AIOM POST ASCO-GI Review
Updates and news from the Gastrointestinal Cancers Symposium
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Liver and biliary tract cancers

ASCO Poster review

Francesco Leone
Università degli studi di Torino
Dipartimento di Oncologia

American Society of Clinical Oncology
Making a world of difference in cancer care

Fondazione del Piemonte per l'Oncologia

Prognostic and predictive markers in HCC

- Tumor MET expression
- Circulating MET, HGF, AFP
- VEGF, HIF-1α SNPs

Simultaneous targeting of MET and VEGFR-2 in advanced HCC: phase 1b/2 study.

J.J. Harding

Abs. 300

BACKGROUND

- Activation of the hepatocyte growth factor (HGF)/mesenchymal-epithelial transition factor receptor (MET) pathway plays a key role in tumorigenesis and promotes tumor growth, invasion and dissemination.[1,2]
- MET is upregulated in response to anti-vascular endothelial growth factor (VEGF) therapies, and simultaneous inhibition of the MET and VEGF pathways leads to reduced tumor growth, invasion, and metastasis *in vivo*.[3,4]
- Emibetuzumab (LY2875358) is a humanized IgG4 bivalent monoclonal antibody that binds to and inhibits ligand-dependent and ligand-independent activation of MET.[5,6] Emibetuzumab demonstrated tolerability and preliminary evidence of antitumor activity in patients with advanced and/or metastatic cancer.[7]
- Ramucirumab is a human IgG1 VEGFR-2 targeting antibody that has shown evidence of single-agent antitumor activity and an acceptable safety profile in a phase II study in patients with advanced HCC.[8]

Simultaneous targeting of MET and VEGFR-2 in advanced HCC: phase 1b/2 study.

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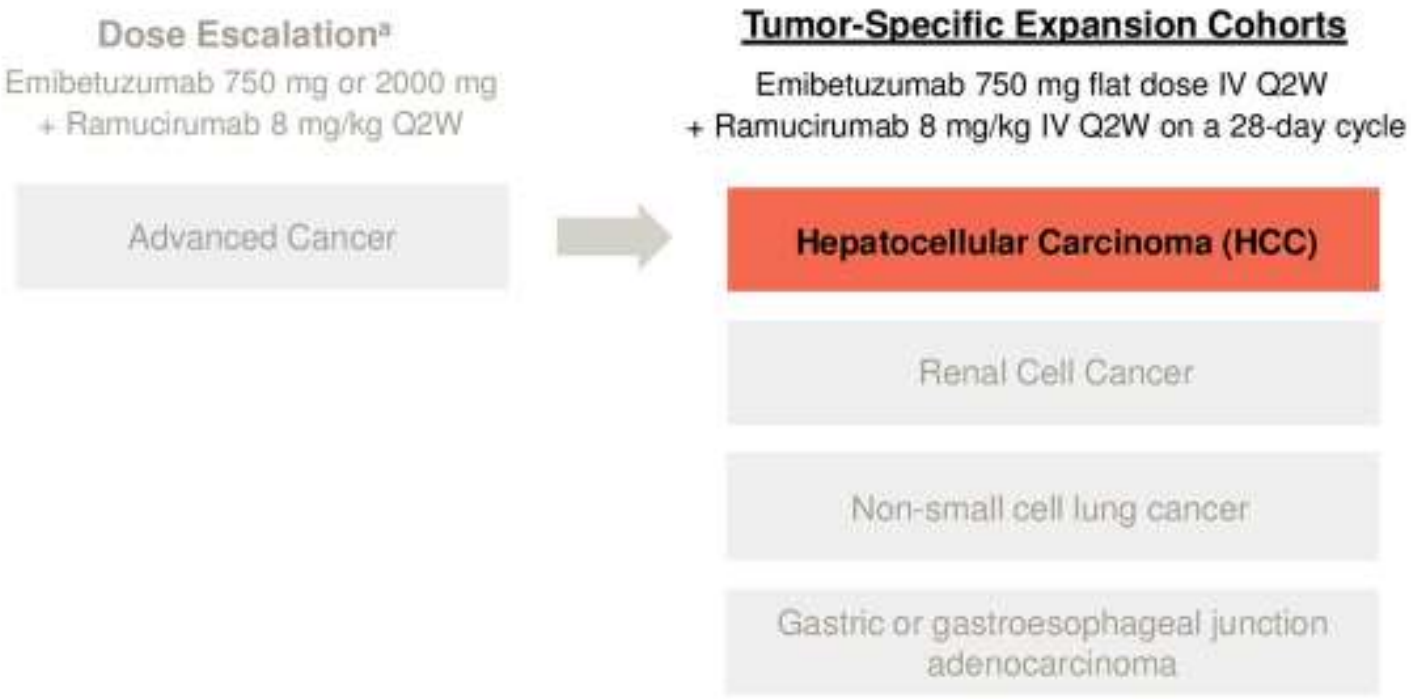
Figure 2. Study Design

- Phase 1b/2, multicenter, nonrandomized, open-label, 3+3 dose-escalation study with tumor-specific expansion cohorts (approximately 15 patients each)



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Simultaneous targeting of MET and VEGFR-2 in advanced HCC: phase 1b/2 study.

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Key Eligibility Criteria

HCC Expansion Cohort

- Advanced and/or metastatic HCC (excluding fibrolamellar carcinoma)
- Have exhausted available options with standard therapies or are not eligible for standard therapies
- Availability of a fresh tumor biopsy sample taken prior to study treatment but after progression (or discontinuation) on the most recent line of systemic tumor therapy
- Have at least 1 measurable lesion (by RECIST v1.1 criteria[11])
- Patients with Child-Pugh Stage B and C disease were excluded
- Patients with liver cirrhosis and/or chronic HBV or HCV were eligible
- ECOG PS ≤1
- Adequate organ function
- Patients with symptomatic central nervous system metastasis were not eligible
- Patients receiving therapeutic anticoagulation agents were not eligible (prophylactic, low-dose anticoagulation therapy was permitted)

Simultaneous targeting of MET and VEGFR-2 in advanced HCC: phase 1b/2 study.

