

Effect of 3-5 years of scheduled CEA and CT follow-up to detect recurrence of colorectal cancer: FACS randomized controlled trial.

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Background: Intensive long-term follow-up after surgery for colorectal cancer is common practice but neither the actual benefit nor the optimal methodology is known. **Methods:** Pragmatic factorial randomised controlled trial in 39 UK hospitals, comparing minimum follow-up (which included a single CT scan at 12-18 months) with 3-6 monthly blood carcinoembryonic antigen (CEA) testing and 6-12 monthly computerised tomography (CT) imaging of the chest, abdomen and pelvis following 1202 participants for 3-5 (mean 3.7) years. **Results:** The proportion of participants with recurrence treated surgically with curative intent was lower than predicted (6.0% overall) but was about 3x higher in the more intensive than minimum follow-up arms ($p=0.019$). The adjusted odds were 2.7 for CEA only ($p=0.035$) and 3.4 for CT only ($p=0.007$); the absolute differences in detection rate in the more intensive arms compared to minimum follow-up were 4.3-5.7% (5.8-8.0% per protocol). Combining CEA and CT provided no additional benefit (adjusted odds for CT+CEA arm = 2.9). The absolute difference in the proportion of participants with recurrence treated surgically with curative intent in the factorial comparison was 1.4% for CEA ($p=0.28$) and 2.8% for CT ($p=0.04$). There was no statistical difference in colorectal cancer deaths nor overall deaths in the minimum compared to the intensive follow-up arms. **Conclusions:** Both regular CEA measurement and CT scanning result in significantly higher rates of diagnosis of operable recurrent colorectal cancer compared to minimal follow up. There is no benefit in monitoring with both CEA and CT. To date no difference in the overall mortality has been demonstrated. CEA monitoring combined with a single CT scan at 12-18 months seems likely to be cost effective. Clinical trial information: 41458548.

Phase III randomized, placebo (PL)-controlled, double-blind study of intravenous calcium/magnesium (CaMg) to prevent oxaliplatin-induced sensory neurotoxicity (sNT), N08CB: An alliance for clinical trials in oncology study.

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Background: Cumulative neurotoxicity commonly leads to early discontinuation of oxaliplatin-based therapy. In a relatively small, prematurely-discontinued, randomized study, IV CaMg was associated with reduced oxaliplatin-induced sNT (Grothey, JCO, 2011). N08CB was designed to definitively test whether IV CaMg significantly decreases cumulative oxaliplatin-related sNT. **Methods:** 353 pts with colon cancer undergoing adjuvant therapy with FOLFOX were randomized to 3 arms: IV CaMg (1g calcium gluconate, 1g magnesium sulfate) before and after oxaliplatin vs PL before and after vs CaMg before and PL after. The primary endpoint was cumulative sNT repeatedly measured by the sensory subscale of the EORTC QLQ-CIPN20. Secondary endpoints, using CTCAE 4.0 and an oxaliplatin specific neurotoxicity scale, were also assessed. Acute neuropathy data were also collected for 5 days following each oxaliplatin dose. The area under the curve (AUC) of the sensory subscale during the treatment cycles was used as summary measures for comparison. The Wilcoxon rank-sum tests were conducted for each treatment versus placebo arm, at 2.5%, adjusting for multiplicity using Bonferroni's approach. **Results:** CaMg did not reduce cumulative sNT. Primary and secondary analyses data are summarized in the Table. In addition, there were no significant differences between arms regarding oxaliplatin administered doses or chemotherapy discontinuation rates. Also, there were no substantial differences in acute neuropathy scores or side-effects between study arms. **Conclusions:** This study does not demonstrate any activity of IV CaMg as a neuroprotectant against oxaliplatin-induced neurotoxicity. Clinical trial information: NCT01099449.

Arm/measure	CaMg/CaMg (n=118)	CaMg/PL (n=116)	PL/PL (n=119)	P value between CaMg/CaMg vs PL/PL	P value between CaMg/PL vs PL/PL
Primary endpoint: CIPN-20 sensory scale mean AUC (sd) (higher scores better)	89.2 (8.5)	87.1 (9.9)	88.3 (9.7)	0.727	0.292
CTCAE, median days to grade 2 sNT	171	171	173	0.748	0.848
Oxaliplatin- specific neuropathy scale, median days to grade 2 sNT	140	139	148	0.953	0.942

Maintenance treatment with capecitabine and bevacizumab versus observation after induction treatment with chemotherapy and bevacizumab in metastatic colorectal cancer (mCRC): The phase III CAIRO3 study of the Dutch Colorectal Cancer Group (DCCG).

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Background: The optimal duration of chemotherapy and bevacizumab in mCRC is not well established. The CAIRO3 study investigated the efficacy of maintenance treatment with capecitabine plus bevacizumab versus observation in mCRC pts not progressing during induction treatment with capecitabine, oxaliplatin and bevacizumab (CAPOX-B). **Methods:** Previously untreated mCRC pts, PS 0-1, with stable disease or better after 6 cycles of CAPOX-B, not eligible for metastasectomy and eligible for future treatment with oxaliplatin, were randomized between observation (arm A) or maintenance treatment with capecitabine 625 mg/m² bid daily continuously and bevacizumab 7.5 mg/kg iv q 3 weeks (arm B). Upon first progression (PFS1), pts in both arms were treated with CAPOX-B until second progression (PFS2, primary endpoint). For pts not able to receive CAPOX-B upon PFS1, PFS2 was considered equal to PFS1. Secondary endpoints were overall survival (OS) and time to second progression (TTP2), which was defined as the time to progression or death on any treatment following PFS1. All endpoints were calculated from the time of randomization. **Results:** A total of 558 pts were randomized. Median follow-up is 33 months. The median number of maintenance cycles in arm B was 9 (range 1-54). The median PFS1 in arm A vs B was 4.1 vs 7.4 months (HR 0.44, 95% CI 0.37-0.54, p<0.0001). Upon PFS1, 72% of pts received CAPOX-B in arm A and 44% in arm B. The median PFS2 was 10.4 vs 10.4 months (HR 0.86, 95% CI 0.7-1.04, p=0.12). The median TTP2 in arm A vs B was 11.5 vs 15.4 months (HR 0.58, 95% CI 0.48-0.72, p<0.0001), and the median OS was 17.9 vs 21.7 months (HR 0.77, 95% CI 0.62-0.96, p=0.02), respectively. **Conclusions:** Maintenance treatment with capecitabine plus bevacizumab after 6 cycles CAPOX-B did not significantly prolong PFS2, which may be due to the lower number of pts in arm B that received CAPOX-B following PFS1. Maintenance treatment significantly prolonged PFS1, TTP2 and OS. Our data support the use of bevacizumab plus capecitabine until progression or unacceptable toxicity. Updated results will be presented. Clinical trial information: NCT00442637.

Bevacizumab continuation versus no continuation after first-line chemo-bevacizumab therapy in patients with metastatic colorectal cancer: A randomized phase III noninferiority trial (SAKK 41/06).

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Background: Chemotherapy plus bevacizumab is a standard option for first-line treatment in metastatic colorectal cancer patients. We assessed whether no continuation is non-inferior to continuation of bevacizumab after stop of first-line chemotherapy. **Methods:** In an open-label, phase 3 multicenter study conducted in Switzerland, patients with unresectable metastatic colorectal cancer having non-progressive disease after 4-6 months of standard first-line chemotherapy plus bevacizumab were randomly assigned in a 1:1 ratio to continuing bevacizumab (7.5 mg/kg every 3 weeks) or no treatment. CT scans were done every 6 weeks between randomization and disease progression. The primary endpoint was time to progression (TTP). A non-inferiority limit for hazard ratio (HR) of 0.727 was chosen to detect a difference in TTP of 6 weeks or less, with a one-sided significant level of 10% and a statistical power of 85%. **Results:** The per-protocol population comprised 262 patients. Median follow-up is 28.6 months (range, 0.6-54.9 months). Median TTP was 17.9 weeks (95% CI 13.3-23.4) for bevacizumab continuation and 12.6 weeks (95% CI 12.0-16.4) for no continuation; HR 0.72 (95% CI 0.56-0.92). Median progression free-survival and overall survival, both measured from start of first-line treatment, was 9.5 months and 24.9 months for bevacizumab continuation and 8.5 months (HR 0.73 (95% CI 0.57 - 0.94)) and 22.8 months (HR 0.87 (95% CI 0.64 - 1.18)) for no continuation. Median time from randomization to second-line treatment was 5.9 months for bevacizumab and 4.8 for no continuation. Grade 3-4 adverse events in the bevacizumab continuation arm were uncommon. **Conclusions:** Non-inferiority could not be demonstrated. The 95% confidence intervals for the TTP HR indicate superiority of bevacizumab continuation after stop of first-line chemotherapy. The median differences in TTP and in time between randomization and start of second-line treatment were of moderate magnitude being less than 6 weeks. The results of an accompanying cost analysis will be presented at the meeting. Clinical trial information: NCT00544700.

A randomized clinical trial of chemotherapy compared to chemotherapy in combination with cetuximab in k-RAS wild-type patients with operable metastases from colorectal cancer: The new EPOC study.

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Background: Resection of liver metastases from colorectal cancer with or without neoadjuvant chemotherapy is the standard of care. The EPOC study (Nordlinger et al, Lancet 2008) randomised patients between surgery and surgery with chemotherapy and demonstrated an improvement in 3 year progression free survival (PFS) of 7.3% (from 28.1% to 35.4%). As a rational extension to the EPOC study data, the New EPOC study evaluates the benefit of cetuximab, an EGF receptor antibody, in addition to standard chemotherapy in patients with operable liver metastases. **Methods:** 272 patients were randomised between February 2007 and November 2012 into the New EPOC study. Eligible patients were required to be k-RAS wild type, have operable liver metastases and to be sufficiently fit for chemotherapy and surgery. Patients with the primary tumour in situ, and those who required short course rectal radiation were eligible. Patients were randomised to receive a fluoropyrimidine and oxaliplatin plus or minus cetuximab for 12 weeks before, then 12 weeks following surgery. Patients who had been treated with adjuvant oxaliplatin could receive irinotecan and 5 – fluorouracil. **Results:** Following a recommendation from the Independent Data Monitoring Committee on 19/11/2012, the New EPOC study was stopped when the study met a protocol pre-defined futility analysis. With 45.3% (96/212) of the expected events observed, progression free survival was significantly worse in the cetuximab arm (14.8 vs 24.2 months, HR (95%CI) 1.50037 (1.000707 to 2.249517) $p < 0.048$). The result of a pre-planned analysis excluding the 23 patients treated with irinotecan based chemotherapy was similar (15.2 vs 24.2 months, HR 1.565546 (1.014967-2.414793) $P < 0.043$). **Conclusions:** Although the data are immature, the accumulation of more events is unlikely to change this result. In patients with resectable liver metastases and K-RAS wt tumours the addition of cetuximab to chemotherapy is not beneficial. Clinical trial information: ISRCTN22944367.

FOLFOXIRI/bevacizumab (bev) versus FOLFIRI/bev as first-line treatment in unresectable metastatic colorectal cancer (mCRC) patients (pts): Results of the phase III TRIBE trial by GONO group.

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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). **Methods:** Eligibility criteria included: measurable and unresectable mCRC, age 18-75 years, no prior CT for advanced disease. Pts 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. Pts 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) 12%/12%. At a median follow-up of 26.6 mos 424 pts progressed and 244 died. Median PFS and OS in the intention to treat (ITT) population were 10.9 and 30.9 mos. FOLFOXIRI/bev significantly increased PFS (median 9.7 vs 12.2 mos, HR 0.73 [0.60-0.88] $p=0.0012$). Subgroup analyses based on stratification factors (PS, prior adj) and baseline characteristics (site of primary, liver only disease, resection of primary, Kohne score) did not evidence significant interactions between treatment and analyzed factors. A trend toward a more consistent effect of FOLFOXIRI/bev was reported in no prior adj (HR 0.68 [0.55-0.83]) compared to prior adj group (HR 1.18 [0.67-2.08], p for interaction=0.071). 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%, $p=0.823$). **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. Clinical trial information: NCT00719797.

LBA3506

Oral Abstract Session, Sat, 3:00 PM-6:00 PM

Randomized comparison of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment of KRAS-wildtype metastatic colorectal cancer: German AIO study KRK-0306 (FIRE-3).

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The full, final text of this abstract will be available at abstract.asco.org at 7:30 AM (EDT) on Saturday June, 1, 2013, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2013, issue of *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Saturday edition of *ASCO Daily News*.

Pharmacodynamic and efficacy analysis of the BRAF inhibitor dabrafenib (GSK436) in combination with the MEK inhibitor trametinib (GSK212) in patients with BRAFV600 mutant colorectal cancer (CRC).

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Background: The BRAF V600 mutation occurs in 5-10% of metastatic CRC, predicts poor prognosis, and may predict lack of response to standard therapy. The combination of inhibitors of BRAF (dabrafenib; D) and MEK (trametinib; T) has shown significant efficacy in BRAF-mutant melanoma. The safety, efficacy, and pharmacodynamic effects of this combination were studied in BRAF-mutant CRC patients (pts). **Methods:** BRAF mutant CRC pts were enrolled to an initial efficacy cohort of 26 pts and a subsequent pharmacodynamic (PD) expansion cohort that included biopsies of 15 pts at screening and at steady state. So far, 36 pts have enrolled, including 10 in the PD cohort. Eligible pts had previously-treated BRAFV600E mutant stage IV CRC. Pts were treated with D (150mg BID) and T (2mg QD). Additional analyses were performed on available archival tissues. **Results:** Data are available for 36 pts: ECOG performance status 0 (58%) or 1 (42%), 81% had received ≥ 2 prior chemotherapy regimens, 36% had received prior EGFR inhibitor treatment, and 83% had ≥ 1 biologic therapy. Among 34 pts with >1 restaging assessment as of November 2012, 1 (3%) achieved a complete response (confirmed, on study >12 m), 3 (9%) achieved a partial response (1 confirmed to date), and 18 (53%) had stable disease (SD). Minor responses were seen in 7/18 pts (39%) with SD. Median PFS was 3.5 mo (95% CI: 1.8-4.9); overall duration on study range: 0.03–15.2 mo 7 pts (24%) remained on study for ≥ 6 cycles with 9 pts still on study. The most frequent AEs, any grade, included pyrexia (67%), nausea (56%), fatigue (53%), chills (47%), vomiting (39%), headache (31%), peripheral edema (31%), anemia (28%), and decreased appetite (28%). 2 pts (6%) discontinued due to AEs. Decreased pERK staining vs pre-dose samples was seen in all post-dose samples leading to absolute ($49\% \pm 29\%$) and relative ($69\% \pm 28\%$, normalized to total ERK) reduction in pERK. **Conclusions:** Further investigation is needed, as this combination is tolerable at full monotherapy doses of each drug, with manageable toxicities, and has activity in a subset of BRAF mutant pts. Updated safety, efficacy, and correlative data will be presented. Clinical trial information: NCT01072175.

A randomized, placebo-controlled, phase I/II study of tivantinib (ARQ 197) in combination with cetuximab and irinotecan in patients (pts) with *KRAS* wild-type (WT) metastatic colorectal cancer (CRC) who had received previous front-line systemic therapy.

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Background: Tivantinib (ARQ 197) selectively inhibits the MET receptor tyrosine kinase, which is implicated in tumor cell migration, invasion, and metastasis. Resistance to EGFR inhibitors has been associated with activation of alternative pathways including MET. **Methods:** Pts with advanced *KRAS* WT CRC that progressed on or after 1 prior line of chemotherapy and no previous treatment with an EGFR inhibitor were eligible. Pts were randomized 1:1 to receive cetuximab (500 mg/m²) and irinotecan (180 mg/m²) on days 1 and 15 every 28 days, plus oral tivantinib (360 mg twice daily [BID]) or placebo. The primary endpoint was progression-free survival (PFS); additional endpoints include safety, objective response rate, overall survival (OS) and exploratory biomarker analyses. **Results:** Between Jul 2010 and Feb 2012, 122 pts were randomized; 117 pts were eligible for analysis (60 tivantinib, 57 placebo). Mean age was 57 years (range, 27-79 years); ECOG PS 0/1 55%/45%; and 81% received prior oxaliplatin. Median PFS was 8.3 months in the tivantinib arm vs 7.3 months in the placebo arm (hazard ratio [HR] = 0.85; 95% CI, 0.55-1.33; *P* = 0.38). Objective response rate (95% CI) was 45% (33%-58%) in the tivantinib arm and 33% (23%-46%) in the placebo arm. Median OS has not yet been reached but is trending in favor of tivantinib vs placebo (HR = 0.67). Among pts with prior oxaliplatin therapy, median PFS was 8.4 months for tivantinib and 7.2 months for placebo (HR = 0.67; 95% CI, 0.44-1.00; *P* = 0.1). The most common grade 3/4 adverse events (≥ 10%) were neutropenia, diarrhea, and nausea. Correlation of clinical outcomes with additional factors including mutation status and immunohistochemical analysis of tumor MET expression will be presented. **Conclusions:** Outcomes in this trial trended towards improvement with tivantinib (360 mg BID) plus cetuximab and irinotecan, particularly in the subgroup who had previous oxaliplatin. Further studies are needed to identify the CRC population most likely to benefit from addition of tivantinib to standard therapy. Clinical trial information: NCT01075048.

Comprehensive pharmacogenetic profiling of advanced colorectal cancer.

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Background: Inherited genetic factors may influence a patient's response to, and side effects from, chemotherapy and biological therapies. Here, we sought to generate a comprehensive inherited pharmacogenetic profile for advanced colorectal cancer (aCRC). **Methods:** We analysed 260 potentially functional coding region and promoter variants in genes within the 5-FU, capecitabine, oxaliplatin, EGFR and DNA repair pathways in 2183 patients with aCRC treated with oxaliplatin-fluoropyrimidine chemotherapy \pm cetuximab (from the MRC COIN and COIN-B trials). Primary outcomes assessed were 12-week response, skin rash (SR) (for those receiving cetuximab), dose-reduction or delay in treatment due to any toxicity and peripheral neuropathy (PN). **Results:** For variants with minor allele frequencies $>20\%$, we had $>85\%$ power to detect an effect on response / toxicity with an OR of 1.3. In patients treated with chemotherapy + cetuximab, 5 and 4 coding region variants in the EGFR pathway were associated with response and SR, respectively. The most significant associations were with variants in members of phosphatidylinositol 3-kinase regulatory subunit. In patients treated with chemotherapy \pm cetuximab, 8 coding region variants in the 5-FU, capecitabine, oxaliplatin or DNA repair pathways were associated with response, 8 with any toxicity and 5 with PN. The most significant associations for response were with variants in DNA repair genes and, for any toxicity, with common variants in DPYD. **Conclusions:** Our study highlights the difficulty in identifying inherited biomarkers for the treatment of aCRC - despite using samples from the largest reported randomised trial for aCRC, with considerable power to detect alleles of small effects, none of the associations remained significant after rigorous correction for multiple testing.

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Poster Discussion Session (Board #2), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**Validation of *DPYD* variants *DPYD**2A, I560S, and D949V as predictors of 5-fluorouracil (5-FU)-related toxicity in stage III colon cancer (CC) patients from adjuvant trial NCCTG N0147.**

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Background: Prediction of 5-FU-related adverse events (5FU-AEs) continues to be problematic. Pharmacogenetic studies on the rate-limiting enzyme in 5-FU metabolism, dihydropyrimidine dehydrogenase (DPD), suggest a link between three variants and both decreased enzyme activity and increased toxicity: c.1905+1 G>A (*DPYD**2A; rs3918290), c.1679 T>G (I560S; *DPYD**13; rs55886062), and c.2846A>T (D949V; rs67376798). Since the adverse impact of *DPYD* variants on 5-FU toxicity remains controversial, we determined associations between the three known *DPYD* variants and 5FU-AEs in stage III CC patients receiving FOLFOX or FOLFIRI (+ cetuximab) after curative resection. **Methods:** 2886 patients were genotyped by multiplexed single-base extension assays using the IPLEX Gold Kit and analyzed on the Sequenom MassARRAY system. Grade 3+ AEs were recorded per CTCAE v3. Fisher's exact test, unequal variance two-sample t-test, and Wilcoxon rank sum test were used to compare categorical variables, continuous variables, and counts between patients with wild-type and mutant status. Logistic regressions were used to assess univariate and multivariate associations. **Results:** Patients displayed the following characteristics: male gender 53.2%, median age 58 [19-86], proficient DNA mismatch repair status 88.6%, PS-0 76.6%, + irinotecan 8.1%, and + cetuximab 45.9%. A total of 27 (0.9%), 4 (0.1%), and 32 (1.1%) patients carried the *DPYD**2A, I560S, and D949V variants, respectively. Analysis identified significant associations between *DPYD**2A and D949V variants and toxicity, with grade 3+ 5FU-AEs identified in 22 *DPYD**2A carriers (OR=11.9, 95% CI 4.0-32.7, p<0.0001) and 22 D949V carriers (OR=5.5, 95% CI 2.5-12.1, p< 0.0001). No interaction effect was found between *DPYD**2A and D949V on grade 3+ 5FU-AEs (p = 0.98), nor on overall grade 3+ AEs (p = 0.97). No significant association was identified between I560S and grade 3+ 5FU-AEs. **Conclusions:** In the largest study to date, statistically significant associations were found between *DPYD**2A and D949V variants and increased incidence of grade 3+ 5FU-AEs, suggesting utility in 5-FU toxicity prediction.

Analysis of *KRAS*/*NRAS* and *BRAF* mutations in the phase III PRIME study of panitumumab (pmab) plus FOLFOX versus FOLFOX as first-line treatment (tx) for metastatic colorectal cancer (mCRC).

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Background: Analysis of a phase III pmab monotherapy study indicated that *KRAS* and *NRAS* mutations beyond *KRAS* exon 2 may be predictive of pmab efficacy (Peeters et al, 2013). **Methods:** The primary objective of this prospectively defined retrospective analysis of PRIME was to assess the effect of pmab + FOLFOX vs FOLFOX on overall survival (OS) in pts with mCRC based on *RAS* (*KRAS* or *NRAS*) or *BRAF* mutation status. "Gold standard" bidirectional Sanger sequencing and WAVE-based SURVEYOR Scan Kits from Transgenomic (conducted independently) were used to detect mutations in *KRAS* exon 3, exon 4; *NRAS* exon 2, exon 3, exon 4; and *BRAF* exon 15. **Results:** *RAS* ascertainment rate was 90%. Tx HRs for pts with WT *RAS* were 0.78 (95% CI, 0.62 - 0.99; $p = 0.04$) for OS (median gain of 5.8 months in the pmab arm) and 0.72 (95% CI, 0.58 - 0.90; $p = < 0.01$) for PFS. Tx HRs for WT *KRAS* exon 2/mutant (MT) other *RAS* were 1.29 (95% CI, 0.79 - 2.10; $p = 0.31$) for OS and 1.28 (95% CI, 0.79 - 2.07; $p = 0.32$) for PFS. Tx HRs for pts with WT or MT *BRAF* were inconsistent with a predictive biomarker (Table). Prognostic effects of the tested biomarkers will be presented. **Conclusions:** A statistically significant OS benefit was observed in pts with WT *RAS* mCRC treated with pmab + FOLFOX vs FOLFOX. Pmab is unlikely to benefit pts with any *RAS* mutations. In this analysis, *BRAF* mutation had no predictive value. Clinical trial information: NCT00364013.

	Pmab + FOLFOX (N = 320)	FOLFOX (N = 321)	HR (95% CI)	Descriptive p value
WT <i>RAS</i> ^a - n	259	253		
Median OS - mos (95% CI)	26.0 (21.7 - 30.4)	20.2 (17.7 - 23.1)	0.78 (0.62 - 0.99)	0.04
Median PFS - mos (95% CI)	10.1 (9.3 - 12.0)	7.9 (7.2 - 9.3)	0.72 (0.58 - 0.90)	< 0.01
MT <i>RAS</i> ^b - n	272	276		
Median OS - mos (95% CI)	15.6 (13.4 - 17.9)	19.2 (16.7 - 21.8)	1.25 (1.02 - 1.55)	0.04
Median PFS - mos (95% CI)	7.3 (6.3 - 7.9)	8.7 (7.6 - 9.4)	1.31 (1.07 - 1.60)	0.01
WT <i>RAS</i> and <i>BRAF</i> - n	228	218		
Median OS - mos (95% CI)	28.3 (23.7 - not estimable)	20.9 (18.4 - 23.8)	0.74 (0.57 - 0.96)	0.02
Median PFS - mos (95% CI)	10.8 (9.4 - 12.4)	9.2 (7.4 - 9.6)	0.68 (0.54 - 0.87)	< 0.01
MT <i>BRAF</i> - n	24	29		
Median OS - mos (95% CI)	10.5 (6.4 - 18.9)	9.2 (8.0 - 15.7)	0.90 (0.46 - 1.76)	0.76
Median PFS - mos (95% CI)	6.1 (3.7 - 10.7)	5.4 (3.3 - 6.2)	0.58 (0.29 - 1.15)	0.12

^aWT in *KRAS* and *NRAS* exons 2, 3, and 4. ^bMT in any *KRAS* or *NRAS* exon 2, 3, or 4.

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Poster Discussion Session (Board #4), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**Heterogeneity of acquired KRAS and EGFR mutations in colorectal cancer patients treated with anti-EGFR monoclonal antibodies.**

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Background: Although KRAS and EGFR extracellular domain acquired mutations were detected in two small cohorts and correlated with acquired resistance to anti-EGFR monoclonal antibodies (MAb), the frequency, co-occurrence, and distribution of these acquired mutations is unknown. In this study we evaluated the presence of acquired KRAS and EGFR mutations in cfDNA from CRC patients (pts) treated with anti-EGFR monoclonal antibody. **Methods:** Plasma was collected from EGFR-MAb refractory mCRC pts as part of the ATTACC (Assessment of Targeted Therapies Against Colorectal Cancer) program. Eligible pts had documentation of pre-treatment KRAS wild type tumor. The cfDNA was extracted from the plasma and analyzed by BEAMing technology for acquired KRAS and EGFR mutation. **Results:** The plasma from 55 patients was analyzed for EGFR and KRAS mutation. The S492R EGFR mutation was detected in 4 pts (7%) treated with cetuximab. Acquired KRAS mutations were detected in 26 of the 55 KRAS wt samples analyzed (47%). Although codon 61 and 146 mutations are rare in untreated CRCs (2% and 1% of the MDACC population, respectively), these atypical KRAS mutations predominated in acquired resistance (Q61H=33% and A146T=10%). Mutations in more than one KRAS codon are exceedingly rare in the primary tumor. In our study we detected more than one KRAS or EGFR mutation in 30% of the population ($p<0.001$), suggesting the development of multiple independent clones in individual patients. Compared to 8 patients with known KRAS mutations, the average number of mutant reads in the 26 patients with acquired mutation was substantially lower ($p<0.01$) despite similar tumor burden. Of note, acquired concomitant KRAS mutations were also found in a BRAF V600 mutant patient previously treated with anti-EGFR MAb and a BRAF inhibitor. **Conclusions:** KRAS and EGFR acquired mutation are present at low concentrations in cfDNA from mCRC pts refractory to anti-EGFR MAb and they are not mutually exclusive, suggesting heterogeneity of the resistant clones. Anti-EGFR MAb refractory patients showed a higher incidence of atypical KRAS mutation and higher incidence of multiple codon KRAS mutations compared with overall CRC patient.

3513

Poster Discussion Session (Board #5), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM***EGFR* and *KRAS* mutations during anti-*EGFR* monoclonal antibody treatment in metastatic colorectal cancer: Clinically relevant?**

Lucie Karayan-Tapon, Aurelie Ferru, Ulrich Cortes, Claire Villalva, Jean Marc Tourani, Christine Silvain, Pierre Levillain, David Tougeron; Department of Molecular Oncology, Poitiers, France; Department of Oncology, Poitiers University Hospital, Poitiers, France; INSERM U935, CHU de Poitiers, Poitiers, France; Department of Gastroenterology, Poitiers University Hospital, Poitiers, France; Department of Pathology, Poitiers University Hospital, Poitiers, France

Background: It is well-established that only patients with wild-type *KRAS* metastatic colorectal cancer (mCRC) benefit from treatment with an epidermal growth factor receptor monoclonal antibody (anti-*EGFR* mAb). Recently, in patients with tumor progression after anti-*EGFR* mAb, occurrence of *EGFR* mutation (n=2/10) [Montagut C et al., Nat Med 2012] or *KRAS* mutation (n=6/10) [Misale S et al., Nature 2012] in metastases has been identified. These mutations could explain treatment resistance but still need to be confirmed with simultaneous analysis of *KRAS* and *EGFR* mutations. **Methods:** We analyzed 37 tumor samples after anti-*EGFR* mAb treatment for mCRC (34 from metastasis lesions and 3 from primary tumors). We analyzed *KRAS* (codons 12 and 13), *BRAF*^{V600E} and *EGFR*^{S492R} mutations using a highly sensitive technique, pyrosequencing (TheraScreen *KRAS* Pyro Kit, Qiagen). All tumors were *KRAS*, *BRAF*^{V600E} and *EGFR*^{S492R} wild-type before anti-*EGFR* mAb treatment. **Results:** The majority of patients were treated using anti-*EGFR* mAb in first-line chemotherapy (70%) and combined with cytotoxic chemotherapy (96%). Cetuximab was used in 86% and panitumumab in 14% of the cases. Among the 37 tumor specimens, 8 were collected after disease progression, and the others after disease control. No *EGFR*^{S492R} mutation was detected. No tumors developed *BRAF* mutation but one tumor acquired a *KRAS* mutation. Nevertheless, the *KRAS* mutation in this patient (G12V) was detected, after 5-fluorouracil plus cetuximab therapy, only in the primary tumor in the colon but not in the liver metastasis. Moreover, there was a disease control (partial response). **Conclusions:** Our results suggest that *EGFR*^{S492R} and acquired *KRAS* mutations during anti-*EGFR* mAb therapy are not the only factors accounting for anti-*EGFR* resistance. Moreover, occurrence of *KRAS* mutation during anti-*EGFR* therapy could differ between primary tumor and metastases.

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Poster Discussion Session (Board #6), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**Analysis of plasma protein biomarkers from the CORRECT phase III study of regorafenib for metastatic colorectal cancer.**

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Background: In the CORRECT phase III trial, the multikinase inhibitor regorafenib (REG) demonstrated significant improvement in overall survival (OS) and progression-free survival (PFS) vs placebo (Pla) in patients with metastatic colorectal cancer (mCRC) whose disease had progressed on other standard therapies. An exploratory biomarker subanalysis was conducted to identify protein biomarkers with potential predictive or prognostic value. **Methods:** Fifteen proteins of interest, many of which are involved in angiogenesis, were quantified by multiplex immunoassay or ELISA in baseline plasma samples collected at study entry from 80% (611/760) of patients. Potential predictive and prognostic effects were evaluated. **Results:** The biomarker subpopulation was representative of the overall study population in terms of OS and PFS. Using OS as the clinical endpoint, Tie-1 was the only protein whose level demonstrated significant correlation with efficacy (low protein group: REG/Pla, HR 0.87; high protein group, HR 0.56; interaction, $p=0.035$). Using PFS as the clinical endpoint, von Willebrand factor (VWF) was the only protein whose level demonstrated significant correlation with efficacy (low protein group: REG/Pla, HR 0.39; high protein group, HR 0.60; interaction, $p=0.02$). Following correction for multiple testing, neither Tie-1 nor VWF data retained statistical significance. Baseline levels of IL-8 and placental growth factor (PlGF) were found to have prognostic value for OS (IL-8: high/low protein levels, HR 3.48, $p<0.001$; PlGF: HR 1.81, $p=0.002$). IL-8 was also prognostic for PFS (high/low protein levels: HR 1.63, $p<0.001$). **Conclusions:** None of the plasma proteins examined showed significant predictive value for REG efficacy after multiple testing correction. The association between baseline levels of Tie-1/VWF and REG efficacy may be a hypothesis to be tested in further trials. Clinical trial information: NCT01103323.

3515

Poster Discussion Session (Board #7), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**Maintenance therapy with bevacizumab with or without erlotinib in metastatic colorectal cancer (mCRC) according to KRAS: Results of the GERCOR DREAM phase III trial.**

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Background: The primary analysis of DREAM demonstrated that a maintenance therapy (MT) with bevacizumab (Bev) + EGFR TKI erlotinib (E) significantly improved progression-free survival (PFS) after a 1st-line Bev-based induction therapy (IT) in patients (pts) with unresectable mCRC. **Methods:** Pts were randomized to MT after an IT with FOLFOX-bev or XELOX-bev or FOLFIRI-bev between Bev alone (Bev 7.5 mg/kg q3w; arm A) or Bev+E (Bev 7.5 mg/kg q3w, E 150 mg/d ; arm B) until PD or unacceptable toxicity. Primary endpoint was PFS on MT. Secondary endpoints included PFS from inclusion, overall survival (OS) and safety. The impact of KRAS tumor status on treatment efficacy was evaluated in an exploratory analysis. **Results:** 700 pts were registered and 452 pts were randomized (228 in arm A, 224 in arm B). KRAS status was available for 413/452 (91%) pts. The median duration of MT was 3.6 m. Results for MT are presented below (Table). In the registered population, median OS was 24.9m (22.5 – 27.3). **Conclusions:** Maintenance treatment with bev + erlotinib increases PFS over maintenance with bev alone in pts with mCRC but does not prolong OS. Further follow-up will determine the impact of 2nd or 3rd line anti-EGFR Mabs in this study. Contrasting with anti-EGFR Mabs, KRAS tumor status is not mandatory to select pts with mCRC for treatment with erlotinib. Clinical trial information: NCT00265824.

GERCOR DREAM study: KRAS analysis.

