Conclusions. Our preliminary data showed that the combination of MWA and TACE for the treatment of intermediate and large-sized HCCs is a feasible and safe method, not burdened by an increase of toxicity, with encouraging results in terms of efficacy.

Q41 SOMATOSTATINE ANALOGS (SSA) OCTREOTIDE LAR AND LANREOTIDE LAR TREATMENT IN G1-G2 GASTROENTEROPANCREATIC NEUROENDOCRINE TUMORS (GEP-NET): SINGLE INSTITUTION EXPERIENCE

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Background. In a recent study, 85 patients with advanced midgut neuroendocrine tumors (NETs) and predominantly low-volume disease were randomly assigned to receive treatment with octreotide long-acting release or placebo. Patients randomly assigned to the octreotide arm had a significantly longer median time to progression than patients assigned to the placebo arm (14.3 vs 6 months, respectively; p <.01) at a planned interim analysis, leading to early termination of the study, giving the evidence of antitumor activity associated with SSA. In this study we analyze our experience with SSA in metastatic G1-G2 GEP-NET.

Materials and methods. A retrospective analysis was conducted on 103 patients (pts) with advanced GEP-NETs treated upfront with octreotide LAR (30 mg 1 fl every 28 days) or lanreotide LAR (120 mg 1 fl every 28 days) until disease progression: 37 pancreatic (P) NET pts (29 treated with octreotide LAR, 8 with lanreotide LAR), 66 gastrointestinal (G) NET pts (45 treated with octreotide LAR, 21 with lanreotide LAR).

Results. In 29 P NET pts group treated with octreotide LAR, mPFS was 24.97 months: in this group, mPFS was 28.67 months in pts with a single metastatic organ and 21.78 months in pts with >1 metastatic organ. In 8 P NET pts group treated with lanreotide LAR, mPFS was 25.10 months: in this group, mPFS was 22.28 months in pts with a single metastatic organ and 22.40 months in pts with >1 metastatic organ. In 45 GNET pts group treated with octreotide LAR, mPFS was 22.9 months: in this group, mPFS was 42.23 months in pts with a single metastatic organ and 19.67 months in pt with >1 metastatic organ. In 21 GNET pts group treated with lanreotide LAR, mPFS was 18.61 months: in this group, mPFS was 75.25 months in pts with a single metastatic organ and 16.08 months in pts with >1 metastatic organ.

Conclusions. Octreotide LAR and lanreotide LAR showed comparable efficacy in terms of PFS in both PNET and GNET, especially in pts with limited metastatic involvement.

Q41 - Table

NET	Treatment	Patients	mPFS	mPFS in patients with 1 metastatic organ	mPFS in patients with >1 metastatic organ
PNET	Octreotide LAR	29	24.97	28.67	21.78
	Lanreotide LAR	8	25.1	22.28	22.4
GNET	Octreotide LAR	45	22.9	42.23	19.67
	Lanreotide LAR	21	18.61	75.25	16.08

Session R • Psychological and psychosocial aspects, rehabilitation problems

R1* MONITORING AND PREVENTING BURNOUT IN THE WORKPLACE: THE ROSA/13 STUDY

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Background. The 'Burnout'' term was introduced by Freudenberger (1974) to describe a state of psychological distress related to work in health care employees, due to prolonged contact with suffering and death. The aim of the present study is to monitor and prevent the occurrence of high levels of work-related stress, through the implementation and verification of the effectiveness of an intervention specifically designed, in the health workforce of the Medical Oncology Unit at the Tor Vergata University Clinical Center (PTV) in Rome and the Day Hospital of the AOU of Salerno P.O. "Giovanni da Procida" (Dh SA).

Materials and methods. Thirteen physicians (median age 36.50 yrs, range 26-62) and 11 nurses (median age 38.5 yrs, range 32-62), were assessed through both Maslach Burnout Inventory (MBI) and General Health Questionnaire (GHQ). The administration of the questionnaires and the training course was carried out by the psycho-oncologists of either units to Dh Sa by the group of Rome in February 2013, and to PTV by the group of Salerno in March 2013. The two groups were randomly allocated: the first group including 8 physicians (median age 36 yrs, range 26-60) and 4 nurses (median age 56 yrs, range 44-62) was subjected to prevention intervention, consisting of 6 hours training; the second group including 5 physicians (median age 34 yrs, range 29-54) and 7 nurses (median age 41 yrs, range 32-61), represented the control and did not participate in the training session. Both groups were asked to answer the questionnaire within 30 days. Subsequently, evaluation will be carried out monthly for a year. Here we present the preliminary results for the pre-intervention assessment and evaluation after a month.

Results. In the group receiving the intervention, the average values reported to Total MBI decreased significantly ($p = 0.32$). Accordingly there was also a statistically significant change as a median value ($p = 0.39$) in the sub-scale Personal Accomplishment. Conversely the control group showed crescent values in the subscale of the MBI Depersonalization ($p = 0.19$), this was not evident for the median value of the subscale Emotional Exhaustion ($p = 0.048$).

Conclusions. These preliminary data suggest the advantage of the interventional program, developed in order to reduce work-related stress in health care personnel in comparison to the simple detection.

R2* LIVING A "NEW" LIFE WITH ADVANCED BREAST CANCER (ABC): THE PATIENTS' EMOTIONAL PERSPECTIVE

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Background. The possibility of having more time to live with cancer highlights the importance of enhancing the quality of this renewed time among ABC patients (pts). Patients use different criteria to judge life expectations and drug effectiveness, and for them the quality of life (QoL) is extremely important. Little attention has been paid up to now to how pts experience their "time with cancer" and give value and meaning to it, in particular at an advanced phase. On this basis, the present study aimed at giving voice to ABC pts, in order to investigate how they represent and give sense to their time and to cast light on their experiences, that help them in feeling lively and active.

Methodology. The research, conducted in Italy, foresaw a mixed 2 phases methods. A first phase was based on the collection of 14 emotional diaries and 12 in depth interview to ABC patients. A second phase based on the collection of 81 questionnaires involving a statistically representative sample of ABC patients.

Results. Although traumatic and emotionally devastating, the diagnosis of ABC offers the occasion to re-orient patients approach to life. Patients declared that the illness helped them in take the most from the "essence" of human being, by finding a renewed life enthusiasm, body and "soul" awareness and by changing value priorities in a more ethical and realistic way. After the diagnosis, pts changed their criteria for measuring QoL and quality of time: pts declared to live a more "intense" life at present (72% of the sample), and indicated the possibility of "feeling well with themselves" as crucially important for maintaining a good QoL and psychological endurance (87% of the sample). However, public opinion is perceived as not well fine-tuned with this renewed "will of life" and women suffer to be treated as "terminal pts" instead of "persons with an intense joy of life"(67% of the sample). Moreover the availability for them to have an innovative therapy is linked to hope for future and to the ability to plan projects. Nowadays innovation means for pts a treatment that guarantees time advantage together with good QoL.

Conclusions. These results underline ABC patients' need for qualifying a good time with cancer. The pts showed the capacity to live with intensity and their need for playing and maintaining an active role in the community. The health care system should take into consideration also the pts perspective in treatment decision making process.

R3* SEARCHING FOR CAREGIVERS' NEEDS: THE PRELIMINARY EXPERIENCE OF THE ONCOLOGY DEPARTMENT OF POLIAMBULANZA FOUNDATION

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Background. Caregivers play a key-role in the management of cancer patients (pts). Some studies have suggested that caregivers of people with cancer may have even more unmet needs than patients.

Material and methods. From 20/2/2012 to 31/1/2013, in an attempt to better identify the needs and the changes in lifestyle of the caregivers in our practice and to plan a targeted support project to decrease caregiver burden, we administered to 200 consecutive caregivers of cancer pts accessing to our day-hospital/MAC a 35-item questionnaire (Weitzner et al., modified Italian version) assessing psychological well-being, relationship with health care, administration and finances, lifestyle disruption and positive adaptation. Caregivers' main characteristics were: gender (female/male) 123/77; median age: 52 years (range 21-79); parentage: husband 53 (26%), wife 47 (24%), daughter 42 (21%) and son 13 (6%); job/occupation: worker 98 (49%), retired 56 (28%), housewife 34 (17%), unemployed 10 (5%) and student 4 (2%); education: high school 80 (40%), middle school 66 (33%), primary school 31 (16%) and university 23 (12%). Patients' main characteristics were: gender (female/male) 116/84; median age: 63 years (range 18-89); stage of disease: metastatic 118 (59%), locoregional and radically resected 82 (41%); site: breast 56 (28%), colorectal 38 (19%), pancreas 21 (11%) and lung 21 (11%).

Results. As expected in metastatic setting, fatigue and depression were the most frequently reported symptoms by caregivers' group (19.7 and 5.7%, respectively). Moreover, our preliminary data showed that caregiving negatively affected the female gender mostly, with an increased risk of anxiety and depression (17.2 vs 2.3%), a worsening of sexual activity (29.5 vs 13.9%), and creates a financial burden for family members by increasing costs and decreasing the number of remunerated manhours (9.8%). On the other hand, caregivers reported being proud and pleased of their caregiving role (93.5%).

Conclusions. Finally, we strongly believe that an early palliative care directed not only at patient symptoms relief but also at caregiver support may improve quality of life in this population. At this time, we are making a targeted support project to decrease caregiver burden.

R4 EVALUATION OF PSYCHOPHYSICAL WELL-BEING IN CANCER PATIENTS

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Background. The healing power of nature has always been well known. The term Healing Gardens was coined at the end of last century in the U.S.A. to identify therapeutic gardens within care facilities. Recent medical studies prove that being in contact with nature enhances the body response. Examples of oncology Garden Therapy in Italy are:

- oncologic verandas at Carrara Hospital, whose benefits resulted into a lower use of analgesic drugs;
- therapeutic garden for oncological patients at Niguarda Hospital, Milan;
- equipped garden at Istituto Regina Elena, Rome, for patients and family members.

Material and methods. Our study involved the aforementioned hospices where patients can relax after undergoing therapy and it evaluated the effect of garden environment on patients well-being during chemotherapy. From August to October 2012, in the Oncology Unit of Fivizzano Hospital (Carrara Department) 100 patients under chemotherapy treatment have been divided into two groups: 50 underwent chemotherapy both inside the hospital and in the garden; the other 50 just inside the hospital. Each patient received a self-assessment questionnaire (A.De.Ss.O Test) about psychological variables related to the oncological disease: anxiety, depression, somatic symptoms, hostility. Physical parameters were also measured: heart rate, blood pressure, oxygen saturation. All measurements were taken both at the beginning and at the end of chemotherapy.

Results. In both groups anxiety decrease was statistically significant ($p < 0.0001$) after treatment. The main difference, however, concerns aggressiveness: in patients undergoing chemotherapy in the garden the drop is statically significant ($p < 0.01$) when compared both to the same patients treated inside the hospital and to the other group always treated indoor. There are no significant differences between the two groups about depression and somatic symptoms, as well as for physical parameters: saturation and blood pressure stay steady after treatment, while heart rate decreases in both groups.

Conclusions. We are aware that this is a first exploratory study that requires further surveys and thorough investigations; however, we observe that undergoing oncological treatments in a garden environment seems to contribute in reducing patients anger. Regarding the decrease of anxiety in both groups, we assume that this could be determined by doctor/patient relationship variables.

R5 EMOTIONAL DISTRESS AS AN USEFUL AND EARLY INDICATOR OF MOOD DISORDERS AND QUALITY OF LIFE IN HOME PALLIATIVE CARE CANCER PATIENTS

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Background. A considerable amount of advanced cancer patients suffers from emotional distress, anxiety and depression. Psychological disorders have a heavy impact on patients care and on their quality of life, so in the home care setting physicians need a quick and feasible instrument to provide an early monitoring of patients emotional state. In this study, we analyzed the prevalence of emotional distress, anxiety and depression in a sample of oncological home palliative care patients. Correlation between distress levels, mood disturbances and quality of life scores were analyzed as well. We finally determined the sensitivity and specificity of an emotional distress instrument, to find out if it can be used to detect concomitant high levels of anxiety and depression.