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Table 1. Baseline Patient and Disease Characteristics

Parameter	HCC N=16
Median Age (range)	60 (46-82)
Male, n (%)	13 (81.3)
Race[a], n (%)	
Caucasian	12 (75.0)
African descent	1 (6.3)
Asian	2 (12.5)
ECOG PS, n (%)	
0	9 (56.3)
1	7 (43.8)
Viral-mediated disease, n (%)	
Positive for Hepatitis B surface antigen	3 (18.8)
Positive for Hepatitis C antibodies	3 (18.8)
Baseline AFP level[a], n (%)	
< 400 µg/L	7 (43.8)
≥ 400 µg/L	7 (43.8)
Prior anti-cancer therapies[a]	
Prior systemic therapy, n (%)	11 (68.8)
Median # of prior systemic therapies (range)	2 (1-6)
Prior sorafenib, n (%)	9 (56.3)
Prior radiotherapy, n (%)	5 (31.3)

[a]At the time of data cutoff, data was not available for race for 1 patient, AFP for 2 patients, and prior therapies for 5 patients

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Table 2. Adverse Events Related to Treatment

Treatment-related Adverse Event, n	Grade 1	Grade 2	Grade 3	Grade 4	All grades[a] (%)
Patients with ≥1 event	3	6	4	0	13 (81.3)
Fatigue	3	3	1	0	7 (43.8)
Peripheral edema	5	2	0	0	7 (43.8)
Hypertension	3	0	1	0	4 (25.0)
Hypophosphatemia	2	2	0	0	4 (25.0)
Thrombocytopenia	2	1	0	0	3 (18.8)
Leukopenia	0	1	1	0	2 (12.5)
Decreased appetite	2	0	0	0	2 (12.5)
Hypoalbuminemia	0	2	0	0	2 (12.5)
Hypocalcemia	2	0	0	0	2 (12.5)
Blood bilirubin increased	2	0	0	0	2 (12.5)
Constipation	2	0	0	0	2 (12.5)

[a] Includes treatment-related events occurring in 2 or more patients

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Simultaneous targeting of MET and VEGFR-2 in advanced HCC: phase 1b/2 study.

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Table 3. Summary of Best Overall Response

Best Overall Response[a] , n (%)	HCC (N=16)
Complete Response (CR)	0 (0)
Partial Response[b] (PR)	2 (12.5)
Stable Disease (SD)	7 (43.8)
Progressive Disease (PD)	3 (18.8)
Not assessed[c]	4 (25.0)
Disease Control Rate (DCR) (CR+PR+SD)	9 (56.3)
Overall Response Rate (ORR) (CR+PR)	2 (12.5)

[a] Best overall response according to RECIST v1.1[11]
[b] Confirmed PRs
[c] No tumor restaging was performed due to early clinical progression (n=3) or patient decision to discontinue early (n=1)

Simultaneous targeting of MET and VEGFR-2 in advanced HCC: phase 1b/2 study.

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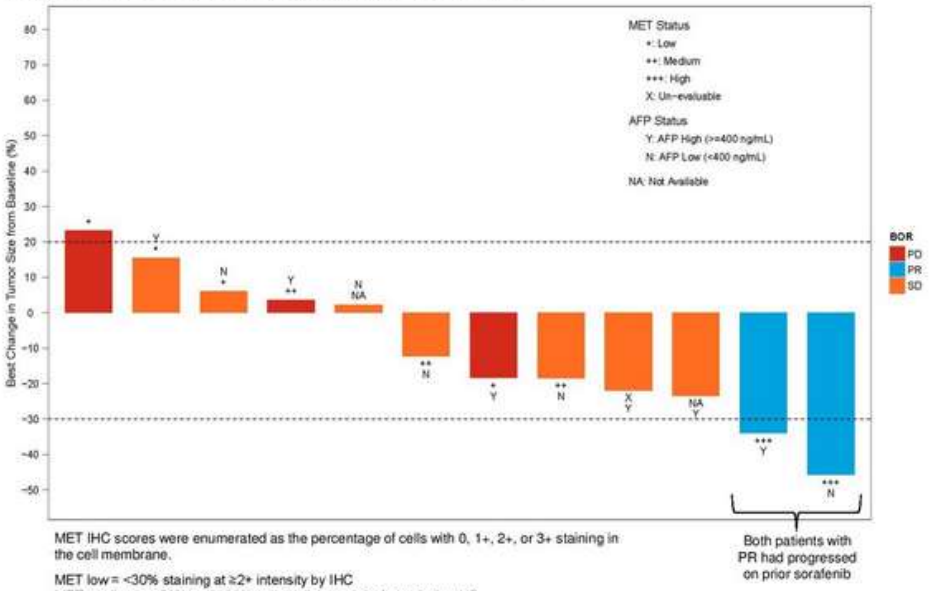
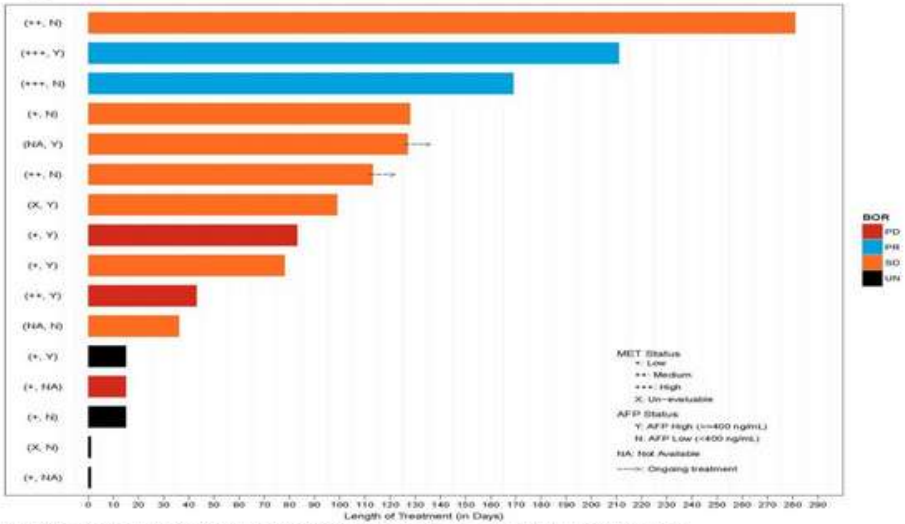
Figure 3. Best Change in Tumor Size



MET IHC scores were enumerated as the percentage of cells with 0, 1+, 2+, or 3+ staining in the cell membrane.