Endpoints, months (95% CI)	Arm A	Arm B	HR (95% CI)	P value
Maintenance population (MP) (n = 452)	n = 228	n = 224		
Median maintenance PFS	4.8 (4.1 - 5.7)	5.9 (4.5 - 6.4)	0.76 (0.61-0.94)	0.010
Median PFS	9.3 (8.7 - 10.1)	10.2 (9.5 - 11.5)	0.76 (0.61 - 0.94)	0.009
Median OS	27.9 (24.1 - 31.1)	28.5 (25.1 - 33.9)	0.89 (0.70-1.12)	0.312
MP - WT KRAS (n = 111)	n = 111	n = 129		
Median maintenance PFS	5.9 (4.0 - 6.5)	6.0 (4.5 - 7.8)	0.86 (0.64-1.16)	0.135
Median PFS	9.7 (8.7 - 11.0)	10.9 (9.8 - 12.6)	0.83 (0.61 - 1.11)	0.197
Median OS	31.5 (27.5 - 38.0)	31.8 (26.6 - 37.8)	0.92 (0.66 - 1.30)	0.644
MP - Mut KRAS (n = 173)	n = 95	n = 78		
Median maintenance PFS	4.4 (3.9 - 5.3)	4.7 (3.6 - 7.1)	0.77 (0.54 - 1.08)	0.124
Median PFS	9.9 (8.6 - 10.8)	9.8 (8.4 - 12.2)	0.80 (0.57 - 1.13)	0.212
Median OS	26.9 (22.4 - 33.2)	26.3 (21.0 - 34.4)	1.06 (0.72 - 1.55)	0.767

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Poster Discussion Session (Board #8), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**FOLFIRI plus bevacizumab (bev) as second-line therapy in patients (pts) with metastatic colorectal cancer (mCRC) who have failed first-line bev plus oxaliplatin-based therapy: The randomized phase III EAGLE study.**

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Background: The phase III ML18147 study (NCT00700102) showed a survival benefit for the continuation of bev after 1st-line bev-containing therapy in pts with mCRC. Continuation of bev beyond disease progression in this setting was approved by the FDA in Jan 2013. In the randomized, phase II SPIRITT study (NCT00418938) assessing 2nd-line treatment for mCRC, progression-free survival (PFS) was longer in the bev arm compared with the panitumumab arm, but the difference was not statistically significant. We describe the results of EAGLE, a multicenter, randomized phase III study evaluating the optimal dose of 2nd-line bev in Japan (UMIN000002557). **Methods:** Pts were randomized 1:1 to receive bev 5 mg/kg (Arm A) or 10 mg/kg (Arm B) plus FOLFIRI Q2W. Key eligibility criteria: age ≥ 20 years, mCRC, ECOG PS ≤ 1 , and treatment failure to prior 1st-line bev plus oxaliplatin-based therapy (≥ 4 cycles). The primary endpoint was PFS. Secondary endpoints included time to treatment failure (TTF), PFS from 1st-line therapy, response rate (RR) and safety. The planned sample size was 370 pts to detect 30% risk reduction with 90% power assuming a two-sided significance level of 0.05. **Results:** 387 pts were randomized between Sep 2009 and Jan 2012; 367 pts formed the full analysis set (Arm A 179 pts; Arm B 188 pts). Baseline characteristics were well balanced between the treatment arms. Respectively for Arm A and B, PFS was 6.2 and 6.3 months (HR 1.03, 95% CI: 0.82-1.30; $p=0.815$), TTF 5.3 and 5.3 months (HR 1.08, 95% CI: 0.87-1.33; $p=0.485$), PFS from 1st-line therapy 17.6 and 17.8 months (HR 0.99, 95% CI: 0.78-1.25; $p=0.919$) and RR 11.7% and 10.1%. Frequently reported AEs in Arm A and B, respectively, were: hypertension (13.0%, 18.1%), proteinurea (36.8%, 35.2%), GI perforation (4.7%, 3.1%), grade 3/4 neutropenia (46.1%, 39.9%), grade 3/4 fatigue (7.8%, 10.9%), and grade 3/4 anorexia (5.7%, 5.2%). Treatment-related deaths occurred in 2 pts in each arm. **Conclusions:** The study did not meet its primary endpoint. PFS in Arm A was comparable to that reported in the ML18147 study. Safety in both arms was consistent with previously reported studies. Clinical trial information: UMIN000002557.

Effectiveness of bevacizumab added to gold standard chemotherapy in metastatic colorectal cancer (mCRC): Final results from the Itaca randomized clinical trial.

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Background: Evidence from available RCTs indicates that the addition of bevacizumab (B) to chemotherapy (CT) results into an improved survival in metastatic colorectal cancer (mCRC). However, the magnitude of this effect is different across trials, with marginal benefit observed when gold standard CT regimens are used. With these premises we performed a phase III randomized clinical study to evaluate the effectiveness of gold standard mCRC first line CT + B. This study was funded by the Italian Ministry of Health. **Methods:** mCRC patients candidate were randomized to receive first line CT + B or first line CT alone. CT regimens included FOLFOX4 (oxaliplatin 85 mg/m² d1, folinic acid FA 100 mg/m² dd1,2, 5FU 400 mg/m² iv bolus dd 1,2 plus 5FU 600 mg/m² 22-h ic dd1,2 – Q14 days) or FOLFIRI (irinotecan 180 mg/m²d1, FA and 5FU as in FOLFOX4, Q 14 days); B 5 mg/kg was administered Q 14 days. The primary end point was Progression Free Survival (PFS). Secondary endpoints included Overall Survival (OS), Response Rate (ORR) and safety. Three hundreds ten events were required to statistically differentiate PFS between groups with 80% power. **Results:** Between 11/2007 and 03/2012, 376 patients were randomized. Patient characteristics were well balanced between the two arms. FOLFOX4 was used in 60% of the patients and FOLFIRI in 40%. After a median follow up of 18.4 months, 313 progressions and 179 deaths were observed. No statistically significant differences in PFS, OS and ORR were observed (see table). B containing regimens were associated with more frequent hypertension, bleeding, proteinuria and asthenia. **Conclusions:** The addition of B to a gold standard CT for mCRC does not result into an improved prognosis in terms of PFS, ORR, OS. ITACA's results (control arm) suggest that the chemotherapeutic schedules used in some of the previously published bevacizumab trials might be suboptimal. Clinical trial information: 2007-004539-44.

	CT+Beva (n=179)	CT (n=197)	HR (95% CI) P value
Median PFS mos (95%CI)	9.2 (8.0-10.0)	8.4 (7.0-8.9)	0.88 (0.70-1.10) 0.265
Median OS mos (95%CI)	20.6 (15.3-22.6)	20.6 (18.2-23.3)	1.18(0.88-1.58), 0.278
ORR % (95% CI)	54.2 (46.7-62.3)	48.1 (40.8-55.4)	0.286

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Poster Discussion Session (Board #10), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**Noninferiority of S-1 to UFT/LV as adjuvant chemotherapy for stage III colon cancer: A randomized phase III trial (ACTS-CC).**

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Background: The ACTS-CC trial is a phase III trial designed to validate non-inferiority of S-1 to UFT/LV, a standard treatment in Japan as adjuvant chemotherapy for stage III colon cancer. This is the first report which evaluated the efficacy of S-1 as adjuvant therapy for colon cancer. **Methods:** 20-80 aged patients with stage III colon cancer who underwent curative surgery were randomly assigned to receive S-1 (80, 100, or 120 mg/day according to BSA on days 1 to 28, followed by 14 days rest, 4 courses) or UFT/LV (UFT: 300 to 600 mg/day according to BSA and, LV: 75 mg/day on days 1 to 28, followed by 7 days rest, 5 courses). Primary endpoint was DFS. Sample size was 1,480 determined with one-sided alpha of 0.05, power of 0.80, and non-inferiority margin of hazard ratio (HR) of 1.29. **Results:** Among 1535 enrolled patients between Apr. 2009 and Jun. 2010, 1518 patients (758 in S-1 group, 760 in UFT/LV group) were included in the efficacy analysis. Median follow-up was 41.3 months, the mean age at enrollment was 64.5 years, wide lymph node dissection (D3) was done in 79.8%, the median number of dissected lymph nodes was 17, and stage IIIA/IIIB/IIIC were 15%/71%/14%. The 3-year DFS rate was 75.5% in S-1 group and 72.5% in UFT/LV group. The HR of DFS was 0.85 (95%CI: 0.70-1.03) and non-inferiority of S-1 was demonstrated ($p < 0.0001$). The completion rate of the protocol treatment was 76.5% in S-1 group and 72.5% in UFT/LV group. The overall incidence of grade ≥ 3 adverse events (AEs) in S-1 group and UFT/LV group were 16.0% and 14.4%: 4.4% and 5.5% for diarrhea, 4.9% and 3.5% for anorexia, 0.7% and 0.4% for leucopenia, 0.9% and 0.1% for anemia, 0.1% and 0.4% for thrombocytopenia, 1.2% and 1.5% for hyperbilirubinemia, 0.8% and 2.1% for AST elevation, and 1.1% and 3.3% for ALT elevation, respectively. **Conclusions:** Adjuvant therapy of S-1 for stage III colon cancer was demonstrated to be non-inferior in DFS to that of UFT/LV. Although AE profiles differed between S-1 group and UFT/LV group in this trial, incidence and degree of AEs were acceptable, and the completion rate of the protocol treatment was high. Adjuvant chemotherapy using S-1 will be a treatment option for stage III colon cancer. Clinical trial information: NCT00660894.

A randomized phase III trial of S-1/oxaliplatin (SOX) plus bevacizumab versus 5-FU/LV/oxaliplatin (mFOLFOX6) plus bevacizumab in patients with metastatic colorectal cancer: The SOFT study.

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Background: Several studies of oxaliplatin plus S-1 combination therapy (SOX) conducted in Asia have shown promising efficacy and safety for metastatic colorectal cancer (mCRC), suggesting the potential to replace mFOLFOX6. We performed a randomized phase III trial to determine whether SOX plus bevacizumab (SOX+Bev) is non-inferior to mFOLFOX6 plus bevacizumab (mFOLFOX6+Bev) in terms of progression-free survival (PFS). **Methods:** The SOFT study was a randomized, open-label, phase III trial. Chemotherapy-naïve patients (pts) with mCRC, an ECOG PS of 0-1, and adequate organ functions were randomized to receive either mFOLFOX6+Bev (5 mg/kg of bevacizumab, followed by 200 mg/m² of l-leucovorin given simultaneously with 85 mg/m² of oxaliplatin, followed by a 400 mg/m² bolus of 5-FU on day 1 and then 2,400 mg/m² of 5-FU over 46 h, every 2 weeks) or SOX+Bev (7.5 mg/kg of bevacizumab, 130 mg/m² of oxaliplatin on day 1, and 40–60 mg of S-1 twice daily for 2 weeks, followed by a 1-week rest). The primary endpoint was PFS. A sample size of 225 pts per group was estimated to be necessary based on a median PFS of 10.0 months in each group and an 80% power to demonstrate non-inferiority of SOX+Bev with a 2.5-month margin (hazard ratio, HR = 1.33) and a 2-sided alpha of 0.05. **Results:** A total of 512 pts were enrolled from February 2009 to March 2011. Data were analyzed after confirming >388 events as planned. Demographic factors were well balanced. Pts received a median of 12 cycles (1 cycle = 2 weeks) of mFOLFOX6+Bev and 8 cycles (1 cycle = 3 weeks) of SOX+Bev (range: 1–16). Median PFS was 11.5 months (95% CI: 10.7–13.2) with mFOLFOX6+Bev and 11.7 months (95% CI: 10.7–12.9) with SOX+Bev. The adjusted HR for PFS was 1.043 (95% CI: 0.860–1.266), and the p value for non-inferiority was 0.0139. Response rate was 62.7% with mFOLFOX6+Bev and 61.5% with SOX+Bev. Grade 3/4 toxicities (%) with mFOLFOX6+Bev/SOX+Bev were leukopenia 8.4/2.4, neutropenia 33.7/8.8, anorexia 1.2/5.2, and diarrhea 2.8/9.2. **Conclusions:** SOX+Bev is non-inferior to mFOLFOX6+Bev with respect to PFS as 1st-line treatment for mCRC and thus can replace mFOLFOX6+Bev. Clinical trial information: JapicCTI-090699.

Prognostic value of early objective tumor response (EOTR) to first-line systemic therapy in metastatic colorectal cancer (mCRC): Individual patient data (IPD) meta-analysis of randomized trials from the ARCAD database.

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Background: EOTR has been suggested as a potential surrogate for overall survival (OS) in patients (pts) with mCRC and allows early assessment of treatment efficacy, facilitating adaptive trial design. We assessed at the individual patient level, the correlation between EOTR (complete or partial response) at 6, 8 and 12 weeks (wk), OS and progression free survival (PFS) in pts with mCRC treated with 1st line chemotherapy with or without a targeted agent as a first step in a surrogacy demonstration. **Methods:** IPD from 13,949 pts enrolled on 15 randomized Phase III trials in 1st line mCRC were used; 8 trials included targeted (anti-angiogenic and anti-EGFR) agents. EOTR prognostic value was assessed by landmark analyses using Cox models stratified by treatment assignment. P-values <0.01 were considered statistically significant to account for multiple comparisons. **Results:** Of 13,949 pts, 11,987 had sufficient response data to be included in the analysis. Median OS was 21.7 months (mo) in pts with an EOTR vs. 16.5 mo without EOTR at 6 wk (p<.0001, Hazard Ratio [HR] 0.64, 95% confidence interval [CI] 0.58-0.70, c statistic [c] 0.55). HRs were similar whether pts were treated with targeted therapies (p<.0001, HR 0.68, 95% CI 0.58-0.80, x 0.54) or non-targeted therapies (p<.0001, HR 0.61, 95% CI 0.55-0.69, x 0.55). Median PFS was 8.4 mo in pts with EOTR at 6 wk vs. 7.0 mo in pts without EOTR (p<.0001, HR 0.79, 95% CI 0.73-0.85). EOTR at 8 and 12 wks were also significantly associated with longer OS and PFS. The prognostic value of EOTR at 6, 8 and 12 wks remained significant (p<0.0001) after adjusting for age, gender, performance status and location of metastatic disease (lung or liver). Overall tumor response (to 26 wk) however provided superior OS prediction (p<.0001, HR 0.51, 95% CI, 0.47-0.56, CS 0.61) vs. EOTR. **Conclusions:** Early response measured at 6, 8 or 12 wk after starting 1st line treatment was a strong and independent predictor of both OS and PFS in patient with mCRC and warrants further consideration as a potential endpoint for future trials, particularly randomized phase II trials.

Efficacy and safety according to age subgroups in AVEX, a randomized phase III trial of bevacizumab in combination with capecitabine for the first-line treatment of elderly patients with metastatic colorectal cancer.

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Background: Elderly patients (pts) are underrepresented in clinical trials. The open-label phase III trial AVEX evaluated the benefit of adding bevacizumab (BEV) to capecitabine (cape) in elderly pts with previously untreated metastatic colorectal cancer (mCRC). This analysis explores clinical outcomes by age subgroup. **Methods:** In AVEX, 280 pts ≥ 70 y with mCRC for whom single-agent chemotherapy was deemed appropriate, were randomized to first-line cape (1000 mg/m² bid days 1–14) alone (n=140) or with BEV (7.5 mg/kg) q3w (n=140). The primary end point was progression-free survival (PFS). Secondary end points were overall survival (OS), overall response rate, and safety. The study was powered to show a difference in PFS but not OS. A post hoc analysis was conducted to assess PFS, OS, and safety in pts 70–74 y, 75–79 y, and ≥ 80 y. **Results:** Median age was 76 y (range, 70–87). In the overall population, BEV + cape significantly prolonged PFS compared with cape (median 9.1 vs 5.1 mo; hazard ratio [HR], 0.53; 95% confidence interval [CI], 0.41–0.69; $p < .001$). Differences in OS did not reach statistical significance in the overall population (HR, 0.79; 95% CI, 0.57–1.09; $p = .182$). Treatment was well tolerated. Results according to age are shown (Table). **Conclusions:** The addition of BEV to cape was associated with significant improvements in PFS in the overall elderly mCRC population and within age subgroups. The safety profile of BEV + cape was consistent across age groups. Clinical trial information: NCT00484939.

	70–74 y		75–79 y		≥ 80 y	
	Cape + BEV n=55	Cape n=46	Cape + BEV n=57	Cape n=66	Cape + BEV n=28	Cape n=28
Median PFS, mo (95% CI)	7.6 (6.0–11.8)	5.0 (4.0–6.5)	9.8 (7.1–11.4)	5.1 (4.1–7.4)	10.5 (5.0–14.5)	5.1 (2.2–7.1)
PFS HR (95% CI)	0.52 (0.32–0.83) <.001		0.60 (0.40–0.89) 0.16		0.36 (0.19–0.71) 0.03	
Median OS, mo (95% CI)	20.7 (13.7–26.1)	22.2 (9.7–42.7)	19.8 (13.8–27.3)	17.4 (11.9–23.0)	19.7 (7.5–26.9)	12.6 (6.6–17.0)
OS HR (95% CI)	0.91 (0.50–1.66) .55		0.79 (0.48–1.30) .37		0.62 (0.31–1.24) .24	
Best ORR (%)	25.5	10.9	15.8	12.1	14.3	3.6
Fisher's exact p	.076		.607		.352	
Grade ≥ 3 adverse events, %	n=54 63.0	n=46 41.3	n=53 54.7	n=64 40.6	n=27 59.3	n=26 57.7

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Poster Discussion Session (Board #14), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**BRAF and KRAS mutations as additional risk factors in the context of clinical parameters of patients with colorectal cancer.**

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Background: The BRAF and KRAS mutations have been proposed as prognostic markers in colorectal cancer (CRC). Of them, only the BRAF V600E mutation has been validated as prognostic for overall survival and survival after relapse, while the value of KRAS mutation is still unclear. **Methods:** In a cohort of 1423 stage II-III patients from the PETACC-3 clinical trial, the prognostic value of the BRAF and KRAS mutations was retrospectively assessed in all possible stratifications defined by the 5 factors (T and N stage, tumor site and grade, and microsatellite instability status), by log rank test for overall survival (OS), relapse-free survival (RFS), and survival after relapse (SAR). The presence of interactions was tested by Wald test. The significance level was set to 0.01 for Bonferroni-adjusted p-values (P^*), and a second level for a trend towards statistical significance was set at 0.05 for unadjusted p-values (P). **Results:** BRAF mutation was a marker of poor OS only in microsatellite stable (MSS) and left-sided tumors, with no prognostic value in microsatellite instable (MSI-H) or right-sided tumors. In MSS/left-sided tumors, BRAF mutation represents a marker of higher risk than previously reported: OS HR=6.4 [95% CI: 3.6-11.5], $P^* < 0.0001$. For SAR, BRAF was prognostic in more stratifications, with higher risk in MSS/left-sided tumors (HR=3.9 [95% CI: 2.1-7.2], $P^* = 0.0002$) than in MSS/right-sided (HR=2.3 [95% CI: 1.2-4.4], $P=0.01$). A novel observation was that BRAF mutation was prognostic also for RFS, but only in MSS/left-sided tumors (HR=3.6 [95% CI: 2-6.3], $P^*=0.0005$). Additionally, heterogeneity in OS and RFS among BRAF mutants was observed. In general, KRAS mutation did not reach the significance level required, but showed a trend to become a prognostic marker for RFS in MSS tumors with early lymph node involvement (N1) (HR=1.6 [95% CI: 1.1-2.2], $P=0.01$). **Conclusions:** The prognostic utility of the BRAF and KRAS mutations has to be interpreted in the context of other factors. For the BRAF mutation, a clear interaction with MSI status and tumor site was observed, with BRAF mutation indicating a much higher risk in MSS/left-sided tumors than previously considered.

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Poster Discussion Session (Board #15), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**Prognostic impact of *KRAS* and *BRAF*^{V600E} mutations stratified by tumor site in resected stage III colon cancer patients treated with adjuvant mFOLFOX6 with or without cetuximab: NCCTG N0147 (Alliance).**

Frank A. Sinicrope, Michelle R. Mahoney, Thomas C. Smyrk, Stephen N. Thibodeau, Richard M. Goldberg, Garth D. Nelson, Daniel J. Sargent, Steven R. Alberts, North Central Cancer Treatment Group (Alliance); Mayo Clinic, Rochester, MN; Mayo Clinic College of Medicine, Rochester, MN; Division of Medical Oncology, Ohio State University School of Medicine, Columbus, OH

Background: The association of *KRAS* or *BRAF*^{V600E} mutations with prognosis in colon cancers has been inconsistent. Since primary tumor site may influence outcome, we analyzed *KRAS* and *BRAF*^{V600E} stratified by tumor site in resected stage III colon cancers from a randomized adjuvant trial of mFOLFOX6 + cetuximab chemotherapy (N= 2,686) where no survival difference by treatment was found. **Methods:** 2,580 tumors were analyzed for mutations in *BRAF*^{V600E} (exon 15) or *KRAS* (codons 12, 13), and for deficient DNA mismatch repair (dMMR). Cox models were used, adjusting for mutation status, age, sex, treatment, T-stage, histologic grade, nodal status, tumor site, and MMR. After study initiation, eligibility was restricted to patients (pts) with *KRAS* wild-type (WT) tumors. At a median follow-up 4.1 yrs, 83% of pts are alive. **Results:** *KRAS* and *BRAF*^{V600E} mutations were detected in 716 (28%) and 346 (14%) tumors, respectively; dMMR was found in 314 (12%). Proximal (to splenic flexure) tumors (50%) were associated with older age and were more likely to be high grade (33 vs 18%), T-stage_{3,4} (88 vs 82%), mutated for *KRAS* (33 vs 23%) or *BRAF*^{V600E} (23 vs 4%), and dMMR (21 vs 3%) [all p < 0.02]. Pts with distal vs proximal tumors showed improved disease-free survival (DFS) [HR 0.7, 95% CI (0.6-0.9); p < 0.01 unadjusted for *KRAS* or *BRAF*]. Mutant *KRAS* [HR=1.5 (1.2-1.7); p < .0001] or mutant *BRAF* [HR=1.4 (1.1-1.7); p=0.02] were each independently associated with worse DFS. The *KRAS* and tumor site interaction was significant (unadjusted p_{interaction}=0.02; adjusted p_{interaction}=0.07), with poorer DFS among distal tumors having mutant *KRAS* [HR 1.7 (1.3-2.2); p < .0001]. No interaction was observed for *BRAF*^{V600E} and tumor site, despite worse DFS for mutant *BRAF*^{V600E} among proximal tumors [HR 1.3 (1-1.8); p=0.04]. **Conclusions:** The adverse prognostic impact of *KRAS*, but not *BRAF*^{V600E}, mutations was confined to the distal colon. This finding underscores the importance of tumor site in the interpretation of the prognostic impact of *KRAS* status, and motivates similar analyses in pts with advanced disease.

Effect of adding oxaliplatin to adjuvant 5-fluorouracil/leucovorin (5FU/LV) in patients with defective mismatch repair (dMMR) colon cancer stage II and III included in the MOSIAC study.

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Background: The MOSAIC study (André T, N Engl J Med, 2004) demonstrated that adding oxaliplatin to adjuvant 5FU and LV improved three-year disease-free survival (DFS) in stage II and III resected CC. Efficacy of FOLFOX4 in pts with dMMR stage III was suggested in a retrospective study (Zaanan A, Ann Oncol 2010). **Methods:** Of the 2,246 pts included in MOSAIC study, formalin-fixed, paraffin-embedded (FFPE) tissue blocks or slides from 1,019 pts were obtained. Thirty-three samples with insufficient tumor tissue were excluded from this translational study. MMR status was determined by immunohistochemistry (IHC) analysis of the protein products of MLH1, MSH2, PMS2, and MSH6 genes. **Results:** A total of 986 pts (44%) were evaluable for MMR status and MMR status was not evaluable for 1,260 pts (56%). Relapse-free survival (RFS), DFS and overall survival (OS) were similar in both, MMR and MMR not evaluable population. Ninety (9.1%) and 896 (90.9%) pts had dMMR and proficient MMR (pMMR) CC, respectively. Of the patients with 90 dMMR CC, 45 pts had stage II and 45 stage III. Hazard Ratios (HRs) for stage II and III dMMR are 0.52 (0.21–1.28) for RFS, 0.52 (0.24–1.14) for DFS, and 0.45 (0.19–1.05) for OS, respectively. HR for stage III dMMR are 0.56 (0.19–1.61) for RFS, 0.51 (0.18–1.41) for DFS, and 0.44 (0.15–1.34) for OS, respectively. HR for stage II dMMR are 0.64 (0.11–3.70) for RFS, 0.60 (0.17–2.09) for DFS, and 0.52 (0.13–2.10) for OS, respectively. **Conclusions:** Analyses of colon cancer MMR status in pts included in the MOSAIC study support the use of FOLFOX4 in pts with dMMR stage III cancer. Clinical trial information: NCT00275210.

Three-year RFS and DFS and 5- and 10-year OS for patients with dMMR CC.

	3-year RFS	3-year DFS	5-year OS	10-year OS
Stage II and III dMMR (n=90)				
FOLFOX4 (n=40)	90.0% ± 4.7%	87.5% ± 5.2%	90.0% ± 4.7%	87.2% ± 5.4%
LV5FU2 (n=50)	79.8% ± 5.7%	78.0% ± 5.9%	82.0% ± 5.5%	70.9% ± 6.6%
Stage III dMMR (n=45)				
FOLFOX4 (n=17)	82.4% ± 9.2%	82.4% ± 9.2%	88.2% ± 7.8%	88.2% ± 7.8%
LV5FU2 (n=28)	67.9% ± 8.8%	67.9% ± 8.8%	71.3% ± 8.6%	63.0% ± 9.4%
Stage II dMMR (n=45)				
FOLFOX4 (n=23)	95.7% ± 4.2%	91.3% ± 5.8%	91.3% ± 5.8%	87.0% ± 7%
LV5FU2 (n=22)	95.2% ± 4.6%	90.9% ± 6.3%	95.5% ± 4.4%	81% ± 8.6%

3525^APoster Discussion Session (Board #17), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**Subgroup analyses results of the PETACC8 phase III trial comparing adjuvant FOLFOX4 with or without cetuximab (CTX) in resected stage III colon cancer (CC).**

Julien Taïeb, Josep Tabernero, Enrico Mini, Fabien Subtil, Gunnar Folprecht, Jean-Luc Van Laethem, Joseph Thaler, John A. Bridgewater, Evaristo Sanches, Lone Petersen, Laurence Collette, Eric Van Cutsem, Karine Le Malicot, Philippe Rougier, Ramon Salazar, Laurent Bedenne, Jean Francois Emile, Pierre Laurent-Puig, Come Lepage; Georges Pompidou European Hospital, Paris, France; Vall d'Hebron University Hospital, Barcelona, Spain; Unità di Chemioterapia, Dipartimento di Farmacologia, Università degli Studi di Firenze, Firenze, Italy; Fédération Francophone de la Cancérologie Digestive, Dijon, France; University Hospital Carl Gustav Carus, University Cancer Center / Medical Department I, Dresden, Germany; Erasme University Hospital, Brussels, Belgium; Department of Internal Medicine IV, Klinikum Kreuzschwestern Wels, Wels, Austria; University College London Cancer Institute, London, United Kingdom; Instituto Portugues de Oncologia, Porto, Portugal; Department of Oncology, Rigshospitalet, København, Denmark; EORTC Headquarters, Brussels, Belgium; University Hospital Gasthuisberg, Leuven, Belgium; Fédération Francophone de la Cancérologie Digestive Faculté de Médecine, Dijon, France; European Hospital George Pompidou, Paris, France; Translational Research Laboratory and Department of Medical Oncology, Institut Catala d'Oncologia-IDIBELL, Hospitalet de Llobregat, Spain; University Hospital, Dijon, France; Service d'Anatomie Pathologique Hôpital Ambroise Paré, Boulogne Billancourt, France; Hôpital Européen Georges Pompidou (HEGP), Assistance Publique Hôpitaux de Paris (APHP), Paris, France; Centre Hospitalier Universitaire Bocage, Dijon, France

Background: Potential benefit of adding CTX to the current standard treatment for stage III CC, was assessed. Subgroup analyses of demographic, clinical and molecular data may improve our understanding of this patient population. **Methods:** Patients (pts) were randomized 28-56 days following resection. They received 12 biweekly cycles of oxaliplatin 85 mg/m² day (d) 1, with leucovorin 200 mg/m², 5-FU 400 mg/m² bolus IV, followed by 5-FU 600 mg/m² 22-hr IV on d1-2 (FOLFOX4), without (arm A) or with weekly CTX (arm B) 250 mg/m² (initial dose 400 mg/m²). Primary endpoint was disease free survival time (DFS). Secondary endpoints included overall survival (OS), treatment compliance and safety. Enrolment was restricted to *KRAS* wt pts in 06/2008. Planned accrual of 1,407 *KRAS* wild-type (wt) pts provided 90% power to detect a hazard ratio (HR) of 0.75 with 2-sided $\alpha=0.05$, with interim analyses after 65% of planned events. Preplanned subgroup analyses were performed. **Results:** 1,602 *KRAS* wt pts (811 arm A, 791 arm B) and 742 mutated (m) *KRAS* (prior to the amendment), were randomized. *BRAF* status was determined in 1134 (71%) *KRAS* wt pts. Median follow-up was 40 months. This interim analysis showed no difference between arms for DFS (HR 1.05, 95% CI 0.85-1.29; p=0.66) or OS (HR 1.09, 95% CI 0.81-1.47; p=0.55) in *KRAS* wt pts or for DFS (HR 0.99, 95% CI 0.75-1.28; p=0.91) or OS (HR 0.98, 95% CI 0.67-1.44; p=0.92) in *KRAS/BRAF* wt pts (n=984). Similar results were seen in *KRAS* mutant (mt) pts without any detrimental effect. In *KRAS* wt pts worse outcomes were seen with CTX in pts >70 years (n=149, DFS: HR 1.97, 95% CI 0.99-3.93; p=0.05), in females (n=666, HR 1.45, 95% CI 1.03-2.03; p=0.03) and in pts with right-sided CC (n=570, HR 1.40, 95% CI 1.01-1.94; p=0.04). Conversely, a better outcome was seen in pts with pT4pN2 CC (n=146, HR 0.55, 95% CI 0.35-0.89; p=0.01). **Conclusions:** Adding CTX to FOLFOX4 offered no benefit to pts with resected stage III *KRAS* wt, *KRAS/BRAF* wt and *KRAS* mt CC. Subgroup analyses suggest that *KRAS* wt pts with pT4pN2 tumors may derive benefit from CTX. MSI status determination is ongoing to explore its potential interaction with poor outcome in female and/or with right-sided tumors pts. Clinical trial information: NCT00265811.

3526

Poster Discussion Session (Board #18), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**Proximal and distal colon tumors as distinct biologic entities with different prognoses.**

Edoardo Missiaglia, Bart Jacobs, Antonio Fabio Di Narzo, Charlotte Soneson, Arnaud Roth, Fred Bosman, Giovanni d'Ario, Dirk Klingbiel, Pu Yan, Mauro Delorenzi, Sabine Tejpar; SIB Swiss Institute of Bioinformatics, Lausanne, Switzerland; Center for Human Genetics, University Hospital Gasthuisberg, Leuven, Belgium; University Hospital Geneva, Geneva, Switzerland; Department of Pathology, Lausanne, Switzerland; SAKK - Swiss Group for Clinical Cancer Research, Coordinating Center, Berne, Switzerland; Department of Research, Lausanne University Hospital, Lausanne, Switzerland; University Hospitals Leuven, Leuven, Belgium

Background: It has been shown that tumors arising in the proximal and distal colon, defined by the embryological midgut and hindgut, have distinctive clinical and molecular features, but very little is known concerning the differences in the mechanism of tumorigenesis and the effect that this could have on therapy. **Methods:** The distribution of clinico-pathological and molecular features was evaluated between proximal (N = 1110 - Caecum to hepatic flexure) and distal colon (N = 1728 - splenic flexure down to sigmoid) in patients included in the PETACC3 trial. Gene expression profile was also available from 783 tumors and 32 normal colon. A further set of 473 metastatic patients treated with cetuximab combined with chemotherapy (De Roock Lancet Oncol. 2010) was used to test tumor location with response. **Results:** Pathological features, such as tumor differentiation, and mucinous histology as well as molecular characteristics, such as MSI status, BRAF, PIK3Ca mutations and LOH18q loss show higher frequency in proximal compared to distal colon (N = 1214; Fisher test, $P < 0.001$). Proximal tumors showed a significantly worse overall survival (N = 2838; HR = 1.4 [1.18 - 1.64] $P < 0.001$) and survival after relapse (N = 861; HR = 1.97 [1.65 - 2.35] $P < 0.001$) only if they were stage III at diagnosis, while no difference was observed for relapse free survival. Microarray profiling identified 997 genes differentially expressed between the two anatomical sites, after adjustment for age, gender, mucinous histology, BRAF, KRAS and MSI status. Only 20 of those were present in normal colon site comparison indicating tumor specificity. Data mining analysis of the differentially expressed genes showed that the distal colon is characterized by an enrichment for MAPK activated pathways as well as for the cetuximab response gene signature (Khambata-Ford JCO 2007). In fact, cetuximab treated KRAS/BRAF wild-type tumors in distal colon had prolonged PFS and a 2-fold higher response rate than proximal. **Conclusions:** Proximal and distal colon tumors have distinctive patterns of clinical-pathological and molecular features. These biological differences likely have significant prognostic and therapeutic implications.

3527

Poster Discussion Session (Board #19), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**Gene expression profiles and tumor locations in colorectal cancer (left vs. right vs. rectum).**

Martin K. H. Maus, Diana L. Hanna, Craig Stephens, Peter Philipp Grimminger, Melinda Epstein, Stephanie H. Astrow, Dongyun Yang, Fotios Loupakis, Jack Hsiang, Gary Zeger, Takeru Wakatsuki, Afsaneh Barzi, Heinz-Josef Lenz; Department of General, Visceral, and Tumor Surgery, University of Cologne, Cologne, Germany; USC Norris Comprehensive Cancer Center, Los Angeles, CA; Response Genetics, Inc., Los Angeles, CA; Department of General, Visceral, and Cancer Surgery, University of Cologne, Cologne, Germany; University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; U.O. Oncologia Medica 2, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy; Keck School of Medicine, Department of Pathology, University of Southern California, Los Angeles, CA

Background: Recent data suggests that CRC from different locations show distinct genetic profiles. Right-sided tumors have a worse prognosis and may have less benefit from targeted therapies. We investigated the tumor locations and genetic profiles (KRAS and BRAF mutation status and ERCC1, TS, EGFR and VEGFR2 mRNA expression) in 580 CRC tumors. **Methods:** FFPE tumor specimen from 580 patients with advanced CRC adenocarcinoma were microdissected and DNA and RNA were extracted. Specifically designed primers and probes were used to detect 7 different base substitutions in codon 12 and 13 of KRAS, V600E mutations in BRAF and the mRNA expression levels of ERCC1, TS, EGFR and VEGFR2 by RT-PCR. These values were analyzed according to tumor location (left vs. right vs. rectum). **Results:** BRAF mutations were significantly more common in the right colon (15%), followed by rectum (3.8%) and left colon (2.5%). KRAS mutations occurred at similar frequencies throughout the colon. Gene expression of ERCC1 was significantly higher in right-sided than left-sided colon tumors in KRAS wild-type colon cancers. The highest expression levels for all genes were seen in rectum. These differences reached significant levels for ERCC1 (rectum vs. right and rectum vs. left, $p<0.001$), TS (rectum vs. left, $p<0.036$) and VEGFR2 (rectum vs. right and rectum vs. left, $p<0.001$). **Conclusions:** Tumor location in CRC is associated with specific mutation and expression profiles. Differences in chemosensitivity may be explained by mutation status and mRNA levels in right vs. left CRC. Rectum cancers showed a distinct genetic profile when compared to colon which indicates different tumor biology and may be related to differences in the microflora.

Location of colon cancer (right-sided [RC] versus left-sided [LC]) as a predictor of benefit from cetuximab (CET): NCIC CTG CO.17.