Methods. Were used the Distress Thermometer to measure distress (DT), Hospital Anxiety Depression Scale and EORTC QLQ-C30 for quality of life. Sample included 66 oncological pa-

tients (39% male; medium age 54.6; D.S. 13.2) in a home palliative care setting.

Results. 81% of patients showed significant distress levels (DT cut off score >4). More than half subjects (55%) reported high levels of anxiety (HADS cut off score >8), and high levels of depression are present in 81% of patients (HADS cut off score >8). Statistical analysis showed that distress was strongly correlated to anxiety and depression. Regarding quality of life, DT was negatively correlated with emotional functioning, general health state, physical and cognitive functioning and, relatively to symptoms, to fatigue and pain. ROC curves analysis showed that a DT cut off score >4 identified patients with high levels of anxiety and depression (HADS score: 15 or more) with a very high sensitivity (0.97) and a moderate specificity (0.58).

Conclusions. It is important to have an easy indicator for the presence of psychological problems in advanced cancer patients. Considering the high correlation between Distress Thermometer and anxiety, depression and some quality of life domains, and its sensitivity to detect mood disturbances, the assessment of emotional distress is a quick and feasible way to individuate which patients are at higher risk of psychological issues. An early monitoring of emotional distress may represent the first step of subsequent and more complete assessments, and it's an easy way to integrate a brief psychological evaluation in physician's home visits.

R6 EFFECT OF ACCEPTANCE AND COMMITMENT THERAPY (ACT) ON WEIGHT LOSS AND BODY IMAGE IN BREAST CANCER PATIENTS

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Background. The weight gain affects a high number of breast cancer patients, during and after the treatments. The Acceptance and Commitment Therapy (ACT) offers strategies in order to increase psychological flexibility, and has shown to be effective in reducing and maintaining weight. The aim is to evaluate the effect of ACT on weight loss in breast cancer patients with BMI ≥28.

Methods. The intervention consists in a set of eight bi-monthly encounters and six monthly maintenance phase encounters. At the first, eighth and last encounter patients' weight is reported and questionnaires on clinical state (RSCL, PWBQ, Distress Thermometer), eating behaviour (TFE.Q-51), psychological flexibility (AAQ-2, Bull's-eye) and on the body image acceptance (BIAAQ) are administered.

Results. Thirty-one breast cancer patients attending the oncological out-patient clinic of the Verona General Hospital, with a BMI = 28 were enrolled in the intervention. Eleven patients have completed the entire protocol, while the other 21 (the second and third group) are finishing the intervention. The mean age was 56 (SD 6.6); the mean BMI was 35 (SD 7). Data showed high mean scores of physical symptoms, psychological symptoms, quality of life (RSCL M = 23.9; SD 9.9, M = 25.3; SD 3.4, and M = 3.2; SD 1.2 respectively) and distress level (M = 5.7; SD 2.8). A high degree of acceptance (AAQ2 M = 48.7; SD 14), consistency with the values (Bull-eye M = 5.5; SD 1.4) and psychological well being (PWBQ M = 72.7; SD 11.3) was observed. An improvement of acceptance of body image (BIAAQ post increased >21 points (SD = 17)) was observed after the intervention. The attendance rate was 89% and patients showed a weight loss of 6.5% at the end of the eighth encounter, corresponding to a mean of 5.4 kg (SD 3.5 kg), and a weight loss of 9.5% at the follow-up (1 year).

Conclusions. The ACT works on the psychological processes that influence the decision-making, and acts on the emotion and thought discrimination, value clarification, implementing committed action. Patients adhered to the encounters and collaborated actively, showed to be able to manage their own thoughts in a less judgmental way, and have shown an improvement in the acceptance of body image. The good results obtained on weight loss, then appear a secondary outcome related to the commitment action to achieve their personal goals, focused on the physical and psychological health, and relational aspects.

R7 DISTRESS IN PRE-CHIRURGICAL AND PRE-CHEMOTHERAPY PHASES IN WOMEN WITH BREAST CANCER: PSYCHOLOGICAL IMPLICATIONS AND RISK FACTORS

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Background. The purpose of this study was:

1) to describe the women's experiences after having received a breast cancer diagnosis in terms of anxiety, depression and distress in two phases along the cancer journey: the pre-surgery phase and the pre-chemotherapy phase;

2) to model predictors of distress in the two groups, using a cross-sectional methodology of the following variables: age, stage of the disease, education, employment status, level of anxiety and depression.

Methods. The data were collected in the Breast Unit of the Istituto Clinico S. Anna, Brescia, via a psychological screening program. Of 227 consecutive patients, 196 gave consent and completed responses for the administration of three questionnaires: BDI-II (Beck et al., 1996), STAI (Spielberger et al., 1983) and PDI (Morasso et al., 1996). 106 patients were assigned to Group A (pre-surgery phase) and 90 patients were assigned to Group B (pre-chemotherapy phase). Anxiety, depression and socio-demo variables (age, education, employment status, stage of the disease) were entered in a stepwise multiple regression analysis to predict the perceived distress level.

Results. In Group A, 48.2% of the women reported a significant level of anxiety and 38.5% reported at least a mild to moderate level of depression; in Group B the levels of anxiety and depression were respectively 44.3% and 37.3%. The Mean of PDI score was 26.13 in Group A (SD = 9.13) and 26.77 in Group B (SD = 8.39). In Group A, the prediction model ($F(2.92) = 71.180$, $p < .001$) showed anxiety and depression as significant predictors and accounted for approximately 60% of the variance of PDI scores. In Group B, depression and age emerged as pre-

dictors, and this model (F (2.86) = 71.798, p <.001) explained 62% of the variability in the PDI scores.

Conclusions. There were no significant differences between the mean of Group A and that of Group B in terms of anxiety, depression and distress. In both A and B groups, correlations were identified between the presence of distress and anxiety and depression, but not with socio-demographic variables. However, differences were noticed in the predictors of distress in the two phases: in the Group A, anxiety and depression are the components that emerge with greater strength in determining the perception of the level of distress. In the Group B the level of anxiety was excluded from the model and the predictive variables were depression and younger age.

Thanks to Priamo Association, Brescia.

R8 CAREGIVING WORRIES AND NEGATIVE HEALTH OUTCOMES IN FAMILY CAREGIVERS OF ONCOLOGICAL PATIENTS ASSISTED AT HOME

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Background. Caregiving to a family member with cancer might have health implications. However, limited research has investigated the psychophysical health of family caregivers of oncological patients staying at home. In our previous study it has been demonstrated that a prolonged and intense worry in daily life is a crucial variable compared to caregivers' well-being, determining important consequences in terms of psychophysical symptomatology. This research was designed to further examine the well-being of family caregivers, investigate the domains of worry and assess to what extent "content-dependent" worry could adversely affect the caregivers' health.

Material and methods. The sample consisted of 100 family caregivers (73 female, 27 male) of oncological patients assisted at home. Participants completed a battery of self-report questionnaires, including the Penn State Worry Questionnaire, the Worry Domain Questionnaire, the Hospital Anxiety and Depression Scale, the Family Strain Questionnaire Short Form and the Psychophysiological Questionnaire of the Battery CBA 2.0. They underwent tests during the home-care request.

Results. The level of worry was medium-high among participants (M 53.56; Sd 11.09) and it resulted that caregivers worry more about work (M 5.70; Sd 3.54), future (M 5.42; Sd 4.21) and self-confidence (M 4.12; Sd 3.67). Depression (M 9.22; Sd 3.97), anxiety (M 10.37; Sd 3.77) and somatic symptomatology (M 45.62; Sd 12.34) levels resulted mild, while strain level high (M 19.18; Sd 7.23). Statistical analyses confirm the conclusions of the previous study, revealing a significant positive correlation between worry levels and caregivers' psychophysical health. Innovatively, it has been highlighted that who has higher scores of worry about work shows also higher levels of strain ($p = 0.19$), somatic symptoms ($p = 0.12$), anxiety ($p = 0.19$) and depression ($p = 0.05$).

Conclusions. Not only trait-worry ("content-free" measure), but also "content-dependent" worry is associated with strain and negative health outcomes. People may worry about different targets and it might be useful to further investigate what are the specific worries of family caregivers in order to promote their physical and emotional well-being. Health care personnel should identify the 'worriers' caregivers early and treat them properly so that they can maintain their own health and provide the best care possible to the patient.

R9 WHAT PATIENTS THINK ABOUT FOLLOW-UP

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Background. The increasing of long survivors patients (pts) is creating some difficulties in Oncology Departments. It has open a discussion about follow-up (FU) management. The aim of our study was to assess the attitude of patients towards FU.

Materials and methods. We investigated pts personal experience, feelings and mood before FU, main worries and fears, meaning given to the FU and satisfaction about FU procedures. From February 2012 to March 2013, patients in FU were interviewed using an anonymous structured questionnaire, before the visit with their oncologist. Our sample is made of 450 patients: 63.3% female; average age is 62 (range 34-85). Most prevailing pathologies are: gastrointestinal (46.2%) and breast (42.6%). To assess the effects of FU, patients were allocated into three groups, regarding the number of years of their FU: a) less than 5 years (53.5%), b) between 5 and 10 years (33.6%), c) more than 10 years (12.8%).

Results. 62.2% patients feel trust and serenity, 21% feel anxiety, 15% fear and worry. Prevailing worries are linked to the disease recurrence (44.9%), fewer pts are worried about the possibility to face another surgery (15.3%) or another chemotherapy treatment (9.8%). A high percentage of pts is not worried (29.8%). Most important clinical meanings given by pts to FU are: the evaluation of their health situation (37.8%) and the early detection of the disease relapse (22.4%); 25.5% of pts give FU a psychological meaning: maintain the relationship with the oncologist and reassure themselves. 44% pts of group b) and c) live the clinical control more from an emotive perspective; 74.1% of pts of the c) group consider the oncologist as the reference point for all health problems. 72% of pts are satisfied about FU procedures, 9.8 % would prefer to undergo fewer examinations and 11.6% would prefer to have more meetings with the oncologist.

Conclusions. Data show a strong link between pts and oncologist, but also pts difficulties in detaching. Economic difficulties and planning problems will oblige Oncology Departments to think about moving FU to different clinical professionists (practictioners or trained nurses). It's important to increase communication and cooperation between these new figures from the beginning of treatment. The change of professional figures will give pts the feeling of a multidisciplinary team.

R10 DISTRESS, HOPELESSNESS, HELPLESSNESS: MEASURE TO CURE

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Background. Detect and respond to psychological distress in cancer patients is a clear indication that the Italian Scientific Community has explained in the "Guidelines for the psychosocial care of cancer patients-AIOM".

Materials and methods. In March 2013, at Azienda Ospedaliera "Ospedale Maggiore" of Crema has started a systematic screening of distress like sixth vital parameter in patients hospitalized into Medical Oncology Operative Unit. The beginning of the detection, like result of the hospital staff participation to HuCare project, was preceded by a protocol drafting. This protocol is shared between medical and nursing team and psycho-oncology staff and is located into the "Quality System" as Specific Operative Statement of Unit. The identified screening tool is the Distress Thermometer (D.T., cut-off ≥4 indicative of clinical significance) completed by a report containing a psychological evaluation and/or psychopathological diagnosis made by the psychologist/psychotherapist. The evaluation is performed in the first 48 hours of the hospitalization, if compatible with patient clinical conditions.

Results. In two months were completed 84 screenings on 105 hospitalizations. Here under data came out like screening result: 5 surveys were not carried out for patients abstention; 7 surveys received a D.T. = 0 score; 22 surveys received a D.T. ≥4 score (mild distress); 32 surveys received a D.T. 5 to 7 score (moderate distress); 18 surveys received a D.T. ≥7 score (marked distress). After clinical investigation, we found that most of the surveys identified as moderate or marked distress were due to serious worries about the emotional and organizational family "destiny", related to unfavorable diagnosis and/or prognosis (the prevalence of hospitalizations is for diagnostic test or first-line chemotherapy).