MET low = <30% staining at ≥2+ intensity by IHC
MET medium = ≥30% and <80% cells staining at ≥2+ intensity by IHC
MET high = ≥80% of cells staining at ≥2+ intensity by IHC

Figure 5. Treatment Duration



MET IHC scores were enumerated as the percentage of cells with 0, 1+, 2+, or 3+ staining in the cell membrane.

MET low = <30% staining at ≥2+ intensity by IHC
MET medium = ≥30% and <80% cells staining at ≥2+ intensity by IHC
MET high = ≥80% of cells staining at ≥2+ intensity by IHC

- **Exploratory biomarker data show high MET expression in responders**
  - PRs were observed only in patients with high MET tumor expression (≥80% of cells ≥2+ by IHC)
- **Enrollment has been expanded to 40 patients to further explore antitumor activity of emibetuzumab in combination with ramucirumab and any potential association with biomarker status**

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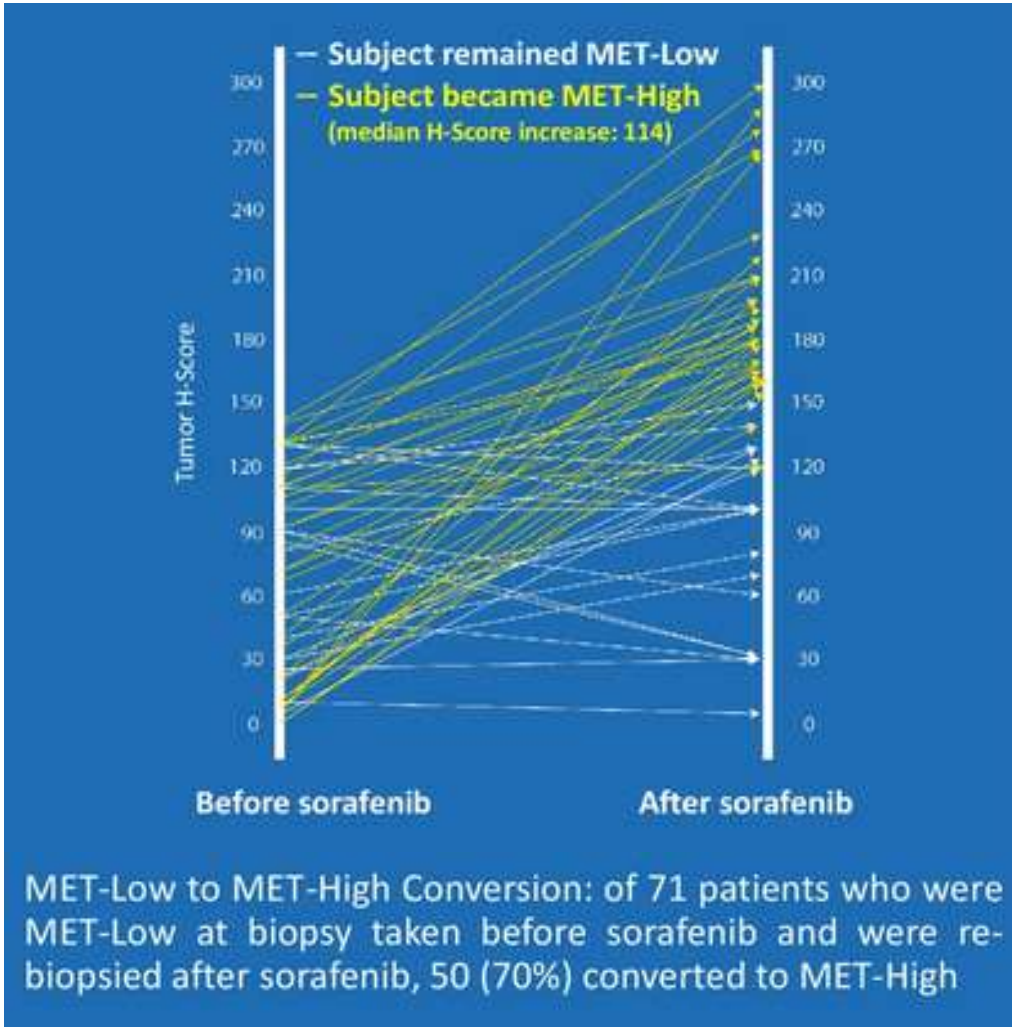
Biomarker analysis from the RCT of tivantinib in second-line HCC

L. Rimassa

Abs. 197

- Circulating MET, HGF, and AFP by 75th percentile hold a prognostic factor
- Circulating MET is a pharmacodynamic biomarker for tivantinib
- Tumor MET is the only prognostic and predictive biomarker, and is more frequently «High» after sorafenib
- This analysis supports the use of tivantinib in MET-High patients only



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Angiogenesis polymorphisms and clinical outcome of HCC pts receiving sorafenib

L. Faloppi

Abs. 280

VEGF and VEGFR genotyping in the prediction of clinical outcome for HCC patients receiving sorafenib: The ALICE-1 study

Mario Scartozzi[1], Luca Faloppi[1], Gianluca Svegliati Baroni[2], Cristian Loretelli[3,4,5], Fabio Piscaglia[6], Massimo Iavarone[7], Pierluigi Toniutto[8], Giammarco Fava[9], Samuele De Minicis[2], Alessandra Mandolesi[10], Maristella Bianconi[1], Riccardo Giampieri[1], Alessandro Granito[6], Floriana Facchetti[7], Davide Bitetto[8], Sara Marinelli[6], Laura Venerandi[6], Sara Vavassori[7], Stefano Gemini[2], Antonietta D'Errico[11], Massimo Colombo[7], Luigi Bolondi[6], Italo Bearzi[10], Antonio Benedetti[2] and Stefano Cascinu[1]