Stephanie Yasmin Brule, Derek J. Jonker, Christos Stelios Karapetis, Christopher J. O'Callaghan, Malcolm J. Moore, Ralph Wong, Niall C. Tebbutt, Craig Underhill, Desmond Yip, John Raymond Zalcborg, Dongsheng Tu, Rachel Anne Goodwin; The Ottawa Hospital, Ottawa, ON, Canada; The Ottawa Hospital Cancer Center, Ottawa, ON, Canada; Flinders Medical Centre and Flinders Centre for Innovation in Cancer, Flinders University, Adelaide, Australia; NCIC Clinical Trials Group, Kingston, ON, Canada; Princess Margaret Cancer Center, University Health Network, Division of Medical Oncology & Hematology, Department of Medicine, University of Toronto, Toronto, ON, Canada; CancerCare Manitoba, Winnipeg, MB, Canada; Austin Health and University of Melbourne, Heidelberg, Australia; Border Medical Oncology, Albury, Australia; Canberra and Calvary Hospitals, Canberra, Australia; Peter McCallum Hospital, Melbourne, Australia

Background: RC and LC differ with respect to biology, pathology, and epidemiology. Further, recent SEER data suggests a mortality difference between RC and LC that varies by stage: stage II and III RC having lower and higher mortality, respectively. We examined if the primary tumour site can also predict for outcome in pre-treated, chemotherapy refractory, metastatic colon cancer (MCC). We compared RC vs. LC as a predictor for efficacy of EGFR inhibition with CET. **Methods:** Using CO.17 (CET vs. BSC), we coded the primary tumour site for 399 pts as RC (cecum to transverse colon) or LC (splenic flexure to rectosigmoid). Fisher's exact test assessed the association between site of cancer and baseline characteristics. Univariate and multivariate analyses of overall survival (OS) and progression free survival (PFS) by site of cancer were performed using Cox regression models. **Results:** Pts with RC (150/399) had more poorly differentiated tumours, mutant KRAS status, and peritoneal rather than liver and lung metastases, and they more often entered the study less than two years after initial diagnosis. Among pts receiving BSC, tumour location (RC vs. LC) was not prognostic for PFS (HR 1.07 [0.79, 1.44], $p=0.67$) or OS (HR 0.96 [0.70, 1.31], $p=0.78$). Among pts with KRAS wild type tumour status, site of cancer was a predictor of benefit from CET, with much greater PFS observed for LC (interaction $p=0.002$). **Conclusions:** In refractory MCC, tumour location within the colon (RC vs. LC) is not a prognostic factor, but is a strong predictor of PFS benefit from CET therapy. Additional research is needed to understand the molecular differences between RC and LC and their interaction with EGFR inhibition.

KRAS WT subset	Median survival (months) CET vs. BSC	Benefit CET vs. BSC HR (95% C.I.), p value	Predictive effect Interaction p value
PFS			
LC	5.4 vs. 1.8	0.28 (0.18, 0.45), $p<0.0001$	0.002
RC	1.9 vs. 1.9	0.73 (0.42, 1.27), $p=0.26$	
OS			
LC	10.1 vs. 4.8	0.49 (0.31, 0.77), $p=0.002$	0.25
RC	6.2 vs. 3.5	0.66 (0.36, 1.21), $p=0.18$	

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Poster Discussion Session (Board #21), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**MET overexpression as a hallmark of the epithelial-mesenchymal transition (EMT) phenotype in colorectal cancer.**

Kanwal Pratap Singh Raghav, Hesham M. Amin, Wenting Wang, Ganiraju C. Manyam, Bradley Broom, Cathy Eng, Michael J. Overman, Scott Kopetz; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Epithelial-mesenchymal transition (EMT) has been identified as a dominant molecular subtype of colorectal cancer (CRC). This EMT phenotype as recognized by complex gene signatures is prognostic and associated with chemoresistance, but a biomarker for EMT suitable for clinical utilization has not yet been validated. The purpose of this study was to compare MET protein expression with protein/gene expression of EMT markers and to evaluate its impact on overall survival (OS). **Methods:** We performed an exploratory analysis of 139 untreated primary CRC samples using data from The Cancer Genome Atlas. Protein and gene expressions were measured using reverse-phase protein array (RPPA) and RNA-sequencing, respectively. MET high/overexpressed group was defined by protein level in the highest quartile. Mann-Whitney U-test and Spearman rank correlation was used to determine association between MET protein expression and protein/gene expression of EMT markers and EMT gene signature scores. Regression tree method and Kaplan-Meier estimates were used to assess overall survival (OS). **Results:** The MET protein distribution is right skewed, demonstrating a unique population of MET high expressing tumors ($P < 0.01$). Colon tumors had higher MET protein levels compared to rectal tumors ($P < 0.01$). MET overexpression was associated with decreased OS (HR 2.92; 95% CI: 1.45 - 5.92). MET protein expression correlated strongly with protein expressions of SLUG (transcription factor for EMT) ($r = 0.6$) and ERCC1 (a marker for oxaliplatin chemo-resistance) ($r = 0.6$) ($P < 0.01$). Higher MET protein levels were associated with higher gene expression of 28 EMT markers including *AXL*, *VIM*, *ZEB1*, *ZEB2*, *FGF1*, *TGFB111* and *MMP11* ($P < 0.05$). Higher MET protein levels were also associated with higher gene scores derived from three published EMT gene signatures ($P < 0.05$). MET protein expression did not correlate with MET gene expression ($r = 0.16$). **Conclusions:** Increased MET protein expression strongly correlates with a molecular EMT phenotype and poor survival in patients with CRC. MET protein expression may be used as a surrogate biomarker to represent and select for this unique molecular subset of CRC driven by EMT biology.

3530

Poster Discussion Session (Board #22), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**Association of colorectal cancer intrinsic subtypes with prognosis, chemotherapy response, deficient mismatch repair, and epithelial to mesenchymal transition (EMT).**

Ramon Salazar, Paul Roepman, Josep Tabernero, Andreas Schlicker, Ian Majewski, Victor Moreno, Robert Rosenberg, Scott Kopetz, Lodewyk F. A. Wessels, Rene Bernards, Iris Simon; Translational Research Laboratory and Department of Medical Oncology, Institut Catala d'Oncologia-IDIBELL, Hospitalet de Llobregat, Spain; Agendia NV, Amsterdam, Netherlands; Medical Oncology Department, Vall d'Hebron University Hospital, Barcelona, Spain; Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands; Netherlands Cancer Institute, Amsterdam, Netherlands; IDIBELL, Institut Catala d'Oncologia, L'Hospitalet de Llobregat, Spain; Department of Surgery, Kantonsspital Baden, Baden, Switzerland; Department of Gastrointestinal Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX; Department of Molecular Carcinogenesis, the Netherlands Cancer Institute, Amsterdam, Netherlands

Background: Unbiased genome-wide analyses of gene expression patterns have been successfully used for molecular classification of breast cancer into subtypes that have clear relevance for prognosis and treatment. A similar classification is still missing for colorectal cancer (CRC). **Methods:** Using full genome expression data of 188 stage I-IV CRC patients, an unsupervised clustering revealed three major subtypes (A-, B-, C-type). A molecular subtype classification was developed and validated in 543 stage II and III patients. The subtypes were analyzed for correlation to clinical information, mutations in the kinome, known molecular markers status and chemotherapy response. In addition, subtypes were determined on 173 samples from The Cancer Genome Atlas (TCGA) colon dataset with Agilent genome expression data. **Results:** C-type patients have the worst outcome, a mesenchymal phenotype, and show no benefit from adjuvant chemotherapy treatment. Patients having A- or B-type tumors have a better clinical outcome, a more proliferative and epithelial phenotype and benefit from adjuvant chemotherapy. A- and C-type groups are enriched for tumors having oncogenic *BRAF* mutations and a deficient DNA mismatch repair system. B-type tumors showed a low overall kinome mutation frequency (1.6%), while both A- and C-type patients harbor a higher mutation frequency (respectively 4.2 and 6.2%), in agreement with their mismatch repair deficiency. Finally, CRC subtyping was confirmed in the colon TCGA dataset with 26 samples classified as A-type, 110 as B-type and 37 as C-type. In agreement with the different aggressiveness of the subtypes, A-type tumors were less prevalent in stage IV while C-type were less prevalent in stage I CRC. **Conclusions:** The heterogeneity of the intrinsic subtypes is largely based on three biological hallmarks of the tumor: an epithelial-to-mesenchymal transition, deficiency in mismatch repair genes that result in a high mutation frequency associated with MSI, and cellular proliferation. These subtypes are clinically relevant, as they differ in their underlying biology and might require different treatment strategies.

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Poster Discussion Session (Board #23), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine and oxaliplatin versus capecitabine alone in locally advanced rectal cancer: First results of the PETACC-6 randomized phase III trial.**

Hans-Joachim Schmoll, Karin Haustermans, Timothy Jay Price, Bernard Nordlinger, Ralf Hofheinz, Jean-Francois Daisne, Jozef Janssens, Baruch Brenner, Peter Schmidt, Hans Reinel, Stephan Hollerbach, Karel Caca, Florian W.B. Fauth, Carla Hannig, John Raymond Zalcberg, Niall C. Tebbutt, Murielle E. Mauer, Carlo G. M. Messina, Manfred P. Lutz, Eric Van Cutsem, for the EORTC GITCG, AIO, AGITG, EORTC ROG, BGDO, FFCD; Martin Luther University Halle-Wittenberg, Halle, Germany; University Hospital Gasthuisberg, Leuven, Belgium; The Queen Elizabeth Hospital, Woodville, Australia; Hopital Ambroise Paré, Boulogne, France; University Hospital Mannheim, Mannheim, Germany; Clinique et Maternité Sainte Elisabeth, Namur, Belgium; AZ Turnhout, Turnhout, Belgium; EORTC, Brussels, Belgium; Städtisches Klinikum Neunkirchen, Neunkirchen, Germany; Leopoldina Krankenhaus, Schweinfurt, Germany; Allgemeines Krankenhaus Celle, Celle, Germany; Klinikum Ludwigsburg, Ludwigsburg, Germany; Onkologische Schwerpunktpraxis, Hanau, Germany; Schwerpunktpraxis für Hämatologie und Onkologie, Bottrop, Germany; Peter McCallum Hospital, Melbourne, Australia; Austin Health and University of Melbourne, Heidelberg, Australia; EORTC Headquarters, Brussels, Belgium; UZ Leuven, Gasthuisberg Campus, Leuven, Belgium

Background: The PETACC-6 trial investigates whether the addition of oxaliplatin to preoperative oral fluoropyrimidine-based chemoradiation (CRT) followed by postoperative adjuvant fluoropyrimidine-based chemotherapy (CT) improves disease-free survival (DFS) in locally advanced rectal cancer. We present results of the early secondary endpoints. **Methods:** Between 11/2008 and 09/2011, patients with rectal cancer within 12 cm from the anal verge, T3/4 and/or node-positive, with no evidence of metastatic disease and considered either resectable at the time of entry or expected to become resectable after preoperative CRT, were randomly assigned to receive 5 weeks of preoperative CRT (45 Gy in 25 fractions) with capecitabine (825 mg/m² twice daily), followed by 6 cycles of adjuvant CT with capecitabine (1000 mg/m² twice daily/days 1-15 every three weeks) (arm 1) or to receive the same regimen with the addition of oxaliplatin before (50 mg/m²/days 1, 8, 15, 22, 29) and after surgery (130 mg/m²/day 1, every three weeks) (arm 2). Additional RT before surgery (5.4 Gy/days 36-38) using the same fields or as a boost with capecitabine was an option. Primary endpoint is DFS. **Results:** 1094 patients were randomized (547 in each arm). 98% and 92% of patients, respectively, received at least 45 Gy of preoperative RT in arm 1 and arm 2. More than 90% of full dose concurrent CT was delivered in 91% and 63% of patients, respectively, in arm 1 and arm 2. Preoperative grade 3/4 toxicity occurred in 15.1% of patients in arm 1 vs. 36.7% in arm 2; 1 vs. 3 patients died before surgery. R0 resection rate was 92.0% in arm 1 and 86.3% in arm 2. The pCR rate (ypT0N0) was equal in both arms with 11.3% in arm 1 and 13.3% in arm 2 (p=0.31). The anal sphincter was preserved in 70% vs. 65% (p=0.09) in arm 1 and 2. Postoperative complications were not different between arms (38% vs. 41%; 5 vs. 4 patients died following surgery). Definitive numbers will be presented at the congress. **Conclusions:** The addition of oxaliplatin to preoperative fluoropyrimidine-based CRT led to decreased treatment compliance and increased toxicity, but did not improve surgical outcome. Clinical trial information: NCT00766155.

3532

Poster Discussion Session (Board #24), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**Tumor-related and treatment-related colostomy-free survival (CFS) following chemoradiation (CRT) using mitomycin (MMC) or cisplatin (CisP), with or without maintenance 5FU/CisP chemotherapy (CT) in squamous cell carcinoma of the anus (SCCA): Results of ACT II.**

Robert Glynne-Jones, Latha Kadalayil, Helen Meadows, David Cunningham, Leslie M. Samuel, Ian Geh, Charles Lowdell, Roger David James, Sandy Beare, Rubina Begum, Jonathan A. Ledermann, David Sebag-Montefiore, on behalf of the ACT II Study Group; Mount Vernon Centre for Cancer Treatment, Middlesex, United Kingdom; Cancer Research UK Institute for Cancer Studies/UCL Cancer Trials Centre, London, United Kingdom; The Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom; Aberdeen Royal Infirmary, University of Aberdeen, Aberdeen, Scotland, United Kingdom; Queen Elizabeth Hospital, Birmingham, United Kingdom; Imperial College Healthcare NHS Trust, London, United Kingdom; No affiliation - now retired, Tonbridge, United Kingdom; University College London Cancer Institute, University College London Cancer Hospital, London, United Kingdom; St James Institute of Oncology, Leeds, United Kingdom

Background: Concurrent CRT is standard treatment for patients (pts) with SCCA. We explore tumor- and treatment-related CFS in a phase III trial (ACT II), which mandated standardised radiation fields and a uniform dose (50.4Gy in 28 daily fractions of 1.8Gy). **Methods:** The ACT II trial (940 pts) compared both CisP (n=468) versus MMC (n=472) combined with 5-FU/CRT, and 2 cycles of maintenance CT (Maint, n=448) versus none (No-maint, n=446). We investigated the association between CFS and baseline factors (age, sex, T stage, size of tumour, nodal status) and treatment using Cox regression. CFS events included baseline colostomies not reversed at first follow up after treatment and post-treatment colostomies. **Results:** Median follow-up (all pts) was 5.1 years. Median age: 58 years; tumour site – canal (84%), margin (14%); stage T1-T2 (52%), T3-T4 (46%); N+ (32%), N0 (62%). Of 884 evaluable patients only 20/118 (17%) baseline colostomies were reversed within 8 months, and 37 later. 112 pts had a post-treatment colostomy due to persistent disease (98) or morbidity (14). The 5-year CFS rates by stage were 86% T1, 77% T2, 57% T3 and 47% T4; 72% N0, 60% N+; by treatment arm 68% MMC/Maint, 70% CisP/Maint, 68% MMC/No-maint and 65% CisP/No-maint respectively. The 5-year CFS rates were 72% and 60% for N0 and N+ respectively. The most significant predictors of colostomy in multivariable Cox regression analyses were T stage, sex and baseline haemoglobin ($p < 0.001$ for all). Men were more at risk than women (adjusted HR 1.64; 95% CI: 1.26, 2.14). Age, site of primary or treatment did not impact on CFS. Although significant in univariate analysis, nodal status did not influence CFS when adjusted for other baseline factors. **Conclusions:** In the largest trial in anal cancer, neither the type of CRT (5FU/CisP vs. 5FU/MMC) nor maintenance chemotherapy improved CFS. 34% (61/177) of all colostomies were baseline fashioned prior to treatment and never reversed after all treatments. The major predictive factors for CFS were T stage, sex and haemoglobin levels. Clinical trial information: NCT00025090.

Individual patient data (IPD) analysis of progression-free survival (PFS) versus overall survival (OS) as an endpoint for metastatic colorectal cancer (mCRC) in modern trials: Findings from the 16,700 patients (pts) ARCAD database.

Qian Shi, Aimery De Gramont, Marc E. Buyse, Axel Grothey, Hans-Joachim Schmoll, Matthew T. Seymour, Richard A. Adams, Leonard Saltz, Richard M. Goldberg, Cornelis J. A. Punt, Jean-Yves Douillard, J. Randolph Hecht, Herbert Hurwitz, Eduardo Diaz-Rubio, Rainer Porschen, Niall C. Tebbutt, Charles S. Fuchs, John Souglakos, Alfredo Falcone, Daniel J. Sargent, for the ARCAD Group; Mayo Clinic, Rochester, MN; Hospital Saint Antoine, Paris, France; International Drug Development Institute, Louvain la Neuve, Belgium; Martin Luther University Halle-Wittenberg, Halle, Germany; Cancer Research UK Clinical Centre, Leeds, United Kingdom; School of Medicine, Cardiff University, Cardiff, United Kingdom; Memorial Sloan-Kettering Cancer Center, New York, NY; Ohio State University Medical Center, Columbus, OH; Academic Medical Center, Amsterdam, Netherlands; ICO Centre René Gauducheau, Saint-Herblain, France; David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA; Duke University Medical Center, Durham, NC; Hospital Clinico San Carlos, Madrid, Spain; Klinikum Bremen-Ost, Bremen, Germany; Austin Health and University of Melbourne, Heidelberg, Australia; Dana-Farber Cancer Institute, Boston, MA; University of Crete, School of Medicine, Heraklion, Greece; Medical Oncology, S. Chiara Hospital, Pisa, Italy

Background: PFS has previously been established as a surrogate for OS based on IPD from first-line mCRC trials conducted before 1999. As mCRC treatment (trt) has advanced in the last decade and OS has increased from 1 to 2 years, this surrogacy required re-examination. **Methods:** IPD from 16,762 pts, median age 62, 62% male, 53% ECOG PS 0 were available from 22 1st line mCRC studies conducted from 1997-2006; 12 tested targeted (anti-angiogenic and/or anti-EGFR) regimens. The relationship between PFS (first event of progression or death) and OS was evaluated at patient-, trt-arm-, and trial-levels using correlation (corr.) coefficients and R^2 (closer to 1 the better) from weighted least square (WLS) regression of arm-specific survival rates and trial-specific hazard ratios (HRs), estimated using Cox and Copula bivariate models. The concordance of significance (CoS) of the treatment effects (TEs) on both endpoints was calculated. **Results:** 44% pts received a targeted regimen. Median PFS was 8 and OS was 18 months. The corr. between PFS and OS was modest at all three levels with low CoS in TE comparisons (see Table). Analyses limited to trials testing targeted trts, non-strategy trials, or superiority trials did not improve surrogacy. **Conclusions:** In modern mCRC trials, where survival post-first progression exceeds time to first progression, PFS TEs do not reliably predict TEs on OS. Nonetheless, until alternative endpoints of clinical benefit can be validated, PFS remains a relevant primary endpoint for 1st line mCRC trials, as our data demonstrate that the ability for any agent to produce an OS benefit from a single line of therapy is challenging.

Class (n. of trials)	Overall (22)	Targeted (12)	Nonstrategy (18)	Superiority (16)
Pt level				
Rank corr.	.51 (.50 - .52)	.55 (.54 - .56)	.53 (.52 - .54)	.51 (.50 - .52)
Trt arm level				
[6m PFS vs. 12m OS rates]				
R^2 WLS	.69 (.58 - .79)	.70 (.48 - .91)	.73 (.62 - .83)	.71 (.59 - .83)
Trial level				
[HRPFS vs. HROS]				
R^2 WLS	.54 (.33 - .75)	.52 (.24 - .80)	.54 (.32 - .76)	.51 (.24 - .77)
R^2 Copula	.46 (.24 - .68)	.45 (.16 - .75)	.48 (.24 - .71)	.54 (.31 - .78)
Concordance	67%	64%	68%	63%

3534

Poster Discussion Session (Board #26), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM

Randomized controlled trials (RCTs) examining continuous (CS) versus intermittent strategies (IS) of delivering systemic treatment (Tx) for untreated metastatic colorectal cancer (mCRC): A meta-analysis from the Cancer Care Ontario program in evidence-based care.

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Background: Given the varying impact on efficacy demonstrated in individual RCTs of CS vs IS of delivering systemic Tx for mCRC, a meta-analysis of the available RCTs was performed. **Methods:** RCTs that compared a CS versus IS of delivering systemic Tx were identified by a systematic search (MEDLINE, EMBASE and ASCO and ESMO proceedings) and review. The results of identified trials were clinically homogeneous (Table) so the data was pooled using Review Manager software (RevMan 5.2). Overall survival (OS) hazard ratios were extracted directly from the most recently reported trial results. A random effects model was used for all pooling. **Results:** 10 RCTs were identified (n= 4,296). After an induction period, the maintenance Tx patients received during the IS was: none (5 trials, n=2,562), fluoropyrimidine (F) (2 trials, n=759), biologic (B) (2 trials, n=852), F+B (1 trial, n=123). Results of the meta-analysis are summarized in the Table (HR>1 favors CS). Sensitivity analyses performed demonstrate results are robust independent of the induction or maintenance Tx used. QOL (data from 2 trials) was either the same in both arms (single Tx induction trial with no maintenance Tx, n=354) or improved in the IS arm (combination tx induction trial with no maintenance Tx, n=1,630). **Conclusions:** IS of delivering systemic Tx for mCRC do not result in a statistically significant reduction in OS compared to a CS of delivery whether or not maintenance therapy is included. QOL is the same or better with an IS.

All trials	OS HR (95% CI)	Test for overall effect - Z	Heterogeneity chi ² (df)	I ² (%)
All trials (n=4,296)	1.02 (0.95 - 1.10)	0.50 (p=0.62)	5.18 (6) (p=0.52)	0
Trials with no maintenance Tx (n=2,562)	1.01 (0.89 - 1.14)	0.10 (p=0.92)	4.38 (3) (p=0.22)	31
Trials with maintenance Tx (n=1,734)	1.00 (0.88 - 1.14)	0.01 (p=0.99)	0.69 (2) (p=0.71)	0

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General Poster Session (Board #1A), Sun, 8:00 AM-11:45 AM

Prospective analysis of UGT1A1 genotyping for predicting toxicities in advanced colorectal cancer (aCRC) treated with irinotecan (IRI)-based regimens: Interim safety analysis of a Japanese observational study.

Wataru Ichikawa, Keisuke Uehara, Keisuke Minamimura, Chihiro Tanaka, Yasumasa Takii, Sotaro Sadahiro, Hideaki Miyauchi, Katsunori Shinozaki, Takuya Miyagaki, Toshio Otsuji, Takeshi Kambara, Satoshi Morita, Yuichi Ando, Yukihiro Okutani, Masahiro Sugihara, Toru Sugiyama, Yasuo Ohashi, Yuh Sakata; National Defense Medical College, Tokorozawa, Japan; Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan; Mitsui Memorial Hospital, Tokyo, Japan; Gifu Prefectural General Medical Center, Gifu, Japan; Niigata Cancer Center Hospital, Niigata, Japan; Tokai University, Isehara, Japan; Graduate School of Medicine, Chiba University, Chiba, Japan; Division of Clinical Oncology, Hiroshima Prefectural Hospital, Hiroshima, Japan; Nishijin Hospital, Kyoto, Japan; Dongo Hospital, Yamatotakada, Japan; Chugoku Central Hospital, Hiroshima, Japan; Yokohama City University Medical Center, Kanagawa, Japan; Clinical Oncology and Chemotherapy, Nagoya University Hospital, Nagoya, Japan; Daiichi Sankyo Co., Ltd., Tokyo, Japan; Iwate Medical University, Morioka, Japan; Department of Biostatistics, School of Public Health, University of Tokyo, Tokyo, Japan; Misawa City Hospital, Misawa, Japan

Background: *UGT1A1**6 and *UGT1A1**28 are risk factors for severe IRI-related toxicities in Asians, but recommended IRI doses based on *UGT1A1* genotypes and other risk factors are unclear. We conducted a prospective analysis to examine the correlation between *UGT1A1* genotypes and the efficacy and safety of IRI-based regimens in Japanese aCRC patients (pts), (NCT 01039506). **Methods:** Pts who had histologically confirmed aCRC, PS of 0–2, received IRI-based regimens (FOLFIRI, IRI+S-1, IRI monotherapy), were *UGT1A1* genotyped, and provided written informed consent were included. *UGT1A1* polymorphisms were analyzed and categorized into 3 groups: wild (*1/*1), hetero (*1/*6, *1/*28), and homo (*6/*6, *6/*28, *28/*28). Detailed toxicities in the first 3 months of treatment were prospectively recorded. For interim safety analysis, incidences of grade 3–4 (severe) toxicities were compared among *UGT1A1* genotypes and a logistic regression model was used to predict the risk of severe toxicities. Severe toxicities and associated risk factors were predicted using a nomogram and bootstrap validation was performed. **Results:** We enrolled 1376 pts between October 2009 and March 2012. At the time of abstract submission, toxicity data of 504 pts were available; 46% pts had wild, 44% hetero, and 11% homo polymorphisms. FOLFIRI was administered to 63% pts. Severe neutropenia developed during the first 3 months of treatment in 33% pts: 36% in hetero [OR, 1.5; 95% CI, 1.0–2.3], 47% in homo (OR, 2.3; 95% CI, 1.2–4.4), and 28% in wild. Severe diarrhea incidence was 5%, which did not correlate with *UGT1A1* genotypes. Multiple logistic regression model included regimen, initial IRI dose, gender, age, *UGT1A1* genotype, and PS as predictors of severe neutropenia in the first treatment cycle. The resulting nomogram demonstrated good accuracy in predicting severe neutropenia, with a bootstrap-corrected concordance index of 0.74. **Conclusions:** Considering *UGT1A1* genotype along with other clinical factors is important for managing pts undergoing IRI-based regimens. Our presentation will provide analysis of data from more than 1000 pts. Clinical trial information: NCT01039506.

Prognostic factors of recurrence of colorectal cancers with microsatellite instability after curative resection: An AGEO retrospective multicenter study.

David Tougeron, Gaelle Sickersen, Thierry Lecomte, Aziz Zaanani, Gaetan Des Guetz, Cedric Lecaille, Aurelie Ferru, Estelle Cauchin, David Sefrioui, Romain Coriat, Thomas Aparicio, Pascal Artru, Isabelle Trouilloud, Tamara Matysiak-Budnik, Julien Taïeb, Pierre Michel, Jean Marc Tourani, Pierre Levillain, Christine Silvain, Lucie Karayan-Tapon; Department of Gastroenterology, Poitiers University Hospital, Poitiers, France; Poitiers university Hospital, Poitiers, France; Centre Hospitalier Trousseau, Tours, France; HEGP, Paris, France; Oncology Department, Bobigny, France; Clinique Bordeaux Nord, Bordeaux, France; Department of Oncology, Poitiers University Hospital, Poitiers, France; Nantes University Hospital, Nantes, France; Rouen University Hospital, Rouen, France; Cochin Teaching Hospital, AP-HP, Paris Descartes University, Paris, France; Avicenne Hospital, Bobigny, France; Hôpital Privé Jean Mermoz, Lyon, France; Service d'Hépatogastroentérologie, Nantes, France; Hôpital European Georges Pompidou, Paris, France; Digestive Oncology Unit, Rouen, France; Department of Pathology, Poitiers University Hospital, Poitiers, France; INSERM U935, University of Poitiers, Poitiers, France

Background: Microsatellite instability (MSI) phenotype is found in approximately 12% of colorectal cancers (CRC). MSI CRC is associated with a low recurrence rate and 5-fluorouracil chemoresistance in adjuvant setting. Clinical and pathological prognostic factors of recurrence are well-identified after surgery of CRC but not in the subgroup of MSI CRC. **Methods:** This multicenter retrospective study included patients with stage I, II and III MSI CRC. The following prognostic factors were studied: age, sex, perforation, occlusion, tumor location, tumor differentiation, T4 stage, lymph node invasion, VELIPI criteria (vascular emboli, lymphatic invasion and perinervous invasion), *BRAF* mutation and adjuvant chemotherapy. Disease-free survival (DFS) was calculated using the Kaplan-Meier method. Prognostic factors of DFS were analyzed in multivariate analysis using Cox model. **Results:** A total of 294 MSI CRC patients were analyzed, including 10%, 49% and 41% stage I, II and III, respectively. Mean age was 67.2 ± 16.0 years. Occlusion was observed in 10% of cases. VELIPI criteria were found in 39%, including 26% with vascular emboli. *BRAF* mutation was detected in 27% of cases. All in all, 40% of patients received adjuvant chemotherapy, predominantly stage III (74%). Mean follow-up was 39.2 ± 33.2 months. The disease recurrence rate was 3%, 8% and 21% in stage I, II and III patients, respectively. The 3-year DFS rate was 85%. In univariate analysis, age, occlusion, lymph node invasion, T4 stage, vascular emboli and perinervous invasion were associated with decreased DFS ($p < 0.05$). In multivariate analysis, only occlusion (RR=3.0; 95% CI 1.2-7.7, $p=0.02$) and vascular emboli (RR=4.5; 95% CI 1.6-12.7, $p < 0.01$) were associated with decreased DFS. Recurrence rates for MSI CRC with and without vascular emboli were respectively, 22% versus 5% for stage II and 33% versus 15% for stage III. **Conclusions:** Occlusion and vascular emboli were independently associated with recurrence of MSI CRC but not lymph node invasion. We advocate vascular emboli analysis in routine clinical practice to facilitate adjuvant chemotherapy decision-making in MSI CRC.

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General Poster Session (Board #1C), Sun, 8:00 AM-11:45 AM

Treatment outcome according to tumor ERCC1 expression status in OPUS study patients with metastatic colorectal cancer (mCRC) randomized to FOLFOX4 with/without cetuximab.

Carsten Bokemeyer, Claus-Henning Köhne, Igor Bondarenko, Anja von Heydebreck, Hans Juergen Grote, Christopher Stroh, Heinz-Josef Lenz; University Medical Center Hamburg-Eppendorf, Department of Oncology, Hematology and BMT with section of Pneumology, Hamburg, Germany; Onkologie Klinikum Oldenburg, Oldenburg, Germany; Municipal Institution Dnipropetrov, Dnipropetrovsk, Ukraine; Merck KGaA, Darmstadt, Germany; University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA

Background: The OPUS study showed that the addition of cetuximab to infusional 5-fluorouracil/folinic acid + oxaliplatin (FOLFOX4) significantly improved progression-free survival (PFS) and response in the first-line treatment of patients (pts) with *KRAS* wild-type (wt) mCRC. High level expression in tumors of ERCC1, a protein involved in nucleotide excision repair, has been associated with resistance to platinum-based chemotherapy in a range of tumor types. This analysis assessed outcome according to ERCC1 expression level and treatment group in OPUS study pts. **Methods:** ERCC1 expression level was assessed by immunohistochemistry (IHC) in all available formalin-fixed paraffin-embedded tumor samples from OPUS study pts. An ERCC1 IHC score on a continuous scale of 0–300 was calculated for each tumor, based on the intensity of nuclear staining and proportion of positive cells. The median IHC score was used to define low (<median) and high (\geq median) ERCC1 expression levels and outcome was assessed in low vs high expression groups in both treatment arms. **Results:** Of 337 OPUS study intention to treat pts, 97 (29%) were evaluable for ERCC1 expression. Pts in the FOLFOX4 arm in the high ERCC1 expression group (n=27) had shorter PFS (median 5.8 vs 9.2 months; hazard ratio, HR 1.63, 95% CI 0.80–3.34) and overall survival (median 11.5 vs 18.5 months; HR 1.75, 95% CI 0.90–3.40) and a lower response rate (33.3% vs 39.1%) compared with those in the low ERCC1 expression group (n=23). To assess the effect of adding cetuximab to FOLFOX4 according to ERCC1 expression level, outcome was assessed in the *KRAS* wt subgroup of pts. Although low pt numbers precluded the drawing of definitive conclusions, PFS in the high ERCC1 expression group was longer in the FOLFOX4 + cetuximab arm (n=14) compared with the FOLFOX4 arm (n=13; median 7.7 vs 5.8 months), survival was longer (median 19.7 vs 12.0 months) and the response rate was higher (71.4% vs 30.8%). **Conclusions:** High tumor ERCC1 expression was associated with poor outcome in pts with mCRC receiving first-line platinum-based chemotherapy. The addition of cetuximab to FOLFOX4 may mitigate this effect in those with *KRAS* wt tumors. Clinical trial information: NCT00125034.

Cetuximab and chemotherapy in the treatment of patients with initially “nonresectable” colorectal (CRC) liver metastases: Long-term follow-up of the CELIM trial.

Gunnar Folprecht, Thomas Gruenberger, Wolf Bechstein, Hans-Rudolf Raab, Juergen Weitz, Florian Lordick, Joerg Thomas Hartmann, Hauke Lang, Tanja Trarbach, Jan Stoeblmacher-Williams, Torsten Liersch, Detlev Ockert, Dirk Jaeger, Ulrich Steger, Thomas Suedhoff, Claus-Henning Kohne; University Hospital Carl Gustav Carus, University Cancer Center / Medical Department I, Dresden, Germany; Department of General Surgery, Medical University of Vienna, Vienna, Austria; Goethe University Hospital, Frankfurt, Germany; Klinikum Oldenburg, Oldenburg, Germany; University Hospital Carl Gustav Carus, University Cancer Center / Surgical Department, Dresden, Germany; Universitätsklinikum Leipzig, Universitäres Krebszentrum (UCCL), Leipzig, Germany; Kiel University Hospital, Kiel, Germany; Universitätsmedizin Mainz, Mainz, Germany; West German Cancer Center, Department of Medical Oncology, University Duisburg-Essen, Essen, Germany; Department of General and Visceral Surgery, University Medical Center, Georg-August-University, Göttingen, Germany; Krankenhaus der Barmherzigen Brüder, Trier, Germany; National Center for Tumor Diseases, University of Heidelberg, Heidelberg, Germany; Chirurgische Klinik und Poliklinik I, University of Wuerzburg, Wuerzburg, Germany; Klinikum Passau, Passau, Germany; Onkologie Klinikum Oldenburg, Oldenburg, Germany

Background: CRC liver metastases can be resected after downsizing with intensive chemotherapy schedules, with a strong correlation between the response and resection rates. Cetuximab plus chemotherapy has been shown to increase the rates of tumor response and resection of liver metastases. (Van Cutsem et al, JCO 2011). **Methods:** Patients (pts) with technically non-resectable and/or with > 4 liver metastases were randomized to treatment with FOLFOX/cetuximab (arm A) or FOLFIRI/cetuximab (arm B) and evaluated regarding resectability every 2 months. Resection was offered to all patients who became resectable during the study. K-ras and b-raf status were retrospectively evaluated. Data on tumor response and resection were reported earlier (Folprecht et al, Lancet Oncol 2010). Overall and progression free survival were analyzed in December 2012. **Results:** Between Dec 2004 and March 2008, 56 pts were randomized to arm A, 55 to arm B. For the current analysis, 109 pts were evaluable for overall survival (OS), and 106 patients for PFS. The median OS was 35.7 [95% CI: 27.2-44.2] months (arm A: 35.8 [28.1-43.6], arm B: 29.0 [16.0-41.9], HR 1.03 [0.66-1.61], p=0.9). The median PFS was 10.8 [9.3-12.2] months (Arm A: 11.2 [7.2-15.3], Arm B: 10.5 [8.9-12.2], HR 1.18 [0.79-1.74], p=0.4). Patients with R0 resection had a better OS (median: 53.9 [35.9-71.9] mo) than patients without R0 resection (27.3 [21.1-33.4] mo, p=0.002) and a better PFS (median 15.4 [11.4-19.5] and 8.9 [6.7-11.1] mo in R0 resected and not R0 resected pts, p<0.001). The 5 year survival in R0 resected patients is 46.2% [29.5-62.9%]. **Conclusions:** This study confirmed a favourable long term survival of patients with initially “nonresectable” CRC liver metastases treated in a multidisciplinary approach of neoadjuvant chemotherapy with cetuximab and subsequent metastasectomy in pts who became resectable. Clinical trial information: NCT00153998.