Conclusions. The low percentage of denials suggests that the treatment has been well received by patients. The collaboration between medical and nursing team and psycho-oncology staff has guaranteed a continuous multidisciplinary treatment of patients. Our data will be deeply investigated in the future months in order to evaluate the impact of suggested psychological treatment on the basis of D.T. score.

R11 THERAPEUTIC INFORMATION AND EDUCATION IN ELDERLY PATIENTS AFFECTED BY LUNG CANCER UNDERGOING ORAL CHEMOTHERAPY TREATMENT

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Background. More than 50% of lung tumor affected patients aged 65 years; more than 30% aged 70 years. Despite this data elderly patients are poorly represented in clinical studies primarily due to restrictions imposed by inclusion and exclusion criteria regarding comorbidity and low performance status. The use of antiblastic drugs has been normal practice for years in the treatment of neoplastic conditions. It is a dramatic event for the patient who must confront this new experience with questions, doubts and uncertainties. Primary objective: to evaluate the patient's perception of oral chemotherapy; to evaluate the frequency of humour disturbance in elderly oncology patients. Secondary objective: to develop a reliable method in terms of communication and therapeutic education to use in the assistance of elderly oncology patients undergoing oral chemotherapy; to reduce psychological problems in elderly oncology patients and to increase compliance with treatment through intervention to demonstrate efficacy by early identification of the most vulnerable patients and to improve their psychosocial health.

Material and methods. Two groups of subjects were used for the present research, one being used as a research sample and the other as comparison. The research sample consisted of 51 subjects already treated in first-line for lung cancer having undergone cycles of chemotherapy with navelbine, who underwent a battery of tests at two different times: at the beginning of the study and after 3 months from first evaluation. Therapeutic education and psychological support were given. The control group consisted of 30 subjects affected by lung cancer treated with navelbine who underwent only the psychodiagnostic battery. An interview was prepared to investigate the level of information on diagnosis, satisfaction with the information received, perception of oral chemotherapy and clinical characteristics and the needs of the patients. Emotional state was evaluated with the GDS and a patient was defined as depressed with a points total of 7, quality of life was evaluated with a multidimensional questionnaire; functional state was investigated by the ADL scale, comorbidity by the Charlson scale, cognitive function by the MMS.

Results. Preliminary results suggest that informative intervention significantly reduces anxiety and depression improving patient satisfaction regarding information received and favoring a better acceptance of oral chemotherapy treatment.

R12 PSYCHOLOGICAL SUPPORT AND INFORMATION POINT FOR PATIENTS AND FAMILY IN PNEUM-ONCOLOGY DH: THE PROJECT "UN COLORE PER LA CURA"

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Background. To improve patient communication within oncology wards, to encourage their involvement in decisions and disease management. Accordingly the pneumo-oncology DH has, from 2007, launched the project "Un colore per la cura": psychological support and information point for patients and family in pneumo-oncology DH. The project has been designed to contribute to greater understanding and involvement when dealing with decisions in the oncological field, producing a better interaction between patients and medical staff. Primary endpoints are: to provide information on all aspects of the disease; to provide, to the patient and family, an area where information is available, to address doubts, to discuss emotional issues and interpersonal relationships, providing psychological and/or psychiatric support to patients following diagnosis and/or during chemotherapy treat-

ment in order to minimize psychological suffering and to help rehabilitation.

Material and methods. The study was conducted on a group of 685 patients, heterogeneous in respect to age, sex and level of education, attending the pneumo-oncology department at A.O Monaldi Hospital in Naples, affected by lung cancer and undergoing multimodal treatment. A waiting area was designated as an information point with appropriate informative poster material addressing the most commonly experienced collateral effects of therapy and methods of dealing with them with the constant presence of a psychologist. During the first access to the DH unit the patients undergo a psychological assessment with the psychologist with the compilation of the 'thermometer of distress' and a test for evaluating anxiety and depression. At the conclusion of the discussion with the psychologist the patients receive a letter explaining the implications of the disease and points of reference to access psychological support whenever necessary and an information form on collateral effects of therapy. A full assessment is provided to the doctor regarding the psychological state of the individual patient. For patients exhibiting significant psychological issues a further assessment is carried out with immediate psychological support to enable better coping with the disease, reducing both physical and emotional difficulties.

Results. Preliminary data suggests that prompt intervention regarding information and psychological support significantly reduces anxiety and depression improving patient satisfaction.

R13 ANALYSIS OF MARITAL DISTRESS BEFORE AND AFTER LABORATORY NARRATIVE MEDICINE, IN COUPLES WITH A SPOUSE RECEIVING CHEMOTHERAPY. DS12 STUDY

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Background. The DS12 study is an observational study, without a control group, performed at the Day Hospital "G.da Procida" of Salerno. The aim of the study was to see how and what affects the distress in a relationship when a devastating event such as cancer occurs and whether using the narrative medicine occur, if possible, mechanisms of adaptive coping.

Materials and methods. Between January 2011 and January 2012, twenty couples, in which one partner was diagnosed with cancer and had to start adjuvant chemotherapy, were enrolled in the DS12 study. The twenty pairs were composed of 10 men diagnosed with colon cancer and 10 healthy women and 10 women diagnosed with breast cancer and 10 healthy men. The DS12 study uses the Distress Thermometer (DT) and the Psychological Distress Inventory (PDI). The patient and his respective spouse, drew up the DT and the PDI, in two stages, the starting day of chemotherapy (T0), and at the end of treatment (TX). After administration of the TD and the PDI at time zero, the patients and their spouse were sent to a group of narrative medicine. The TD and the PDI were administered for the second and last time TX. The group of narrative medicine was divided into one monthly meeting for a period of 6 months. Each meeting was attended by four pairs: 2 with their sick husband and wife with two healthy and the sick wife and healthy husband.

Results. The results of the DS12 study show that the cancer event is related to high levels of distress, not only for the patients, but also in the couple because their partners showed significant levels of emotional distress related to fear of illness, loss of a spouse/in a lifetime, the increase of responsibility for the education of children and of everyday life. Problems with sexuality were found in all the 4 groups examined. After the narrative medicine laboratory have been shown significantly lower levels of distress in all the 4 groups examined and the problems connected with sexuality and physical appearance have considerably improved.

Conclusions. The significant decrease in the observed values of TD and the PDI cannot be charged at the end of chemotherapy, because the tests were administered during the last administration of the drugs, but the narrative medicine laboratory has stimulated patients and their spouses to develop adaptive coping strategies to deal with the stressor events of the disease and to reduce the negative emotional reactions.

R14 PSYCHOLOGICAL MORBIDITY IN INFORMAL FAMILY CARE GIVERS

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Background. Psycho-oncologic interventions on cancer patients have been reported to be associated with significant, small-to-medium effects on emotional distress and quality of life (QoL) but little is known about the way psycho-oncologic interventions on informal caregivers (CGs) could affect cancer patients global care. Informal, unpaid, family CGs provide the majority of cares for cancer patients in Southern Italy. As caring for an ill or disabled family member imposes a well-documented burden on the CG, physical, psychological, emotional, and social sufferings are very likely to happen in cancer informal CGs, affecting both CGs' QoL and their ability to take care of the patient. We speculate that CGs' psychosocial distress is often underestimated in our community and that interventions improving CGs' ability to cope with stress situations could finally result in some benefits for cancer patients. Comprehensive support for patients and their family CGs should be introduced early, so the purpose of this study was first to investigate the incidence of psychological morbidity, such as anxiety and depression, in CGs of cancer patients referring to Oncologic centres of Cosenza Azienda Sanitaria Provinciale.

Materials and methods. From January to April 2013, 71 CGs were recruited: 67 from Castrovillari, Paola and Rossano Medical Oncologic centres and from Psyconcology Unit, and 4 from Cassano hospice. All CGs (14 males and 57 females) but one were family CGs; median age was 47 (range 24-79) years. In all participants anxiety and depression were measured with Hamilton anxiety rating scale and with Hamilton rating scale for depression, respectively.

Results. Forty-four (61%) CGs had at least a clinically relevant anxiety and/or a slight-to-severe depression. A slight depression was detected in 37 (52%) CGs; 7 CGs had a moderate depression and only one was found to have severe depression. Fourteen (19%) CGs showed clinically relevant anxiety, while anxiety was not clinically relevant in 35 CGs.

Conclusions. Results of the first step of this study suggest that psychological morbidity affects informal family CGs. According to these preliminary screening on anxiety and depression, in the following step CGs will be offered some psychological interventions. The hypothesis we warrant to test is that promoting CGs physical and emotional well-being should finally result in the best care possible for cancer patients.

R15 PATIENT AND COMPANION CHARACTERISTICS AND THEIR CONTRIBUTION TO QUESTION ASKING IN FIRST ONCOLOGICAL BREAST CANCER CONSULTATIONS

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Background. Companions often accompany patients to cancer consultations and participate in the encounter. While several Italian surveys have been conducted on cancer patients, general information needs, the characteristics of patients and companions and their contribution to question asking in cancer consultations have not been approached.

Aim. To provide first descriptive evidence on: 1) the characteristics of unaccompanied and accompanied Italian breast cancer patients and their expressed information needs, and 2) the role of companions and their contribution to questions asked during the consultation.

Method. Seventy female patients with breast cancer at their first consultation with the oncologist were recruited in the first six months of 2010 in the out-patient clinic of the Medical Oncology Unit of the Hospital Trust of Verona. Either for the patient or the companion pre-consultations were collected sociodemographic data, state anxiety inventory, general health questionnaire, patient health questionnaire depression scale, control reference scale, decision self efficacy scale and post-consultation (shared decision making questionnaire, satisfaction with decision scale) measures. Information needs were defined by the number and type of questions asked during the consultation. Companion's questions were also classified in terms of function.

Results. In our sample 69% of patients were accompanied, usually by one close family member, either husband or adult child. Non-employed or retired patients and those with a preference for a passive role in decision making were more likely to be accompanied. Unaccompanied patients and accompanied patients were equally active in asking questions which in number went far beyond those reported for other cancer patients in the literature (a mean of 18, 12 when excluding administrative questions, compared to 9). Companions asked fewer questions than patients and their presence did not suppress patients question asking. They often added new topics to discuss about.

Conclusions. The verbatim analysis of questions posed by patients and companions can help oncologists to better target their information needs. In our study companions showed to play a relevant role in supporting and sharing information with the patient, contributing positively to question asking, without suppressing the information needs of their kin patient.

R16 COUNSELLING FOR THE CAREGIVER OF ONCOLOGICAL PATIENT IN ADVANCED PHASE OF ILLNESS

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Background. The caregiver's burden depends on affective involvement and difficulties to manage the prescribed therapies. The questionnaire that we use for survey has the target to investigate how the caregiver can manage intramuscular and subcutaneous therapy of his patient. How does the family member engage this perspective?

Material and methods. The survey has developed in 2 months and the questionnaire has been delivered to 20 caregivers. The pattern reflects the reality of our ward: the turn over of patients from ward to domicile and from domicile to ward, the recruitment of caregivers is based on these conditions:

- patients of caregivers had to be admitted at Dh or at hospitalization;
- the board discharge letter of patients must provide administration of medicine through intramuscular way or subcutaneous way.

The questions of questionnaire were:

- In the board discharge letter from DH or hospital admission has the doctor prescribed for your family member drugs to administer by injection?
- If your family member needs an injection and you are not able to do it, who must you contact?
- During the access at DH or at hospital admission of your family member, has anyone taught to do injection?
- Do you know the difference between intramuscular and subcutaneous injections?
- Is it important that the person who takes care of a family member has to be trained to do injections?

Results. The caregiver is mainly female (25% male, 75% female) and is 50-60 years old. The data from the reading of questionnaires show that a lot of caregivers of discharged patients can't do injections even if they have been prescribed by the doctor as home therapy. The difference between intramuscular and subcutaneous injections is quite plain: 15 caregivers have answered that they know the difference while only 5 caregivers don't know it. A lot of them empower an expert person or a worker of health branch. The caregiver asks to be practiced but at the fifth question 56% say that the person who takes care of a patient be trained in performing injection. 33% say that practice is quite important and only 11% consider it not important.