IJC International Journal of Cancer 2014

- VEGF have been shown to predict clinical outcome in HCC patients treated with sorafenib.
- SNPs may represent a clinical tool to better identify HCC patients more likely to benefit from sorafenib

Angiogenesis polymorphisms and clinical outcome of HCC pts receiving sorafenib

L. Faloppi

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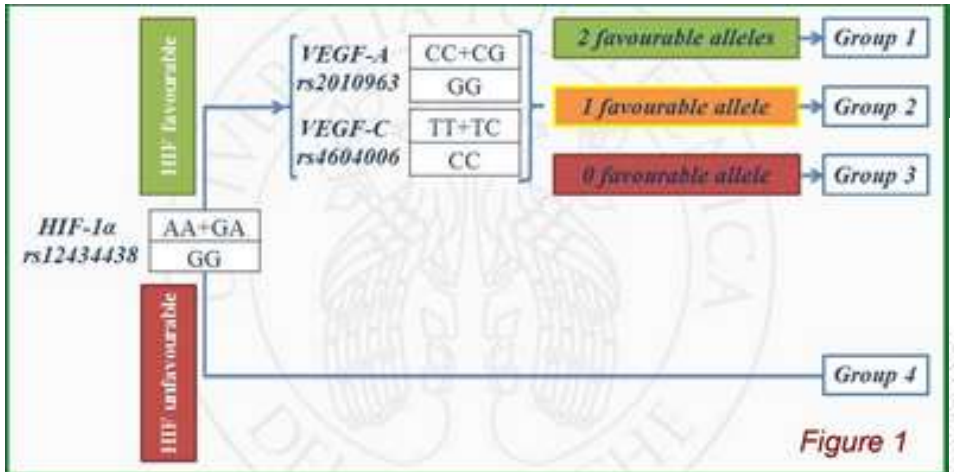
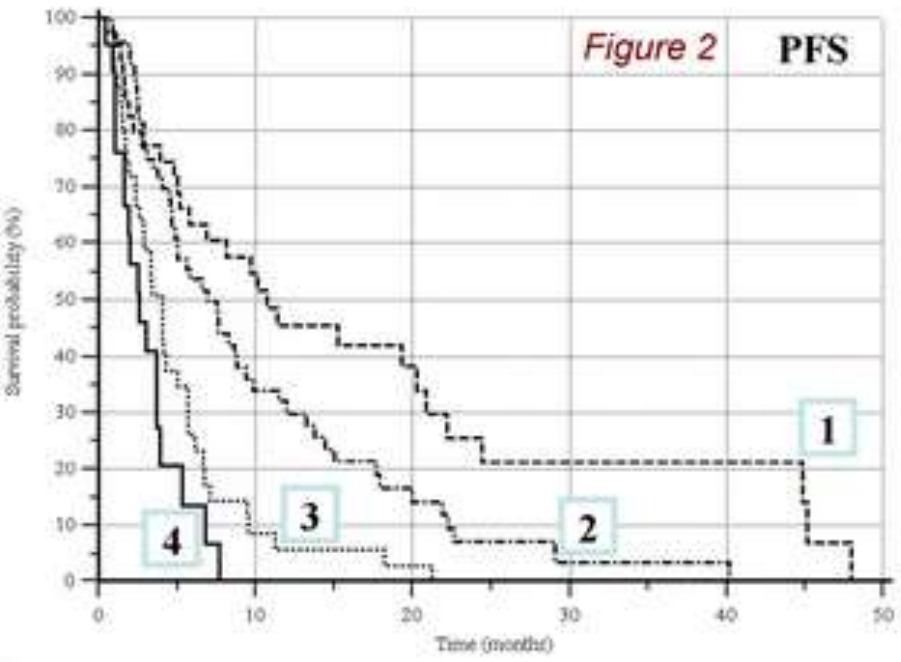


Figure 1

Table 1	PFS (months)	OS (months)
Group 1	10.8	19.0
Group 2	5.6	13.5
Group 3	3.7	7.5
Group 4	2.6	6.6



rs12434438 of HIF-1α, rs2010963 of VEGF-A and rs4604006 of VEGF-C have been confirmed as independent factors; rs12434438 of HIF-1α select a population with a particularly poor outcome.

Actionable molecular subgroups in biliary cancer (future therapies)