Estimated OS and PFS.

	SD	N	1y	2y	3y	4y	5y
OS	All pts	109	90%	62%	48%	34%	28%
	K-RAS wt	69	88%	68%	53%	40%	33%
	Arm A	54	89%	63%	49%	35%	28%
	Arm B	55	91%	62%	47%	34%	28%
	R0 resected	36	89%	78%	64%	53%	46%
PFS	No R0 resection	70	91%	54%	39%	24%	19%
	All pts	106	43%	15%	6%	5%	5%
	K-RAS wt	67	49%	18%	6%	5%	5%
	R0 resected	36	69%	25%	11%	8%	8%

A phase II study of combination epigenetic therapy in metastatic colorectal cancer (mCRC): A phase II consortium (P2C)/Stand Up 2 Cancer (SU2C) study.

Nilofer Saba Azad, Anthony B. El-Khoueiry, Michelle R. Mahoney, Douglas Adkins, Patrick J. Flynn, Nathan Bahary, George P. Kim, Henry Clement Pitot, Charles Erlichman, Ross C. Donehower, James Gordon Herman, Stephen Baylin, Nita Ahuja, P2C; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; Mayo Clinic, Rochester, MN; Washington University School of Medicine in St. Louis, St. Louis, MO; Metro Minnesota Community Clinical Oncology Program, St. Louis Park, MN; University of Pittsburgh Medical Center, Pittsburgh, PA; Mayo Clinic, Jacksonville, FL; Johns Hopkins University School of Medicine, Baltimore, MD; The Johns Hopkins University, Baltimore, MD; The Johns Hopkins Hospital, Baltimore, MD

Background: Therapy with decitabine and entinostat (ENT: HDAC inhibitor) shows synergistic effect in re-expression of tumor-suppressor genes and growth inhibition in CRC cell lines and in vivo studies. **Methods:** We conducted a phase II, multi-institutional study of SQ 5-azacitidine (AZA) and oral ENT in mCRC pts. A 28 day cycle included: AZA at 40 mg/m² d1-5 and 8-10 with ENT 7 mg d3 and 10. Initial eligibility criteria included: ECOG PS 0-1, good end organ function, and biopsiable disease for cohort A (CoA). An interim analysis indicated that toxicity which crossed pre-specified safety boundary was secondary to disease. A 2nd cohort B (CoB) with eligibility restrictions: <2 prior regimens in KRAS-mutated CRC pts, <3 prior regimens if KRAS wild-type, and liver disease limited to <30% of volume was accrued. Serial tumor biopsies and research blood were collected to assess for methylation/expression changes in circulating tumor DNA and biopsies, respectively. The primary endpoint was response as measured by RECIST criteria using a 2-stage Simon design. **Results:** 47 pts were initially enrolled (24 CoA, 23 CoB). Pts received a median of 2 cycles on both cohorts (1-16 CoA, 2-6 CoB). Pts had a median of 4 prior therapies for CoA (range 2-9) and 3 for CoB (range 2-6). Gr 4 AEs attributable to treatment for CoA included hyperglycemia (1) and hypokalemia (1); other common Gr 3 AEs included anemia (3), decreased lymphocytes (7), fatigue (3), and nausea (3). CoB pts experienced grade 3 chest pain (1), neutropenia (2), leucopenia (2), urinary tract obstruction (1), and hypophosphatemia (1). No responses have been observed. Results of translational objectives will be presented at the meeting. **Conclusions:** SQ AZA and ENT therapy does not have clinical activity as defined by confirmed response in aCRC. Follow-up for survival, response to subsequent therapy, and correlative analysis are ongoing. Supported in part by N01-CM-2011-00099. Clinical trial information: NCT01105377.

Patient outcome (N=46).

Cohort	Follow-up	PD	Deaths	Median PFS*	Median OS
A (n=24)	26 mos (22-23.3)	21	22	1.8 (1.7-4)	5.6 (3.7-12.6)
B (n=22)	11 mos (0.2-12)	19	13	1.9 (1.8-2.2)	8.3 (6.1-NA)

* Kaplan-Meier estimates, time in months, with 95% confidence interval.

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General Poster Session (Board #1F), Sun, 8:00 AM-11:45 AM

Using quantitative sensory testing as an early predictor of chronic oxaliplatin neuropathy in gastrointestinal cancer patients.

Sangeetha Meda Reddy, Nancy Kwon, Irene B. Helenowski, Robert Norm Harden, Judith A. Paice, Halla Sayed Nimeiri, Mary Frances Mulcahy, Al B. Benson, Maxwell Thomas Vergo; Northwestern University, Feinberg School of Medicine, Chicago, IL; Northwestern University, Chicago, IL; Northwestern University Department of Preventive Medicine, Chicago, IL; Rehabilitation Institute of Chicago, Chicago, IL; Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL; Dartmouth Hitchcock Medical Center, Lebanon, NH

Background: Acute oxaliplatin neurotoxicity has been shown to be predictive of chronic neuropathy, a devastating irreversible adverse effect of oxaliplatin. Our study was designed to test the utility of quantitative sensory testing (QST) to measure acute oxaliplatin neurotoxicity at early time points to identify those at risk for developing chronic neuropathy. **Methods:** Gastrointestinal cancer patients receiving 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) chemotherapy were evaluated over a 1 year period for development of acute and chronic oxaliplatin neurotoxicity: before starting FOLFOX, 1 hour into oxaliplatin infusion, before cycles 2, 4 and 12, and 1 year after start of treatment. Patients underwent QST to measure thermal and mechanical sensitivities, vibration detection, pain sensation, and fine motor skills. Chronic neuropathy was measured using National Cancer Institute Common Toxicity Criteria for Adverse Events version 4. **Results:** We conducted analysis of 18 patients that have reached the 1 year followup period. We found thermal QST measured during cycle 1 infusion, which is indicative of acute neurotoxicity, to be predictive of 1 year neuropathy. Decreased cold detection intrainfusion during cycle 1 relative to baseline scores yielded a significant correlation to chronic neuropathy scores ($r_s = -0.53$, $p = 0.03$) and predicted grade 2 or 3 neuropathy ($p = 0.048$). Furthermore, decreased cold detection scores intrainfusion showed trend towards correlation to neuropathy scores ($r_s = -0.45$, $p = 0.07$) and prediction of grade 2 or 3 neuropathy ($p = 0.07$). Additionally, patients with higher tolerance to cold and heat intrainfusion were at higher risk for grade 1 or higher neuropathy ($p = 0.057$ for cold pain, $p = 0.03$ for heat pain). We also found decreased mechanical detection scores using von frey filaments as early as cycle 2 were correlated to 1 year neuropathy scores ($r_s = 0.52$, $p = 0.03$) and predicted development of grade 2 or 3 neuropathy ($p = 0.008$). **Conclusions:** We can use QST to identify high risk patients that are likely to develop chronic neuropathy at 1 year, allowing for targeted use of preventive measures to decrease the incidence of this debilitating adverse effect.

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General Poster Session (Board #1G), Sun, 8:00 AM-11:45 AM

Beyond VEGF inhibition: Comparative efficacy analysis of novel VEGF and non-VEGF therapeutic agents in phase I trials for patients with metastatic colorectal cancer (mCRC).

Sukeshi R. Patel, Norma Ketchum, Brad H. Pollock, John Sarantopoulos, Steven Weitman, Devalingam Mahalingam; University of Texas Health Science Center at San Antonio, San Antonio, TX; University of Texas Health Sciences Center at San Antonio, San Antonio, TX; Institute for Drug Development, University of Texas Health Science Center, San Antonio, TX; Institute For Drug Development, University of Texas Health Science Center at San Antonio, San Antonio, TX; Institute for Drug Development, Cancer Therapy and Research Center, University of Texas Health Science Center at San Antonio, San Antonio, TX

Background: Recently, regorafenib (RGF), an oral multikinase inhibitor, was approved for patients (pts) with mCRC who have failed standard therapies. Compared to placebo, the phase III CORRECT study showed RGF improved median overall survival (mOS) from 5.0 to 6.4 months (mo) and median progression-free survival (mPFS) from 1.7 to 1.9 mo, regardless of K-Ras status. This suggests further VEGF inhibition is crucial in controlling mCRC progression. Many mCRC pts enroll on phase I studies with efficacy reported by some; however, a collective efficacy assessment aimed solely for mCRC in relation to class of agents has not been done. **Methods:** A historical cohort analysis included pts with mCRC enrolled amongst 28 phase I trials at the IDD, from 7/2008 – 9/2012. PFS and OS were estimated from Kaplan-Meier curves and groups were statistically compared with the log rank test. The magnitude of association between dichotomous factors and survival was estimated with the hazard ratio (HR). **Results:** A total of 75 pts were included. Median age 59 (33–80), males 61 %, K-ras mutated 39 %. ECOG PS 0–1 96 %. ≥ 3 prior lines of therapy 68 %. Class of drugs included: VEGF Inhibitors 32 %, Cytotoxic 25 %, Microenvironment Inhibitors 13 %, Apoptosis/Autophagy Inhibitors 11 %, EGFR/Growth Factor TKIs 8 %, others 11 %. For the whole cohort of 75 pts, mPFS was 2.8 mo (95% CI: 2.0–3.7). As of 12/1/12, among 65 pts, mOS was 5.6 mo (95% CI: 4.4–7.0). In subgroup analysis, mPFS was 3.4 (95% CI: 1.4–4.5) vs 2.8 months (95% CI: 2.0–3.5) for pts on VEGF and non-VEGF Inhibitors (HR 0.79, 95% CI: 0.43–1.44, $p = 0.44$), respectively. VEGF Inhibitor treated pts had a mOS of 5.5 months (95% CI: 1.6–10.0 months) vs 5.6 months (95% CI: 4.4–7.6) with non-VEGF Inhibitors (HR 1.02, 95% CI: 0.58–1.78, $p = 0.96$). Efficacy was similar regardless of K-Ras status. **Conclusions:** In pretreated mCRC, median PFS and OS for pts enrolled in phase I trials, irrespective of agent, was comparable to efficacy of RGF. Therefore, after failure of standard therapies, mCRC pts should be encouraged to enroll in clinical trials with efficacy reported in both VEGF and non-VEGF inhibitors.

5FU/LV with or without irinotecan in patients with resected stage II-III rectal cancer: Final analysis of R98 intergroup study.

Catherine Delbaldo, Marc Ychou, Ayman Zawadi, Jean-Yves Douillard, Thierry André, Veronique Guerin-Meyer, Céline Lepère, Olivier Dupuis, Roger Faroux, Annie Jouhaud, Emmanuel Quinaux, Pascal Piedbois; Service Oncologie, Hôpital des Diaconesses, Paris, France; Montpellier Cancer Institute, Montpellier, France; Radiothérapie, Centre Hospitalier Départemental, La Roche Sur Yon, France; ICO Centre René Gauducheau, Saint-Herblain, France; Hôpital Saint Antoine, Paris, France; Service Oncologie Médicale, Centre Paul Papin, Angers, France; Hôpital Européen Georges Pompidou, Paris, France; Service de Radiothérapie, Centre Jean-Bernard, Le Mans, France; Centre Hospitalier Départemental Les Oudairies, La Roche sur Yon, France; Service Radiothérapie, Hôpital Henri Mondor, Créteil, France; International Drug Development Institute, Louvain-la-Neuve, Belgium; Service Oncologie Médicale, Hôpital Henri Mondor, Créteil, France

Background: The goal of the study was to test whether adding Irinotecan to a 5-FU/LV adjuvant regimen improves disease free survival (DFS) or overall survival (OS) in optimally resected stages II-III rectal cancers. Primary end-point was DFS. **Methods:** Six hundred patients were planned to be randomized between 5-FU/LV (control arm) or 5-FU/LV + irinotecan (experimental arm). As only 357 patients had been included from 03/1999 to 12/2005 (178 in control and 179 in experimental arm), the IDMC recommended to close accrual. The trial was stratified by control arm: Mayo-Clinic regimen (A: LV 20 mg/m², 5-FU 425 mg/m² bolus days (d) 1- 5 repeated at d29,57,92,127 and 162) or LV5-FU2 regimen (A': LV 200 mg/m², 5-FU 400 mg/m² bolus and 5-FU 600 mg/m² 22-hours infusion d1-2, q 2 w for 12 cycles). The experimental arm (B) was LV5-FU2 + irinotecan 180 mg/m² d1. **Results:** All 357 randomized patients were evaluable for efficacy. Patient characteristics were well balanced (median age 62 years, stage II 31 %, stage III 69 %, N0 31 %, 68 % received preoperative radiotherapy, and 80 % had sphincter conservation). With follow-up of 156 months, DFS and OS are not statistically increase (81vs 92 events for DFS in experimental and control arm, hazard ratio (HR)=0.805, p=0.154; 63 vs 72 events for OS, HR=0.874, p=0.433). Patients allocated to the experimental arm had more grade 3-4 neutropenia when compared with the LV5FU2 control (33 % vs 16 %, p=0.03), but not when compared with the Mayo Clinic arm (32% vs 36%, p=0.84). Grade 3-4 diarrhea tend to be higher in the experimental arm, but analyses stratified by control arm or by radiotherapy failed to show significant differences across strata (test for interaction p=0.44). **Conclusions:** In patients with resected stage II-III rectal cancer, adding irinotecan to 5FU/LV led to a non significant increase of DFS and OS. The analysis was planned to have a 60 % power to detect a significant difference with 220 events. With a long term follow up of 8 years only 173 events were observed in our trial. Lack of power and good patient prognosis (thirty one percent of node negative patients) may have impacted the results.

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General Poster Session (Board #2A), Sun, 8:00 AM-11:45 AM

Phase II trial of target-guided personalized chemotherapy in first-line metastatic colorectal.

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Background: Chemotherapy (Ch) options for patients (pts) with colorectal cancer (CRC) have increased in the last years. However, there are no validated prospective molecular markers in CRC to select which agents are better to treat any individual case. The aim of this study was to determine the efficacy in terms of progression free survival (PFS) of a biomarker panel to guide treatment selection in this setting. **Methods:** Treatment naive, ECOG 0-1, metastatic CRC pts were accrued. Pts were prospectively analyzed with a predefined set of 10 molecular targets, including: *KRAS*, *BRAF*, and *PI3K* mutations and Topoisomerase-1(Topo-1), ERCC-1, Thymidylate synthase (TS) and Thymidine phosphorylase (TP) expression by immunohistochemistry (IHC) performed in a tumor biopsy. Ch combination schema plus Cetuximab (C) or Bevacizumab (B) at standard doses was customized based on: Topo-1 +:Irinotecan (I). Topo-1- and ERCC-1 -:Oxaliplatin(O). Topo-1- and ERCC1 +:investigator option (I or O). TS -:Fluoropyrimidines (FP).TS +:No FP. TP -:5-FU, TP +:Capecitabine. Maintenance C or B treatment was allowed. Primary outcome measure was PFS. **Results:** 74 pts were accrued and all of them received biomarker guide treatment. All of them began personalized. Interim analysis on 61 pts (38 males, median age 65) showed.Topo-1 + in 33 pts (54%),ERCC-1- in 36(59%) TS + in 44 (73%), TP – in 61 (100%), K-ras nativein 34 (55%), BRAf mutated in 2 (3,2%). With a median follow up time of 9,1 months (m). Median PFS (95% CI) is 8,6 (6,2-10,9) m, with a 41,3% (27,4-55,2) 12mPFS . Overall clinical benefit (Response + Stabilizations) was 74,5% (65,6-83,4).Toxicities Grade \geq 3 included 18% neutropenia, 4,9% asthenia and 3,3% anemia. 12 pts (23%) received loco-regional treatment (surgery or radiosurgery). Median Overall survival has not been reached. **Conclusions:** Target- Guided Personalized Ch in first line CRC pts is feasible and results in promising PFS with low toxicity. Update of final results and more detailed data will be presented. Clinical trial information: NCT01453257.

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General Poster Session (Board #2B), Sun, 8:00 AM-11:45 AM

Use of RAS pathway activation or KRAS mutation status to predict cetuximab response in CRC patient-derived xenografts.

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Background: Cetuximab was approved for treating EGFR-expressing metastatic colorectal carcinoma (mCRC) without patient stratification. Subsequent retrospective clinical studies resulted in an exclusion criterion for patients with KRAS mutations at codons 12 and 13. However, only a fraction of patients with wtKRAS benefit from the treatment. Recent analyses indicated that patients with KRAS mutation at codon 13 can also benefit. We set out to investigate whether KRAS mutations, or any other factors, are good biomarkers for CRC-cetuximab therapy patient stratification. **Methods:** We have established patient derived xenografts (PDX) from treatment-naïve Asian CRC patients to discover biomarker predictive of cetuximab response. We conducted a clinical trial style study ("patient avatar trial") of cetuximab using a randomly selected cohort of 26 EGFR+ PDXs. The antitumor activities were analyzed against KRAS mutation status and a published expression-signature. **Results:** We identified 12/26 (~46%) as cetuximab responders and 14/26 non-responders (defined by 50% tumor growth inhibition threshold). All 14 non-responders are mutated for one or more of KRAS, BRAF (V600E), EGFR, AKT and PIK3CA oncogenes. In contrast, 5/11 responders analyzed are wild-type for all these genes. Importantly, 5/11 responders have activating KRAS mutations at codons 12/13, contradictory to the currently practiced clinical exclusion criteria, but consistent with more recent clinical findings. Most interestingly, the observed cetuximab activity in this cohort of 26 PDXs has a surprisingly strong correlation to a published RAS pathway score. **Conclusions:** Our results indicated strong predictive power of cetuximab-CRC-PDX trial and RAS signature, and warrant prospective clinical studies for further confirmation.

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General Poster Session (Board #2C), Sun, 8:00 AM-11:45 AM

ALK and ROS1 gene rearrangements detected in colorectal cancer (CRC) by fluorescence in situ hybridization (FISH).

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Background: Activation of *ROS1* and *ALK* tyrosine kinases through gene fusions lead to unchecked cell proliferation and transformation. *ROS1* and *ALK* gene fusions were found in about 5% and 2% of lung adenocarcinomas and are highly sensitive to specific tyrosine kinase inhibitors. This study aimed at identifying the presence of *ROS1* and *ALK* rearrangements in CRC using FISH technology. **Methods:** Arrayed specimens of metastatic CRC (mCRC) patients were tested with a 4-target, 4-color break-apart FISH probe set (Abbott Molecular) designed to simultaneously evaluate the genomic status of *ROS1* and *ALK*. Fused 3'/5' signals of each gene were considered negative for rearrangement; single 3'/single 5' (for *ROS1*) and split 3'-5' or single 3' (for *ALK*) were considered positive for rearrangement. **Results:** Among 236 mCRC patients tested, two were positive for *ROS1* (single 3' *ROS1* signals in 39% and 61% of tumor cells) and one was positive for *ALK* rearrangement (single 3' *ALK* in 41% of tumor cells). The upper cut-off for positive FISH patterns in the negative specimens was identified as <15% both for *ROS1* and *ALK*. Interestingly, the *ALK*⁺ patient displayed intra-tumoral heterogeneity, detected in the tissue cores and confirmed in two resection blocks. The fusion partner for *ALK* was identified as *EML4* by PCR-based tests and sequencing. The fusion partner(s) for *ROS1* remains to be identified by other technologies. A small fraction of specimens presented duplicated or clustered copies of native *ALK* and *ROS1*. **Conclusions:** The novel FISH probe set was effective to identify the first cases of *ROS1* rearrangements in CRC and re-confirm the occurrence of *ALK* rearrangements. This supports further evaluation of mCRC cases for *ROS1* and *ALK* gene fusions as these may represent new targets for evaluation in clinical trials. Tumor heterogeneity in the *ALK* rearrangement must be addressed for screening tests. (Partially supported by research grant from Abbott Molecular and the Colorado CCSG P30CA046934).

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General Poster Session (Board #2D), Sun, 8:00 AM-11:45 AM

Stereotactic body radiotherapy response and local control rates for hepatic oligometastases.

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Background: Stereotactic body radiation therapy (SBRT) is a non-invasive, effective technique in the treatment of hepatic oligometastases from solid tumors. We present response and local control rates from our single institution experience. **Methods:** We treated 79 metastatic liver lesions from 64 different patients using stereotactic body radiation therapy. One colorectal cancer patient was treated three times and four patients were treated twice. Among the 79 metastatic liver lesions treated, 85% had prior chemotherapy. The primary cancer site included: Colorectal 66%, Non-colorectal GI 14%, Breast 6%, Ovarian 5%, NSCLC 3%, and other 6%. The mean GTV size was 37.3 (cc). The mean GTV diameter was 3.1 (cm). The median total dose was 54 (Gy) with the minimum and maximum total dose being 30 and 60 (Gy). **Results:** The overall local control rate was 94.2%, with estimates at 12, 24, 36, and 48 months being 96.1%, 87.9%, 87.9% and 87.9% following SBRT treatment. When comparing colorectal cancer patients vs all other primary cancer sites, the one year local control rate was 93.4% and 100%. The two and three year local control rates for colorectal cancer vs other primary cancer sites were 84.9% vs 90.9%. Best response was examined as a 4 level response (CR,PR,SD,PD) per the RECIST criteria. Overall, 67% of patients had a response, and less than 3% of patients had progression with SBRT treatment. For colorectal cancer patients, 79% had a response to treatment. Only 21% of colorectal cancer patients did not respond, however, the majority of these patients still had stable disease following treatment. Non-colorectal primary site cancers had a response in 50% of the lesions following SBRT treatment. The remaining 50% of non-colorectal primary cancers were stable following SBRT treatment and none progressed. The median dose for CR, PR, or SD was 54 Gy. The median dose for patients with progressive disease was less than 50 Gy. The observed CTC toxicities were limited with mostly grade 1-2 toxicity and only two grade 4 and one grade 5 toxicity. **Conclusions:** Stereotactic body radiation therapy is an effective treatment option for patients with hepatic oligometastases with a limited toxicity profile.

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General Poster Session (Board #2E), Sun, 8:00 AM-11:45 AM

Effect of oxaliplatin-containing neoadjuvant chemotherapy on tumor volume in locally advanced rectal cancer and sensitivity of surviving tumor cells to radiotherapy.

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Background: The use of oxaliplatin (OXA) is well established in adjuvant and palliative treatment of colorectal cancer (CRC), but its role in neoadjuvant treatment of locally advanced rectal cancer (LARC) is controversial. Data from the ACCORD 12/0405, STAR-01 and NSABBP R-04 trials suggest no additional clinical benefit of adding OXA to fluoropyrimidine-based preoperative chemoradiotherapy (CRT) in LARC. However, the possibility of reducing risk of systemic recurrence and the use of OXA-containing neoadjuvant chemotherapy (NACT) in liver metastasis warrant further clarification of the role of OXA in neoadjuvant treatment of LARC. **Methods:** We report results from a non-randomized phase II trial of neoadjuvant treatment of 72 LARC patients, receiving two courses of the Nordic FLOX regimen prior to CRT (25 x 2 Gy; weekly OXA; daily capecitabine). Tumor volumes were calculated from MRI scans taken before and after NACT and 4 weeks after CRT completion. Using OXA resistant human CRC cell lines, the impact of previous OXA exposure on radiosensitivity (1-5 Gy) was examined. **Results:** Median baseline tumor volume was 16.6 cm³ (1.1-293 cm³). All tumors, except one, responded to NACT, leaving a median tumor volume of 5.3 cm³ (0.2-157 cm³), representing a median volume reduction of 63%. In all but three patients, additional tumor volume reduction was observed following subsequent CRT (median tumor volume 5.3 cm³; 0.02-119 cm³; median volume reduction of 68%). Exposure of cell lines to increasing concentrations of OXA resulted in resistance towards the drug. OXA resistant models exhibited increased radiosensitivity compared to OXA sensitive counterparts. **Conclusions:** OXA-containing NACT led to substantial tumor volume reduction. Additional tumor volume reduction was observed in almost all cases, suggesting that pretreatment with OXA-containing NACT did not preclude tumor response to CRT. Results from experimental models rather suggest that pretreatment with OXA might enhance radiosensitivity of surviving OXA resistant cells. Taken together, our results are in favor of continued exploration of OXA-containing NACT in LARC. Clinical trial information: NCT00278694.

3548

General Poster Session (Board #2F), Sun, 8:00 AM-11:45 AM

Cochrane systematic review and meta-analysis of adjuvant chemotherapy for stage II colon cancer.

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Background: Colon cancer is potentially curable by surgery in the early stages of the disease. Adjuvant chemotherapy improves disease-free and overall survival in patients with stage III disease, but the magnitude of benefit in stage II colon cancer is less clear. A previous Cochrane systematic review and meta-analysis (SR/MA) found improved disease-free, but not overall survival (Figueredo et al., 2008). An updated SR/MA was performed to determine the effects of adjuvant chemotherapy on disease-free and overall survival in patients with stage II colon cancer. **Methods:** Relevant databases (MEDLINE, EMBASE, and Cochrane) were independently searched by all authors, using the same search strategy employed in the original study (1/1988 to 9/2012). Randomized trials containing data on stage II colon cancer patients undergoing adjuvant 5-fluorouracil (5FU) chemotherapy versus observation were included. Pooled results were expressed as hazard ratios (HR) whenever possible, or risk ratios (RR), with 95% confidence intervals (95%CI) using a random effects model. **Results:** Seven studies were identified, and included in the final SR/MA. Six of the 7 studies were included in the disease-free survival analysis (n=4587). Adjuvant 5FU was associated with better disease-free survival (RR 0.84 (95%CI 0.75-0.94)). All 7 studies (n=5353) were included in the overall survival analysis showing an improvement with adjuvant 5FU (HR 0.87 (95%CI 0.78-0.97)). There was no evidence of heterogeneity across the studies ($I^2 = 0\%$ for all analyses). **Conclusions:** In stage II colon cancer, adjuvant 5FU chemotherapy statistically improves both disease-free and overall survival. Our SR/MA demonstrates, for the first time, an overall survival advantage with adjuvant chemotherapy in stage II colon cancer.

The frequencies and clinical implications of mutations in 33 kinase-related genes in locally advanced rectal cancer.

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Background: Locally advanced rectal cancer, LARC (T3/4 and/or N+) is currently treated with pre-operative chemoradiotherapy (pCRT), but responses are not uniform. The phosphatidylinositol 3-kinase (PI3K), MAP-kinase (MAPK) and related pathways have been implicated in rectal cancer tumorigenesis. Here, we investigated the association between genetic variations in these pathways and clinical outcomes in LARC. **Methods:** We genotyped a total of 239 Single Nucleotide Polymorphisms (SNPs) including potentially clinically relevant mutations in 33 cancer related genes including PIK3CA, PIK3R1, AKT, STK11, KRAS, BRAF, MEK, CTNNB1, EGFR, MET and NRAS using the Sequenom platform. DNA samples utilized herein were extracted from pre-treatment rectal cancer biopsies of 201 patients who were then treated with long-course pCRT followed by surgical resection. **Results:** 62 different mutations were detected in 15 genes, with the highest frequencies occurring in KRAS (n=93, 47%), PIK3CA (n=29, 14%), MET (n=27, 13%), STK11 (n=13, 6.3%), CTNNB1 (n=12, 6%), BRAF (n=8, 4%) and NRAS (n=7, 3.5%). Mutations were also detected in AKT, PIK3R1, EGFR, GNAS, MEK1, PDGFRA, ALK and TNK2, but at frequencies of less than 2%. Pathologic complete response (pCR) was associated with excellent (97%) 5-year Recurrence-Free Survival (RFS) (Hazard ratio [HR], 0.076; 95% CI, 0.01-0.50, P=0.001). We found: 1) Mutations in PI3K pathway-related genes (PIK3CA, AKT, STK11) were significantly associated with absence of pCR (odd ratio [OR], 5.40; 95% CI, 1.24-23.54, P=0.024). However, mutations in MAPK pathway-related genes (KRAS, BRAF, NRAS, MEK) was not found to be significantly associated with pCR (P=0.805). 2) In contrast, in patients who did not achieve pCR (non-pCR), mutations in PI3K pathway-related genes were not associated with RFS. However, KRAS G12V and KRAS G12S mutations were significantly associated with an increased risk of recurrence (HR, 2.115; 95% CI, 1.077-4.156, P=0.030). **Conclusions:** These results suggest that mutations in kinase signaling pathways may modulate treatment responsiveness and clinical outcomes in locally advanced rectal cancer and thus may constitute rational targets for novel therapies.

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General Poster Session (Board #2H), Sun, 8:00 AM-11:45 AM

Molecular characteristics and prognostic implication of mucinous histology in colorectal cancer patients treated with adjuvant FOLFOX.

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Background: There have been controversies in prognostic impact of mucinous histology in colorectal cancer (CRC) and its implication in pts treated with adjuvant FOLFOX is unclear. This study aimed at elucidating the molecular characteristics and prognostic implication of mucinous histology in pts treated with adjuvant FOLFOX. **Methods:** Stage II and III CRC pts who received adjuvant FOLFOX were analyzed. Pts were grouped according to the mucinous content: > 50%, mucinous adenocarcinoma (MAC); < 50%, adenocarcinoma with intermediated mucinous component (AIM); and without any mucinous component, nonmucinous adenocarcinoma (NMA). Clinicopathologic features, MSI status (N = 518), CpG island methylator phenotype (CIMP) (N = 322) BRAF mutation (N = 269) and disease-free survival (DFS) were compared. **Results:** Among a total of 521 pts, 27 (5.2%) had MAC, 41 (7.9%) AIM, and 453 (86.9%) NMA. MAC and AIM had higher frequency of proximal location and lower angiolymphatic invasion. MAC had higher proportion of T4 tumors. AIM had higher frequency of age \geq 65 years and female. In terms of molecular characteristics, MAC and AIM showed similarly higher proportion of MSI-high and CIMP-high compared to NMA. BRAF mutation also showed similar trend. In contrast to the similarities between MAC and AIM, DFS was significantly different. MAC showed significantly worse DFS compared with AIM and NMA, whereas AIM and NMA showed similar DFS. Multivariate analysis revealed MAC as an independent negative prognostic factor of DFS (adjusted HR 7.96, 95% CI 3.76-16.8). **Conclusions:** AIM and MAC has distinct clinico-pathologic features and molecular characteristics compared with NMA. Only MAC but not AIM has an adverse prognostic impact on stage II or III CRC treated with adjuvant FOLFOX compared with NMA.

	MAC (%)	AIM (%)	NMA (%)	P values		
				MAC vs NMA	AIM vs NMA	AIM vs MAC
Age \geq 65	29.6	46.3	28.3	-	0.015	-
Female	40.7	68.3	37.5	-	<0.001	0.025
Proximal	59.3	61.0	30.9	0.002	<0.001	-
T4	40.7	14.6	13.0	<0.001	-	0.015
Angiolymphatic invasion	22.2	29.3	45.3	0.019	0.048	-
MSI-high	14.8	14.6	5.6	0.073	0.022	-
CIMP-high	35.3	25.0	4.6	<0.001	<0.001	-
BRAF mutation	5.3	6.7	2.1	-	-	-
3-year DFS	57	87	86	<0.001	-	0.01

-, >0.10

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General Poster Session (Board #3A), Sun, 8:00 AM-11:45 AM

Proof-of-concept study of Sym004, an anti-EGFR monoclonal antibody (mAb) mixture, in patients (pts) with anti-EGFR mab-refractory KRAS wild-type (wt) metastatic colorectal cancer (mCRC).

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Background: KRAS wt mCRC pts progressing on chemotherapy and anti-EGFR mAbs have limited treatment options. Sym004 is a first-in-class drug mixture of two mAbs targeting non-overlapping epitopes on the EGFR, causing its internalization and degradation. With this unique mechanism of action, Sym004 overcomes acquired resistance to anti-EGFR mAbs in preclinical studies. **Methods:** Open-label, multicenter trial assessing safety (primary endpoint) and efficacy of 2 dose levels of Sym004 in KRAS wt mCRC pts with prior clinical benefit to anti-EGFR mAbs and subsequent progression during or within 6 months after treatment cessation. Sym004 was administered until disease progression or unacceptable toxicity. Tumor responses were evaluated centrally according to RECIST criteria. Paired skin and tumor biopsies were obtained at baseline and week 4. **Results:** In total, 42 pts were enrolled at 9 mg/kg (13) and 12 mg/kg (29). Median age was 66 years and median number of prior treatment lines 3. Central radiology review was performed in 12/13 (92%) pts at 9 mg/kg and 27/29 (93%) pts at 12 mg/kg. Tumor shrinkage > 10% was documented in 4/12 (33%) pts at 9 mg/kg, with partial response (PR) in 1/12 (8%) and stable disease (SD) in 9/12 (75%). At 12 mg/kg, 7/27 (26%) pts had > 10% tumor shrinkage, with PR in 3/27 (11%) and SD in 15/27 (56%). Median progression-free survival was 13.6 weeks (95% CI: 5.3-23) and 13.7 weeks (95% CI: 5.9-18.6), respectively. Duration of response for pts with PR was 5.6-17.6 weeks. Grade 3 or higher toxicity included skin rash in 26/42 (62%), hypomagnesemia in 16/42 (38%) and diarrhea in 2/42 (8%). Adverse events were manageable with dose reduction and supportive medication. There were no indications of immunogenicity. Pharmacodynamic analysis in serial tumor samples showed profound down-regulation of EGFR and reduction in proliferation marker Ki67. **Conclusions:** Sym004 at weekly doses of 9 and 12 mg/kg showed significant clinical activity in anti-EGFR treatment-refractory KRAS wt mCRC pts, clearly demonstrating proof-of-concept. Serial biopsies confirmed its mechanism of action. No unexpected adverse events were observed. Clinical trial information: NCT01117428.

Association of DNA promoter hypermethylation of decoy receptor 1 (DCR1) with poor response to irinotecan in metastatic colorectal cancer.