Conclusions. The caregiver considers important to be practiced to take care come better of his family member: the answer of caregiver to this question has to be a motivation for our work. There is a dissatisfied need that the nurse can satisfy by a specific counselling that through the practice can give practical support and psychological support, conducing to decrease caregiver's anxiety.

Session S • Miscellanea

S1 MONOINSTITUTIONAL STUDY ON THE ACCESS TO MEDICAL TREATMENTS IN RELATION TO THE SOCIAL STATUS OF THE CANCER PATIENT CURED AT THE VENETO ONCOLOGY INSTITUTE OF PADUA (IOV)

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Background. The National Health Service (NHS) in Italy is a public system of universal nature that guarantees health care to all citizens. Few Italian studies relate the therapy received by a cancer patients with their socio-economic status, so we decided to analyze the situation of the Veneto Oncology Institute of Padua (IOV).

Materials and methods. It is an observational monoinstitutional study conducted on 886 patients (pts) treated at the IOV from May 2006 to December 2011. They were selected from the Onco-AIFA, a web-based national Italian registry used to monitor anticancer high-cost therapies. The socio-demographic data were obtained from medical records. We verified if there are differences in access to treatments (number of diagnostic tests, chemotherapy treatments, specialist and follow visits) in association with the socioeconomic determinants. We analyzed the survival differences in connection with demographic and clinical characteristics. The statistical analysis was performed using the Kruskal-Wallis test and the Cox model.

Results. There are 520 pts evaluable of the 886 pts selected: 42% suffering from colorectal cancer, 28% lung cancer and 30% breast cancer. The median age is 63 years (41% male). With regard to the profession the sample is divided as follows: 34% traders/artisans/workers, 25% technical professions/office workers, 14% highly specialized occupations, 25% retired/housewives. The statistical analysis shows no significant differences in the number of exams and medical services in relation to the profession, except one that regards the mean number of chemotherapy infusions (25 manual professions vs 20 other professions, $p = 0.007$). The socioeconomic variables do not affect survival, unlike the age [hazard ratio (HR) 1.42, $p < .001$] and the type of cancer (HR 0.72, $p < .001$). The average cost of benefits per pt is about 4,600.00 euro/year, there is a major expense for traders/artisans/workers compared to other professions (+19%).

Conclusions. The analysis of the sample of cancer pts did not reveal significant differences if it comes to access to care, so the system does not seem discriminatory. Probably these differences are homogenized by the state of economic well-being enjoyed so far by pts of the IOV.

S2 THE ONCOLOGY AND THE HOSPITAL CARE IN PIEDMONT AND VALLE D'AOSTA: 10 YEARS OF ONCOLOGY NETWORK

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Introduction. The Oncology Network of Piedmont and Valle d'Aosta (ROPVdA) has the goal of treating and assisting cancer patients along the pattern of care by offering multi-disciplinary and administrative assistance through the Case Management Services (CAS). The Oncology Network aims to: overcome the regional heterogeneity; achieve increasingly higher standards of treatment; simplify the access to services; bring the services to the context of the life of the person in need of care; identify uniform and consistent diagnostic and therapeutic patterns of care; develop an activity of cutting-edge research with the consequent transfer of the results obtained to the clinical setting.

Materials and methods. To monitor the activity of ROPVdA, activity indicators based on administrative data were analyzed.

Results. Between 2001 and 2011 the weight of cancer care on overall hospital care has been reduced (inpatient days for cancer care decreased from 12.8% to 10.4%). The general reduction in hospital care (-9% of admissions and length-of-stay) was more marked for cancer treatments (-17% of admissions and -20% of patient days). In 2011 cancer care represents the 13.1% of total hospital admissions and 13.7% of total patient days. The weight in terms of DRGs reimbursement tariffs reaches the 16.5% due to the major complexity. Usage of day services for cancer care has been stable in the past 5 years (about 40% of daily accesses). Between 2001 and 2011 hospitalization rates due to cancer among residents decreased in a homogeneous way in all the ASL, with a reduction of heterogeneity. Migrations to other regions for cancer care are stable over the analyzed time-period (7.9% in 2001 and 7.6% in 2011) with a degree of heterogeneity between the ASL of residence. Usage of CAS and GIC by newly diagnosed cases among residents in Piedmont has increased from 2006 (18%) to 2011 (30%), with wide differences among the type of cancer (from almost 60% for breast to 12% for bladder).

Conclusions. The systematic identification and estimate of indicators will allow critical evaluation and the return to the hospital management for any corrective action. The goal is to improve patterns of care for patients, providing them with correct information on the quality of our services and provide access to useful information.

S3 PHARMACOGENOMIC ASSESSMENT OF TAXANE-BASED REGIMENS TOXICITIES: A SINGLE-CENTER EXPERIENCE

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Background. Taxanes are active agents widely used to treat many solid tumors. However, the utility of taxane-based therapy could be limited by gastrointestinal toxicities, hematological toxicities, hypersensitivity and cumulative neurotoxicity. Taxanes are metabolized by CYP3A4 and CYP3A5 isoenzymes, and they are a substrate for the ATP binding cassette multidrug-transporters ABCB1. Metabolic pathways of these antitumor agents need a thorough evaluation to understand why some patients experience severe adverse effects. Aim of our study was to evaluate the association between taxane-related toxicities and their metabolism-related genetic polymorphisms in patients affected by solid cancers undergoing taxane-based chemotherapy regimens.

Patients and methods. We examined 182 adult patients, ECOG performance status ≤1, affected by solid tumors who un-

derwent treatment with taxane-based regimens in adjuvant or metastatic setting, planned for at least 3 courses of therapy. Through a peripheral venous blood sampling we genotyped them for selected polymorphisms and ABC-transporters that may influence cellular sensitivity to taxanes: CYP3A4*1B (A>G), CYP3A5*3 (G>A) and ABCB1 (1236 C>T; 3435 C>T). SNPs (single nucleotide polymorphisms) were characterized by pyrosequencing. 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 evaluated in 182 patients (12 males and 170 females). Median age of patients was 59 (range 30-82). Patients who received taxanes were 95 in adjuvant setting and 87 in the metastatic one. We observed a significant association between normal homozygous genotype for ABCB1 polymorphism (3435 C>T) and lower toxicity during therapy with taxane-based regimens ($p = 0.012$). An association between mutant homozygous and normal homozygous genotypes with dose limiting toxicities was demonstrated, even though not statistically significant ($p = 0.058$). A larger cohort of patients must be investigated. The multivariate analysis results were independent from the different taxane-based regimens adopted, from the age and stage of disease.

Conclusions. ABCB1 3435 C>T seems a toxicity predictive biomarker for taxanes. On the other hand, a larger cohort of patients must be investigated to define the role of CYP3A4, CYP3A5 and ABCB1 (1236 C>T) polymorphisms.

S4 BRCA1-BRCA2 MUTATIONS IN FAMILIAL BREAST AND OVARIAN CANCER DETECTED IN GENETIC COUNSELING ONCOLOGY (CGO) OF MANTOVA. RECURRENT AND NEW MUTATIONS VERSUS FAMILY PHENOTYPES

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Background. Germline autosomal mutations in *BRCA1/BRCA2* genes predispose to breast and ovarian cancer. The mutational spectrum varies among ethnic groups and geographic regions.

Patients and subjects. In 8 years 812 families were selected for risk of hereditary breast and ovarian cancer. We identified 56 pathogenic mutations among 138 index cases and SIGU guidelines were used.

Methods. Genomic DNA was extracted from peripheral blood. *BRCA1/2* exons and intronic-exon boundary regions were directly sequenced and large genomic rearrangements (LGRs) were performed by Multiplex Ligation-dependent Probe Amplification.

Results. We identified 56 pathogenic mutations among 138 index cases studied, 29 in *BRCA1* and 27 in *BRCA2*.

BRCA1: we found 1 intronic mutation (IVS), 6 large genomic rearrangements (LGR), 4 frame-shift mutations (F), 6 non-sense mutations (N), 8 missense mutations (M) and 6 missense mutations are unknown variants (UV). The *BRCA1* mutations with higher recurrence were in exon11. Ten of these mutations were detected in probands with a family history of breast cancer (BC) plus ovarian cancer (OC). In *BRCA1* we identified 3 novel mutations: c.1918C>T (p.Gln640Ter) in exon11; c.2231T>G (777Stop) in exon11; c.2531G>A (p.Ser844Asn) in exon11 associated with a large delection of exon3. In pBRCA1, the amino acid residue Trp1837 is involved in the formation of BRCA1-MLH1 complex and the mutation p.Trp1837Arg (c.5509T>C in exon24) was found to be responsible of substantial modifications for the BRCA1 structure (Quaresima et al., 2006). This mutation occurs in a proband with individual history of breast, ovarian an colorectal cancer (BC + OC + CCR). We observed the delection of exon24, the loss of all amino acid residues of the BRCA1-MLH1 interaction site, in a proband with BC and a family history of CCR.

BRCA2: we found 1 intronic mutation (IVS), 11 frame-shift mutations (F), 2 non-sense mutations (N), 11 missense mutations (M), 10 of which are UVs. The *BRCA2* mutations with higher recurrence were in exon11 (14/27). In *BRCA2* we identified 5 novel mutations: c.7372dupT (p.His2455Serfsx4) exon14; c.7987delG (2663Stop) exon18; c.902A>G (p.Asp301Gly) exon10; c.3090C>T (p.Phe1030Leu) exon11; c.3709G>C (p.Ala1237Pro) exon11. Two novel mutations occurred in probands with BC+OC.

Conclusions. In our small mutated and affected population no correlations occurred with type of mutations, cancer phenotypes, age of diagnosis, hormonal status and her-2 status.

S5 CLINICAL PHARMACOGENETICS OF DPD FOR PRETREATMENT SCREENING OF PATIENTS TO BE TREATED WITH FLUOROPYRIMIDINE THERAPY

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Background. DPD deficiency is the result of loss-of-function mutations within the DPYD gene. The IVS14+1G>A and 2846A>T variants are associated with severe DPD impairment as a result of a 165-bp deletion in the DPD mRNA or a change of the acidic aspartic acid to the aliphatic valine, respectively. In this study, we describe the spectrum of toxicities of fluoropyrimidines in patients carrying the IVS14+1G>A and 2846A>T variants.

Methods. Data were collected from 550 patients with gastrointestinal, breast and pancreatic cancers. They were evaluated for DPD genotype upon development of grade 2 non-hematologi-

cal and 3 hematological toxicities (CTCAE v.4) after standard fluoropyrimidine-containing regimens. DNA was extracted from blood and IVS14+1G>A and 2846T>C DPD variants were screened on a Real-Time Life Sciences 7900 HT platform. The study was approved by the local Ethics Committee.

Results. A total of 26 IVS14+1GA, five 2846AT, one IVS14+1AA and one 2846TT subjects were identified. Toxicities in all subjects were G3/4 diarrhea (100%), G3/4 mucositis (48%), febrile neutropenia (45%), G3/4 thrombocytopenia (38%), G3/4 anemia (24%), G2/3 hand-foot syndrome (14%), G3 dermatitis (7%) and G2/4 alopecia (7%). The IVS14+1AA patient showed G3 diarrhea, G3 mucositis, G3 thrombocytopenia, febrile neutropenia, complete alopecia and *Staphylococcus aureus* sepsis. This patient required 20 days of hospitalization and management with antibiotics and supportive care. The patient survived because she was given a reduced 5-FU 250 mg/m^2 test dose without folates, while the 2846TT patient deceased after the first cycle of FOLFOX4 treatment because of G3 diarrhea, G4 mucositis, febrile neutropenia and G4 thrombocytopenia.

Conclusions. Patients carrying the deleterious IVS14+1G>A and 2846T>C variant alleles display severe toxicities which are fatal in homozygous variant subjects. Although the frequency of IVS14+1G>A allele is low, the screening for DPD mutation is clinically relevant to avoid the severe toxicities or death in patients treated with fluoropyrimidine-containing regimens. This finding suggests the usefulness of pre-treatment screening of DPD in patients candidates to fluoropyrimidine treatment.

Study supported by the Italian Association for Cancer Research (AIRC) and the Istituto Toscano Tumori (ITT).