- IDH1
- FGFR2
- PD1
- TGFβ/SMAD4
- mTOR
- ROS1

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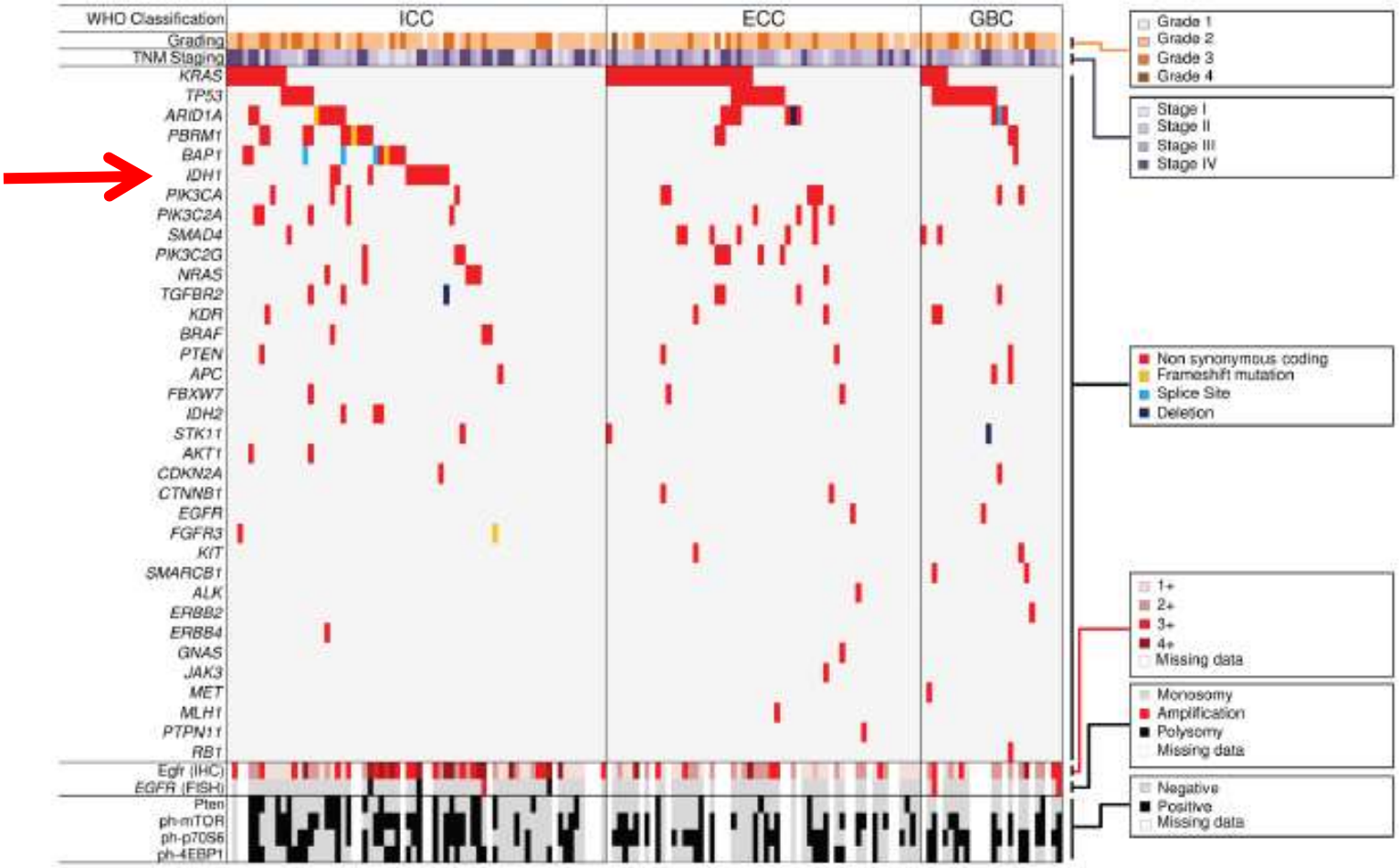
Actionable molecular subgroups in biliary cancer



Simbolo M, Oncotargets 2014

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Mutations in IDH1 in advanced BTC pts who received gemcitabine and cisplatin

D.H Ahn

Abs. 287

Mutant IDH inhibits HNF4α to block hepatocyte differentiation and promote biliary cancer

Nature. 2014

Supriya K. Saha[1,*], Christine A. Parachoniak[1,*], Krishna S. Ghanta[1], Julien Fitamant[1], Kenneth N. Ross[1], Mortada S. Najem[1], Sushma Gurumurthy[1], Esra A. Akbay[2], Daniela Sia[3,4,5], Helena Cornella[3], Oriana Miltiadous[4], Chad Walesky[6], Vikram Deshpande[1], Andrew X. Zhu[1], Aram F. Hezel[7], Katharine Yen[8], Kim Straley[8], Jeremy Travins[8], Janeta Popovici-Muller[8], Camelia Gliser[8], Cristina R. Ferrone[1], Udayan Apte[6], Josep M. Llovet[3,4,9,10], Kwok-Kin Wong[2], Sridhar Ramaswamy[1,11], and Nabeel Bardeesy[1,12]

IDH mutations in liver cell plasticity and biliary cancer

Cell Cycle 2014

Supriya K Saha, Christine A Parachoniak, and Nabeel Bardeesy*

Cancer Center and Center for Regenerative Medicine; Massachusetts General Hospital; Department of Medicine; Harvard Medical School, Boston, MA USA

Mutant isocitrate dehydrogenase 1/2 (IDH) acts through a novel mechanism of oncogenesis, producing high levels of the metabolite 2-hydroxyglutarate, which interferes with the function of α-ketoglutarate-dependent enzymes that regulate diverse cellular processes including histone demethylation and DNA modification.

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Mutations in IDH1 in advanced BTC pts who received gemcitabine and cisplatin

D.H Ahn

Abs. 287

Table 3. Univariate Cox Regression Model for Overall Survival

Tumor somatic variant	Incidence (%)	Hazard Ratio	95% CI	P-value
ARID1A	13.75	1.737	(0.75, 3.35)	0.1993
BAP1	10	1.645	(0.32, 2.58)	0.2028
BRAF	10	0.827	(0.29, 2.37)	0.7234
CDKN2A	30	0.639	(0.27,1.51)	0.3069
FGFR2	13.75	0.131	(0.0178, 0.96)	0.0453
IDH1	12.5	0.459	(0.16, 1.30)	0.1435
KRAS	23.75	1.431	(0.72, 2.83)	0.3038
PIK3CA	16.25	0.668	(0.2710, 1.71)	0.3994
TP53	27.5	1.797	(0.86, 3.78)	0.1219

Somatic mutations in **IDH1** (11 of 80 pts; 13%) (HR 0.31; p = 0.035) **were associated with improved overall survival (OS) and progression free survival (PFS)**

IDH1 is a therapeutic target of interest, where ongoing clinical trials are assessing the clinical activity in targeting IDH1 in biliary cancers (NCT02073994, NCT02273739)

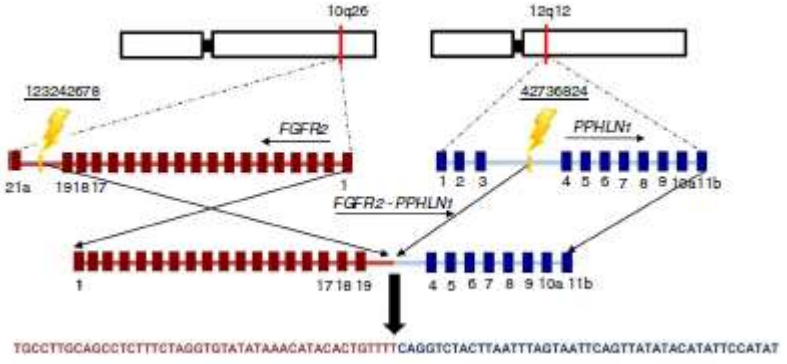
BGJ398 in pts with advanced or metastatic FGFR-altered cholangiocarcinoma