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Background: Heterogeneity in the biology of colorectal cancer (CRC) is associated with variable responses to standard chemotherapy. We aimed to identify DNA hypermethylated genes as predictive biomarkers for irinotecan treatment of patients with metastatic CRC. **Methods:** The presence of DNA methylation for a selected panel of 22 genes was assessed by methylation specific PCR (MSP) on primary tumors of 185 patients with metastatic CRC treated with first-line capecitabine (CAP, n=90) or a combination of capecitabine and irinotecan (CAPIRI, n=95) in the phase 3 CAIRO trial. Methylation status of each gene was correlated to progression free survival (PFS) by treatment regimen. Genes for which methylation status associated with response to irinotecan, were validated in 166 patients treated with first-line CAP (n=78) or CAPIRI (n=88). **Results:** Decoy Receptor 1 (DCR1) was identified as a novel hypermethylated gene in CRC. In CAPIRI treated patients, DCR1 methylation was correlated to a shorter PFS compared to patients with unmethylated DCR1 (hazard ratio [HR]=0.4 (95%CI =0.3-0.7), p = 0.0009). In patients with methylated DCR1 PFS did not improve with CAPIRI treatment, compared to treatment with CAP (discovery set: HR=0.8 (95%CI=0.5-1.3, p=0.4); validation set: HR=1.1 (95%CI 0.7-1.7, p=0.6)), in contrast to patients with unmethylated DCR1 (discovery set: HR=2.5 (95%CI 1.7-3.3, p=0.0004); validation set: HR=1.7 (95%CI 1.1-2.0, p=0.004)). **Conclusions:** CRC patients with methylated DCR1 did not benefit from adding irinotecan to capecitabine therapy, indicating that DCR1 methylation status may guide selecting metastatic CRC patients for irinotecan-based therapy.

Genetic variations in miRNA binding site of *TPST1* and *ZG16B* associated with prognosis for patients with colorectal cancer.

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Background: MicroRNAs (miRNA) may play important roles in tumorigenesis by regulating the expressions of proto-oncogenes or tumor suppressor genes. Single nucleotide polymorphisms (SNP) located in the 3'-UTR of miRNA target genes might affect miRNA-mediated gene regulation, thereby contributing to the susceptibility or prognosis of cancer. Accordingly, the present study analyzed SNPs located in the putative miRNA-binding sites of the 3'-UTR of various genes and their impact on the prognosis for patients with colorectal cancer by altering miRNA binding efficiency. **Methods:** Eight hundred and thirty-one consecutive patients (discovery cohort, n=309; validation cohort, n=522) with curatively resected colorectal adenocarcinoma were enrolled in the present study. The genomic DNA was extracted from fresh colorectal tissue. One hundred fifty-seven SNPs were selected *in Silico* analysis for the current study, which was based on several miRNA database and HapMap database. The SNP genotyping was performed using the Sequenom MassARRAY. **Results:** The median age of all patients was 65 years, and 468 (56.3%) patients had colon cancer, while 363 (45.1%) patients had rectal cancer. The pathologic stages after the surgical resection were as follows: stage I (n=150, 18.1%), stage II (n=332, 40.0%), stage III (n=333, 40.1%), and stage IV (n=16, 1.9%). In the discovery cohort, 19 SNPs were identified as possible prognostic biomarkers in a multivariate survival analysis [disease-free survival (DFS) and/or overall survival (OS)] adjusted for age, preoperative CEA level, and pathologic stage. In the validation cohort, the *TPST1* rs3757417T>G and *ZG16B* rs12373A>C were significantly associated with prognosis as same direction in the discovery cohort (discovery + validation cohort; *TPST1* rs3757417T>G, DFS, p value=0.0007, OS, p value=0.0091 in recessive model; *ZG16B* rs12373A>C, DFS, p value=<0.0001, OS, p value=0.0009 in dominant model). **Conclusions:** The current study provides evidence that the rs3757417T>G and rs12373A>C polymorphism in the 3'-UTR of *TPST1* and *ZG16B*, respectively, are possible prognostic biomarker for patients with colorectal cancer.

Regular statin users and colorectal cancer (CRC) prognosis.

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Background: Statins are frequently used for the control of hyperlipidemia. Statins have multiple anti-cancer properties and may be associated with lower CRC risks among their users. This study tries to go a step further and explores whether statin use affects the prognosis of curatively resected CRC. **Methods:** We established a population cohort with patients (age ≥ 40 y) who were diagnosed as having stage I or II CRC from 2004 to 2008 and received curative surgery from the database of Taiwan Cancer Registry. Data of medication prescription and co-morbidities were retrieved from the database of National Health Insurance, Taiwan. Regular statin use was defined as taking statins for > 180 days within the observation period from one year before the cancer diagnosis to one year afterward. The database of National Death Registry was used for survival outcomes. Another similar cohort consisting of patients with hepatocellular carcinoma (HCC) was used for comparison. **Results:** In total, 10762 patients with CRC were enrolled; 891 (8%) patients were regular statin users, 812 (8%) patients took statins but were not regular users, and 9059 (84%) patients never used statins. Regular statin users, compared to never users, were more likely to be female ($p < 0.001$), older ($p < 0.001$), have stage I disease ($p < 0.001$) and co-morbidities such as diabetes, coronary artery disease, and renal disease. Adjuvant therapy was less frequently administered in regular statin users. In univariate analysis, cancer-specific survival (CSS) of regular statin users was significantly longer than that of never users (5-y CSS, 87% vs. 84%, $p = 0.022$), but overall survival (OS) was not significantly different (5-y OS, 80% vs. 77%, $p = 0.156$). In multivariate analysis adjusting for age, gender, stage, adjuvant therapy, co-morbidities, and the use of aspirin, regular statin use was an independent predictor both for better CSS (hazard ratio [HR] 0.72, $p < 0.001$) and for better OS (HR 0.71, $p < 0.001$). In contrast, no associations were found between statin use and CSS or OS in the HCC comparison cohort. **Conclusions:** Regular statin use was associated with better prognosis in CRC patients who received curative therapy. (This study was supported by grants DOH-101-TD-B-111-001 and DOH-102-TD-B-111-001).

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General Poster Session (Board #3E), Sun, 8:00 AM-11:45 AM

Colorectal cancer gene expression profiling using nanostring nCounter analysis.

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Background: A more accurate method of identifying stage 2 and 3 colorectal cancer (CRC) patients at highest risk for recurrence after surgical resection is needed. Gene expression signatures utilizing microarray-derived gene expression data from fresh frozen primary CRCs to predict risk of recurrence have been developed by us and others. Advances in technology platforms for gene expression measurements and their applicability to formalin-fixed, paraffin-embedded (FFPE) specimens offer new opportunity to develop clinically useful diagnostics based on molecular profiles. **Methods:** 58 patient FFPE samples of all stages stored from 1-12 years were collected from the Vanderbilt GI SPORE Translational Pathology and Imaging Core and annotated with appropriate clinicopathologic data. 414 genes were selected from our 34-gene prognostic classifier and other published CRC gene signatures, as well as gene elements associated with intestinal stem cell biology and epithelial-to-mesenchymal transition (EMT). RNA was extracted from the tumors, and gene expression analysis was completed using the nCounterplatform. **Results:** Quality of extracted RNA from tumor blocks was similar among the tumors and adequate for analysis. No significant differences were seen in signal strength ($p=0.94$, Kruskal-Wallis test) or intra-class variation (correlation coefficient = 0.99) across material extracted from new and old blocks. Fold change values for the 70 most highly differentially expressed genes on the nCounter platform correlated well with Affymetrix U133 plus 2 microarray ($R^2=0.819$). Genes associated with EMT clustered according to prognosis, with poorer prognoses seen in patients with high TWIST expression or low E-cadherin and SMAD4 expression. There was a trend toward better survival outcomes with high expression of E-cadherin and SMAD4 ($p=0.072$, log-rank test). **Conclusions:** This preliminary study demonstrates the feasibility of this approach to determine gene expression patterns in FFPE tumor tissue samples. Our data suggest that this approach may be applied to identify clinically applicable prognostic gene expression profiles that may be validated in archived patient samples that are well annotated with patient outcome data.

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General Poster Session (Board #3F), Sun, 8:00 AM-11:45 AM

Neoadjuvant chemoradiotherapy (NCRT) using concurrent S-1 and irinotecan in rectal cancer: Impact on long-term clinical outcomes and prognostic factors.

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Background: To assess long-term clinical outcomes of neoadjuvant chemoradiotherapy (NCRT) of rectal cancer using concurrent irinotecan and S-1. **Methods:** One hundred and fifteen patients without distant metastases entered this phase II trial in cT3/T4 rectal cancer (n=104/11). Pelvic radiotherapy was given to 45 Gy in 25 fractions over 5 weeks with concurrent oral S-1 at 80 mg/m² and intravenous irinotecan at 80 mg/m² once weekly. Median follow-up term was 60 months (ranged from 20 to 96 months). **Results:** Adverse effect of Grade 3 was recognized in 7 patients (6%), and completion rate of this NCRT regimen was 87 %. All 115 patients (100%) could undergo R0 surgical resection. Twenty-eight patients (24%) demonstrated a pathologic complete response (ypCR). Local recurrence-free survival was 93%, disease-free survival (DFS) was 79%, and overall survival (OS) was 80%. By the multivariate proportional hazard model for DFS and OS, ypN2 was only remnant independent prognostic factor (P=0.0019 and P=0.0064, respectively). ypN2 was recognized in 9 patients (8%), and prognosis was extremely dismal (8 patients were recurred within 2 years). We again performed the multivariate analysis for 106 cases restricted to ypN0/1, which exhibited 85% of DFS, and both ypT and tumor portion were independent predictors (P=0.0065 and P=0.003, respectively). Combination of them could greatly enrich high risk patients for recurrence (P<0.0001), and dominant recurrences were uniquely found in lung. **Conclusions:** Novel NCRT regimen using S1/irinotecan demonstrated high response rates and excellent long-term survival, with acceptable adverse effects. ypN2 is a definitive indicator of dismal prognosis, and combination of ypT and tumor portion can identify high risk patients among the ypN0/1 patients.

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General Poster Session (Board #3G), Sun, 8:00 AM-11:45 AM

Genes involved in EGFR-degradation to predict for efficacy in metastatic colorectal cancer patients treated with cetuximab.

Sebastian Stintzing, Wu Zhang, Takeru Wakatsuki, Yan Ning, Nico Benjamin Volz, Joseph Ethan Li, Melissa Janae Labonte, Peter M. D. Wilson, Adel Kardosh, Fotios Loupakis, Lisa Salvatore, Marta Schirripa, Heinz-Josef Lenz; University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; USC Norris Comprehensive Cancer Center, Los Angeles, CA; Azusa Pacific University, Azusa, CA; U.O. Oncologia Medica 2, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy; U.O. Oncologia Medica 2, Azienda Ospedaliero-Universitaria Pisana, Istituto Toscano Tumori, Pisa, Italy

Background: As many transmembrane receptors, the epithelial growth factor receptor (EGFR) has a highly regulated turnover leading to inactivation and recycling or degradation after activation. This process can be divided into four different phases: receptor endocytosis, ubiquitination/neddylolation, recycling and degradation. We tested whether functional significant single nucleotide polymorphisms in genes involved in the degradation pathway will predict clinical outcome (response, PFS and OS) in 108 patients with metastatic colorectal cancer enrolled in clinical trials and treated with cetuximab. **Methods:** Genomic DNA was isolated from blood from 108 patients treated with cetuximab enrolled in one of two clinical trials. All patients were KRAS and BRAF wildtyp. 20 SNPs were selected based on the involvement in receptor endocytosis (CBL, CIN85, endophilin) ubiquitination/neddylolation, recycling and degradation (CBL, EPS15, Ubc12, UbcH7). Minor allele frequency had to be higher than 10%. PCR and product sequencing were done using standard procedures. Uni- and multivariate analyses, adjusting for age, gender, rash and racial background, were carried out. **Results:** In univariate analysis, rs895374 (HR: 1.69; p= 0.03), which is located in the exome of UbcH7, was able to separate patient cohorts significantly in perspective of progression free survival (CC = 5.7mo, CA= 3.6mo, AA= 3.4mo). Using multivariate analysis, rs895375 stayed to be a significant predictor of progression free survival with a Hazard ratio of 2.08 (95% CI 1.24 – 3.48) and a p value of 0.005. UbcH7 plays a pivotal role in the process of neddylation (adding NEDD8 to the EGFR), which switch the balance between recycling and degradation of the EGFR towards degradation. **Conclusions:** The process of EGFR recycling is important mechanism of resistance of cetuximab in colorectal cancer. This is the first report suggesting that germline polymorphisms in the degradation process may predict efficacy of cetuximab in patients with metastatic colorectal cancer. Anti-EGFR antibody like Sym004 might overcome this resistance mechanism by preventing EGFR recycling.

Survival after resection plus intra-operative radiofrequency ablation (IRFA) to treat colorectal liver metastases (CLM): Results of an international collaborative study.

Serge Evrard, Abou Diallo, Veronique Brouste, Caroline Lalet, Gregoire Desolneux, Simone Mathoulin-Pelissier, Peter Kissmeyer-Nielsen, Frank Mortensen, Graeme John Poston, Stefan Staettner, Ioannis Konstantinidis, Ronald P. DeMatteo, Michael Ian D'Angelica, Peter J. Allen, William R. Jarnagin, Yuman Fong; Institut Bergonié, Bordeaux, France; Institut Bergonie, Bordeaux, France; Institut Bergonie, Regional Comprehensive Cancer Center, Bordeaux, France; Aarhus University Hospital, Aarhus, Denmark; University Hospital Aintree, Liverpool, United Kingdom; Aintree University Hospitals, Liverpool, United Kingdom; Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY; Memorial Sloan-Kettering Cancer Center, New York, NY

Background: Adding IRFA to parenchymal resection to treat CLM is gaining increasing acceptance in specialized HPB teams treating complex, bilobar disease. Objectives were to confirm the promising results of the prospective *CLOCC* and *ARF2003* trials on a larger international scale. **Methods:** Four centers combined their clinical databases regarding IRFA for CLM. Demographics, treatments, CLM characteristics, complications (Clavien-Dindo), local recurrence, and survivals (liver progression-free, LPFS, relapse-free, RFS and overall, OS) were analyzed. **Results:** 280 patients (38% female, median age 61y) received resection plus IRFA over 2001-2011. 205 had synchronous CLM (73%) and 247 bilateral (88%). 227 patients received pre-operative chemotherapy (173 one line, 37 two lines, 10 three lines, 7 missing); 189 received post-operative chemotherapy (103 one line, 46 two lines, 40 three lines). Median number of tumors resected was 2 (range 1-19) and ablated 2 (1-12). Median size (mm) of largest CLM ablated per patient was 8.5(0.1-50). 96 patients experienced complications: 29 G1, 19 G2, 35 G3, 10 G4, and 3 deaths. 48 patients had local recurrence of ablated CLM. 155 patients developed new CLM, 165 extra-hepatic metastases, and 119 patients died during follow-up. One-year, 3-year and median (months) RFS, LPFS and OS were respectively: RFS 41%(95CI35-47), 14%(95CI9-19), 9m (95CI8-11); LPFS 53%(95CI47-59), 31%(95CI25-37), 15m (95CI11-19); OS 90%(95CI85-93), 58%(95CI51-65), 40m (95CI37-50). Median follow-up was 38m (95CI34-49). **Conclusions:** In this difficult-to-treat group, survival results were good and comparable with rates reported after resection only. IRFA complements resection, enabling to treat more patients, and offers the advantage of sparing healthy parenchyma.

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General Poster Session (Board #4A), Sun, 8:00 AM-11:45 AM

Association between c-Met expression and tumor recurrence in colorectal cancer patients after liver resection.

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Background: c-Met is a receptor for hepatocyte growth factor that has been implicated in the pathogenesis and growth of a wide variety of human malignancies, including colorectal cancer (CRC). The aim of the present study was to clarify the correlation between c-Met protein expression in the primary lesion and relapse-free survival (RFS) in patients who had undergone curative hepatectomy for colorectal metastases. **Methods:** Between January 2004 and December 2009, formalin-fixed paraffin-embedded sections of surgical specimens from 108 CRC patients who had undergone hepatectomy were obtained at a single center. We performed immunohistochemical staining to detect c-Met expression. c-Met expression levels were scored dependent on staining intensity; 0, negative; 1, weak; 2, moderate; 3, strong. We defined scores 0 and 1 as c-Met-low, and scores 2 and 3 as c-Met-high. The Kaplan-Meier method and Cox proportional hazards model were used to investigate relationships between c-Met expression, patient characteristics, and RFS. **Results:** We identified 65 males and 43 females with a median age of 62 years. A total of 53% of patients underwent simultaneous resection of primary and metastatic liver lesions, and the others underwent metachronous resection. High levels of c-Met expression (c-Met-high) in the primary tumor were observed in 52% of patients. There were no differences in terms of size or number of metastatic liver lesions between the c-Met-low patients and the c-Met-high patients. RFS was significantly shorter in the c-Met-high patients (9.7 months) than that in the c-Met-low patients (21.1 months) in primary tumors ($p=0.013$). Multivariate analyses demonstrated that c-Met-high (hazards ratio [HR], 1.73; 95% confidence interval [95% CI], 1.08-2.79 for c-Met-high vs. c-Met-low) and hepatic resection for synchronous disease (HR, 2.17; 95% CI, 1.36-3.46 for synchronous vs. metachronous resection) were associated with worse RFS. **Conclusions:** High levels of c-Met expression in the primary tumor were associated with shorter RFS after hepatic metastasectomy.

Preoperative radiotherapy (preop RT) in rectal cancer: Impact of chemotherapy on the outcome—Long-term results of the randomized 22,921 phase III trial of EORTC.

Jean Francois Bosset, Gilles Calais, Laurent Mineur, Philippe Maingon, Ljiljana Radosevic-Jelic, Alain Daban, Etienne Bardet, Alexander Beny, Jean Claude Ollier, Michel Bolla, Dominique Marchal, Jean Luc VAN Laethem, Vincent Klein, Jordi Giral, Pierre Clavere, Pascal Cellier, Laurence Collette; Besançon University Hospital, Besançon, France; Centre Hospitalier Régional Universitaire de Tours, Tours, France; Radiotherapy and Oncology GI and Liver Unit, Institut Sainte-Catherine, Avignon, France; Georges-François Leclerc Cancer Center, Dijon, France; Institute of Oncology and Radiology, Belgrade, Serbia; Hopital Universitaire Jean Bernard, Poitiers, France; Institut Gustave Roussy, Villejuif, France; Rambam Health Care Campus, Haifa, Israel; Centre Paul Strauss, Strasbourg, France; Centre Hospitalier Régional Grenoble, La Tronche, Grenoble, France; Intercommunal De Sante Publique Du Pays De Charleroi, Charleroi, Belgium; Hôpital Universitaire ERASME, Bruxelles, Belgium; Clinique Oceane, Vannes, France; Hopital General Val D Hebron Barcelone, Barcelone, Spain; Chru Limoges, Limoges, France; Centre Paul Papin, Angers, France; EORTC Headquarters, Brussels, Belgium

Background: This 2x2 factorial design clinical trial evaluated the addition of Fluorouracil-based chemotherapy (CT) to preop RT and the use of adjuvant CT in patients with resectable T3-T4 M0 rectal cancer. The 5-year results showed that adding CT preoperatively or postoperatively had no significant effect on overall survival (OS) nor on disease-free survival (DFS) but a divergence seemed to emerge respectively at 2 and 5 years in the postop CT group. We report results with a median of 10.4 years. **Methods:** A total of 1011 patients were allocated in four treatment arms: preop RT ; preop RT + 2 CT courses ; preop RT + 4 postop CT courses ; preop RT-CT + postop CT. Preop RT was 45 Gy over 5 weeks. A one 5-day course of CT consisted of 5-Fu 350 mg/m²/d and Leucovorin 20 mg/m²/d. The effect of preop CT and adjuvant CT on OS and DFS was assessed by Logrank test (2-sided 5% significance level) stratified respectively for postop and for preop treatment. Written informed consent was obtained from all patients before randomization. **Results:** There is no significant difference in OS, nor in DFS between the groups receiving preop CT or not ($p = 0.91$ and $p = 0.38$ respectively). There is no significant difference in OS nor in DFS between the groups treated by postop CT or not ($p = 0.32$ and $p = 0.29$ respectively). The 10-year cumulative incidence of local recurrences is ~9 % in all the CT groups and 17.4 % in the preop RT alone group ($p = 0.0044$). The 10 year cumulative incidence of distant metastases (DM) is ~35 % in all treatment groups. **Conclusions:** With more that 10-years follow-up there is no benefit in rectal cancer by adding Fluorouracil-based chemotherapy preoperatively nor postoperatively to preop RT in terms of OS, DFS, nor in term of DM. Clinical trial information: 00002523.

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General Poster Session (Board #4C), Sun, 8:00 AM-11:45 AM

Efficacy and toxicity of second-line AIO plus irinotecan (IRI) after pretreatment with AIO plus oxaliplatin (L-OHP) in the sequential therapy of metastatic colorectal cancer (CRC).

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Background: The FOLFIRI followed by FOLFOX6 (or vice versa) schedule has been considered as the gold standard of sequential treatment in CRC (Tournigand C. JCO 2004). In contrast to those bi-weekly schedules, the wide-spread weekly chemotherapy administration (e.g. AIO regimen), has not been investigated as yet for second-line treatment. The AIO + IRI schedule has provided promising results in the first-line treatment of CRC (Köhne C.-H. JCO 2005). Therefore, we now investigated the efficacy and toxicity of this schedule in second-line treatment in a phase II study. **Methods:** From 5/02 to 6/10, 60 palliative patients (pts.) with histologically proven CRC were enrolled in an oligocentric phase II study based on the following regimen: weekly IRI (80 mg/m² i.v.) as 1h-infusion (inf.): d1, 8, 15, 22, 29, 36, qd 57 followed by 5-FU (2000 mg/m² i.v.) combined with sodium folinic acid (500 mg/m², d1, 8, 15, 22, 29, 36, qd 57) as a 24h-inf. via port-a-cath. This study focused on the efficacy and toxicity of second-line treatment with AIO + IRI. **Results:** Last date of evaluation: November 30, 2012; evaluable for efficacy: n = 58 pts., evaluable for toxicity: n = 59 pts.; men/women: 28/72%; median age: 65y; primary tumor location: rectum/colon: 45/55%; toxicity data: higher grade toxicity (grade 3-4): leukocytopenia: 5.1%; thrombocytopenia: 1.7%; vomiting: 3.4%; diarrhea: 13.5%; hand-foot-syndrome: 1.7%; alopecia (grade 2) 3.4%; efficacy data: PFS: 4.2 m; median OS 14.2 m, RR: 10%; AIO + IRI following AIO + L-OHP achieved a median OS of 25.0 months. **Conclusions:** In the field of second-line treatment of CRC the AIO plus IRI regimen offers both a favorable toxicity profile and promising results in terms of efficacy compared with the FOLFIRI regimen.

Hsa-miR-31-3p expression in FFPE tumor samples as a predictor of anti-EGFR response in patients with metastatic colorectal cancer.

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Background: In metastatic colorectal cancer (mCRC), KRAS mutations are associated with resistance to anti-EGFR antibodies. To identify, in wild-type KRAS mCRC patients, markers that predict response to anti-EGFR antibodies, we focused on miRNAs. **Methods:** Expression profile of 1145 miRNAs was done on 84 colorectal tumors and 5 normal colon mucosae. Correlations between miRNAs expression level and survival were based on frozen samples of a training set from a retrospective series of 33 patients treated by cetuximab and irinotecan and of two validation set from prospective collections of 38 patients treated by cetuximab or panitumumab based chemotherapy or by panitumumab and irinotecan as third-line, using an adjusted Cox proportional hazards model. Validation on FFPE samples was done on 39 patients treated with panitumumab and irinotecan as third-line. **Results:** A predictive signature of 11 miRNA linked to the PFS was identified ($p < 0.01$) but only one, hsa-miR-31-3p, exhibited significant different expression level between tumor from bad prognosis and good prognosis from the training set. We tested expression of this miRNA on the training set, and found a HR of 1.9 CI95% [1.1-2.9]. In validation set, the prognostic impact of hsa-miR-31-3p the HR was estimated to 1.9 CI95% [1.1-3.1]. Using multivariate model obtained from the training set to the two validation set, we predict the PFS of the patients (accuracy of prediction: AUC = 0.77). We classified the validation set according to a free PFS score ($P = 0.005$) with a specificity of 62% CI95% [38%-82%] and a sensitivity of 82% CI95% [56%-96%] for the prediction model. A nomogram, established taking into account hsa-miR-31-3p expression level, predicted the progression risk ($P < 0.0001$). Confirmation of the predictive value of hsa-miR-31-3p expression on survival risk progression was done on FFPE sample ($p = 0.0006$). **Conclusions:** This is the first tool to select individual patients with a wild-type KRAS tumor for anti-EGFR therapy from frozen or FFPE samples.

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General Poster Session (Board #4F), Sun, 8:00 AM-11:45 AM

Phase I study of the HSP90 inhibitor AUY922 in combination with capecitabine as treatment for patients with advanced solid tumors.

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Background: Heat shock protein 90 (HSP90) is a molecular chaperone involved in the maintenance and function of client proteins, many of which are integral to key oncogenic processes. AUY922 is a competitive inhibitor of HSP90. Preclinical evidence suggests potential synergy between HSP90 inhibition and fluorouracil. This phase I study was designed to determine the maximum tolerated dose (MTD) of AUY922 in combination with standard dose of capecitabine as treatment for patients with advanced solid tumors. **Methods:** Pts with refractory solid tumors received AUY922 with capecitabine in a standard 3+3 dose escalation. Dose levels were capecitabine 1000mg/m² PO BID d 1-14 of 21-day cycles, with escalating doses of AUY922 IV days 1, 8, and 15; the 6th dose level combined the MTD of AUY922 with capecitabine 1250mg/m². Dose-limiting toxicities (DLTs), safety, and efficacy were evaluated. **Results:** 23 pts were treated at 6 dose levels: 22mg/m² (*n* = 3); 28mg/m² (*n* = 3); 40mg/m² (*n* = 3); 55mg/m² (*n* = 5); 70mg/m² (*n* = 3); 70mg/m² with capecitabine 1250mg/m² (*n* = 6). No DLTs were observed until the 6th dose level (grade 3 diarrhea). Related adverse events (% grade 1/2; % grade 3/4) included: diarrhea (43%; 17%), fatigue (30%; 13%), nausea (39%; 0), hand-foot skin reaction (30%; 5%), anorexia (30%; 4%), vomiting (30%; 0), and darkening vision (26%; 0). Vision darkening, a class effect of HSP90 inhibitors, was reversible with drug hold and retreatment was possible. Two pts (9%) had hematologic G 3/4 events of neutropenia. Of the 19 pts evaluable for response, partial response was noted in 4 patients (colorectal, 2; breast, 1; stomach, 1); 2 had progressed on prior fluorouracil, and remained on treatment for 13-35 wks. Stable disease was noted in 8 pts (35% [colorectal, 5; pancreas, 2; breast, 1]) with a median duration of 25.5 wks (range: 11-44+). All 5 colorectal pts were refractory to 5-FU. **Conclusions:** The addition of AUY922 to standard dose capecitabine was well-tolerated at doses of up to 70mg/m². Preliminary efficacy is encouraging, particularly as seen in pts previously resistant to fluorouracil, and warrants further investigation of this regimen. Clinical trial information: NCT01226732.

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General Poster Session (Board #4G), Sun, 8:00 AM-11:45 AM

EGFL7 polymorphism to predict tumor response in metastatic colorectal cancer (mCRC) patients (pts) treated with FOLFIRI and bevacizumab (BV).

Joseph Ethan Li, Wu Zhang, Fotios Loupakis, Dongyun Yang, Takeru Wakatsuki, Yan Ning, Sebastian Stintzing, Rita Elie El-Khoueiry, Nico Benjamin Volz, Federica Marmorino, Marta Schirripa, Lisa Salvatore, Carlotta Antoniotti, Chiara Cremolini, Heinz-Josef Lenz; USC Norris Comprehensive Cancer Center, Los Angeles, CA; University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; U.O. Oncologia Medica 2, Azienda Ospedaliero-Universitaria Pisana, Istituto Toscano Tumori, Pisa, Italy

Background: Angiogenesis involves endothelial cell (EC) sprouting, proliferation, and differentiation and recruitment of mural cells to stabilize new vessels. The proteins Epidermal Growth Factor Domain-Like 7 (EGFL-7) and Activin Receptor-like Kinase 1 (ALK1) play critical roles. EC-secreted EGFL7 antagonizes Notch to promote EC proliferation, sprouting, and motility. EGFL7 also regulates mural cell recruitment and extracellular matrix deposition. ALK1 is an EC-restricted TGF- β Type 1 receptor with downstream repression of Vascular Endothelial Growth Factor (VEGF) signaling. ALK1 also promotes pericyte-EC adhesion. EGFL7 or ALK1 inhibition enhances antitumor efficacy when combined with BV in murine models. Both are overexpressed in many cancers and may be critical for efficacy of anti-VEGF therapy. We tested whether EGFL7 (rs1051851, rs2297538) and ALK1 polymorphisms (rs2293094, rs11169953, rs706819) will predict efficacy of BV-based therapy in mCRC pts. **Methods:** Genomic DNA was extracted from peripheral whole blood samples from 455 mCRC pts treated with first-line BV and FOLFIRI. SNPs were analyzed by PCR-based direct DNA sequencing and evaluated for association with tumor response rate (RR), overall survival (OS), and progression free survival (PFS). **Results:** Male/female: 272/183; median age: 62 (range: 25-81); median PFS and median OS: 10.9 (95%CI: 10.1-11.6) and 29.9 (95%CI: 25.9-34.6) months, respectively; response to therapy: 59% (215 pts); median follow-up: 23.6 (range: 1.8-60.4) months. Pts carrying the EGFL7 rs1051851 G/G alleles had a 62% RR versus 56% in pts with A/G and 29% in patients with A/A ($p=0.0130$, Cochran-Armitage trend test). The result remained significant after adjustment for baseline pt characteristics ($p=0.026$, Multivariable logistic regression test). There was no statistically significant association between tested polymorphisms and OS or PFS. **Conclusions:** The EGFL7 SNP rs1051851 may predict tumor response in mCRC pts treated with FOLFIRI and BV. To our knowledge, this is the first study demonstrating predictive significance of genetic variations in EGFL7. Prospective validation of this study is warranted.

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General Poster Session (Board #4H), Sun, 8:00 AM-11:45 AM

Use of genetic variants in pericyte-driven tumor vessel maturation genes to predict treatment efficacy in mCRC patients treated with FOLFIRI/bevacizumab.

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Background: Angiogenesis is maintained by the presence of PDGFB (platelet derived growth factor beta) which binds to the receptor, PDGFRB on pericytes, signaling them to stabilize stalk cells adjacent to tip cells. PDGFB signaling by endothelial tip cells promotes proliferation, migration, and stabilization of pericytes which are closely associated with endothelial cells. VEGF driven angiogenesis in response to tumor hypoxia relies on several genes. Previously, studies showed RALBP1, RGS5, and CSPG4 greatly impact the structure of blood vessels during angiogenesis. Recognizing these genes are important in angiogenesis through pericytes, we investigated the correlation between polymorphisms in these genes and clinical outcomes in patients with mCRC treated with FOLFIRI/bevacizumab (BV). **Methods:** Genomic DNA was extracted from 455 patients' blood or tissue treated with first-line BV + FOLFIRI and prospectively enrolled in a prospective pharmacogenomic translational study. Median follow up is 24 months and median PFS and OS were 10.5 and 29.9 months, respectively. Eight functionally significant SNPs; RGS5 (rs1056515, rs2661280), PDGFRB (rs2229562, rs2302271), CSPG4 (rs8023621, rs1127648), and RALBP1 (rs10989, rs329007) were analyzed by PCR-based direct sequencing. All candidate SNPs were analyzed for association with tumor response rate (RR), progression free survival (PFS), and overall survival (OS). **Results:** Four SNPs showed significant results in the univariate analysis of either OS or PFS. PDGFRB rs2302273 remained significant upon multivariate analysis. Univariate analysis of PDGFRB rs2302273 concluded patients with any T (CT/TT) allele were significantly associated with longer PFS compared to those with CC genotypes (median 10.2 vs 11.6 months, HR=0.78 [95%CI: 0.63-.98], $p=0.031$, log-rank test) which remained significant upon multivariate analysis (HR=0.73 [95% CI: 0.57-0.92], $p=0.008$, log-rank test). **Conclusions:** Our results show that the PDGFRB polymorphism rs2302273 may serve as a prognostic marker for the efficacy of FOLFIRI + BV treatment in patients with mCRC. Studies to confirm and update these preliminary findings are ongoing.

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General Poster Session (Board #5A), Sun, 8:00 AM-11:45 AM

Use of genetic variants in immune response genes to predict clinical outcome in mCRC patients treated with cetuximab-based therapy.

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Background: Cetuximab is a monoclonal antibody targeting the EGF receptor. One of its anti-tumor mechanisms is the stimulation of the immune system via ADCC (Antibody-Dependent-Cell mediated Cytotoxicity). Immune response through T-cell activation may also play a role in antitumor efficacy of chemotherapy. CTLA4, PDL1, IDO1 and CD24 are inhibitory co-receptors or ligands that may downregulate the immune system through suppression of T-cell response. We tested whether Germline polymorphisms in these genes are involved in the cetuximab dependent immune response pathway and thus predict outcome in mCRC patients treated with cetuximab. **Methods:** DNA was isolated from blood of 108 patients with mCRC treated with either irinotecan+cetuximab (n=73) or single agent cetuximab (n=35). Twelve prospectively functionally relevant SNPs; IDO1(rs9657182, rs3739319, rs1010866), PD1(rs2227981, rs7421861), PDL1(rs2297137, rs2297136, rs10122089, G>C), CTLA4(rs231777, rs231775), and CD24(rs8734) were analyzed by PCR-based direct sequencing and evaluated for association with tumor response, overall survival (OS), and progression free survival (PFS). **Results:** Results are attached. There were 65 men and 43 women with a median PFS of 3.7 (95%CI: 2.8, 4.6) months and a median OS of 10.5 (95%CI:7.7, 13.3) months. Median follow up was 16.3 (range:1.2, 42.4) months. **Conclusions:** Our results show that immune response related SNPs may predict efficacy of cetuximab treatment in patients with mCRC. To the best of our knowledge this is the first data linking PDL1(rs2297137) to cetuximab efficacy in mCRC patients.

Significant results in OS, PS, or tumor response.