S6 "VANDA PROJECT": A SCREENING PROGRAM FOR CERVICAL AND BREAST CANCER IN TANZANIA. DATA COLLECTION, MONITORING AND ANALYSIS

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Rationale. In the sub-Saharian Africa the 1st and 2nd leading causes of cancer death among women are respectively cervix and breast cancer. Early diagnosis is the only possibility to timely treat these cancers. The region of Mwanza covers an area of approximately 14 million inhabitants: females represent 51% of the population. In this area, no screening and/or prevention programs are available. There is a strong need to sensitize the female population to undergo clinical and instrumental tests for cervical and breast cancers early diagnosis.

Objectives. Vanda Project's aim is to screen women aged 15-64 years living in the 12 districts of Mwanza and to create a structured data base to collect the main cervix cancer risk factors (HPV positivity, number of pregnancies, age of the first sexual intercourse, use of oral contraceptives) and breast cancer risk factors (genetic, hormonal and reproductive issues).

Methods. Local media invite women to meet the multidisciplinary team operating within the districts using a mobile unit. Pap smear, clinical breast examination and training of the local physicians along with training of the population to perform breast self examination are the main activities of the team. Biopsy samples are locally examined while the biological characterization of positive cases is carried out at the Romagna Cancer Institute (IRST, Italy). Clinical, laboratory and epidemiological data are entered into the database and are periodically sent to the IRST Biostatistics Unit for monitoring and statistical analysis.

Results. From May to December 2012, 2155 women from 5 districts took part in the program: 91 of them (4%) had clinically evident cervical cancer. An exceptionally high stage distribution at diagnosis was observed: 30% in stage III and 20% in stage IV. To date 408 randomly selected samples have been analyzed by cytology, only 4% with inadequate material. Cytological data of the remaining 392 cases are: 85 (22%) normal; 216 (55%) infections (chiefly mycotic); 72 (18%) precancerous lesions (50% H-SIL according to Bethesda classification); 19 (5%) positive for cancer (mainly stages III-IV). Data entry is ongoing and breast cancer processing is planned for the next months.

Conclusions. This project clearly shows the high feasibility of a cervical and breast cancers screening program in a population at high risk and the opportunity to analyze the widespread major risks factors.

S7 SCREENING CAMPAIGNS FOR CERVICAL AND BREAST CANCER IN UGANDA: A TWO YEARS EXPERIENCE OF ONCOLOGY FOR AFRICA ONLUS

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Background. Cervical cancer (CC) and breast cancer (BC) are the most frequent female malignancies in Uganda (incidence 45.6/100,000; 23.4/100,000 respectively). The 5-yr cancer survival is poor (19% and 45% respectively) because of lack in screening programs and public health facilities. Oncology for Africa is an Italian non-profit organization that cooperates in Uganda. Aim of this study is to evaluate the clinical effectiveness of three screening campaigns and to verify if this experience is sustainable and reproducible by the local medical staff.

Methods. Three missions were held from January 2011 to November 2012 in urban (Kampala, Nsambya Hospital) and in rural (Kitgum, Northern Uganda) areas. Each campaign included a preliminary phase of information consisting into population sensitizing by brochures and radio ads; the second phase includes gynecological inspection and breast palpation according to local methods. Local staff was trained only during the first and second campaign; in particular three nurses were trained during the second mission by local colleagues skilled in the first one. The third mission has been exclusively performed by the local medical staff with a logistic help.

Results. A total of 4752 women were screened, belonging to any religion, with a range of accrual from 49 to 188 pts/die. The major findings are reported in the Table.

Conclusions. Our data demonstrate a growing accrual during the campaigns. An increasing number of PAP test has been performed, probably due to our progressive training addressed to local medical staff. By ameliorating screening procedures we also surveyed a higher rate of precancer lesions and cancer. The present data seem to confirm a 4-fold higher breast and cervical cancer incidence if compared to the official data. At present the local staff is planning a further screening campaign autonomously

managed. This suggests the effectiveness of the training "in loco" and the viability and reproducibility of this screening model, that has been conceived and planned in collaboration with local Health Units.

S7 - Table

	January 2011 pts 884	January 2012 pts 1888	November 2012 pts 1980
Abnormal findings by			
VIA TEST	78 (9.2%)	75 (3.9%)	52 (2.6%)
Breast examination	29 (3.4%)	13 (0.7%)	29 (1.5%)
Second level examination			
PAP TEST	30 (38%)	52 (69%)	41 (78%)
Biopsy/colposcopy	30 (38%)	22 (29%)	12 (23%)
Precancer lesions	10 (33%)	4 (18%)	5 (41%)
Cervical cancer	2 (0.2%)	4 (0.2%)	6 (0.3%)
Breast cancer	1 (0.1%)	2 (0.1%)	6 (0.3%)
Compliance of population	84%	98%	95%

S8 QUICK ELIGIBILITY SCREENING FOR CLINICAL TRIALS (QU.E.S.T.): A NEW STRATEGY TO IMPROVE ACCRUAL IN CLINICAL TRIALS

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Background. Clinical trials (CTs) are the cornerstone for advancing treatments in cancer. However, CTs recruitment remains a considerable challenge even for leading academic cancer centers. According to the Cancer Cooperative Coalition Groups, although 20% of patients (pts) meet CTs eligibility criteria, only 3% are enrolled. Surprisingly, about 30% of accrual sites have no systematic approach for CTs screening, which frequently results in CTs early closure. Here we evaluate the potentiality of QuEST, a software tool that we developed as an aid to CTs accrual.

Materials and methods. For CTs screening only four variables are required by QuEST, three of which are fixed (cancer site, setting and biology) and one is trial specific. Patients, who result potentially eligible, are then referred to the leading CT investigator. QuEST is available to the medical staff at the "Centro Accoglienza e Servizi" (CAS), which is an out-patients office that triages patients with a recent cancer-related diagnosis. Patient characteristics and recruitment rate resulting by QuEST introduction were analysed using the SPSS 17.0.

Results. During February 2013, before QuEST introduction, 71 pts were evaluated by the CAS medical staff. Of these, 45 pts were suitable for oncologic treatment. The most frequent cancer types were colon-rectum (24%), breast (16%), lung (16%), head-neck (13%) and hematological (22%). Eleven (24%) had localized disease and 34 (76%) had advanced disease. Twenty-nine (64%) of the advanced cancer pts were eligible for first-line treatment. Thirty-seven (82%) of these pts started therapy at our center: only four (11%) were considered for CTs eligibility. In the month following QuEST implementation, 30 pts were screened through the software QuEST and ten (33%) pts were referred to the leading CT investigators. Although screening failure occurred in four (13%) pts (detection of CNS metastasis and HCV infection in two pts, rapid progressive disease and refusal of the experimental therapy in the others), a total of six (20%) pts started cancer therapy in CTs. Based on this preliminary results, the CTs screening rate was 3.0 higher after QuEST introduction (33% vs 11%, p <0.001).

Conclusions. QuEST represents an organized and efficient strategy to create a systematic and easy approach for CTs screening. If adopted by others centers, QuEST may help clinical researchers working in a nearby geographic area to realize a network for improving CTs accrual.

S9 PRELIMINARY RESULTS OF REGINE PROJECT: A SURVEY ON RARE CANCERS IN AN ITALIAN REGION

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Background. Epidemiologic data on rare cancers is scarce and their definition is still controversial. One of the most important problems is that their burden of care has not been adequately estimated although they constitute a relevant public health problem. Improving the quality of care for these cancers is a public health priority. Starting from these assumptions an outcome research project has been planned to establish a network of specialized hospitals in an Italian region to produce an epidemiologic picture on frequency, management and outcomes of a sample of rare cancers.

Methods. It is an outcome study to survey all patients affected by GIST, NET, and kidney during a period of 12 months. A dedicated web-page (accessible only to participants) has been created to collect data. Epidemiological, clinical and therapeutic information have been collected at the baseline and at follow-up visits (at 3, 6, 12 months). All the data were anonymous: patients were identified by a numeric code.

Results. A network of 10 hospitals has been established and data of 263 patients have been included. Among our sample 168 patients were males (63.9%) and 171 under 60 years old (65%). The distribution by cancer type showed that during the study period, 147 patients presented a kidney cancer (55.9%), 82 NET (31.2%) and 34 a GIST (12.9%). Patients with kidney cancer are for 74.1% males and in 52.4% of cases right kidney was involved. In 82.6% of cases it was a clear cell cancer and underwent a surgical intervention. Only 33 patients received a medical treatment. Among 34 patients with GIST, 55.9% were males and 22 over 60 years old. Stomach and intestine the most frequently involved sites: a surgical intervention was done to 28 patients (90.3%) and 15 patients (60%) received imatinib because at moderate or high risk of relapse. Among the patients with NET, 67% were over 60 years old and 53.7% were males: the most involved sites resulted lung (26 patients) and intestine (23 patients). Forty-seven patients (66.2%) received a surgical intervention and 40 (48.8%) received drugs. The data of follow-up were collected for 78 patients at 3 months, at 6 months for 54, at 9 months for 35 and at 12 months for 21 patients.

Conclusions. The results of this preliminary phase documented the feasibility of the study and confirmed the great interest of clinicians. This study represented a promising attempt in the assessment of epidemiological and clinical data in an area without a regional cancer registry.

S10 LONG TERM CANCER SURVIVORS. A MONOINSTITUTIONAL CLINICAL EXPERIENCE

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Background. In recent years, the medical and scientific progresses make possible long disease-free periods after cancer treatments, and long survivorship has become a distinct phase of cancer care including surveillance for recurrences, evaluation of medical and psychosocial consequences of treatment, evaluation of the quality of life after treatment, recommendations for screening for new primary cancers and for health promotion. The impact of the treatment on the long-term health of the survivors is substantial. After treatment, the patients are at risk for physical and psycological sequelae depending on stage and treatment modalities. Late effects include organ damage and functional disabilities like cardiorespiratory system dysfunction, neurocognitive problems, premature menopause, gastrointestinal system dysfunction, sexual impairment, infertility, chronic fatigue and secondary malignancies.

Methods. A multidisciplinary team formed by Medical hematologists/oncologists and psychologists was established within the Department of Medical Oncology at the National Cancer Institute of Aviano in 2008. This cancer survivors clinic (O.RA project -Oncologia Riabilitativa- supported by ISS) is devoted to long term cancer survivors (all persons who are previous affected by haematological/solid cancer and treatments-free since at least 5 years), in addition to standard oncological follow-up through a both clinical and rehabilitative standard. This projetc involves a multidisciplinary team: oncologist/hematologist, psychologist, nurse, other physician if necessary (i.e. cardiologist, gynecologist, etc.) and offers a unique clinical approach.

Results. In the last five years we have evaluated 195 patients (29% HD, 26% NHL, breast 19%, other 26%). The cardiorespiratory system dysfunction, thyroid disfunction, osteoporosis are the main late effects found. We have registered in our population 15 pregnancies in 8 women, 16 conceptions in 9 men, and 3 new primary cancers (1 thyroid carcinoma, 2 skin cancers). About psychosocial consequences of treatment, the lymphoma survivors seem to be more fatigued than normal population. Quality of life appears to be poorer in survivors than in normal population in many aspects (i.e. physical and social function, mental health).

Conclusions. In conclusion this program could favourably impact on the new evaluation of hematological follow-up with re-evaluation of the lifestyles and the reintroduction in social life and working activities.

S11 PROPOSAL FOR AN INTEGRATED CARE APPROACH FOR DISABILITY IN ONCOLOGY: A SINGLE INSTITUTION REPORT

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Background. In the last decade survival in cancer patients (pts) has improved with an increased need for health, economic and welfare benefits. The disability assessment (DA) is carried out by Commissions for Assessment of Disability (CAD) of the competent Azienda Sanitaria Locale (AUSL). In Emilia Romagna (ER), CAD can be integrated by a medical specialist (MS) (ER Law (L) 19/02/2008, N4). Patients must be evaluated by CAD within 15 days after submission of the disability request (DR) (L 9/03/2006, N80) and the results of CAD evaluation and relative benefits are immediate. Finally from 01/01/2010, the general practitioner or MS can proceed to request benefits for disability for their own pts by electronic form on INPS (Istituto Nazionale di Previdenza Sociale) web site (L 3/08/09, N102).