M.M. Javle

Abs. 335

Massive parallel sequencing uncovers actionable *FGFR2–PPHLN1* fusion and *ARAF* mutations in intrahepatic cholangiocarcinoma

Daniela Sia[1,2,3], Bojan Losic[3,4], Agrin Moeini[1], Laia Cabellos[3], Ke Hao[3,4], Kate Revill[3], Dennis Bonal[3], Oriana Miltiadous[3], Zhongyang Zhang[3,4], Yujin Hoshida[3], Helena Cornella[1], Mireia Castillo-Martin[3], Roser Pinyol[1], Yumi Kasai[4], Sasan Roayaie[5], Swan N. Thung[3], Josep Fuster[1], Myron E. Schwartz[3], Samuel Waxman[3], Carlos Cordon-Cardo[3], Eric Schadt[4], Vincenzo Mazzaferro[2] & Josep M. Llovet[1,3,6]



The transforming and oncogenic activity of the FGFR2–PPHLN1 fusion can be successfully inhibited by a selective FGFR2 inhibitor (BGJ398) in vitro

NATURE COMMUNICATIONS 2015

- Ongoing phase 2, open-label study of oral BGJ398 125 mg once daily (3-week-on/1-week-off) in BTC pts with FGFR2 fusions who progressed after cisplatin/gemcitabine (NCT02150967).
- The primary endpoint is ORR.
- 30 pts were enrolled.

BGJ398 in pts with advanced or metastatic FGFR-altered cholangiocarcinoma

M.M. Javle

Abs. 335

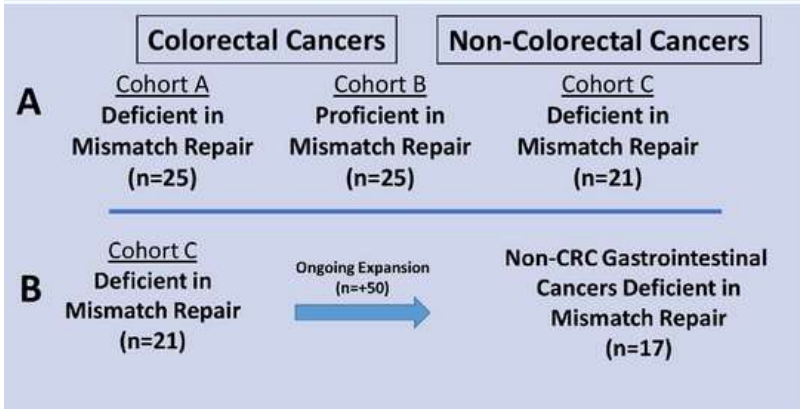
- Common adverse events (AEs; ≥ 20% of pts), were hyperphosphatemia (50%), fatigue (42%), constipation (38%), cough (23%), and nausea (23%). Grade 3/4 AEs were hyper/hypophosphatemia, lipase increase, and hyponatremia.
- Among 22 pts evaluable, 3 achieved partial response and 15 had stable disease, including 10 with tumor reductions (-41%, n = 1; -2% to -29%, n = 9). **Overall DCR was 82%.** As of the cutoff date, 18 pts remained on therapy, of which 13 were on for > 120 days. Kaplan-Meier estimated lower limit (95% CI) of median time on study was 143 days.
- BGJ398 shows impressive anti-tumor activity and a manageable safety profile in pts with advanced FGFR-altered CCA.

PD-1 blockade in mismatch repair deficient non-colorectal gastrointestinal cancers

D.T. Le

Abs. 195

Figure 2 . Study Design



- Anti-PD1 (Pembrolizumab) was administered at 10 mg/kg, every 2 weeks.
- The primary endpoints were immune-related objective response rate and the 20-week immune-related progression-free survival rate
- Mismatch repair testing consisted of IHC for MMR proteins or PCR-based MSI testing
- An expansion was open for cohort C **(Figure 2B)**

Table 1. Baseline Patient Characteristics

Characteristic	MMR-deficient GI non-CRC n=17 (%)
Median Age – years	60
Gender-female	5 (29)
ECOG PS-zero	5 (29)
Tumor Type	
Pancreas	4 (23)
Ampullary	4 (23)
Biliary	3 (18)
Small bowel	3 (18)
Gastric	3 (18)
Metastatic	17 (100)
Liver Mets	11 (65)
Median Prior Regimens	2

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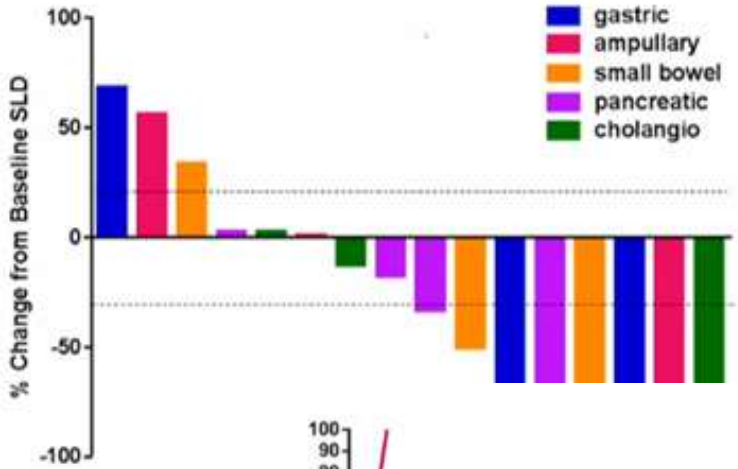
PD-1 blockade in mismatch repair deficient non-colorectal gastrointestinal cancers