SNP	N	OS	P (multivariate)
		Median, mo (95%CI)	
IDO1rs9657182			0.009
A/A	24	12.0 (5.7, 20.4)	
A/G	55	15.0 (7.8, 15.9)	
G/G	25	8.5 (5.1, 10.8)	
IDO1rs3739319			0.045
A/A	27	10.8 (4.4, 15.0)	
A/G	51	8.7 (6.3, 12.0)	
G/G	27	17.9 (8.5, 26.4)	
CD24rs8734			0.001
G/G	54	7.8 (5.7, 10.5)	
G/A	36	13.1 (8.7, 17.9)	
A/A	5	2.3 (1.8, 11.3)	
		PFS	
		Median, mo (95%CI)	
CTLA4rs231777			0.017
C/C	65	4.1 (3.3, 5.3)	
C/T	34	2.6 (2.3, 4.4)	
		Tumor response	
		PR	SD+PD
PDL1rs2297137			0.029
G/G	60	9 (16%)	49 (84%)
G/A	36	7 (19%)	29 (81%)
A/A	9	5 (56%)	4 (44%)

Abbreviations: PR, partial response, SD, stable disease, PD, progressive disease.

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General Poster Session (Board #5B), Sun, 8:00 AM-11:45 AM

Use of genetic variants in wnt signaling pathway to predict gender and tumor location dependent survival in metastatic colorectal cancer (mCRC) patients (pts) treated with first-line FOLFIRI and bevacizumab (BEV).

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Background: CRC is generally characterized by aberrant Wnt signaling. Wnt signaling pathway genes AXIN2 and TCF7L2 complex control the proliferation and differentiation of intestinal epithelial cells. Previous study showed polymorphisms in TCF7L2 and AXIN2 were associated with increase risk of colon cancer. We tested the hypothesis whether single nucleotide polymorphisms (SNPs) in TCF7L2 (rs7903146) and AXIN2 (rs2240308, rs3923087) will predict clinical outcome in a cohort of mCRC pts treated with first line FOLFIRI/BEV. **Methods:** Genomic DNA were extracted from blood of 455 mCRC pts which prospectively enrolled in a pharmacogenetic translational study. Females(n=172) and males(n=252); Median follow up is 24 months, median PFS and OS were 10.5 and 29.9 months, respectively. Candidate SNPs were analyzed by PCR-based direct sequencing. **Results:** In the overall population analysis, TCF7L2 and AXIN2 polymorphisms were not associated with OS and PFS, but our data showed that 2 polymorphisms may predict clinical outcome when adjusted by pts gender and tumor location: 1) In right-sided tumors, male pts with any T allele of TCF7L2rs7903146 were associated with significantly worse PFS in comparison to those carrying C/C genotype (HR: 2.15; 95% CI: 1.09-4.22; P = 0.027, log-rank test). However, female pts with any T allele reversly showed better PFS compared with those carrying C/C variants (HR: 0.39; 95% CI: 0.17-0.94; P = 0.035, logrank test). 2) In women, pts with AXIN2 rs2240308 any A allele had better PFS and OS in right-sided tumors compared to those with any A allele but located in left side($p_{\text{interaction}}=0.047$)(PFS) and ($p_{\text{interaction}}=0.025$)(OS), respectively. **Conclusions:** Our data show for the first time Wnt signaling pathway gene polymorphisms TCF7L2 rs7903146 and AXIN2 rs2240308 may predict PFS and OS in mCRC pts treated with first-line FOLFIRI/BEV. More importantly, this predictive value is dependent on gender and tumor location, suggesting a different role of Wnt signaling in female vs male and in right vs left side tumor. Our preliminary data warrants clinical trial validation.

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General Poster Session (Board #5C), Sun, 8:00 AM-11:45 AM

Adjuvant chemotherapy (AC) outcomes in young (YP) and elderly patients (EP) with high-risk stage II colon cancer (CC).

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Background: High-risk stage II CC is defined as those presenting with T4 stage, obstruction or perforation, <12 lymph nodes retrieved, positive resection margins, and lymphovascular or perineural invasion. Our prior findings suggest that improved outcomes from AC are limited to specific high risk features, such as T4 disease (Kumar et al, ASCO 2012). It is unclear if this benefit is seen across all ages. Our aim was to compare patterns of AC use and outcomes in YP and EP with high risk stage II CC. **Methods:** All patients diagnosed with high risk stage II CC from 1999 to 2008 and evaluated at any 1 of 5 regional cancer centers in British Columbia were categorized into YP (age <70 years) or EP (age ≥70 years). Kaplan-Meier methods and Cox regression were used to correlate receipt of AC with overall survival (OS), disease specific (DSS) and relapse free survival (RFS), stratified by age group. **Results:** A total of 1,236 patients were identified: 636 (51%) YP and 600 (49%) EP among whom 363 (57%) and 85 (14%) received AC, respectively. Individuals who received AC in either age group had better performance status than those who did not (ECOG 0/1 47% vs. 34%, p=0.02). After adjusting for known prognostic factors, a significant advantage in OS, but not DSS or RFS, from AC was observed for both YP and EP (Table). The impact of AC on these outcomes was similar across age groups (p interaction of age and treatment = 0.46, 0.64 and 0.69 for OS, DSS and RFS, respectively). In the entire cohort, individuals with T4 lesions had significantly improved OS (HR 0.50, 95%CI 0.33-0.77, p=0.002), DSS (HR 0.59, 95%CI 0.37-0.93, p=0.03), and RFS (HR 0.63, 95%CI 0.42-0.95, p=0.03). The effect of AC in the T4 subgroup was also similar for both YP and EP in terms of OS, DSS and RFS (p interaction of age and treatment = 0.41, 0.71 and 0.77, respectively). **Conclusions:** In this population-based cohort of high risk stage II CC, improvements in outcomes from AC were seen mainly in those with T4 disease, regardless of age.

Age group	Hazard ratios (and 95% CI) of events in patients receiving AC vs. no AC					
	OS	p value	DSS	p value	RFS	p value
YP	0.72 (0.52-0.99)	0.04	0.79 (0.54-1.16)	0.23	0.75 (0.53-1.05)	0.09
EP	0.59 (0.40-0.88)	0.01	0.69 (0.42-1.13)	0.14	0.84 (0.53-1.33)	0.45

Adjuvant chemotherapy with oxaliplatin/5-fluorouracil/leucovorin (FOLFOX) versus 5-fluorouracil/leucovorin (FL) in patients with locally advanced rectal cancer after preoperative chemoradiotherapy followed by surgery: A randomized phase II study (The ADORE).

Yong Sang Hong, Byung-Ho Nam, Kyung Hae Jung, Jae-Lyun Lee, Kyu-Pyo Kim, Young Suk Park, Joon Oh Park, Sun Young Kim, Tae-You Kim, Jee Hyun Kim, Joong Bae Ahn, Tae Won Kim; Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Cancer Registration and Biostatistics Branch, Center for Clinical Trials, Research Institute and Hospital, National Cancer Center, Goyang, South Korea; Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Center for Colorectal Cancer, Research Institute and Hospital, National Cancer Center, Goyang, South Korea; Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea; Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea; Department of Internal Medicine, Cancer Metastasis Research Center, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea

Background: Preoperative chemoradiotherapy (Pre-CRT) with fluoropyrimidines (Fp) followed by surgery is one of the standard treatments for patients (pts) with locally advanced rectal cancer (LARC); however, the role of adjuvant chemotherapy is still controversial. The aim of this study is to investigate the efficacy of adjuvant FOLFOX for LARC pts who underwent Fp-based Pre-CRT and complete total mesorectal excision (TME). **Methods:** This randomised phase II study accrued LARC pts whose ypStage was II (ypT3-4/ypN0) or III (any ypT/ypN1-2) after Fp-based Pre-CRT followed by TME. Pts were randomly assigned (1:1) to receive adjuvant chemotherapy either with FL (5-FU 380 mg/m², leucovorin 20 mg/m² on D1-5 q 4 weeks X 4 cycles) or FOLFOX (oxaliplatin 85 mg/m², leucovorin 200 mg/m² on D1, 5-FU bolus 400 mg/m² on D1, 5-FU infusion 2400 mg/m² for 46 hours q 2 weeks X 8 cycles). The primary endpoint was disease-free survival (DFS). **Results:** A total of 320 pts were randomly assigned (161 FL and 159 FOLFOX) between November 2008 and June 2012, the arms were balanced. By intent-to-treat analysis, estimated 2-year DFS rate was 82.0% in FOLFOX arm and 69.4% in FL arm (HR 0.46 [95% CI, 0.28-0.76], *p*=0.002) after the median follow-up duration of 22.5 months. The statistical improvements of DFS were maintained regardless of ypStage: 2-year DFS rate was 89.7% (FOLFOX) vs 76.4% (FL) in pts (*n*=122) with ypStage II (HR 0.32 [0.10-0.98], *p*=0.035), and 78.1% (FOLFOX) vs 64.4% (FL) in pts (*n*=198) with ypStage III (HR 0.49, [0.27-0.86], *p*=0.011). All grade leucopenia (32% vs 22%), neutropenia (70% vs 46%), thrombocytopenia (26% vs 2%) and sensory neuropathy (71% vs 5%) were more frequently observed in FOLFOX arm; however, grade 3/4 adverse events (AE) were not different between arms. **Conclusions:** Adjuvant FOLFOX improved 2-year DFS relative to FL for LARC pts whose ypStage II or III after Fp-based Pre-CRT followed by TME. Significant AEs were not different between arms. The DFS results will be updated in the presentation. Clinical trial information: NCT00807911.

Tumor perivascular PDGFbR as an independent prognostic factor in metastatic colorectal cancer.

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Background: New vessel formation is an essential factor for tumor growth and metastasis. Tumor vessels show reduced and variable pericyte coverage. Several pericyte markers have been identified, including platelet-derived growth factor receptor beta (PDGFbR), smooth muscle α -actin (ASMA) and desmin. Variability in pericyte status and its prognostic significance remains largely uncharacterized in colorectal cancer (CRC). The aim of the present study was to perform a preliminary analysis of the variability in expression of the three pericyte markers and to investigate the potential prognostic significance of perivascular PDGFbR (PV-PDGFbR). **Methods:** A population-based cohort was used for double-staining, performed on 100 tumors with CD34 and above-named pericyte markers. For the rest of the study a metastatic CRC (mCRC) collection from the phase III NORDIC-VII study was used. Analyses were performed on a tissue microarray with tumor material from 328 out of the 566 patients in the intention to treat population. All tumors and corresponding normal tissue were scored by immunohistochemistry (IHC) with regard to PV-PDGFbR. 255 and 97 cases were analyzed by IHC with regard to perivascular ASMA and microvessel density (MVD), respectively. **Results:** Analyses of the double-staining revealed independent and variable expressions of all three pericyte markers. Analyses of the NORDIC-VII cohort revealed two prognostic groups with low and high PV-PDGFbR expression. Median OS was 14.3 mo for PV-PDGFbR-low tumors (N=22) vs. 22.9 mo for PV-PDGFbR-high (N=306) tumors (HR=1.95; 95% CI 1.20-3.16; log-rank p=0.007). Multivariate analysis, including WHO performance status, alkaline phosphatase level and BRAF mutation status confirmed PV-PDGFbR as an independent prognostic factor of OS (HR=1.75; 95% CI 1.07-2.84; p=0.025). PV-PDGFbR was not significantly linked to perivascular ASMA or MVD. PV-PDGFbR in normal tissue was not associated with survival. **Conclusions:** CRC display a previously un-recognized variability in pericyte characteristics. Low tumor PV-PDGFbR level is associated with worse prognosis in patients with mCRC, in a manner independent of performance status, alkaline phosphatase levels and BRAF status.

Primary tumor location and expression of mir-664 as a combined biomarker for bevacizumab effectiveness in metastatic colorectal cancer.

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Background: We aimed to identify tissue microRNAs (miRs) that could predict outcome for patients with metastatic colorectal cancer (mCRC) treated with first line bevacizumab (BEV) and chemotherapy (CT) but not for patients treated with CT alone. **Methods:** Patients with mCRC treated with first line capecitabine and oxaliplatin (CT) with or without BEV at ten hospitals were identified and data was extracted retrospectively. Formalin-fixed paraffin-embedded tissue samples from primary tumors were collected and RNA was purified from 3 x 10 µm sections, without micro-dissection. miR expression was measured using Applied Biosystems TaqMan Custom LDA cards profiling 22 selected miRs in duplicate. The 22 miRs were selected from a previous discovery study profiling 754 miRs. miR expression was related to time to disease progression (TTP) and overall survival (OS) in multivariate analyses using Cox proportional hazards models with adjustment for age, prior adjuvant treatment, and no. of metastatic sites. We have previously found that patients with primary tumors originating in the sigmoid colon and rectum (S+R) experienced a better outcome than patients with other primary tumor locations (caecum to descending colon) when treated with BEV, so our analyses were stratified by primary tumor location. **Results:** miR expression was measured in samples from 399 patients: 155 samples from the original CT+BEV discovery study, 119 samples from a new CT+BEV cohort, and 125 samples from a CT alone cohort. Expression of miR-664 showed a significant positive association with increasing TTP, OS, and response rate (RR), but only in the cohort of patients with sigmoid colon- and rectal primary tumors treated with CT+BEV (n=183). **Conclusions:** We have identified a subgroup of patients with mCRC that are likely to benefit from BEV addition to first line CT using the combined information of location of the primary tumor and expression level of miR-664.

Treatment	CT	CT+BEV	CT	CT+BEV	CT	CT+BEV
Primary tumor location	All	All	S+R	S+R	S+R	S+R
MIR-664 expression level	All	All	All	All	Highest quartile	Highest quartile
RR (CR+PR), %	-	37	-	40	-	48
Median TTP, mo	8.4	9.5	8.1	10.3	7.3	11.3
Median OS, mo	16.4	24.4	16.8	28.4	15.3	33.9

On-treatment progression-free survival analysis of ziv-aflibercept/FOLFIRI treatment within 28 days of end of treatment in metastatic colorectal cancer: Updated efficacy results from the VELOUR study.

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Background: The phase III VELOUR study demonstrated that adding the novel antiangiogenic agent ziv-aflibercept (known as aflibercept outside the United States) to FOLFIRI in patients with metastatic colorectal cancer previously treated with oxaliplatin significantly improved overall survival, progression-free survival (PFS), and overall response rate vs placebo/FOLFIRI. We performed an additional analysis of PFS “on-treatment,” censoring events that occurred more than 28 days after last treatment dose. **Methods:** Patients were randomized to receive ziv-aflibercept 4 mg/kg or placebo every 2 weeks in combination with FOLFIRI. An independent review committee determined progression based on radiologic review. PFS was estimated using Kaplan-Meier analysis, with censoring of events after the last dose plus 28 days. Treatment groups were compared using a log-rank test and were stratified by Eastern Cooperative Oncology Group performance status and prior bevacizumab therapy. Hazard ratio (HR) and confidence interval (CI) were estimated using a Cox proportional hazard model. **Results:** On-treatment analysis showed significantly increased PFS for patients treated with ziv-aflibercept/FOLFIRI compared with placebo/FOLFIRI (Table). More patients were censored in the ziv-aflibercept arm due to adverse events. **Conclusions:** The on-treatment PFS analysis demonstrates a significantly improved treatment effect of the addition of ziv-aflibercept to FOLFIRI (HR=0.55) over what was observed in the primary analysis suggesting that continuing treatment with ziv-aflibercept up to disease progression provides additional benefit. Clinical trial information: NCT00561470.

PFS, months	Placebo/FOLFIRI n=614	Ziv-aflibercept/FOLFIRI n=612	Hazard ratio
PFS per primary analysis, number of events	454	393	HR=0.76 (95% CI, 0.66-0.87) P=0.00007
Median (95% CI)	4.67 (4.21-5.36)	6.90 (6.51-7.20)	
On-treatment PFS, number of events	320	208	HR=0.55 (95% CI, 0.46-0.66) P<0.00001
Median (95% CI)	5.29 (4.37-5.49)	8.31 (7.23-9.50)	

Analysis of overall survival and safety during the course of the phase III VELOUR trial comparing FOLFIRI and ziv-aflibercept or placebo in mCRC patients who progressed on prior oxaliplatin treatment.

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Background: VELOUR, a large, international, randomized, placebo (pbo)-controlled study, compared efficacy and safety of FOLFIRI with ziv-aflibercept (known as aflibercept outside the United States) or with pbo in 1,226 metastatic colorectal cancer patients who received prior oxaliplatin treatment. Ziv-aflibercept demonstrated statistically significant, clinically meaningful improvements in median overall survival (OS) (13.5 vs 12.06 mos; hazard ratio [HR]=0.817, P=0.0032), progression-free survival, and response rate. This analysis estimates treatment effect and safety over time course of the study. **Methods:** HRs by 6-mo time periods were estimated using piecewise Cox proportional hazard model. NCI-CTCAE v3.0 was used to grade adverse event (AE) severity. **Results:** HR improved over time (Table), consistent with survival curves that continue to separate past the median time point, indicating that the magnitude of ziv-aflibercept treatment effect continues to increase over time. Incidence of grade 3 AEs (45.1% vs 62.0%) was higher in the ziv-aflibercept/FOLFIRI arm; incidences of grade 4 AEs were 17.4% (pbo) vs 21.4% (ziv-aflibercept). More common AEs only occurred in a small proportion of ziv-aflibercept/FOLFIRI cycles (eg, grade ≥ 3 hypertension and diarrhea occurred in 3.6% and 2.8% of cycles, respectively). The majority of grade 3/4 AEs occurred in early treatment (first 3-4 cycles). Most patients experienced only a single episode of grade ≥ 3 AEs with ziv-aflibercept/FOLFIRI. Importantly, AEs in VELOUR did not impact patients' ability to receive chemotherapy. **Conclusions:** Treatment with ziv-aflibercept/FOLFIRI showed continuous, consistent improvement in OS over time. While combined grade 3/4 AEs were higher with ziv-aflibercept, AEs occurred early in treatment in a small proportion of total cycles; the majority were single-episode in nature. Clinical trial information: NCT00561470.

OS (mos), piecewise Cox model with predefined intervals (per 6 mos) (ITT population).

Parameter	Time (mos)	HR (95% CI vs pbo + FOLFIRI)
OS	t \leq 6	0.860 (0.664-1.114)
OS	6 < t \leq 12	0.838 (0.673-1.043)
OS	12 < t \leq 18	0.782 (0.582-1.050)
OS	t > 18	0.676 (0.463-0.988)

Results of a phase III, randomized, double-blind, placebo-controlled trial of pegfilgrastim (PEG) in patients (pts) receiving first-line FOLFOX or FOLFIRI and bevacizumab (B) for colorectal cancer (CRC).

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Background: The literature reports that adding biologics to chemotherapy (ctx) may increase the incidence of clinically significant neutropenia. This trial was conducted to evaluate the efficacy of PEG in reducing the incidence of febrile neutropenia (FN) in pts with locally-advanced (LA) or metastatic (m)CRC receiving first-line treatment with either FOLFOX/B or FOLFIRI/B. **Methods:** Key eligibility: ≥ 18 years old; measurable, nonresectable CRC per RECIST 1.1. Pts were randomly assigned 1:1 to either placebo or 6 mg PEG ~ 24 h after ctx/B. The study treatment period included four Q2W cycles, but pts could continue their assigned regimen until progression. Pts were stratified by region (North America vs rest of world), stage (LA vs mCRC), and ctx (FOLFOX vs FOLFIRI). Estimated sample size ($N = 800$) was based on the expected incidence of grade 3/4 FN (primary endpoint) across the first 4 cycles of ctx/B, powered for PEG superiority over placebo. Other endpoints included overall response rate (ORR), progression-free survival (PFS), and overall survival (OS). **Results:** 845 pts were randomized (Nov 2009 to Jan 2012) and received study treatment; 783 pts completed 4 cycles of ctx/B. Median age was 61 years; 512 (61%) pts were male; 819 (97%) had mCRC; 414 (49%) received FOLFOX, and 431 (51%) received FOLFIRI. Grade 3/4 FN (first 4 cycles) for placebo vs PEG was 5.7% vs 2.4%; OR 0.41; $p = 0.014$. A similar incidence of other \geq grade 3 adverse events was seen in both arms (28% placebo; 27% PEG). See table for additional results. **Conclusions:** PEG significantly reduced the incidence of grade 3/4 FN in this pt population receiving standard ctx/B for CRC. Follow-up is ongoing. Clinical trial information: NCT00911170.

	Placebo (n=423)	PEG (n=422)	Placebo vs PEG
Grade 3/4 FN (95% CI)	5.7% (3.7, 8.3)	2.4% (1.1, 4.3)	Diff = -3.3% (-6.6, 0.0) OR=0.41 (0.19, 0.86) $p=0.014$
ORR* (95% CI)	238/420 [†] ; 56.7% (51.8, 61.5)	244/420 [†] ; 58.1% (53.2, 62.0)	Diff = 1.4% (-6.5, 9.3) OR = 1.06 (0.81, 1.39) $p=0.683$
Median PFS* (95% CI), mo	10.1 (9.3, 11.1)	9.7 (9.2, 10.8)	HR = 1.05 (0.88, 1.26) $p=0.552$
Median OS* (95% CI), mo	24.6 (21.3, NR)	21.8 (18.5, 25.6)	HR = 1.05 (0.81, 1.36) $p=0.704$

*Immature data. [†]Measurable disease.

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General Poster Session (Board #6B), Sun, 8:00 AM-11:45 AM

Detection of the BRAF^{V600E} protein in human colon carcinomas by a mutation-specific antibody.

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Background: BRAF encodes a serine-threonine kinase that is a downstream effector of activated RAS. A point mutation (V600E) in BRAF occurs in a subset of colorectal cancers (CRCs) and is associated with adverse outcome and may predict non response to anti-EGFR antibodies. Detection of a BRAF^{V600E} mutation in a CRC with microsatellite instability indicates a sporadic origin and excludes Lynch Syndrome. While BRAF^{V600E} mutation status is determined using a DNA-based assay, antibodies against the BRAF^{V600E} protein have recently been developed. We examined mutant BRAF^{V600E} protein expression and its concordance with mutation status. **Methods:** Primary stage III colon carcinomas (50 BRAF^{V600E} mutation carriers and 25 wild-type cases) were studied from a completed phase III adjuvant trial comparing FOLFOX +/- cetuximab (NCCTG N0147). In archival resection specimens, immunohistochemistry (IHC) was performed using a pan-BRAF antibody and a V600E mutation-specific antibody raised against an immunogenic synthetic peptide derived from the internal region of the BRAF^{V600E} protein. BRAF^{V600E} mutations in codon 15 were analyzed in extracted DNA using a multiplex, allele specific PCR-based assay. BRAF staining was scored independently by two pathologists blinded to mutation status. **Results:** In primary colon carcinomas stained with a pan-BRAF antibody, diffuse cytoplasmic staining for BRAF proteins was detected in 74 of 75 carcinomas with one case deemed non-evaluable. Using the mutation-specific BRAF^{V600E} antibody, diffuse cytoplasmic staining was detected in 49 of 74 tumors without appreciable heterogeneity of expression. Among these 49 tumors expressing mutant BRAF^{V600E} proteins, all (100%) were found to carry a BRAF^{V600E} mutation according to a DNA-based assay. In contrast, absent BRAF^{V600E} staining was observed in all 25 tumors that were found to have wild-type copies of BRAF^{V600E} detected using a PCR-based assay. **Conclusions:** For the detection of mutant BRAF^{V600E}, complete concordance was found between IHC and a DNA-based method in colon carcinomas. This finding supports the use of IHC as a simplified strategy to screen CRCs for mutant BRAF^{V600E} proteins in routine clinical practice to inform clinical decision-making.

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General Poster Session (Board #6C), Sun, 8:00 AM-11:45 AM

Thymidylate synthase (TS) expression as a prognostic molecular marker in stage II/III colon cancer.

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Background: Studies on the association between colorectal cancer (CC) outcome and thymidylate synthase expression have provided inconsistent results. In this study we attempted to resolve the issue by assessing the associations between TS expression and outcome in a population of primary CC patients (pts), who after resection were randomized to 5-FU/FA vs. FOLFIRI adjuvant therapy. **Methods:** Immunohistochemical staining for TS protein was successfully performed for 1211 pts in the PETACC3 trial. TS immunoreactivity was scored as high expression ($\geq 75\%$ positive) and low expression ($< 75\%$ positive). Gene expression respectively copy number data were available for 853 respectively 306 of these samples. Twelve single nucleotide polymorphisms (SNPs) close to the *TYMS* gene were assessed in 923 pts. Association of variables with relapse-free (RFS) and overall survival (OS) was assessed using Cox regression models. **Results:** High TS expression and RNA level were strongly associated (log fold change 0.65, $p < 0.001$). Both were significantly higher in proximal CC. As expected, both were associated with other characteristics of proximal CC: MSI, BRAF mutation, high tumor grade. RNA was significantly correlated with gene copy number, distal CC showing more frequent allelic loss. Three SNPs were associated with gene expression which was validated in data from the 1000 genomes project, but none with survival. High TS expression was more strongly associated with better OS in pts receiving FOLFIRI (HR 0.4, 95% CI 0.3–0.6, $p < 0.001$), than 5-FU/FA (HR 0.8, 95% CI 0.5–1.1, $p = 0.13$), with a significant interaction ($p = 0.05$). Similar results were observed for RFS (HR 0.5, $p < 0.001$ vs. HR 0.7, $p = 0.07$; interaction $p = 0.11$). TS expression is still highly prognostic in multivariate models adjusting for factors associated with risk or proximal tumors in FOLFIRI treated pts (OS: HR 0.5, $p = 0.008$; RFS: HR 0.6, $p = 0.02$), but not in 5-FU/FA treated pts (OS and RFS: HR = 1, $p = 1$). **Conclusions:** TS expression is lower in distal CC, partly due to deletion of the *TYMS* locus. Pts with high TS expression have longer RFS and OS, notably when treated with FOLFIRI. For these pts addition of irinotecan to 5-FU/FA adjuvant chemotherapy might be considered. Clinical trial information: NCT00026273.

Risk of second primary cancers after treatment for locoregional rectal cancer.

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Background: The risk of second primary colorectal cancers among rectal cancer patients has been described, but little is known about the risk of non-colorectal malignancies that may occur in the field of radiation. We attempted to quantify the risk, using data from the large population-based California Cancer Registry (CCR). **Methods:** We analyzed the CCR data for surgically-treated locoregional rectal cancer cases, diagnosed during the period 1988–2009. We excluded cases with second primary tumor (SPT) diagnosed within 12 months of initial diagnosis. Radiation treatment used was external beam radiation therapy. Standardized incidence ratios (SIR) with 95% confidence intervals (CI) were calculated to evaluate risk as compared to the underlying population after matching for age, sex, ethnicity, and time. **Results:** Of the study cohort of 13,418 rectal cancer cases, 1572 cases of SPTs were observed. The SIR was increased for small intestine cancer among cases receiving radiation treatment (4 cases observed vs. 1.01 cases expected; SIR=3.94, 95% CI 1.07-10.10) but not among cases lacking radiation treatment (4 observed vs. 4.45 expected; SIR=0.90, 95% CI 0.24-2.30). Among females treated with radiation, the SIR was increased for uterine cancer (12 observed vs. 5.59 expected; SIR=2.15, 95% CI 1.11 to 3.75) but not among cases lacking radiation therapy (23 observed vs. 26.17 expected; SIR=0.88, 95% CI 0.56-1.32). Among males receiving radiation treatment, the SIR for prostate cancer was decreased (23 observed vs. 69.78 expected; SIR=0.33; 95% CI 0.21 to 0.49) but of borderline significance among males lacking radiation therapy (243 observed vs. 276.97 expected; SIR=0.88, 95% CI 0.77-0.99). No significant differences were observed for cancers of the vagina, cervix, ovary, kidney, bladder, penis, testes, or leukemia based on prior radiation treatment for rectal cancer. **Conclusions:** Patients receiving pelvic radiation for treatment of rectal cancer have a subsequently higher than expected incidence of small intestine and uterine cancer. The incidence of prostate cancer appears to fall after pelvic radiation. These unexpected findings suggest complex relationships associated with radiation treatment for rectal cancer and SPT risk.

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General Poster Session (Board #6E), Sun, 8:00 AM-11:45 AM

Influence of sex and anthropometric factors on tumor biologic characteristics of colorectal cancer: A cohort study.

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Background: How body size influences risk of molecular subtypes of colorectal cancer (CRC) remains unclear. In this study, we investigated the relationship between height, weight, BMI, WHR and risk of CRC according to expression of beta-catenin, cyclin D1, p53 and microsatellite instability (MSI) status. **Methods:** Immunohistochemical expression of beta-catenin, cyclin D1, p53 and MSI-screening status was assessed in tissue microarrays with tumours from 584 cases of incident colorectal cancer in the Malmö Diet and Cancer Study. Four anthropometric factors: height, weight, body mass index (BMI), waist-hip ratio (WHR) were categorized by quartiles of baseline anthropometric measurements, and relative risks of CRC according to expression of betacatenin, cyclin D1, p53 and MSI screening status were calculated using multivariate Cox regression models. **Results:** Expression of cytoplasmatic and nuclear betacatenin, cyclin D1, p53 and MSS all revealed a positive association with increased weight and BMI in the overall analysis. Negative expression of the above mentioned factors was more frequently associated with increased height. MSI was not associated with any of the anthropometric factors in overall analysis and according to gender. Gender specific analysis revealed no association between any anthropometric factors and positive and negative cytoplasmatic beta-catenin expression, beta-catenin nuclear negativity, cyclin D1 negativity and p53 positivity. Nuclear beta-catenin positivity, cyclin D1 positivity, p53 negativity and MSS were all associated with increased weight in women. In men, positive expression of cytoplasmatic and nuclear beta-catenin, cyclin D1 positivity and p53 positivity were all associated with increased WHR. Negative expression of betacatenin was associated with increased weight, while there were no associations between any anthropometric factors and cyclin D1 negativity, MSS or MSI status in men. **Conclusions:** Findings from this large prospective cohort study demonstrate an association between obesity, measured as weight and BMI, and risk of CRC according to the expression of beta-catenin, cyclin D1, p53 and MSI status.

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General Poster Session (Board #6F), Sun, 8:00 AM-11:45 AM

Survival benefit and complications of primary tumor resection (PTR) in patients with stage IV colorectal cancer (CRC) in the era of modern chemotherapy: A systematic review and meta-analysis.

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Background: Although there is evidences that PTR in advanced CRC may improve outcome, most studies were conducted during the period of monotherapy with 5-fluorouracil. Limited data is available regarding potential benefits and risk of PTR in patients with stage IV CRC treated with modern chemotherapy (MC). A recent phase II study suggested that outcomes are not compromised by leaving the primary colon tumor intact in such patients (*JCO*.2012;30:3223). **Purpose:**To compare survival of patients with advanced CRC who underwent PTR with patients without resection in the era of MC. The review also aims to determine post-operative mortality and non-fatal complications rates, primary tumor complications rate (PTCR), non-resection surgical procedures rate (NSPR) and quality of life (QOL). **Methods:** A literature search was conducted by using CENTRAL (2012), Medline (1946-2012), and EMBASE (1947-2012). Studies involving patients with stage IV CRC who underwent PTR were selected with restriction to publication dates from 2000, English language and human studies. Screening, evaluation of relevant articles and data abstraction was done in duplication and agreement was assessed. Articles that met the inclusion criteria were assessed for quality by using Ottawa-Newcastle score. Data was collected and synthesized as per protocol. **Results:** Of total of 3,379 reports, 10 retrospective studies were selected with patients population of 2,655. Among 2,655 patients, 1616 (61%) underwent PTR with a median overall survival of 18.7 months (range: 11-30.7) compared with 12.9 months (range: 5.8-22) in the control. The HR for survival was in 0.68 (95% CI: 0.56-0.83) favoring the PTR. Mean 30 days post-operative mortality rate in the PTR group was 3.9% (95% CI: 0-11). Mean PTCR and NSPR in the control group were 27.4% (95% CI: 16.4-38.5) and 27% (95% CI: 12.5-41.6) respectively. No study provided QOL. **Conclusions:** The retrospective data favors PTR in advanced CRC in the era of modern chemotherapy. Future prospective randomized trials are warranted to confirm the findings.

Phase II study of dacarbazine for metastatic colorectal cancer: Final results with MGMT analysis.

Alessio Amatu, Andrea Sartore Bianchi, Catia Moutinho, Katia Bencardino, Erica Bonazzina, Lisa Pietrogiovanna, Filippo Venturini, Alessandra Gambaro, Giovanna Marrapese, Alessandro Belotti, Manel Esteller, Salvatore Siena; Dipartimento Oncologico, Ospedale Niguarda Ca' Granda, Milano, Italy; Institut d'Investigación Biomedica de Bellvitge, Barcelona, Spain; Azienda Ospedaleria Niguarda Ca' Granda, Milano, Italy

Background: O⁶-methylguanine-DNA-methyltransferase (MGMT) is a DNA repair protein removing mutagenic and cytotoxic adducts from O⁶-guanine in DNA. Approximately 40% of colorectal cancers (CRCs) display MGMT deficiency due to promoter hypermethylation leading to silencing of the gene. Alkylating agents, such as dacarbazine, exert their antitumor activity by DNA methylation at the O⁶-guanine site, inducing base pair mismatch, therefore activity of dacarbazine could be enhanced in CRCs lacking MGMT. We conducted a phase II study with dacarbazine in CRCs who had failed standard therapies (oxaliplatin, irinotecan, fluoropyrimidines, and cetuximab or panitumumab if KRAS wild type). **Methods:** All patients had tumor tissue assessed for MGMT as promoter hypermethylation in double-blind for treatment outcome. Patients received dacarbazine 250 mg/m² i.v. qd for 4 consecutive days q21 until PD or intolerable toxicity. We employed a Simon two-stage design to determinate if the ORR would be $\geq 10\%$. Secondary endpoints included association of response, PFS and disease control rate with MGMT status. **Results:** Sixty-eight patients were enrolled from May 2011 to March 2012. Patients received a median of 3 cycles of dacarbazine [range 1-12]. Grade 3-4 toxicities included: fatigue (41%), nausea/vomiting (29%), constipation (25%), platelet count decrease (19%), anemia (18%). Overall, 2 patients (3%) achieved partial response (PR) and 8 patients (12%) had stable disease (SD). Disease control rate (PR+SD) was significantly associated with MGMT promoter hypermethylation in the corresponding tumors. **Conclusions:** Objective clinical responses to dacarbazine in metastatic CRC patients are confined to those tumors harbouring epigenetic inactivation of the DNA repair enzyme MGMT. Clinical trial information: 2011-002080-21.

Impact of nodal metastasis on survival of stage IV colon cancer: Analysis of National Cancer Data Base (NCDB).