Material and methods. We report the experience of Modena AUSL Legal Medicine and Risk Management Service for pts who presented DR in years 2011-12 and were assessed by CAD. The data were retrieved from "Invalidi Civili Web", a software used at Modena AUSL. In 2011-12 the initial DA was not complemented in all cases by MS (in Oncology and/or Hematology).

Results. In 2011-12, 1976 pts with solid or hematological malignancies and assessed according to L80/2006 were included: 1221 pts were evaluated in Modena and Castelfranco district (855 in CAD and 366 at home or during hospitalization by at least 1 member of CAD), 410 in Carpi district (325 and 85, respectively) and 345 in Sassuolo district (210 and 135, respectively).

Conclusions. Our analysis is aimed to show a numerical representation of the phenomenon and to document that the majority of DR occurs in advanced stage of disease, with a failure for pts and families to obtain earlier benefits provided by L. To facilitate the access of DA and to reduce the number of home visits, we propose that CAD should be organized at the outpatient clinics (Divisions of Oncology and Hematology University Hospital (H) Modena; Division of Oncology, H of Carpi and H of Sassuolo). In compliance to ER indications, CAD will be always supplemented by MS, with obvious positive effects on the reconstruction of clinical history and improvement on DA. Moreover, Modena AUSL is working to make the electronic submission of DR possible by MS. This approach applies to a "tailored on the single patient" organization model of care and DA is configured as "taking care of the person with disabilities" through an integrated evaluation by health and social figures.

Session T • Oncology nursing

T1* ASSUMPTION OF PHYTOTHERAPIC TREATMENT AND MANAGEMENT OF SIDE EFFECTS IN PATIENTS UNDERGONE CHEMOTHERAPY AND RADIOTHERAPY

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Background. Complementary therapy in oncology is a topic much discussed. Phytotherapic products are used for symptoms such fatigue, loss of appetite, nausea, vomiting, mucositis, anxiety and to improve the immune system. According to 2010 Istat data, 25% of Italian people consider this therapy as valuable, and 33% of neoplastic patients use it at least once.

Objective. To evaluate the efficacy of phytotherapic treatment for the management of side effects in patients who underwent chemotherapy and radiotherapy.

Materials and methods. In this study, open label, multicenter, we analyzed two cohorts of patients randomized from two hospitals in Turin, Azienda Sanitaria Ospedaliera Universitaria (ASOU) San Giovanni Battista and Ospedale Evangelico Valdese di Torino. First group (called A) used phytotherapic treatment and the second group (called B) used traditional treatments for the management of the side effects. According to literature data, a questionnaire was submitted to a sample of 200 patients (100 patients on A group, 60% ASOU San Giovanni Battista, 40% Ospedale Valdese; 100 patients on B group, 60% ASOU San Giovanni Battista, 40% Ospedale Valdese). The questionnaire was divided into three parts: the first part collects personal data of the patient, the second part uses the rating scale (called WHO) for the analysis of chemo- and radio-therapy side effects; the last part is dedicated to collect data on type and properties of phytotherapic products.

Results. The analysis of data shows that the modal value of the gender was female and that of pathologies was breast cancer. The data recorded in ASOU San Giovanni Battista demonstrate statistical significance on behalf of A group with phytotherapeutic treatment: nausea $p = 0.030$, mucositis $p = 0.024$, pain $p = 0.00001$, asthenia $p = 0.00002$, general illness $p = 0.00001$. The data of the Hospital Valdese demonstrate on behalf of the A group that used phytotherapeutic treatment the following statistical meaningfulness: mucositis $p = 0.00163$, cutaneous toxicity $p = 0.023$, asthenia $p = 0.00548$, general illness $p = 0.00301$. The phytotherapic products most used by the sample were: aloe 96%, calendula 21% and green tea 17%.

Discussion and conclusions. Our data are similar to the literature, especially for the gender of the patients affected, the prevalence of tumoral disease (breast-cancer) and the efficacy of the phytotherapic treatment.

T2* SLEEP-WAKE RHYTHM DISORDER IN PATIENTS UNDERGOING CHEMOTHERAPY

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Introduction. Insomnia affects up to 50% of cancer patients, particularly women, and occurs concurrently with psychological diseases. Symptoms interfering a lot with sleep are flushing, pain, fatigue, breathing disease, chemotherapy adverse reaction and results of paraneoplastic syndromes. Sleep disorder worsens physical, cognitive and work performances and consequently the quality of life (QoL).

Objectives. To investigate sleep-wake rhythm alteration, its influence on perceived QoL in patients undergoing chemotherapy and to highlight the relationship between sleep disorder and predisposing, precipitating and perpetuating factors.

Methods. From May to July 2012 two hundred specific questionnaires were distributed to patients undergoing chemotherapy at Oncology Day Hospital unit of COES service (Centro Onco-Ematologico Subalpino), Azienda Sanitaria Città della Salute e della Scienza in Turin. Only 179 valid questionnaires were returned. Data obtained were statistically analyzed with two-tailed Chi-squared test and showed in graphics and tables.

Results. 79 males and 100 females answered completely the questions. We found out that 65.93% of patients was satisfied about sleep habits and patients older than 60 years complained the greater degree of dissatisfaction. 61.84% of patients referred sleepiness and fatigue during the day ($p = 0.00001$). 45.93% of patients assuming corticosteroids complained about difficulties falling asleep, 47.29% about non-restorative sleep and 36.48% about the time spent sleeping (not enough); comparison between people assuming corticosteroids vs not assuming is statistically significant ($p = 0.03816$). Only 34.87% of total patients assumed hypnotic drugs, mainly females ($p = 0.01703$). A very important discovery is that chemotherapy does not influence sleep disorder ($p = 0.00006$). 16% of patients referred a severe influence on QoL due to sleep disorder and 14% thought it affected their work performances. Finally we found out that patients experienced much tension, fatigue, tiredness, worry and anxiety.

Conclusions. Sleep disorder is perceived less than what reported in literature: we found out a small influence of the disorder on daily life. In agreement with literature sleep-wake rhythm alteration is related with corticosteroids administration, anxiety (emotional impact of diagnosis) and asthenia. Despite the data reported in literature, sleep does not seem to be significantly influenced by chemotherapy.

T3 A RANDOMIZED CLINICAL STUDY ON THE EFFECTS OF LIVE SAX MUSIC ON VARIOUS PHYSIOLOGICAL PARAMETERS, PAIN AND MOOD LEVEL IN CANCER PATIENTS

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Background. Various studies have reported positive results about the use of music in various problematic areas of oncological nursing, especially in pain reduction and promotion of improvements in mood, anxiety level and general quality of life for cancer patients.

Material and methods. The objective of this study was to examine the effects of live sax music on various physiological parameters, pain and mood level in cancer patients. The research design is a sperimental pilot study with randomized controlled trial, structured with one experimental and one control group. Fifth-two patients in Medical Oncology Ward at Policlinico S. Orsola Malpighi in Bologna were chosen to participate in the study and randomized in two groups. The experimental group received standard nursing care as well as a 30-minute live sax performance, while the control group received only the standard nursing care. Systolic and diastolic blood pressure, heart rate, body temperature, glycemia, oxygen saturation, pain level (VASP scale), and level mood (VASM scale), were measured before and after the musical performance, resulting in baseline and post-test values for the patients in the experimental group. The T-test for independent samples, Chi-squared test, and Fisher's exact test were used to examine associations between the two groups on the demographic and clinical variables to be sure of relative sample homogeneity. The Shapiro-Wilk test was used to examine the null hypothesis that the demographic, clinical, vital signs, pain and mood levels were normally distributed. The Mann-Whitney U-test to examine the statistically significant differences in the measured variables between the groups from the baseline to the post-test measurements. The Wilcoxon test to examine statistically significant differences within each group from the baseline to the post-test measurements.

Results. In the experimental group, oxygen saturation ($p = 0.003$), VASP ($p = 0.001$), and VASM ($p = 0.000$) improved significantly from the baseline values, while in the control group no statistically significant change was observed. Further, participants assigned to the test group described their experiences as exceptionally positive.

Conclusions. Live music performed by academically trained medical staff could be introduced to the field of medical care in order to improve cancer patients' quality of life during their hospital stay.

T4 OVARIAN CANCER SYMPTOMS IN 12 MONTHS PRECEDING DIAGNOSIS: MITO-12/ENGOT OV-12 PATHWAY TO DIAGNOSIS OF OVARIAN CANCER

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Background. Early diagnosis of ovarian cancer (OC) remains difficult, with no reliable screening and vague pre-diagnostic symptoms. An intergroup (MITO, MaNGO, NOGGO, BGOG) study was undertaken to describe patient symptoms and sentinel events along pathway to OC diagnosis. First objective of this study was to describe the frequency and duration of symptoms within 12 months previous to OC diagnosis.

Patients and methods. Patients with OC eligible for first-line chemotherapy were recruited to MITO7 (ClinicalTrials.gov Identifier NCT00660842) and MITO12 (NCT01061619) studies, in Italy, Germany, Belgium and France. Consenting patients completed Goff Ovarian Cancer Symptom survey, a self-report instrument describing severity, frequency, duration of 23 symptoms within 8 categories (Table 1).

Results. Between November 2008 and April 2013, 633 patients completed the survey, with median age 60 years (range 21-87). 85% patients were stage III (420, 66%) or IV (115, 18%). At least one symptom in the previous 12 months was reported by 545 (86%) patients (Table 1). Most frequent categories of symptoms reported were "pain" (67%), "abdomen" (67%) and "eating" (57%). Individual symptoms most commonly reported were abdominal bloating (58%), pelvic pain (50%), increased abdominal girth (48%), fatigue (48%). Recruitment into the study is ongoing, through June 2013.

T4 - Table 1
Frequency of symptoms within 12 months previous to diagnosis

Symptom category	N pts (%)
Pain	425 (67%)
Eating	360 (57%)
Abdomen	424 (67%)
Bladder	213 (34%)
Bowels	284 (45%)
Menses	60 (9%)
Intercourse	70 (11%)
Miscellaneous	351 (55%)
Any symptom	545 (86%)

Conclusions. These preliminary data regarding frequency of symptoms in the 12 months prior to OC diagnosis are consistent with results of previous extra-European studies. Further planned analyses, regarding symptom severity, occurrence, duration, and geographical differences among the participating countries will allow a more detailed description.

T5 CONSTIPATION IN CHEMOTHERAPY: PREVALENCE SURVEY OF PATIENTS TREATED AT THE HOSPITAL OF NOVARA

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Background. Constipation is a frequent, untreated and often not reported symptom. Different surveys show a prevalence of this symptom between 10% and 20% in healthy population. These percentages in people who are affected by a cancer until 40%-50%. These surveys aren't conducted on Italian patients, during the advanced stage of illness, during a therapy with opiates. It must value importance that patients give to this symptom and correlation between the symptom self and subjective factors like age, sex and performance status (ECOG) and value ways of action and any benefits. It's necessary to check the system of monitoring symptoms in medical records and correspondence between the shown symptom and notes on the official forms.

Materials and methods. It was built a questionnaire divided into 7 questions, translating the parameters into cognitive elements that are essential for evaluation and measurement of constipation on the basis of National Cancer Institute through the common Toxicity Criteria Adverse Events (V.4.0). It has been made a survey on 100 patients during chemotherapy at the Oncological division in Novara that have been enrolled from 13 to 17/2/12. At the end of the survey their medical records have been analysed and detected useful information through a research form, created for this work. Notes that have been given by patients have been compared with notes of medical records.

Results. The control group is made of 54 women and 46 men with an age between 25 and 83 years (median strip = 61; average = 59.98 +-12.93). 55 patients reported constipation during the last month, 40 of them have never suffered of chronic constipation. Percentage is higher between women. A lot of patients (48/55) call for help specialized persons for the resolution of the symptom, the most asked person is the doctor. About 30% of interviewed declare that they haven't resolved constipation with the adopted cares.