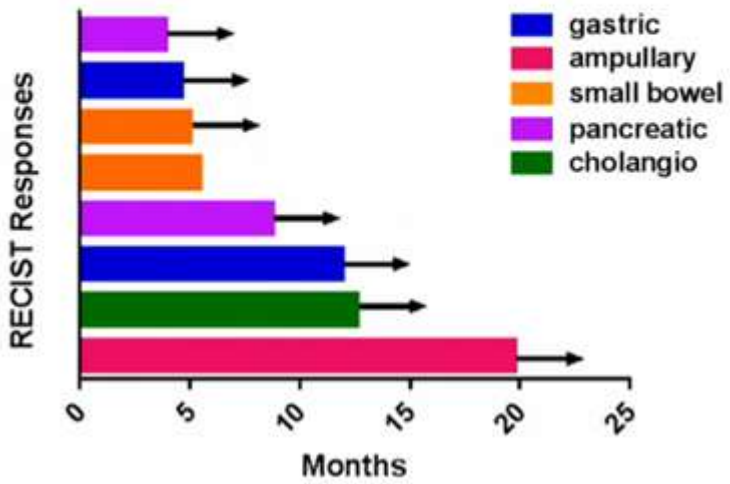
D.T. Le

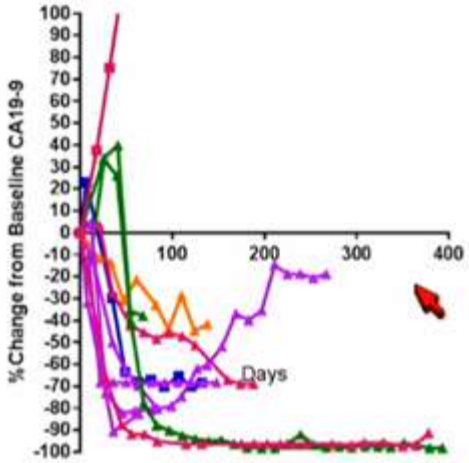
Abs. 195

Target Lesion Measurements



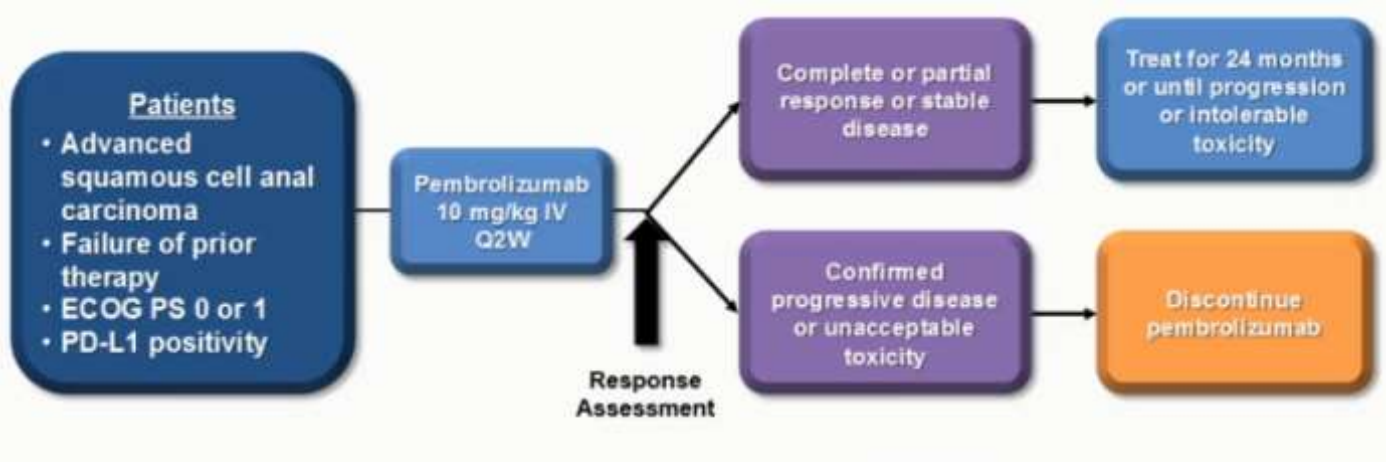
Durability of Response

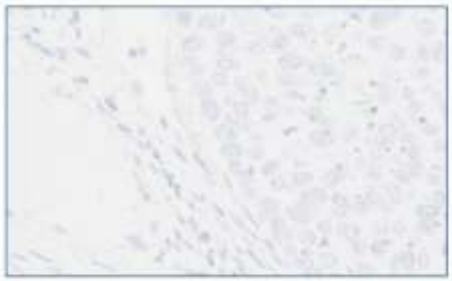




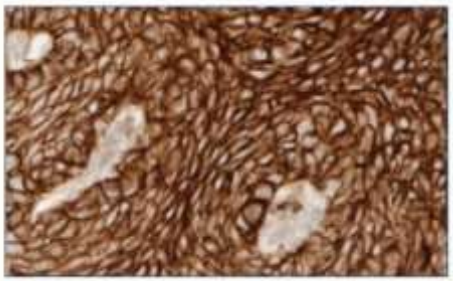
Tumor Marker Kinetics

Study of Pembrolizumab in Advanced Solid Tumors (KEYNOTE-28)





PD-L1 Negative



PD-L1 Positive

- Immunohistochemistry: assessed at a central laboratory using a prototype assay (QualTek) and 22C3 antibody clone (Merck)
- Positivity: membranous PD-L1 expression in ≥1% of cells in tumor and stroma