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Background: Nodal metastasis (mets) is an important prognostic factor in the staging of colon cancer (CCa). However, the significance of nodal mets in stage IV CCa remains undetermined. Therefore, we investigated the impact of nodal mets on 5 year overall survival (5-yr OS) in stage IV CCa. **Methods:** Patients (pts) from the NCDB who had been diagnosed with histologically confirmed Stage IVCCa from 1998-2010 were divided into two groups: with(+ve) or without(-ve) nodal mets and the 5 yr OS was compared using the Kaplan Meier Curves. Multivariate analysis was performed using CoxProportional regression model. An adjusted hazard ratio(aHR) was calculated for pts with nodal mets compared to those without nodal mets after adjusting for age, grade and tumor size. **Results:** 70,387 pts from the NCDB with stage IV CCa were included in our analysis. Of these, 12,363(17.5%) had no nodal mets (TN0M1), 23,052(32.7%) had 1-3 nodal mets (TN1M1), and 34,972 (49.69%) had 4 or more nodal mets (TN2M1) involved at the time of diagnosis (Table 1a). The overall nodal positivity was 82.4%. The 5-yrOS of all stage IV pts was 10.7% (Table 1b); 5 yr OS for node -ve pts was 18.4% versus 9.2% for node +ve pts ($p<0.0001$)(Table1b). The 5 yr OS of N1 and N2 was 12% and 7.2%, respectively. The aHR of pts with nodal mets versus without nodal mets was 1.8 (95% CI of 1.7-1.9), after adjusting other prognostic covariates. **Conclusions:** Stage IV CCa with nodal mets is associated with an increased risk of death compared to node-negative disease. The number of positive lymph nodes at the time of diagnosis is also an important risk factor.

1a. Distribution of nodal status in stage IV.

Nodal status	Number of patients	Nodal positivity
Node negative	12,363	17.6%
Node positive	58,024	82.4%
Total	70,387	100%

1b. Five-year overall survival analysis of stage IV*.

Overall 5yr OS	10.76%
Survival for node-negative pts	18.4%
Survival for node +ve pts	9.2%
Survival for 1-3 LN + pts	12.1%
Survival for 4 and above LN + pts	7.2%

* p value<0.0001.

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General Poster Session (Board #7A), Sun, 8:00 AM-11:45 AM

Use of tumor size to predict long-term survival in colon cancer patients: Analysis of National Cancer Data Base (NCDB).

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Background: Tumor size (TS) is a known prognostic factor in breast, renal, and lung cancers, however, not in colon cancer (CCa). Tumor (T) depth, nodal status (N), and metastasis (M) are used in the TNM staging. Hence, we studied if TS is an independent risk factor for death in CCa. **Methods:** Data included TS, grade, T-stage, N, and M-status from the NCDB for 298,021 CCa pts (1998-2010). We divided pts into 4 groups by TS (<2cm; 2-4cm; 4-6cm; >6cm). Data was analyzed using Spearman's rho correlation (r) and Kaplan-Meier for overall 5-yr survival (5yrOS). Hazard ratios (HR) were calculated using a Cox model adjusting for age, sex, grade, T, N-status and TNM stage. **Results:** Proportion of pts with TS 0-2, 2-4, 4-6 and >6cm were 13.25%, 38.95%, 29.54%, and 18.26% respectively. Median TS was 4cm. TS was positively correlated with grade, T, N-status and TNM stage (p=0.0001) and negatively correlated with 5yrOS (65.5%, 52.4%, 45.5%, and 41.2% for four sizes respectively) (Table). Cox modeling demonstrated TS of 4-6cm and >6cm had HRs of 1.23 (95%CI 1.14-1.34) and 1.7 (95%CI 1.5-1.8) respectively. **Conclusions:** A primary TS of 4-6cm and >6cm is associated with a 23% and 70% increased risk of death, respectively, over 5-yrs in CCa. Prospective studies are needed to evaluate the role of primary TS in CCa prognosis.

Association of tumor size with other variables.

Variable	0-2cm (Col%)	2-4cm (Col%)	4-6cm (Col%)	>6cm (Col%)	Median size (cm)	r(ASE)*
T stage	T1	16,288(41.3)	8,169(7.0)	1,701(1.9)	798(1.4)	1.9
	T2	13,214(33.5)	36,172(31.0)	15,364(17.4)	5,185(9.5)	3.3
	T3	8,563(21.7)	62,274(53.5)	58,260(66.1)	34,814(64.2)	4.5
	T4	1,329(3.3)	9,757(8.3)	12,772(14.5)	13,361(24.6)	5.5
Nodal status	N0	32,732(83.1)	71,773(61.6)	45,657(51.8)	26,557(49.0)	3.5
	N1/N2	6,657(16.9)	44,594(38.3)	42,438(48.1)	27,599(50.9)	4.6
TNM staging	I	2,751(70.0)	39,811(34.2)	14,845(16.8)	5,117(9.4)	3
	II	4,629(11.7)	27,974(24.0)	26,242(29.7)	18,026(33.2)	4.5
	III	4,505(11.4)	25,513(21.9)	20,565(23.3)	12,895(23.8)	4.5
	IV	2,748(7.0)	23,074(19.8)	26,445(30.0)	18,120(33.4)	5
5-yr OS	All	65.5%	52.4%	45.5%	41.2%	

* Chi-square test with p < 0.0001; ASE-asymptotic standard error; Col%-column%.

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General Poster Session (Board #7B), Sun, 8:00 AM-11:45 AM

Primary tumor resection in metastatic colorectal cancer (mCRC): A prospective cohort study.

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Background: The role of primary tumor resection in patients presenting with mCRC remains controversial. Previously reported survival benefits associated with primary tumor resection may not translate in the modern era of systemic therapies. We examined the impact of primary tumor resection on survival in a modern cohort of mCRC patients. **Methods:** Patients were identified using a clinician-designed mCRC registry involving 15 participating Australian sites from mid 2009. Patients were excluded if planned for curative metastasectomy or had incomplete data. Univariate logistic regression and multivariate cox regression was utilized to identify significant associations between resection, clinical variables and survival outcomes. **Results:** We identified 682 mCRC patients with median follow up 20 months. 40% (n = 275) had their primary in-situ. Rates of primary resection were higher for age > 70 years (OR 1.66 95% CI [1.22 – 2.26], p = 0.001) and Charlson score ≥ 3 (OR 1.50 [1.10 – 2.06], p = 0.011). Lower resection rates were observed for rectal v colon primary (OR 0.39 [0.28 – 0.55], p < 0.001), liver metastases (OR 0.59 [0.42 – 0.82], p = 0.002) and ECOG 2 - 4 (OR 0.64 [0.45 – 0.92], p = 0.015). There was a significant survival advantage for pts with primary tumor resection (median OS 21.3 vs 16.8 months; HR 0.63, p < 0.001), even when adjusting for known prognostic factors in a multivariate analysis (HR 0.56 [0.44 – 0.72], p < 0.001). Multivariate analyses also demonstrated that age > 70 years (HR 1.32 [1.03 – 1.71], p = 0.031) and ECOG ≥ 2 (HR 3.17 [2.43 – 4.15], p < 0.001) were significantly associated with poorer outcomes; whereas chemotherapy use (HR 0.61 [0.45 – 0.84], p = 0.002), bevacizumab use (HR 0.68 [0.52 – 0.89], p = 0.005) and rectal primary (HR 0.69 [0.53 – 0.91], p = 0.009) predicted improved survival. **Conclusions:** Our study suggests that primary tumor resection is associated with significant survival advantages for mCRC patients in the modern era of systemic therapies. The 40% of primary cancers in-situ is higher than previous mCRC studies and suggests a tendency for non-operative intervention in Australia. Further analysis aimed at examining the impact of other confounding variables such as tumor burden is ongoing and will be presented.

Small bowel adenocarcinoma phenotyping and prognostic factors.

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Background: SBA is a rare tumor with poor prognosis. Data regarding SBA molecular alterations are lacking. **Methods:** We searched for several candidate oncogenic alterations and characterised the immunophenotype according to the primary tumour location in pts with SBA (all stages; ampullary tumours excluded) treated in 11 centres from 1996 to 2008. Tissue microarrays were constructed from tumour samples, and DNA was extracted from formalin-fixed, paraffin-embedded samples. HER2, β -catenin, TP53, and mismatch repair (MMR) protein expression was assessed by immunohistochemistry. A molecular analysis assessed microsatellite instability, *KRAS* mutation and *BRAFV600E* mutation. **Results:** We obtained samples from 63 SBA pts (median age, 58 years; tumour stage: I-II, n=19 (30%); III, n=22 (35%); IV, n=20 (32%); locally advanced, n=2 (3%)). HER2 overexpression (3+) was observed in 2/62 (3%) pts. Overexpression of TP53 was observed in 26/62 (42%) pts. Abnormal expression of β -catenin was observed in 12/62 (19%) pts. MMR deficiency (dMMR) was observed in 14/61 (23%) pts, consistent with Lynch syndrome in 7/14 (50%) pts. All of the dMMR tumours were in duodenum or jejunum. Only one of dMMR tumour was stage IV. A *KRAS* mutation was observed in 21/49 (43%) pts. *BRAFV600E* mutation was observed in only 1/40 pt. Median overall survival (OS) was 36.6 months (95% confidence interval [CI], 26.9-72.2). In univariate analysis, stage I-II ($p<0.001$) and dMMR phenotype ($p=0.02$) were significantly associated with longer OS. In multivariate analysis, only disease stage independently predicted longer OS ($p<0.001$). For stage IV pts, median OS was 17.9 months (CI, 12.6-36.6). For stage I-III pts median recurrence-free survival (RFS) was 26.7 months (CI: 14.6-42.4). A trend for a better RFS was observed if tumour was dMMR HR: 0.39 (CI, 0.10-1.44], $p=0.15$. **Conclusions:** This large study suggests that molecular alterations in SBA are closer to those in colorectal cancer (CRC) than those in gastric cancer, with low levels of HER 2 overexpression and high rates of *KRAS* mutations. The seemingly higher rate of dMMR than in CRC may be explained by the higher frequency of Lynch syndrome in SBA in pts. A trend for good prognosis was associated with dMMR.

Final results of the AIO 0307 study: A controlled, randomized, double-blind phase II study of FOLFOX6 or FOLFIRI combined with sorafenib (S) versus placebo (P) in second-line metastatic colorectal carcinoma (mCRC) treatment.

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Background: The oral multikinase inhibitor Sorafenib (S) inhibits angiogenesis and tumor growth in preclinical models of CRC. This study investigated the addition of S to standard 2nd line chemotherapy (CTX). **Methods:** Patients (pts) with mCRC and progression after first-line therapy with an oxaliplatin- or irinotecan based fluoropyrimidine containing regimen \pm Bevacizumab (Bev), were randomized to receive chemotherapy (CTX) (FOLFOX6 or FOLFIRI) + S (400 mg bid) or CTX + placebo (P). 240 pts were planned to be enrolled to ensure a power of 80% if median progression-free survival (PFS) with S is increased by 2 months compared to P. **Results:** Between 04/09 and 10/11, 101 pts were enrolled. Recruitment was stopped prematurely due to slow accrual. 97 pts were evaluable in the full analysis set. Median age was 65 years, 60 pts were male, 97% with ECOG 0 or 1. Median PFS was 5.2 months (mths) in S and 5.6 mths in P (HR 0.84, 90% CI 0.58, 1.22, $p=0.439$). Best response rate was 25.6% and 12.2% ($p=0.106$), respectively. Disease control rates were comparable. Median overall survival (OS) was 9.6 mths with S compared to 12.7 mths with P (HR 1.57, 90% CI 1.03, 2.41, $p=0.076$). Difference in OS was even more pronounced in subgroup ($n=41$) with FOLFOX6 backbone (9.6 vs. 13.8 mths, HR 2.37, 90% CI 1.22, 4.60, $p=0.026$). In 69 Bev-pretreated pts OS was 8.4 vs. 14.9 mths (HR 2.30; 90% CI 1.36, 3.88, $p=0.007$) compared to 13.1 vs. 7.4 mths (HR=0.61; 90% CI 0.28, 1.36, $p=0.308$) in 28 pts without Bev pretreatment. Adverse events (AEs) were consistent with the known safety profiles. Most frequent grade 3/4 AEs affected the gastrointestinal tract (diarrhea, mucositis/stomatitis, nausea); other frequent severe AEs included neutropenia and leukopenia, fatigue, fever, sensory neuropathy, and thrombosis. **Conclusions:** No unexpected safety concerns occurred during the course of the study. S did not lead to improved PFS. There was a detrimental effect of S on OS in patients with Bev pretreatment. Clinical trial information: 2008-000803-26.

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General Poster Session (Board #7E), Sun, 8:00 AM-11:45 AM

The MEK inhibitor selumetinib ([SEL], AZD6244, ARRY-142886) plus irinotecan (IRI) as second-line therapy for KRAS-mutated (KRAS_M) metastatic colorectal cancer (CRC).

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Background: There are few therapies for second-line KRAS_M CRC. Inhibiting downstream signal transduction may offer therapeutic options. Use of selumetinib (MEK 1/2 inhibitor; AstraZeneca) is supported by preclinical and clinical evidence. We designed a dose-finding/phase II study of IRI + SEL in KRAS_M CRC. **Methods:** Eligibility included: KRAS_M or BRAF_M CRC with measurable disease progressing after 1st-line therapy with an oxalipatin + bevacizumab regimen; PS 0-1; acceptable organ function. Patients (Pts) were treated with IRI 180 mg/m² iv q2w and SEL 50 or 75 mg po bid. Dose escalation was traditional 3+3 (50 mg bid SEL, then 75 mg bid). In Part B/phase II, primary endpoint was PI-determined response rate (RR) by RECIST. A Simon 2-stage design allowed expansion to 45 pts if ≥1 responses in 20 pts was seen; ≥4/45 responses would be encouraging, when compared to historical RR of 4% (and median PFS 2.5 mo) [EPIC, Sobrero 2008], with approximately 90% power to detect an ORR of 15% at the 10% alpha level (one-sided). **Results:** N = 32 pts entered; 31 treated. Median age was 54 (27-75) yrs; 18 male and 24 Caucasian. The first 3 pts tolerated SEL 50 mg bid without DLT and the remaining 28 were treated at 75 bid. Median number of cycles on study was 3.5 and median PFS was 3.4 mo. Grade 3 AEs included (N): diarrhea 3, fatigue 2, neutropenia 2, and 1 each thrombocytopenia, enteritis, GI bleed, rash. There was one Grade 4 neutropenia. The best PI-reported response included 3 (10%) confirmed PR and 16 (52%) SD [including 1 unconfirmed PR]. 6 patients were on study for more than 6 (up to 22) months. The study was terminated early due to non-protocol considerations. **Conclusions:** In this small study, the RR of 10% and med PFS of 3.4 mo in pts with KRAS_M CRC treated with IRI + SEL in 2nd line are promising compared with prior studies in non-selected patients. MEK inhibition in KRAS_M CRC should be explored further. Supported in part by AstraZeneca.

Peripheral blood monocytes as biomarkers for colorectal cancer.

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Background: Peripheral blood monocytes (PBM) represent a reservoir of inflammatory cells that contribute to cancer progression. When recruited into tumors, monocytes give rise to either macrophages or dendritic cells. Tumor-derived soluble factors can influence the differentiation of tumor-associated macrophages (TAMs) and drive their phenotype to either tumoricidal (M1) or pro-tumorigenic macrophages (M2). We hypothesized that PBM might change their phenotype already when in circulation and can be used as potential markers for early diagnosis of colorectal cancer (CRC) and its progression to metastatic disease. **Methods:** Monocytes were isolated by using magnetic microbeads conjugated to antibodies against CD14. In a monocentric training set we included 55 (27 non metastatic (NM), 38 metastatic (M)) untreated CRC patients. The third group included age and gender matched healthy volunteers (HV). Following RNA extraction, gene expression profiles of PBM were investigated by high throughput screening using Illumina. Statistical analysis was done on the microarray expression data to delineate a disease specific signature. A cut off was set to select the genes showing a minimum fold change of 1,5. A validation study was performed in three additional major oncological centers throughout Europe. **Results:** There was a broad overlap in the gene signature of PBM from NM and M patients, indicating that this signature already exists in an early stage. Then we assessed the performance of the gene signature of cancer versus HV as diagnostic tool, in particular the sensitivity and specificity, which were remarkably high in the ROC analysis. Out of 40 differentially expressed genes, 21 genes were confirmed by qRT-PCR analysis on samples processed independently. In the validation study the number of genes was downsized to a 12 gene signature without loss of specificity and sensitivity. **Conclusions:** This first biomarker study of PBM in CRC suggests an 'imprinting' of PBM by the tumor in CRC patients. Since the imprinting profile might also be reversed, the PBM signature might not only be useful in CRC diagnosis, but also for the follow-up of treated CRC patients. Overall, our data offer new opportunities to develop a non-invasive test for CRC detection and monitoring.

Correlation of hypertension and proteinuria with outcomes in elderly bevacizumab (BEV)-treated patients with metastatic colorectal cancer (mCRC): Analysis of the BECOX and BECA studies.

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Background: Studies suggest a relationship between hypertension, which is common in older patients, and outcome in BEV-treated patients with mCRC. We performed a retrospective analysis of two studies – BECA [Feliu et al BJC 2010; EudraCT 2005-002808-42] and BECOX [NCT01067053] – to determine if hypertension and proteinuria predict outcome in elderly BEV-treated patients. **Methods:** Patients ≥ 70 years received capecitabine 1250 mg/m² bid po on days 1–14 + BEV 7.5 mg/kg on day 1 every 21 days in the BECA study; BECOX patients received capecitabine 1000 mg/m² bid po on days 1–14 with BEV 7.5 mg/kg and oxaliplatin 130 mg/m² on day 1 (oxaliplatin discontinued after cycle 6). Primary endpoints were overall response rate (ORR) in BECA and time to progression (TTP) in BECOX. Correlations were investigated for hypertension and proteinuria with ORR, disease control rate (DCR), overall survival (OS) and TTP. Logistic regression was performed to identify factors associated with hypertension and proteinuria. **Results:** 127 patients were included (BECA n=59; BECOX n=68; 61% male, median age 76 years; ECOG PS 0/1/2 45%/52%/2%). During the study 16% of patients had hypertension and 61% had proteinuria as an adverse event. Hypertension correlated with DCR, OS and TTP but not ORR; proteinuria correlated with ORR and DCR (Table). Development of proteinuria or hypertension in the first 2 cycles did not correlate with efficacy. Risk factors associated with development of hypertension were female gender (odds ratio [OR] 0.241; p=0.011) and greater no. of BEV cycles (OR 1.112; p=0.002); factors associated with proteinuria were diabetes (OR 3.869; p=0.006) and greater no. of BEV cycles (OR 1.181; p<0.0001). **Conclusions:** This analysis of the BECOX and BECA studies suggests that hypertension and proteinuria are associated with outcome in BEV-treated elderly patients with mCRC. Clinical trial information: NCT01067053.

Outcome	Hypertension			Proteinuria		
	Yes (n=20)	No (n=107)	p	Yes (n=77)	No (n=50)	p
Median OS, mo	NR	16.9	0.012 ^a	22.0	20.1	0.211 ^a
Median TTP, mo	14.0	10.6	0.174 ^a	13.0	7.4	0.063 ^a
ORR, %	50	37	0.325 ^b	47	28	0.042 ^b
DCR, %	95	71	0.024 ^b	86	58	0.001 ^b

^aLog-rank test. ^bFisher's exact test. NR, not reached.

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General Poster Session (Board #7H), Sun, 8:00 AM-11:45 AM

Impact of M1a and M1b staging in patients (pts) with metastatic colorectal cancer.

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Background: In 2009, pts with M1 colorectal cancer were divided into two subsets for the American Joint Committee on Cancer (AJCC) 7th edition. Pts with metastases (mets) confined to one organ or site at initial diagnosis became stage M1a while multiple sites or peritoneal mets became M1b. The objectives of the study are to evaluate the impact of site of mets and M1a/b staging among pts with M1 colorectal cancer. **Methods:** All pts referred to the BC Cancer Agency from 1999-2007 with newly diagnosed M1 colon or rectal cancer were included. Demographic, treatment, and outcome data were prospectively collected. The prognostic impact of individual sites of mets was assessed by hazard ratio estimates from univariate Cox models. Multivariable Cox proportional-hazards models were used to determine variables associated with overall survival in the entire cohort and in those undergoing resection of their primary tumor. **Results:** 2,049 pts with M1 disease were included. Median age was 66 years; 71% had colonic origin; 70% had their primary tumor resected; and 69% received chemotherapy. In univariate analysis, solitary mets were associated with improved survival. In multivariable analysis, M1a/b status still had significant prognostic effect. The effect remained significant in the subgroup analysis of pts with resected primary tumors when histology, T and N stage were included. **Conclusions:** Pts with solitary mets, including peritoneum, have superior overall survival as compared to those with multiple sites of mets. AJCC 7th edition staging that includes M1a/b provides significant prognostic information and should be considered in clinical practice and trials of pts with M1 disease who otherwise have few prognostic factors.

Univariate analysis: Site of mets		Multivariate analysis: M1a/b status and standard prognostic variables		
Site of mets	HR [95% CI]	Variable	P value	HR [95% CI]
Multiple	1.0 Referent	Resected yes vs no	<0.0001	0.46 [0.41,0.52]
Solitary liver	HR=0.62 [0.56, 0.69]	M1b vs M1a	<0.0001	1.38 [1.22,1.55]
Solitary lung	HR=0.50 [0.40, 0.62]	Age: >70 vs <=70	<0.0001	1.32 [1.18,1.47]
Solitary peritoneal	HR=0.70 [0.54, 0.91]	ECOG 2 vs 0-1	<0.0001	1.64 [1.43,1.88]
Solitary other	HR=0.70 [0.57, 0.86]	ECOG 3-4 vs 0-1	<0.0001	3.49 [3.02,4.02]

Prognostic stratification of k-RAS wild type colorectal cancer patients receiving irinotecan-cetuximab treatment: Preliminary results of 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. **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:** 31 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.

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General Poster Session (Board #8B), Sun, 8:00 AM-11:45 AM

Association of body mass index (BMI) with overall survival (OS) in patients (pts) with metastatic colorectal cancer (mCRC) who received targeted therapies (TT).

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Background: Preclinical data suggest that adiposity activates pro-inflammatory and insulin-dependent pathways which may lead to resistance to TT, e.g., bevacizumab (Bev) or cetuximab (Cet). Only two retrospective trials have studied the relationship between BMI and outcome for mCRC pts who received TT, with conflicting results. Our aim was to compare OS across BMI groups for mCRC pts treated with TT. **Methods:** Retrospective data, pertaining to clinical characteristics and outcome, were obtained from the South Australian Registry for mCRC from Feb 2006-Oct 2012. The BMI at first treatment was grouped as Normal (N) = 18.5- <25, Overweight (OW) = 25- <30, Obese I(Ob1) = 30- <35, Obese II (Ob2) ≥35. **Results:** Of 1,174 pts, 39% were OW, 15% Ob1 and 7% Ob2. 352 pts received chemo+TT (Bev, Cet, panitumumab (Pan) and/or regorafenib) and 814 chemo alone. Baseline characteristics were similar across all BMI groups except for type of mCRC: N pts were more likely than obese pts to have synchronous CRC (77.9% vs 56-69.7% for obese). On adjustment for age, sex, synchronous disease, metastatic sites, number of lines of chemo and TT, median OS was longer for N versus OW or Ob1 pts with chemo+TT (35.4 vs 24.9 or 22.7 mons, Table) with no difference in OS for chemo alone. Only N gp pts had an improvement in OS on the addition of TT to chemo. On breakdown by type of TT, OW and Ob1 pts had a poorer outcome with Bev but not with EGFR TT. **Conclusions:** The BMI is an independent predictor for a poorer outcome for OW and OB1 pts with chemo+TT, specifically for pts receiving Bev. The OW and OB1 patients may be a target group for lifestyle and nutrition advice to improve OS with TT. Prospective studies are required to validate this finding.

Hazard ratios and median OS.

	HR	P value	95% CI	Median OS (months)
All TT (n=352)				
N	R			35.4
OW	1.86	0.001	1.29-2.69	24.9
Ob1	1.85	0.011	1.15-2.96	22.7
Ob2	1.28	0.435	0.69-2.35	30.6
VEGF TT (n=200)				
N	R			36.1
OW	2.08	0.001	1.35-3.21	17.5
Ob1	2.67	0.004	1.37-5.20	16.0
Ob2	0.81	0.677	0.30-2.21	63.5
EGFR TT (n=106)				
N	R			40.8
OW	1.33	0.356	0.72-2.47	30.3
Ob1	0.95	0.900	0.39-2.27	41.6
Ob2	1.90	0.230	0.67-5.38	31.8

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General Poster Session (Board #8C), Sun, 8:00 AM-11:45 AM

Natural history and outcomes of synchronous and metachronous colorectal cancers (CRC): A population-based analysis.

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Background: Early data suggest that synchronous and metachronous CRC portend a worse prognosis when compared to solitary CRC. Our aims were to 1) characterize the clinical features and treatment patterns of synchronous and metachronous CRC and 2) compare their survival outcomes with those of solitary CRC. **Methods:** All patients diagnosed with non-metastatic CRC between 1999 and 2008 and referred to any 1 of 5 regional cancer centers in British Columbia, Canada were reviewed. Synchronous and metachronous CRC were defined as multiple (2 or more) distinct tumors that were diagnosed within and beyond 6 months of the date of index CRC diagnosis, respectively, during the study period. Patients with liver metastases at initial diagnosis were excluded. Kaplan-Meier and Cox regression analyses were used to estimate survival among the different CRC groups. **Results:** A total of 6360 patients were identified: 6147 (96%) solitary, 178 (3%) synchronous and 35 (1%) metachronous tumors; median age was 68 years (IQR 59-76); 57% were men; and 75% were ECOG 0/1 at the time of index cancer diagnosis. Baseline demographic characteristics were comparable across patients (all $p > 0.05$). Compared with solitary CRC, synchronous and metachronous CRC more commonly affected the colon rather than the rectum (84 vs 85 vs 59%, respectively, $p < 0.001$), but presenting symptoms, treatment approaches, and use of chemotherapy, radiation and surgery were similar among the different tumor groups (all $p > 0.05$). In terms of survival, no differences were observed in 3-year relapse free survival (66 vs 66 vs 56%, $p = 0.20$), 5-year cancer specific survival (69 vs 69 vs 53%, $p = 0.34$) and 5-year overall survival (62 vs 59 vs 49%, $p = 0.74$) for solitary, synchronous and metachronous CRC, respectively. These findings persisted after controlling for known prognostic factors, such as age and ECOG. **Conclusions:** In this large population-based cohort, there were no differences in survival outcomes among solitary, synchronous and metachronous CRC. Patients who present with multiple tumors in the colon or the rectum should be managed similarly to those who present with an isolated tumor.

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General Poster Session (Board #8D), Sun, 8:00 AM-11:45 AM

Estrogen and colorectal cancer incidence and mortality in the Women's Health Initiative clinical trial.

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Background: The preponderance of observational studies associate estrogen alone use with lower colorectal cancer incidence. In contrast, no difference in colorectal cancer incidence was seen in the Women's Health Initiative (WHI) randomized, controlled trial (RCT) of estrogen versus placebo after 7.1 years mean intervention. We now assess the influence of estrogen alone use on longer-term colorectal cancer incidence and mortality after an additional 5.6 years post-intervention follow-up. **Methods:** The WHI study was a randomized, double-blind, placebo-controlled clinical trial involving 10,739 postmenopausal women who had undergone prior hysterectomy and who were randomly assigned to receive daily 0.625 conjugated equine estrogen (n = 5279) or matching placebo (n = 5409). Colorectal cancer diagnosis rates and mortality were assessed after a mean of 7.1 years (standard deviation [SD] 1.1) of intervention and 12.7 years follow-up. **Results:** Colorectal cancer incidence in the treatment and control groups were almost equivalent, 0.15% diagnoses/year v 0.13% in the estrogen therapy arm and the placebo group, respectively (Hazard ratio [HR], 1.12; 95% Confidence Interval [CI], 0.83-1.52; *P* = 0.46). Bowel screening examinations were comparable in both groups throughout. For women age 70-79 at study entry, hormone therapy was associated with an increased risk of colorectal cancer, HR 1.71; 95% CI, (1.02-2.86). For women age 50-59 and 60-69, the respective HR's and 95% CI were 0.86 (0.43-1.71) and 0.98 (0.64-1.49), p-interaction 0.165. For women with a waist circumference of > 88 cm, there was an increased risk of colorectal cancer, HR 1.53; 95% CI, 0.95-2.45 compared to 0.95 (0.66-1.39) for waist circumference of < 88 cm, p-interaction 0.124. Although not statistically significant, there was a higher number of colorectal cancer deaths in the hormone therapy arm (33 v 24 deaths; 0.05% v 0.04%; HR, 1.42; 95% CI, 0.84-2.41; *P* = 0.19). **Conclusions:** There were no significant differences in colorectal cancer incidence or mortality after long-term follow-up in the WHI RCT of conjugated equine estrogen. There was a suggestion of an elevation in colorectal cancer risk among older women randomized to estrogen. Clinical trial information: NCT00000611.

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General Poster Session (Board #8E), Sun, 8:00 AM-11:45 AM

A phase II trial of salvage treatment with gemcitabine and S-1 combination in heavily pretreated patients with metastatic colorectal cancer.

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Background: We conducted a phase II trial of gemcitabine with S-1 to evaluate the activity and toxicity of such a combination in heavily pre-treated patients (pts) with metastatic colorectal cancer (mCRC) who have progressed after treatment with fluoropyrimidines-, oxaliplatin- and irinotecan-containing regimens. **Methods:** 36 pts were enrolled, with the following characteristics: 19 females (53%), median age 57 (28-72), 30 ECOG PS 0-1 (83%). S-1 was given orally (30 mg/m²) b.i.d for 14 consecutive days and gemcitabine (1000 mg/m²) was given on days 1 and 8, every 21 days, until disease progression and for a maximum of 9 cycles. The primary endpoint was objective response rate (ORR). **Results:** The median number of cycles was 5 (range 1-9), ORR was 16.7% (95% confidence interval [CI] 4.5-28.9%) and disease control rate was 61.1% (95% CI 45.2-77.0%) with 6 partial responses and 16 stable diseases. Median duration of disease control was 5.8 months (95% CI 4.1-7.5 months). Median progression-free survival was 3.7 months (95% CI 2.2-5.2 months) and median overall survival was 10.0 months (95% CI 7.4-12.7 months). Grade 3-4 toxicities were rare (neutropenia 12%, anemia 11%, leucopenia 6%, thrombocytopenia 3% and diarrhea 3%). **Conclusions:** Combination chemotherapy with gemcitabine and S-1 was a convenient, well tolerated and efficacious for heavily pre-treated pts with mCRC. This regimen warrants further evaluation in pts with good PS but no further treatment options.

A French multifactorial prospective study of tumor protein and genetic markers in stage I-III colorectal cancer (CRC): Highlight on molecular characteristics related to mismatch repair (MMR) status.

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Background: There is still a need to identify prognostic markers in stage II CRC for setting up adjuvant treatment. The prognostic value of tumor genetic and protein markers was analyzed in CRC patients, as well as relationships between markers. Given the strong prognostic and predictive value of deficient MMR (dMMR), we examined whether dMMR tumors had a distinct protein profile as compared to proficient (pMMR) tumors. **Methods:** This prospective multicentric study involved 251 stage I-II-III CRC patients with complete surgical resection. Primary end-point was disease free survival (DFS, 60 events, median follow-up 88 months). Biomarkers analyzed on frozen primary tumors were: MMR status (bat 25, bat 26), mutations of KRAS (codons 12-13), BRAF (V600E), PIK3CA (exons 9 and 20), APC (exon 15) and P53 (exons 4-9), CIMP status, ploidy, S-phase fraction, LOH (8p, 17p, 18q), EGFR (ligand-binding assay), VEGFA expression (Elisa), thymidylate synthase (TS) enzyme activity and expression (RT-PCR), thymidine phosphorylase (TP) and dihydropyrimidine dehydrogenase (DPD) expressions (RT-PCR). **Results:** 30 stages I, 116 stages II and 105 stages III were included (FUFOL adjuvant treatment in 30 stages II and 61 stages III). 14% were dMMR. Multivariate Cox analyses showed that tumor staging was the only significant predictor of DFS. Log Rank analyses restricted to stage III showed tendencies for a shorter DFS in KRAS-mutated ($p=0.005$), BRAF wt ($p=0.009$) and pMMR tumors ($p=0.036$). dMMR tumors significantly expressed elevated TS (median 3.1 vs 1.4) and TP (median 5.8 vs 3.5) expression relative to pMMR ($p<0.001$) and tended to express higher DPD expression (median 14.9 vs 7.9, $p=0.027$) and EGFR content (median 69 vs 38, $p=0.037$) relative to pMMR. **Conclusions:** The present data, suggesting for the first time that both TS (5FU target) and DPD (FU catabolism enzyme) are overexpressed in dMMR tumors, bring strong arguments to explain the resistance of dMMR CRC tumors to FU-based therapy. The fact that dMMR tumors tend to express elevated EGFR levels and are prone to be KRAS wt suggests that anti-EGFR may be a relevant therapy in these patients. Clinical trial information: 1997.CHUNice-948.

Prognostic significance of tumor stromal and epithelial claudin 2 in metastatic colorectal cancer.

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Background: Tight junctions (TJ) are the most apical epithelial cell-cell adhesions. Claudin super-family trans-membrane proteins, including claudin 2 (cl2), are important components of TJs. Expression of cl2 has been reported to be elevated in colorectal cancer (CRC) and its up-regulation increases tumorigenicity of CRC cells in vitro. The aim of this study was to analyze the prognostic significance of cl2 in CRC. **Methods:** A tissue microarray (TMA) from the stage IV CRC patients of the phase III NORDIC-VII study was used. Cl2 IHC staining was evaluated in a semi-quantitative manner in cancer cells (cl2-C) and in the tumor stroma (cl2-S). Primary fibroblasts were established from human CRC tumor tissue and non-tumor colon tissue, and evaluated by immunoblotting. **Results:** Analyses of the TMA derived from the NORDIC-VII cohort revealed that cancer cell expression and tumor stroma expression of cl2 was associated with shorter OS in a Log-Rank test for trend (cl2-C, n=315, p=0.018; cl2-S, n=319, p=0.020). Expression of cl2-S, but not cl2-C was prognostic in multivariate analysis including WHO performance status, alkaline phosphatase level and BRAF mutation status (HR=1.30; 95% CI 1.08-1.56; p=0.006). When cl2-C and cl2-S expression was combined the prognostic significance was increased. The group with high cl2-C and high cl2-S (N=182), when compared with the rest of the cases (n=129), displayed a worse prognosis in terms of OS (19.1 mo vs 27.2 mo; p=0.003) in univariate analyses (HR=1.55, 95% CI 1.16-2.08, p=0.003) and in multivariate analyses (HR=1.52, 95% CI 1.13-2.05, p=0.006). Immunoblotting analysis of primary cultures of fibroblasts confirmed cl2 expression in fibroblasts from CRC tissue and from non-tumor tissue, with higher expression observed in the tumor fibroblasts. **Conclusions:** CRC display a previously un-reported stromal expression of cl2 of prognostic significance. High cl2-S is associated with worse prognosis in patients with metastatic CRC, in a manner independent of WHO status, alkaline phosphatase levels and BRAF status. Furthermore, high expression of cl2 in both cancer cells and the tumor stroma is also associated with poor prognosis.

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General Poster Session (Board #8H), Sun, 8:00 AM-11:45 AM

Aspirin use and survival outcomes in patients (pts) with PIK3CA mutant colorectal cancer (CRC).