Conclusions. Constipation is a symptom with a high prevalence in oncologic patient during chemotherapy. The note objectively detected is not always similar with subjective perception of constipation. Often there's not correspondence between a reported symptom and the comparison of it in medical records. These notes suggest a necessity of an accurate monitoring and of a standardized valuation of the symptom to increase percentage of success after the treatment and to improve the quality of life of oncological patients.

T6 QUALITY OF LIFE IN PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA DURING CHEMOTHERAPY: EVALUATION WITH EORTC QLQ-C30 (V3.0) QUESTIONNAIRE

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Background. Malignant pleural mesothelioma (MPM) is a highly symptomatic and rapidly progressive malignancy (median survival: 6-18 months in treated patients). Accurate evaluation of the impact of disease and its treatment on quality of life (QoL) is an important goal. Cancer may produce many different symptoms, related to disease or to treatment. EORTC QLQ-C30 (V3.0) questionnaire is an excellent instrument to evaluate patients (pts) functional dimension, symptoms and global health QoL status. The aim of the study was to identify major presenting symptoms (dyspnea, fatigue, pain, and appetite loss) with a validated instrument as EORTC QLQ-C30 (V3.0) questionnaire and the impact in the QoL of pts with MPM during 3 chemotherapy (CT) lines.

Material and methods. From March to May 2013, EORTC QLQ-C30 (V3.0) questionnaire was administrated, every day 1 CT for 3 cycles, to measure QoL in 30 pts with MPM. Twenty-two were men, 8 women; median age 68 years (range 37-84). Sixteen were in first-line (pemetrexed ± platinum compounds), 8 in second chemotherapy (pemetrexed or gemcitabine or vinorelbine), 6 in third (out of second-line clinical trials for progression disease). PS ECOG was 0 (80%) or 1. The change of symptoms and others QoL items during the treatment were analyzed. Clinical stage, response and toxicity to CT were considered.

Results. At first observation more 84% of patients reported pain, dyspnea, fatigue and appetite loss, and 90% had 3 or more symptoms. Pain and dyspnea had a significant effect on global QoL. During CT, changes in QLQ-C30 scores are generally small: we observed moderate reduction of dyspnea, mild reduction of pain and fatigue in pts in first- and second- line CT. Dyspnea increased during third-line CT as so as fatigue and pain. Global health and QoL scale improved during CT in first- and second-line, worsened in third.

Conclusions. The symptoms described in EORTC QLQ-C30 (V3.0) questionnaire capture pts disease experience. First- and second-line CT may have positive effects on the QoL with the control of dyspnea, pain and fatigue (the most important symptoms in pts with MPM). Third-line CT impact on the QoL is not favorable: poor symptoms control and new therapeutic approach is perceived as deterioration of global health. Physician knowledge of pts changes self-evaluated with questionnaire gives the impact of the treatment on pts QoL, and ultimately, whether it should be continued.

T7 WOMEN'S HEALTH PROJECT IN ONCOLOGY DEPARTMENT: A DEDICATED ROOM

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Background. Breast cancer diagnosis and treatment require coordinated efforts of multidisciplinary teams in order to develop and test a new model of intervention, and professional education on assessing optimal methods.

Aims. To increase healthcare and quality of life (QoL) in women with breast cancer, to help them in preparing for chemotherapy, to promote a global approach to the patients, stimulating a process of humanization of the treatment procedures, using complementary therapies (touch therapy, music therapy, massage).

Material and methods. Fifty-two women with breast cancer were enrolled. They had the chemotherapy in two dedicated rooms with particular attention to colors and furniture. The nurses who followed them tried to be in tune with the patients through the "empathic listening" to enhance the emotional closeness and the sense of acceptance perceived by the patients. The patients completed a questionnaire at the fourth chemotherapy's cycle composed by questions about the room's utility (ambient, nurses' presence, music, food's presence in the room and complementary therapies). The patients were followed always by the same nurse.

Results. The results of the satisfaction questionnaire showed that: 98% (51/52) of patients said the room is useful; for 83% (43/52) of patients the affective contact was effective while for 17% (9/52) of them the affective contact was quite satisfactory; for 94% (49/52) of patients it is very important to have always met the same nurses, 64% (34/52) liked very much the room's comfort, 27% (14/52) thought that was very important and the other 8% (4/52) thought it was important; 44% (23/52) liked very much listening to music, 37% (19/52) liked to listen to music.

Conclusions. Many studies have been done and have demon-

strated the usefulness of complementary therapies. Our study also shows that patients have enjoyed this experience. Patients have enjoyed the presence of the same nurse in the room because in this way they felt more confident, more free to express doubts, fears, emotions, they felt more free to express doubts about how manage the side effects at home and so on. What the patients find most helpful is learning as much about the experience as they can. At last but not least our study demonstrated that information from other patients and from dedicated nurses, with a specific preparation, can be useful.

T8 STUDY ON INITIAL NEEDS AND EXPECTATIONS OF THE CAREGIVER (CG) OF ONCOLOGICAL PATIENTS UNDERGOING ANTITUMORAL TREATMENT

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Background. The assistance to oncology patients is given by the CG. The responsibility increases during the illness course. This study was done in order to shed light on problematic situations the CG incurs and their expectations.

Methods. From January to March 2011 in 3 DH in Piedmont the CG responded to anonymous questionnaires at their first contact. The purpose was to discover expectations and knowledge of the CG.

Results. 140 questionnaires: 88% of the CG were family members (68% women, median age 64). There was no significant difference in the results among the 3 DH. 78% declared to be CG out of love, 15% out of obligation, 7% out of circumstances. 27% CG expressed fear and 33% were prepared to fight. 33% CG expected the patient to be healed, 41% an increase of survival, 15% only an improvement in the symptoms, 10% reported to not have specific expectations. On the other hand, the CG believed that 49% of the patients expected to be healed, 24% an increase in survival, 19% only an improvement, 7% believed the patient didn't have any expectations. The CG held a significantly greater expectation of healing than the patients themselves ($p > 0.01$). 53% of CG expected the real diagnosis, 31% a diagnosis without survival, 5% an inaccurate diagnosis, 10% expected to not be informed. 58% CG predicted significant consequences in its daily working, family, and social lives (13% radical and 45% relevant). This information was independent of the stage tumor. Only 66% CG knew the benefits granted from the law 104. 56% CG requested assistance. 57% CG claimed to have confided their emotions, of those 51% with family members, 32% with a psychologist, 17% with the oncology doctor. 50% CG required information in home management of the patient, 26% in managing the therapy effects, 13% in an emergency situation. The majority (87%) believed to have sufficient knowledge pertaining to the collateral effects of the antineoplastic treatment.

Conclusions. No significant difference between the 3 DH. The CG was primarily a female family member. The CG feel fear and fight; they are more pessimistic than the patient about the outcome. The request for assistance overall was <50%. This data reinforces the social and socio-economic priority to invest in CG and support them. CG especially sought assistance for their anxieties and emotions. CG should be more involved in the communication between patients and the health care system. Improving the needs of the CG means improving oncology assistance.

T9 COUNSELLING AND NURSING. NURSE EMOTIONAL IMPACT IN ONCOLOGY

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Background. Counselling is the transmission of skills and competencies to facilitate development of potentialities and improvement of patient resources, and of team, of organizations and community. Counselling skills include understanding of patient needs, welcoming, being authentic, to know how to listen, including and orienting people asking for help. Helping is also to active and press for the full potential of patient, stimulate his activity and removing the obstacles to development, that is "empowerment". The purpose of this study was to collect from nurses the information of their perception about relational and communicative aspects of nursing cancer care.

Materials and methods. An anonymous questionnaire has been developed to evaluate the dynamics and the critical issues about nurses' approach with cancer patients and to explore the emotional nurse impact in front of cancer patient.

This questionnaire was divided into 2 parts:

- on the first one objective data were collected (registry, job and so on);
- on the second one there were questions about communication, nurse perception of disease and the attitude towards the patient and emotional capacity to face death; the questionnaire investigated also about working environment, workloads, and nursing team cohesion and sense of belonging; the last group of questions was about the importance of nurse psychological training.

Results. 180 questionnaires were administered and of these 162 returned. The study showed that a significant percentage (68%) of nurses are able to activate a relationship with patient; 40% of nurses sees the patient as isolated; 36% answers only to physical needs of dying patient. 52% of nurses showed a strong discomfort in management of dying patient. 65% recognizes that training is required for development of skills useful to improve a better perception of patient needs.

Discussion. Nursing is a profession close with suffering: a psychological training aimed to acquisition of informations where the nurse questions itself is very important.

T10 PIACENZA PICC TEAM: OUR FIRST EXPERIENCE

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Background. The patient care requires frequently the avail-

ability of a reliable long-medium term venous access, due to the particular complexity of the chemotherapy regimens, the frequent need for a nutritional or transfusional support and for periodic blood sampling. PICC (peripherally inserted central catheter) and midline are an innovation technology that has substantially changed the approach to the venous system. We describe our first experience in PICC and midline insertion.

Material and methods. Consecutive adult patients attending the oncology-haematology or medical departments were eligible if they needed chemotherapy, nutritional support or long term antibiotic therapy. Four types of possible complications were defined: mechanical, thrombotic, infections and malfunctioning. For insertion no particular position was required, a 7.5 MHz puncturing probe was placed in the inferior third part of the superior harm and a 21 gauge needle was advanced under real-time ultrasound-guidance, preferably into the basilica vein. The Seldinger technique was used to place a 4 French catheter which was advanced into the superior vena cava until insertion into right atrium. In PICC positioning a ECG was performed to verify the correct position of the tip; within two hours after each procedure, an upright chest X-ray, preceded by an ultrasound scanning of the internal jugular vein, was carried out to confirm the PICC position. Catheter-related infections, symptomatic vein thrombosis and malfunctioning were reported.

Results. From June 2011 to April 2013, 223 procedures were applied for 200 onco-haematologic patients (90%) and 23 internistic patients (10%). Nine procedures (4%) have failed; in 169 patients was positioned a PICC (76%) and in 45 patients a midline (20%). A single-needle puncture of the vein was performed in 203 procedures (91%); only 9 attempts failed (4%). Only one nerve and one arterial puncture (without major bleeding) were reported. The main lifespan of PICC was 94 days (range 40-370). Symptomatic deep-vein thrombosis of the upper limbs developed in 5 patients (2.3%). Only three catheter-related infections occurred (0.18/1000 catheter days).

Conclusions. PICC and midline represent the best response to the growing need to get in each patient, both in hospital and at home, a stable and safe venous access, achieved and maintained with the little risk and the best cost-benefit ratio. However, thrombosis remains a major problem, at least in our patients.

T11 NEW ORGANIZATIONAL MODEL FOR OUTPATIENTS AFFECTED BY MULTIPLE MYELOMA TREATED WITH BORTEZOMIB

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Background. During the last 10 years new non-chemotherapeutic drugs with direct impact on cancer cells and the medullary microenvironment have added to the treatment of multiple myeloma (MM). At present the bortezomib (velcade), the first proteasome inhibitor introduced in medical practice, is one of the main new drugs used for treating patients affected by MM. After using the bortezomib for some years, the physicians from the Research Unit on MM at the Seràgnoli Treatment Clinic have valued that almost the 20-30% of patients do not need to have blood drawn before each drug delivery, because, after the laboratory monitoring carried out during the first cycle, no blood toxicity is expected in the following cycles and in the same percentage of patients the medical exam is not necessary as no such neurologic toxicity shows as to benefit from a specialist intervention.

Materials and methods. We addressed this project to patients affected by MM assisted at the hematological out-patient unit and treated with bortezomib in specified days without needing blood drawn and/or medical exam (instead necessary at the beginning of each new treatment cycle). These patients were previously identified and selected by the physicians responsible for this project. Its purpose is to simplify the procedures preceding the infusion of bortezomib, with consequent reduction of the waiting time of patients with respect to the usual delivery times. The conditions of hematological and/or neurological toxicity are verified by a registered nurse. The verification is compared to validated toxicity grading scales used by the main specialized clinics for MM treatment. The nurse will refer to those scales in addition to the patient interview, before proceeding with the infusion of bortezomib.