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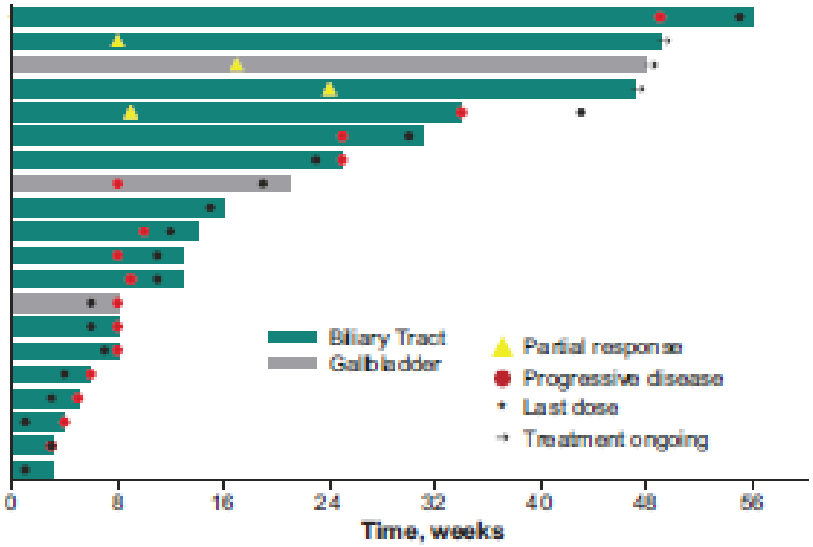
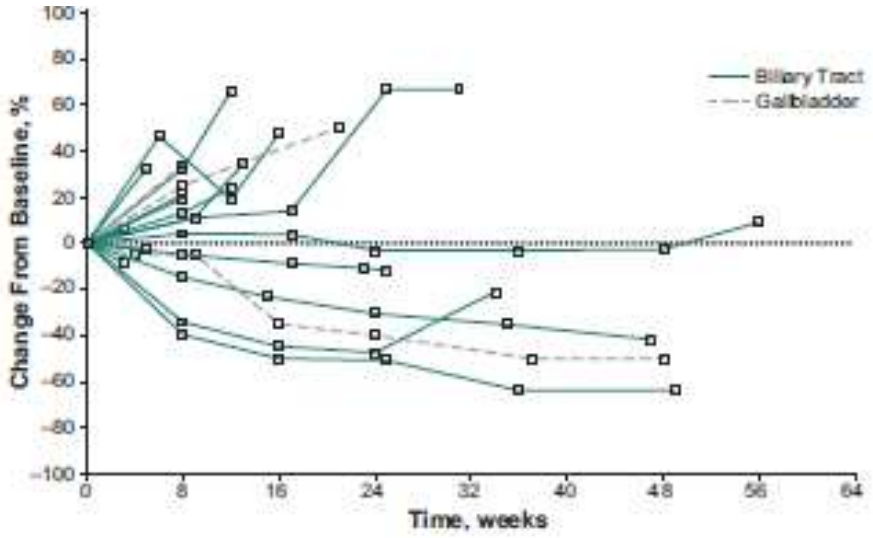
Pembrolizumab in BTC

Best Response	n	% (95% CI)
Complete response	0	0 (0.0–14.8)
Partial response	4	17.4 (5.0–38.8)
Stable disease	4	17.4 (5.0–38.8)
Progressive disease	12	52.2 (30.6–73.2)
No assessment[b]	3	13.0 (2.8–33.6)

N = 24
ORR: 17.4%
(95% CI, 5.0-38.8)
DCR: 34.8%





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Standard of treatment in biliary cancer (current therapies)

- Gemcitabine and platinum compound combinations in 1° line
- No standard therapies for second-line treatment

Systemic therapy in elderly patients with advanced biliary tract cancer

M.G. McNamara

Abs. 382

Table 1. Prospective studies

Bekaii-Saab et al 2011, Journal of Clinical Oncology 29:2357-2363	Selumetinib
Goldstein et al 2010, Cancer Chemotherapy and Pharmacology 67:519-525	Gemcitabine/Cisplatin
Jensen et al 2012, Annals of Oncology 23:2341-2346	Gemcitabine/Oxaliplatin/Panitumumab/Capecitabine
Knox et al 2005, Journal of Clinical Oncology 23:2332-2338	Gemcitabine/Capecitabine
Malka et al 2014, Lancet Oncology 15:819-828	Gemcitabine/Oxaliplatin ± Cetuximab
Moehler et al 2014, European Journal of Cancer 50:3125-3135	Gemcitabine ± Sorafenib
Okusaka et al 2010, British Journal of Cancer 103:469-474	Gemcitabine ± Cisplatin
Rao et al 2005, British Journal of Cancer 92:1650-1654	5-Fluorouracil/Etoposide/Leucovorin versus Epirubicin/Cisplatin/5-Fluorouracil
Shannon et al 2014, Annals of Oncology 25:iv244	Gemcitabine/Cisplatin/Panitumumab
Valle et al 2010, New England Journal of Medicine 362:1273-1281	Gemcitabine ± Cisplatin
Wagner et al 2009, British Journal of Cancer 101:1846-1852	Gemcitabine/Oxaliplatin/5-Fluorouracil

1163 pts were recruited from Jan 97-Dec 13.
Median age of entire cohort was 63 yrs (range 23-85); 260 (22%) were ≥ 70 yrs, 18 (2%) were ≥ 80 yrs.

Table 3. Multivariable analysis for Progression-free (PFS) and Overall survival (OS)

Covariate		PFS <70 years	PFS ≥70 years	OS <70 years	OS ≥70 years
Gender (reference; female)	Female vs Male	HR 1.00 (95%CI 0.84-1.18, P=0.98)	HR 1.14 (95%CI 0.83-1.56, P=0.42)	HR 1.12 (95%CI 0.94-1.33, P=0.22)	HR 1.33 (95%CI 0.97-1.84, P=0.08)
ECOG performance status (reference; 0)	0 vs 1	HR 1.10 (95%CI 0.92-1.32)	HR 0.86 (95%CI 0.60-1.24)	HR 1.08 (95%CI 0.90-1.31)	HR 0.81 (95%CI 0.57-1.16)
	0 vs 2	HR 1.58 (95%CI 1.13-2.20) [P=0.04]	HR 1.03 (95%CI 0.58-1.83) [P=0.65]	HR 2.02 (95%CI 1.45-2.82) [P=0.001]	HR 1.84 (95%CI 1.03-3.28) [P=0.02]
Disease stage (reference; locally advanced)	Locally advanced vs Metastatic	HR 1.46 (95%CI 1.20-1.78, P<0.001)	HR 1.21 (95%CI 0.86-1.69, P=0.28)	HR 1.48 (95%CI 1.20-1.82, P<0.001)	HR 1.49 (95%CI 1.05-2.12, P=0.03)
Treatment (reference; monotherapy)	Monotherapy vs Combination	**HR 0.64 (95%CI 0.53-0.77, P<0.001)**	**HR 0.54 (95%CI 0.38-0.77, P=0.001)**	**HR 0.73 (95%CI 0.61-0.88, P=0.001)**	**HR 0.60 (95%CI 0.43-0.85, P=0.004)**

ISTITUTO DI CANDIOLO

Thank you!

francesco.leone@ircc.it