Results. 134 patients were analyzed following two different procedures depending on they having their blood drawn or not. Waiting times have reduced from 4-5 hours to 2 hours and to 50 minutes.

Conclusions. The advantages for patients having recurring bone pain symptoms and concurrent difficulty in deambulation and autonomy are obvious as well as the large geographical area of origin. Moreover, a further valid consideration concerns the phases of continuing care, where the patient will be cared by the same nurse during the whole treatment period at the out-patient unit. That being so, the supervisor of the treatment process is always the physician whom the nurse refers to in case of need.

T12 REDUCTION OF FEAR AND ACUTE TOXICITY FROM CHEMOTHERAPY WITH A TELEPHONE CALL AFTER THE FIRST CYCLE: A PILOT STUDY OF ONCOLOGY NURSING

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Background. Outpatient chemotherapy shifts the management of side effects from health-care providers to patient and his family. Moreover, chemotherapy toxicity recording is usually performed when patients have recovered from previous cycle side effects and could have forgotten their incidence and/or seriousness. The purpose of this exploration was to determine whether a systematic telephone call 24-48 hours after the first cycle of chemotherapy helps patients to better describe toxicity, prevent possible complication of toxicity and verify the ability to overcome side effects based on oral and written self-care measures previously provided.

Material and methods. One hundred and seventy consecutive patients treated for various cancer types, with different chemotherapy regimens benefited of a telephone call the day after the first cycle of chemotherapy, performed by a nurse and the oncologist. During each call a brief questionnaire was recorded investigating possible side effects and use of drugs as needed. Moreover, at the following visit a satisfactory survey was carried out.

Results. From October 2010 to July 2012 one hundred and seventy calls were done to one hundred and seventy patients;

there were 96 male and 74 female and the mean age was 66 years (range 22-87). Every patient responded and there was not necessity for calling back. Only in 38 cases (23%) it was necessary the intervention of the oncologist to clarify self-care measures for side effects or for patients identified as frail or very anxious. The telephone call was very convenient in reducing acute toxicity of chemotherapy and for psychological support. Indeed eighty-four percent of patients did not require the use of rescue medications. In addition patients and families reported a high rate of satisfaction and resulted more confident with their oncologist and nurse and with the treatment plan, after the call.

Conclusions. We conclude that a systematic telephone call the day after the first cycle of chemotherapy is an easy, feasible and not expensive way to reduce side effects and anxiety for treatment. It provides, at least, an appreciated psychological support and can help in case of usual as well as unusual and/or serious side effects.

T13 ORAL MUCOSITIS IN PATIENTS UNDERGOING CHEMO-RADIOTHERAPY: INTERNAL INVESTIGATION CARRIED OUT IN "FONDAZIONE IRCCS ISTITUTO NAZIONALE TUMORI"

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Background. Oral mucositis (OM) is an inflammation of the oral mucosa, resulting from exposure to chemotherapy agents and radiation therapy and affects 40% of patients treated with standard dose chemotherapy, 90% with radiotherapy of the head-neck area, and 99% of patients undergoing high-dose chemotherapy for bone marrow transplantation. Nurses occupy a key position in supporting patients affected by this type of complication and they must be familiar with the most efficient treatments and when to use them. An internal investigation was carried out in the National Cancer Institute of Milan with the scope of evaluating the treatments administered, either as prophylaxis or cure, as well as the information tools utilized by health operators and those communicated to the patients.

Material and methods. Consultation of international guidelines MASCC and ASCO.

Implementation of a questionnaire related to the management of OM, issued to nurses of the Institute. The 11 operative units (OU) most likely to be exposed to the risk of contracting OM were selected.

Results. Ninety-two questionnaires were distributed of which 51% were completed. Analysis of the results indicated that there is no official and shared tool for treating OM; in fact medical prescription constitutes the only reliable source of treatment (76%). Written information issued to patients by nursing staff occurred in 12% of cases, whereas 86% of the time, oral communication was preferred. Both in the prophylaxis phase and in the care phase could be observed frequent use of mouthwashes containing ethanol which exert a negative action on the epithelium of oral mucosa. There is also a high incidence in the administration of antifungal solutions, however, their use should be strictly limited to cases of confirmed diagnosis of fungal infections.

69% of the nurses interviewed administered brief infusions of 5-FU and melphalan in their OU, while cryotherapy prophylaxis was carried out only in 20% of the cases.

Conclusions. Recognition and identification of the therapy that causes OM is essential so that appropriate treatment strategies can be implemented, allowing the patient to continue with his cancer treatment unhindered by this particular complication.

T14 TRAINING EMPOWERING CANCER: RESULTS OF EXPERIENCE AT THE SALEM ONCOLOGY CENTRE IN HOUSTON

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Background. Nursing education in oncology aims to research and implement care strategies that meet the needs of patients. As a following step after the basic training course, the clinical setting is an excellent forum for learning, allowing to acquire clinical and communication skills. Based on these considerations comes the "Renato project", promoted by the association "Donna come prima" and the "LILT of Naples", whose objectives are: 1.Comparing Italy/U.S as to: a) basic and post-basic university courses; b) organizational models of care. 2. Transferring the experience to nursing students and health workers.

Materials and methods. The project "Renato" was conducted by a nurse graduate from Seconda Università of Naples, Registered Pascale Institute. The project was held at the Salem Oncology Centre in Houston (USA) from 25/01/2013 to 24/02/2013, to which patients with cancer in Day Hospital, receiving chemotherapy are referred. The experience was divided into a first phase of knowledge of the communication modes within the team and patients cared for during the reference period, followed by clinical learning, analysis of training and the adopted care model.

Results

Focus	Italy	USA
Basic training course (period)	3 years	4 years
Post basic training (period)	Oriented management	Clinical specialist
Level of responsibility	Medium	High
Approach to the terminal patient cancer	Palliative care	Palliative care
Model of care	Functional	Primary nursing
Role in decision-making	Borderline	Central
Health system	Social health	Private
Relationships within the team	Fragmented functions	Work processes for highly multidisciplinar integration

Conclusions. In the U.S organizational model nursing skills are advanced and the nursing role is central to the management of cancer patients, thanks to highly specialist training and advanced clinical skills and greater attention to the evaluation of clinical skills, periodically verified and certified, which ensures a highly quality of care and safety for the client. By comparing these two different organizational models, graduated nurse experiences a process of empowerment that helps to develop clinical and decision-making skills.

T15 EVALUATION ON THE PERCEIVED QUALITY, PERCEPTION AND INFORMATION RECEIVED DURING THE FIRST VISIT AT THE RECEPTION AND SERVICE CENTRE AT THE HEMATOLOGY AND ONCOLOGY UNITS, AO CITTA DELLA SALUTE E DELLA SCIENZA, TURIN

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Introduction. The quality is a central element of the health protection system and the patient's perception represents an important resource for health services reorganization in response to the citizens/users expectations.

Objectives. The objective is to evaluate the perceived quality of the welcome and the information received by patients during their first visit to the Reception Centre Services (CAS) of the Cancer Center Hematology subalpine (COES) of the Hospital City Health and Science Molinette in Turin and in particular the role played by the nurse in the context of this service.

Materials and methods. The present study involved 40 patients referred to CAS for the execution of their first visit in the period between May 29 and August 9, 2012. The evaluation of the perceived quality of the welcome and the information received was realized through the distribution of a telephone questionnaire, with 15 closed questions relating to the benefit received, divided into four thematic sections, plus two open-ended questions in order to highlight any critical situation experienced by patients and to collect suggestions for improving the quality.

Results. The results show overall good levels of satisfaction with the organizational aspects of the service (80%), evaluation of information received (70%), the role played by the nurse (71.4%) and the overall service provided (97%). But it has however highlighted a reduced participation of nurses in providing information to patients during the visit, particularly in reference to the possibility of receiving a useful help to deal with any difficulties in daily life; the organizational aspects and the relationship with the operators have come out as areas to which prioritize future interventions, in order to achieve an improvement in the perceived quality of service.

Conclusions. Although the results of this study indicate an overall high level of patient's satisfaction with the service being investigated, we must not forget that in the field of social and health services, the quality objectives are never strictly fixed, which means that performance, such as response to the needs of patients, must surely correspond to their expectations, but the main challenge for quality is not only simply having a satisfied patient, but rather pointing to a patient more than satisfied by offering a service that exceeds his expectations.

T16 PATIENT COMPLIANCE TO ORAL THERAPY: DIFFERENCES BETWEEN CLINICAL TRIALS AND CLINICAL PRACTICE

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Background. The compliance to oral therapy is particularly important in oncology and it mainly depends on the patient, unlike the intravenous therapy. An inappropriate compliance with oral therapy can lead to a loss of efficacy of treatment or to an increased toxicity. The nurse may have a relevant role for the patient compliance to oral therapy.

Materials and methods. We analyzed patients enrolled into six clinical trials and patients treated with oral therapies within standard clinical practice.

The materials used in clinical trials were:

- training of the patients to the oral therapy;
- diary, where the patient daily writes the intake of the oral therapy or the reasons why he did not take the therapy;
- phone numbers for clarifications about adverse events.

Conversely, within routine clinical practice, compliance to the oral therapy can be only deduced from the interview with the patient.

Results. In 48 patients enrolled in 6 clinical trials with oral agents, we found that the diary is an useful tool, easy to fill. It significantly improves the patient compliance to oral therapy and it allows to identify adverse events and if the patient takes the therapy in the right way. Within clinical trials the monitoring and accurate accountability of the oral therapy is higher than the clinical practice setting (98% vs 60%, $p = 0.002$). Furthermore adherence to therapy was 86% in the patients enrolled in a clinical trial using the diary. Conversely, in clinical practice, the estimated compliance was operator-dependent and generally less accurate.

Conclusions. The tools (such as the diary) used in clinical trials help the patient to properly take oral therapies. The results of our study suggest that the use of the diary and an accurate training of the patient performed by the nurse may be also useful in clinical practice in order to understand, to identify adverse events and to empower the patient about oral therapy.

T17 WHY A NURSE IS A MUST. THE ORAL CHEMOTHERAPY ATOR PROJECT IN AREZZO

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Background. ATOr is a clinic entirely dedicated to the management of outpatients in treatment with oral chemotherapy, with the aim to give the best quality of cure. It is open from 10 to 13 from Monday to Thursday. Indeed we check with attention adverse events (AEs), compliance to the treatment and quality of life for each patient. Our ATOr visited 1024 patients in the last year. ATOr started in March 2012 with the only presence of four medical oncologists. The activity has been progressively growing, from 41 outpatients monthly in March 2012 to 97 outpatients in March 2013, with a total number of 1024 outpatients visited. Because the oncologic team felt the need of a nurse with expertise in the ATOr to improve quality of information and education

(considering that patients know they can contact a nurse through the time to express any doubt and to report AEs) we decided in January 2013 to involve in ATOr a team of three nurses. Near future developments will be the involvement of a psychologist to give support every time is needed and of a pharmacist/pharmacologist to manage drug-drug interactions.

Material and method. We reorganize the ATOr with the presence of a nurse, dedicating two hours per day. The nursing activities are: providing treatments and drug outpatient diaries, information about the possible AEs, evaluation of the outpatients drug compliance and quality of life by follow-up phone interview and listening and care. We also evaluate a convenience test of 37 patients with questionnaire about compliance and the analysis of home diaries.

Results. The percentage of drug compliance, since we started follow-up phone interview, was 94%. The medium age of ATOr patients was 67 (range 48-82). About the reported AEs with the related grade, the most common were: fatigue G1, 29%, nausea G1, 24%, diarrhea G1, 27%, hand and foot syndrome G1, 18%, stomatitis G1, 16%. The diary provides accurate data about AEs, not only about the last days before the visit but of the whole period of administration. We believe that the high value of quality and patients satisfaction achieved was due mainly to the effort of the nurses.

Conclusions. We have a nurses team with high motivation and expertise, we use CTCAE as a validated scale of AEs, quality of life instruments such as FACT-P and a home diary. In the near future we have planned to improve these activities developing more detailed instruments for checking compliance and drug safety.

AUTHOR INDEX

See you at the

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