Ben Tran, Robert N Jorissen, Jayesh Desai, Fiona Day, Lara Rachel Lipton, Hui-Li Wong, Jeanne Tie, Ian Faragher, Ian Jones, Oliver Sieber, Peter Gibbs; Royal Melbourne Hospital, Melbourne, Australia; Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia; The Royal Melbourne Hospital, Melbourne, Australia; The Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia; Western Hospital, Footscray, Australia; The Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia

Background: Aspirin has an established role in preventing CRC. Recent data suggests aspirin use may also benefit a subset of pts diagnosed with CRC. In one series, the authors identified PIK3CA mutations as a potential predictive biomarker for aspirin use, reporting that PIK3CA mutant CRC pts receiving aspirin had superior cancer specific survival (CSS) compared to those not receiving aspirin (HR 0.18, $p < 0.001$), whereas in pts with wildtype PIK3CA, aspirin had no survival impact. Our study aims to confirm the survival benefit associated with aspirin use in pts with PIK3CA mutant CRC. **Methods:** A cohort of CRC pts with PIK3CA mutations (Sanger sequencing) was identified. Prospectively collected clinicopathological, treatment and outcome data was available. Aspirin use was confirmed by chart review. CSS and overall survival (OS) analyses were conducted using Cox proportional hazards in univariate and multivariate settings. Recurrence free survival (RFS) analyses were limited to early stage CRC pts (Stage A-C). Statistical differences in 5-year CSS (5YS) rates were calculated using Fisher's exact test. **Results:** From a cohort of 1,019 CRC pts with known PIK3CA mutation status, 121 (12%) harbored PIK3CA mutations. Of these, 112 (92%) had aspirin usage data available: 27 (24%) pts used aspirin, 85 (76%) did not. In the aspirin group, there were 22 (81%) early stage and 5 (19%) metastatic CRC pts; in the no-aspirin group, there were 59 (69%) early stage and 26 (31%) metastatic CRC pts. In univariate analyses, aspirin use was not associated with superior CSS (HR 0.57, $p = 0.21$), OS (HR 0.83, $p = 0.57$), or RFS (HR 0.72, $p = 0.57$). In multivariate analyses, aspirin use was not associated with improved OS (HR 1.07, $p = 0.86$), CSS (HR 1.04, $p = 0.94$) or RFS (HR 0.54, $p = 0.34$). In 69 (62%) pts with mature follow-up, there was a trend towards superior 5YS for aspirin users (69% v 42%, $p = 0.09$), but this may reflect imbalances in stage at diagnosis. **Conclusions:** Our study was unable to confirm the recently reported survival benefit associated with aspirin use in pts with PIK3CA mutant CRC. Given the small numbers of pts, a modest survival benefit associated with aspirin use cannot be excluded. Analyses in an expanded cohort of early stage pts are underway.

Hepatic artery infusion (HAI) of irinotecan, 5-fluorouracil, and oxaliplatin plus intravenous cetuximab (Cet) (Optiliv) after failure on one versus two or three chemotherapy protocols in patients (pts) with unresectable liver metastases from wt KRAS colorectal cancer (LM-CRC) (European phase II clinical trial NCT00852228).

Michel Ducreux, Pasquale F. Innominato, Mohamed Hebbbar, Denis Michel Smith, Céline Lepère, C. N. J. Focan, Rosine Guimbaud, Carlos Carvalho, Salvatore Tumolo, Sameh Awad, Stephanie Truant, Denis Castaing, Abdoulaye Karaboué, Thierry De Baere, Francis Kunstlinger, Mohamed Bouchahda, Valerie Boige, Philippe Rougier, Rene Adam, Francis Levi, ARTBC International; Institut Gustave Roussy, Villejuif, France; INSERM U776, Paul Brousse Hospital, Villejuif, France; Medical Oncology Unit - Hôpital Huriez, Lille, France; Hopital Saint André, Bordeaux, France; Hôpital Européen Georges Pompidou, Paris, France; CHC Clinique Saint Joseph, Liège, Belgium; University Hospital of Purpan, Toulouse, France; Medical Oncology Unit, Hospital Fernando Fonesca, Amadora, Portugal; Medical Oncology Department, S. Maria degli Angeli Hospital, Pordenone, Italy; Radiology Department, Paul Brousse Hospital, Villejuif, France; Centre Hospitalier Universitaire Lille, Lille, France; Hepato-Biliary Centre, Hopital Paul Brousse, Villejuif, France; Centre Hépatobiliaire, Hôpital Paul Brousse, Villejuif, France; Medical Oncology Department, INSERM U776, Paul Brousse Hospital, Villejuif, France; Service d'Hépatogastro-Entérologie, Institut Gustave-Roussy, Villejuif, France; European Hospital George Pompidou, Paris, France; Hepatobiliary Center and INSERM U776, Paul Brousse Hospital, Villejuif, France

Background: Optiliv allowed complete macroscopic resection (R0-R1) of previously unresectable LM-CRC in 28% of the pts, despite failure of 1-3 prior chemotherapy protocols (Lévi et al. Proc ASCO GI 2013). **Purpose:** To assess tolerability and efficacy of Optiliv according to previous chemotherapy exposure. **Methods:** Pts received iv Cet (500 mg/m²) and chronomodulated or conventional HAI of Irinotecan (180 mg/m²), 5-Fluorouracil (2800 mg/m²), and Oxaliplatin (85 mg/m²) q2 wks. Liver surgery was performed according to q6wks multidisciplinary reviews. Pts were categorized according to Optiliv as 2nd (N=29 pts) vs 3rd-4th chemotherapy line (N=35 pts). **Results:** Pt characteristics were similar in both groups. Overall, there were 22F and 42 M, aged 33-76 years, with good PS (0/1/2: 40/22/2) and predominantly liver lesions. LM-CRC were bilateral in 51 pts (79.7%), with a median of 10 metastases (1-50), 6 segments involved (1-8), and largest diameter of 52 mm (15-172). 61 pts (2nd line, 27; 3rd-4th line, 34) received a median of 6 courses (1-15). Grade 3-4 toxicities per pt were similar in both groups except for abdominal pain (2nd line, 15% vs 3rd-4th line, 35%, p=0.07), diarrhea (7% vs 24%, p=0.09), thrombocytopenia and febrile neutropenia (0 vs 9%, p=0.25). Four CR were achieved in 2nd line (15%) vs none in 3rd-4th line. Respective objective response rates were 63% and 38% (p=0.05). R0-R1 resections were performed in 11/27 pts (41%) on 2nd line vs 6/34 pts (18%) on 3rd-4th line (p=0.06), resulting in respective median progression-free survival (PFS) of 14.2 months [7.8 - 20.7] vs 7.3 [5.5 - 9.1] (p=0.002). Median overall survival (OS) was not reached at 3 years in the pts on Optiliv as 2nd line vs 15.2 months in the more heavily pretreated pts (p<0.001). **Conclusions:** Intravenous Cet and triplet hepatic artery infusion resulted in the doubling of secondary surgical resection rate of LM-CRC, PFS and OS in 2nd line as compared to 3rd-4th line. Optiliv now deserves upfront testing. Clinical trial information: NCT00852228.

3600

General Poster Session (Board #9B), Sun, 8:00 AM-11:45 AM

A phase II, randomized, double blind comparison of calcium aluminosilicate clay (CASAD) versus placebo (dibasic calcium carbonate) for the prevention of diarrhea in patients (pts) with metastatic colorectal cancer (mCRC) treated with irinotecan (I).

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Background: CASAD is a naturally occurring calcium montmorillonite clay that serves as a cation exchange absorbent. One of the active metabolites of Irinotecan is SN-38, which is adsorbed by CASAD in vitro. The study hypothesis was that oral CASAD would reduce the rate of grade 3/4 diarrhea in mCRC patients treated with irinotecan. **Methods:** The study is a multicenter, prospective, randomized, double blinded placebo-controlled phase II trial. One hundred patients receiving I-based chemotherapy were randomized equally between CASAD (1000 mg po 4x daily) and placebo in order to have 75% power to detect a difference in the proportions of patients with grade 3/4 diarrhea within 6 weeks at a 1-sided 5% significance level. We also compared symptom burden using the MDASI questionnaire summed over the 13 symptom items for weeks 0, 3, 5, and 6. **Results:** Between 5/2009 and 5/2012, 100 patients were randomized in a 1:1 ratio between study arms. Median age 57 yrs, 54% male, 74% Non-Hispanic White, 93% performance status 0 or 1. Serious diarrhea was less frequent than expected based upon prior studies with Irinotecan. In evaluable patients, no significant difference in the rate of G3/4 diarrhea was seen (the primary endpoint): CASAD arm: 7/43 pts (16%), Placebo arm: 3/32 pts (9%), $p=0.70$. The rate of any diarrhea among all pts was also similar: CASAD arm 64% vs. Placebo arm 70%. The rate of study dropout was 14% in CASAD and 38% for placebo ($p=0.01$; 2-sided). No differences were found in symptom burden or individual symptom items or serious adverse events. **Conclusions:** Compared with placebo, CASAD use was safe but ineffective in preventing diarrhea in mCRC patients treated with irinotecan-containing chemotherapy regimens. There were no favorable or unfavorable signals in terms of the patient experience related to symptoms, but there were significantly more dropouts in the placebo arm. Future CASAD trials are focused on active treatment of diarrhea. Clinical trial information: NCT00748215.

Prevention of 5-FU-induced health-threatening toxicity by pretherapeutic DPD deficiency screening: Medical and economic assessment of a multiparametric approach.

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Background: While 5-FU is the foundation of many in GI oncology treatments, pts with DPD deficiency can experience early-onset severe (5%) even fatal (0.3%) toxicities. This study aimed to confirm the pharmaco-economic benefits of pre-therapeutic screening for DPD deficiency using a multiparametric approach in a multicenter prospective cohort study (NCT01547923). **Methods:** Two parallel cohorts of pts treated with 5-FU-based chemotherapy for colorectal carcinoma were compared: Group A: initial DPD deficiency screening; Group B: no evaluation. Enrollment was based on 5-FU administration guidelines of each institution. DPD deficiency screening combined genotyping and phenotyping (ODPM Tox) (1,2,3). The 2 groups were to be compared in terms of early 5-FU-induced toxicity grade, toxicity cost and DPD screening cost. The enrollment was to be immediately closed in the case of proven 5-FU-related toxic death. **Results:** 1,130 pts were included from 06/01/2008 to 07/31/2012. Group A: no severe toxicity despite 1 pt with complete deficiency (pt not treated with 5-FU), 20 pts with partial deficiency had safe PK-monitored 5-FU (ODPM Protocol) with only one hospitalization due to toxicity. Group B: One death due to complete DPD deficiency, confirmed retrospectively. Enrollment prematurely closed after experts' unanimous decision citing ethical concerns. 21 pts with partial DPD deficiency. 5 reported toxicity-related hospitalizations. Data treatment is ongoing. **Conclusions:** One complete deficiency occurred in both groups: Group A pt had safe treatment whereas Group B pt died due to 5-FU toxicity. Pre-therapeutic DPD deficiency screening using this multi-parametric approach should be performed before 5-FU-based treatment and PK-guided dose adaptation allows for safe treatment of even partially DPD deficient patients. Clinical trial information: NCT01547923.

	DPD screening	No. of patients	Partial deficiency	Complete deficiency	5-FU induced toxic death
Group A	Yes	720	20	1	0
Group B	No	410	21	1	1

Prospective analysis of the early modulation of plasma amphiregulin (AR) during treatment with cetuximab and irinotecan in irinotecan-refractory metastatic colorectal cancer (mCRC) patients (pts).

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Background: The potential role of AR tissue levels in the prediction of benefit from anti-EGFRs in mCRC 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. **Methods:** We designed a prospective confirmatory study in the same setting of mCRC pts. 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 $\alpha=0.05$ 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. Nevertheless, 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. Clinical trial information: 2008-003160-19.

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General Poster Session (Board #9E), Sun, 8:00 AM-11:45 AM

Circulating angiogenic factors as predictors of benefit from bevacizumab (bev) beyond progression in metastatic colorectal cancer (mCRC): Traslational analyses from the phase III BEBYP trial.

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Background: TML and BEBYP trials demonstrated that the strategy of prosecuting bev beyond progression is effective in mCRC. Previous analyses from phase II studies showed that a modulation of plasma angiogenic factors occurs during 1st-line treatment with chemotherapy (CT) + bev and a wide variability in soluble Vascular Endothelial Growth Factor Receptor-2 (sVEGFR-2) levels was observed at the time of progression. Moving from preliminary analyses in murine models we selected a pool of candidate ligands to be tested in the clinical setting. **Methods:** sVEGFR2, Placental Growth Factor (PlGF), Platelet-Derived Growth Factor-C, basic Fibroblast Growth Factor, Angiopoietin-2 and soluble Tie-2 were assessed by ELISA on plasma samples collected at baseline in a cohort of 59 patients enrolled in phase III BEBYP trial of 2nd-line CT ± bev beyond progression to a bev-containing first-line regimen. Plasma levels were defined high or low adopting the median values as cut-off. **Results:** A significant interaction between treatment arm and baseline sVEGFR-2 levels was observed ($p=0.036$). Among 30 patients with high sVEGFR-2 levels, the prosecution of bev was associated with a significant benefit in terms of PFS (median: 10.4 vs 3.4 months, HR 0.37 [95%CI 0.10-0.58], $p=0.0015$), that was not evident among 29 patients with low sVEGFR-2 levels (5.4 vs 5.0 months, HR 0.98 [95%CI 0.45-2.11], $p=0.956$). Despite a trend towards a greater benefit from bev among 30 patients with high PlGF levels (HR 0.45 [95%CI 0.13-0.86]), no interaction between treatment arm and baseline PlGF levels was observed ($p=0.210$). Combined analysis of sVEGFR-2 and PlGF showed that prosecuting bev provided a substantial benefit in PFS in the subgroup with high levels of both ligands (10.5 vs 2.3 months, HR 0.25 [95%CI 0.01-0.45], $p=0.043$). **Conclusions:** sVEGFR-2 levels at the time of first progression may predict benefit from prosecuting bev. Interesting results from simultaneous analysis of sVEGFR-2 and PlGF may be affected by a pronounced subgrouping and should be considered cautiously. Given their potential clinical value, these data need prospective confirmation. Clinical trial information: NCT00720512.

Bevacizumab plus chemotherapy continued beyond first disease progression in patients with metastatic colorectal cancer previously treated with bevacizumab-based therapy: Patterns of disease progression and outcomes based on extent of disease in the ML18147 study.

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Background: ML18147 demonstrated that bevacizumab (BEV) + chemotherapy (CT) continued beyond first disease progression (PD) significantly prolongs overall survival (OS) and progression-free survival (PFS) as second-line treatment for metastatic colorectal cancer (mCRC) [Bennouna et al. Lancet Oncol 2012]. Here we report exploratory analyses of patterns of PD and outcomes based on extent of disease. **Methods:** In ML18147, patients (pts) with unresectable, histologically confirmed mCRC who progressed ≤ 3 months after discontinuation of first-line BEV were randomised to second-line CT \pm BEV. This exploratory analysis evaluated PD patterns, time from discontinuation of study medications to PD, and survival outcome (OS, PFS) based on liver-limited vs extensive disease. **Results:** Details on patterns of PD and outcome by extent of disease are shown in the table. **Conclusions:** These exploratory analyses suggest that pts with liver-limited or extensive disease seem to benefit equally from BEV+CT continued beyond PD. Our findings indicate that the pattern of PD does not appear to differ between the two treatment arms following cessation of BEV treatment in this setting. Clinical trial information: NCT00700102.

Patterns of PD, n (%)	CT alone (n=410)	BEV+CT (n=409)
No. of pts with PD	321 (78.3%)	302 (73.8%)
No. of pts with PD due to new lesion	163 (50.8%)	132 (43.7%)
Site of baseline lesion (in pts with PD due to new lesion)		
Lung Liver	87 (53.4%) 132 (81.0%)	59 (44.7%) 118 (89.4%)
Site of new lesion		
Lung Liver Peritoneum Local lymph nodes Other	74 (45.4%) 53 (32.5%) 10 (6.1%) 7 (4.3%) 48 (29.4%)	51 (38.6%) 55 (41.7%) 13 (9.8%) 8 (6.1%) 26 (19.7%)
	n=345 (84.1%)	n=329 (80.4%)
Time from discontinuation of study medication to PD		
Median	0.4 months	0.5 months
Liver-limited disease		
OS	n=117 (28.5%)	n=109 (26.7%)
Median	9.3 months	11.6 months
PFS		
Median	4.1 months	5.7 months
Extensive disease		
OS	n=292 (71.2%)	n=300 (73.3%)
Median	10.0 months	11.0 months
PFS		
Median	4.1 months	5.6 months

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General Poster Session (Board #9G), Sun, 8:00 AM-11:45 AM

Chemotherapy first, followed by chemoradiation (CRT) and then surgery, in the management of locally advanced rectal cancer (LARC).

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Background: Standard pre-op CRT and post-op chemo for LARC delays the start of optimal systemic therapy by 18-22 weeks. To more promptly address micrometastases that could lead to distant failure, and supported by evidence of excellent primary tumor response to FOLFOX, we began offering FOLFOX as initial treatment for patients (pts) with high-risk LARC. More recently, we have begun offering all planned FOLFOX prior to CRT and surgery. **Methods:** We obtained an IRB waiver to review records of all clinical stage II/III RC pts treated with initial FOLFOX followed by CRT and total mesorectal excision (TME) at our institution between 2007 and 2012. Of approximately 300 rectal pts treated with CMT, 61 received some or all of their planned FOLFOX as initial therapy. **Results:** The median age of these 61 pts was 52 years, 54% male. At diagnosis, 84% had T3N1-2 or T4N0-1 tumors and 16% had T3N0 tumors. Of these, 57 received induction FOLFOX (median 7 cycles) then received pre-op CRT, while 4 pts achieved an excellent response to chemotherapy alone, declined CRT, and went directly to TME. Twelve pts did not undergo surgery; 9 had a complete clinical response and elected to be managed non-operatively; 1 refused recommended surgery despite incomplete tumor regression, 1 had surgery deferred due to comorbidities, and 1 developed distant metastatic disease prior to planned surgery. Of the 61 patients, 19 (31%) had either a pathCR (14) or a complete clinical response (5) leading to non-operative management. Of the 49 pts who underwent TME, all had R0 resections and 23 (47%) had tumor response >90%, including 13 (27%) with pathCR. Of the 28 patients who received all 8 cycles of initial FOLFOX, 8 achieved a pathCR (29%) and 3 achieved a complete clinical responses (11%), managed non-operatively. All patients completed therapy as planned. There were no SAEs requiring delay in treatment during either FOLFOX or CMT. **Conclusions:** FOLFOX before CRT results in substantial tumor regression, a high rate of delivery of all planned therapy, and a substantial rate of pathCRs. Chemo and CMT before planned TME provides a favorable opportunity for consideration of non-operative management.

Chronomodulated hepatic artery infusion (HAI) of irinotecan, 5-fluorouracil (5-FU), and oxaliplatin (I-OHP) plus intravenous (iv) cetuximab (Cet) (Chrono-Optiliv) in patients with unresectable liver metastases from wt KRAS colorectal cancer (LM-CRC) after treatment failure (European Phase II trial NCT 00852228).

Mohamed Bouchahda, Abdoulaye Karaboué, Marie-Christine Etienne-Grimaldi, Etienne Chatelut, Pasquale F. Innominato, Gilles Paintaud, Luana Ricca, Eric Vibert, Yves Ajavon, Sameh Awad, Denis Castaing, C. N. J. Focan, Gerard Milano, Jean Francois Morere, Rene Adam, Francis Levi, ARTBC International; Medical Oncology Department, INSERM U776, Paul Brousse Hospital, Villejuif, France; INSERM U776, Paul Brousse Hospital, Villejuif, France; Laboratoire d'Oncopharmacologie, Centre Antoine Lacassagne, Nice, France; Institut Claudius Regaud, Toulouse, France; Inserm U776, Service de Chronothérapie, Département de Cancérologie, Hôpital Paul Brousse, Villejuif, France; Centre Hospitalier Régional Universitaire de Tours, Tours, France; Centre Hépatobiliaire, Hôpital Paul Brousse, Villejuif, France; Service de Radiologie, Hopital Paul Brousse, Villejuif, France; Radiology Department, Paul Brousse Hospital, Villejuif, France; Hepato-Biliary Centre, Hopital Paul Brousse, Villejuif, France; CHC Clinique Saint Joseph, Liège, Belgium; Centre Antoine Lacassagne, Nice, France; Medical Oncology Unit, Paul Brousse Hospital, Villejuif, Finland; Hepatobiliary Center and INSERM U776, Paul Brousse Hospital, Villejuif, France

Background: Hepatic artery triplet chronotherapy is an effective salvage therapy for pretreated LM-CRC (Bouchahda et al. Cancer 2009). The combination of iv Cet with chrono or conventional triplet HAI allowed complete macroscopic resection (R0-R1) of previously unresectable LM-CRC in 28% of the pts, and median progression-free (PFS) and overall survival (OS) of 8.7 and 25.7 months respectively, despite prior chemotherapy (Lévi et al. ASCO-GI 2013). **Purpose:** To relate tolerability and efficacy of Chrono-Optiliv to pharmacokinetics (PK). **Methods:** 18/64 registered patients received iv Cet (500 mg/m²) and chrono HAI of Irinotecan (180 mg/m²), 5-FU (2800 mg/m²), and I-OHP (85 mg/m²) q2 weeks. Liver surgery was performed according to q6wks reviews. The systemic exposure to the 4 drugs was determined on 1st course in 11 pts, through 16 samples over 56h. **Results:** 8F, 10M, aged 33-72 years had good PS (0/1: 83%/17%), a median of 7 LM-CRC (2-50) in 6 segments (1-8) with median largest diameter of 47 mm (15-130). LM-CRC were bilateral in 13 pts (72%); 10 pts (56%) got Chrono-Optiliv as 3rd-4th line. Main grade 3-4 toxicities were neutropenia (56%), abdominal pain (44%), diarrhea and fatigue (22%). The rate of objective responses was 50% [26.9-73.1], and that of R0-R1 33.3% [11.5 -55.1], resulting in median PFS and OS (months) of 12.6 [8.8 -16.1] and 21.9 [7.4-36.4] respectively. Plasma PK revealed the expected Cet levels and a relevant systemic exposure to the HAI drugs, with median trapezoidal AUC's of 12.4 µg*mn/mL (2.6-38.5) for SN-38, 142 µg*mn/mL (96- 434) for 5-FU and 100 µg*mn/mL (37-189) for free I-OHP. A significant correlation was found between free I-OHP AUC and abdominal pain (p=0.016) and between SN38 AUC and both neutropenia (p=0.018) and response (p=0.028). **Conclusions:** The significant systemic exposure to the HAI drugs together with iv Cet could explain efficacy and lack of early progression on Chrono-Optiliv. The results call for upfront testing of optimized Chrono-Optiliv. Clinical trial information: NCT 00852228.

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General Poster Session (Board #10A), Sun, 8:00 AM-11:45 AM

The distribution of chromosomal and microsatellite instability in colorectal cancers related to inflammatory bowel disease.

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Background: Surveillance for colorectal cancer (CRC) in inflammatory bowel disease (IBD) has so far not been effective. Mucosal or fecal biomarkers may be useful in the selection of high risk patients. The yield may depend on the underlying carcinogenic pathway. In IBD associated CRC (IBD-CRC) the distribution of chromosomal instability (CIN) and microsatellite instability (MSI) is not well documented. Our objective was to determine the distribution of CIN and MSI and the association to clinico-histological factors in a cohort of patients with IBD-CRC. **Methods:** Ploidy was measured by high-resolution image cytometry and MSI by using two markers (BAT 25 and BAT26) in 62 patients with 72 CRC-IBD selected by matching the Norwegian Cancer Registry with IBD cohorts of three university hospitals in Oslo. The association between ploidy/MSI status and clinicohistological factors were analyzed by non-parametric tests. **Results:** Ploidy status was analyzed in 67 (93%), microsatellite stability in 68 (94%) tumors. Forty-nine (73.1%) were non-diploid (43 aneuploid, 1 polyploid, 5 tetraploid), 13 (19.4 %) diploid, five (7.5%) indeterminate. Forty-three (63.2%) were microsatellite stable (MSS), four (5.8%) microsatellite instable (MSI). One tumor was MSI in BAT25 but MSS in BAT26. Twenty (29.5%) tumors showed no PCR-product in at least one of the markers. In 46 tumors, both ploidy and MSI status were available. All non-diploid tumours (36, 78.3%) were MSS and all MSI tumors (4, 8.7%) were diploid. Six (13%) tumors were diploid and MSS. Four patients were treated with 5-ASA prior to diagnosis of CRC. Three developed diploid, one aneuploid cancers. Of the untreated patients, 31 developed aneuploid, 7 diploid cancers ($p=0.036$). We did not find an association between age, gender, type of IBD, duration of IBD, localisation of CRC, TNM-stage and CIN or MSI. **Conclusions:** The majority of CRC-IBD in our cohort seem to present CIN and only a minority MSI. Some CRC-IBD patients present neither CIN nor MSI. Future studies should determine whether these display the CpG island methylator phenotype. Biomarkers for CRC-IBD should be derived from all three pathways.

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General Poster Session (Board #10B), Sun, 8:00 AM-11:45 AM

Phase Ib dose-escalation study of Pexa-Vec (pexastimogene devacirepvec; JX-594), an oncolytic and immunotherapeutic vaccinia virus, administered by intravenous (IV) infusions in patients with metastatic colorectal carcinoma (mCRC).

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Background: Pexa-Vec is an EGFR-targeted vaccinia virus engineered to express granulocyte-macrophage colony stimulating factor (GM-CSF), thereby stimulating direct oncolysis, tumor vascular disruption and anti-tumor immunity (*Nat Rev Cancer* 2009). Dose-dependent IV Pexa-Vec delivery was defined previously (*Nature* 2011). This study was designed to assess the safety, maximal tolerated dose and anti-tumor activity of Pexa-Vec administered IV in patients with mCRC after failure of standard therapies. **Methods:** Nine patients were treated at 1 of 3 dose levels (10^6 , 10^7 or 3×10^7 pfu/kg IV every 2 weeks x 4) in a standard 3+3 dose-escalation design; 6 additional patients were enrolled at the MFD. Anti-tumor activity according to RECIST was determined using serial CT scans. Pharmacokinetic studies were also performed. Data summarized prior to database lock. **Results:** 15 patients with mCRC refractory to irinotecan, oxaliplatin, and 5-FU were treated (median lines of therapy 5; range 2-7); 13 of 15 received prior anti-angiogenic agents, and 11 of 12 KRAS WT tumors failed cetuximab. Adverse events were generally grade 1/2 and included: fever (93%), chills (93%), headache (60%), nausea (60%), and hypotension (40%). No dose-limiting toxicities or grade 3/4 events were reported. Only patients treated at high-dose (Cohort 3 & Expansion) exhibited a pustular rash (n=9; 78%). Pexa-Vec genomes detected in blood acutely were above the dose threshold for systemic delivery. Notably, clearance was not more rapid with repeated IV treatments despite the induction of humoral immunity. Furthermore, patients at the top dose level exhibited increased disease stabilization at Week 4 (89% high-dose (n= 9) versus 33% low-dose (n=6)). A trend (p=0.16) towards increased overall survival at high vs low-dose Pexa-Vec was observed with 78% high-dose patients still alive between 5 and 13 mos. **Conclusions:** Repeat IV Pexa-Vec was well-tolerated with transient flu-like symptoms. Dose-dependent safety, pharmacokinetics and anti-tumor activity were described in treatment-refractory mCRC patients. Clinical trial information: NCT01380600.

Association of KRAS mutation with worse recurrence-free survival and site of metastatic progression after resection of hepatic colorectal metastases.

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Background: There are conflicting results regarding the influence of KRAS mutation status and outcome in patients (pts) with colorectal cancer. A recent report suggested worse outcome in KRAS mutated (MUT) pts who underwent resection of hepatic metastases (Karagkounis et al, ASCO 2012). **Methods:** Recurrence patterns and survival were evaluated in 169 patients who had undergone resection of liver metastases, then received adjuvant hepatic arterial infusion and systemic chemotherapy, and for whom KRAS data were available. Kaplan-Meier methods were used to estimate recurrence free survival (RFS) and overall survival (OS). Log-rank test was used to determine whether survival functions differed by KRAS mutation status. Cumulative incidence function was used to estimate the probability of time from adjuvant therapy to bone, brain, lung and liver metastases separately. Mutations in KRAS (codons 12, 13) were detected using the iPLEX assay (Sequenom, Inc). **Results:** Median follow-up for the entire cohort was 38.8 months. 118 were KRAS wildtype (WT), and 51 were KRAS MUT (45 G12, 5 G13, 1 K117N). The 3 year RFS was 48% [95%CI: 37-58%] for KRAS WT pts and 30% [15-44%] for MUT pts ($p<0.01$). OS at 3 years was 96% [88-98%] for KRAS WT and 80% [61-90%] for MUT pts ($p=0.08$). Cumulative incidence of developing bone, brain, lung, and liver metastases by 2 years is presented in Table 1. The cumulative incidence of metastases to bone at 2 years was 0% and 13.7% in KRAS WT versus MUT pts ($p<0.01$), to brain 0% versus 4.6% for KRAS WT versus MUT ($p=0.05$), and to lung 27% versus 47.5% in KRAS WT versus MUT pts ($p<0.01$). **Conclusions:** In pts who have had liver resection followed by adjuvant therapy, those with KRAS MUT have a worse RFS and seemingly worse OS than those who are KRAS WT. Also, patients with KRAS MUT appear more likely to develop bone, brain, and lung metastases. Further investigation of a larger number of patients is warranted.

Cumulative incidence of development of metastases at 2 years.

Site	N=118 KRAS WT [95%CI]	N=51 KRAS MUT [95%CI]	P value
Bone	0	13.7% [0.3-27.2%]	<0.01
Brain	0	4.6% [0-13.5%]	0.05
Lung	27% [17.5-36.5%]	47.5% [32.4-68.4%]	<0.01
Liver	18% [8-25.8%]	37% [19.3-54.6%]	0.08

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General Poster Session (Board #10D), Sun, 8:00 AM-11:45 AM

Impact of early tumor shrinkage on clinical outcome in KRAS wild-type colorectal liver-limited metastases treated with cetuximab plus chemotherapy: Lessons from a randomized controlled trial.

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Background: Recently, early tumor shrinkage (ETS) was reported to predict outcome in metastatic colorectal cancer treated with cetuximab (cet). This study was to evaluate the impact of ETS on long-term outcome in patients (pts) with wild-type-KRAS unresectable CLLM receiving cet plus chemotherapy (CT, FOLFIRI or mFOLFOX6). **Methods:** 138 pts treated in a randomized controlled trial (70 in armA received CT plus cet and 68 in armB received CT alone) previously reported (Jianmin et al, ESMO 2012, abstract-557, ClinicalTrials.gov, number NCT01564810) were included into this analysis. ETS was defined as a reduction of $\geq 20\%$ in the sum of the longest diameters of target lesions compared to baseline at the first evaluation (8 weeks). Outcome measures were progression-free survival (PFS) and overall survival (OS). **Results:** 132 pts were available for evaluation, and ETS occurred more frequently in armA than that in armB (45/68 vs. 26/64, $p = .003$). Irrespective of treatment arm, pts achieved ETS were associated with longer OS (armA: 38.0 vs. 18.7months, $p < .001$; armB 30.6 vs. 17.7months, $p = .003$) and PFS (armA: 11.8 vs. 4.8months, $p < .001$; armB 8.0 vs. 4.6months, $p = .001$) when compared to pts with no-ETS. Among pts with ETS, there were statistic difference between armA and armB in terms of PFS (11.8 vs. 8.0months, $p = .041$) but not of OS (38.0 vs. 30.6months, $p = .30$); the converted resection rates for liver metastases were 40.0% (18/45) in armA and 19.2% (5/26) in armB, which were no significantly different ($p = .072$). For pts without liver surgery, pts observed ETS also gained an increased survival benefit over those no-ETS in armA with regards to OS ($p = .01$) and PFS ($p < .001$) though it was not full certified in armB (OS: $p = .054$; PFS: $p = .041$). For pts in armA, cet-induced skin toxicity correlated with the occurrence of ETS ($p = .048$). In addition, cox regression for OS using indicated a hazard ratio of 0.39 (95%CI 0.21–0.72, $p = .003$). **Conclusions:** ETS $\geq 20\%$ at 8 weeks may serve as a predictor of favorable outcome in pts with wild-type-KRAS CLLM receiving cet plus CT.

Quality of life (QOL) and toxicity among patients in CALGB 80405.

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Background: CALGB 80405, a phase III trial, was originally designed to compare toxicity and overall survival of metastatic colorectal patients treated with standard chemotherapy (choice of FOLFOX or FOLFIRI) and either: 1) Bevacizumab; 2) Cetuximab; or 3) both Bevacizumab and Cetuximab. Because Cetuximab causes a prominent acneiform skin rash, adverse effects on QOL were anticipated and assessed in a QOL companion. **Methods:** The QOL companion enrolled the first 518 consenting patients randomized to CALGB 80405 between 10/2005-9/2007, the majority prior to amendments that eliminated the dual biologic arm and restricted participation to patients with KRAS *w/tumors*. QOL was assessed at baseline, 6 weeks, and 3, 6 and 9 months post-randomization, using the EORTC QLQ-30 and the Dermatology-Specific Quality of Life (DSQL) Scale. We hypothesized that patients receiving Cetuximab would have lower satisfaction with appearance, reduced social functioning and lower overall QOL at 3 months, (a primary assessment point). **Results:** Patients had a mean age of 59, were predominantly male (58%), performance status 0 (62%), and non-Hispanic White (85%). 83% completed a 3 month assessment. There were no differences in global health functioning ($p=0.164$) or other items/subscales of the EORTC at 3 months by treatment arm. However, significant differences were found across arms in skin symptoms ($p<.0001$), limitations in social activities due to skin condition ($p=0.008$), and concerns about appearance ($p<.0001$), as measured by the DSQL. Patients randomized to Bevacizumab reported fewer skin symptoms, fewer social limitations and appearance concerns than patients receiving Cetuximab alone or Cetuximab + Bevacizumab. The choice of chemotherapy (FOLFOX or FOLFIRI) had no bearing on these results. **Conclusions:** Global QOL, as well as physical, role, social and emotional functioning, were not significantly different across treatment arms. However, Cetuximab recipients reported greater symptoms and QOL concerns relating to their skin than those receiving Bevacizumab alone. Interventions to more adequately address skin problems from Cetuximab treatment are warranted. Participants are still being followed to determine survival differences between the biologics. Clinical trial information: NCT00265850.

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General Poster Session (Board #10F), Sun, 8:00 AM-11:45 AM

Genomic classifier (ColoPrint) to predict outcome and chemotherapy benefit in stage II and III colon cancer patients.

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Background: Although benefit of chemotherapy in stage II and III colorectal cancer patients is significant, many patients might not need adjuvant chemotherapy because they have a good prognosis even without additional treatment. ColoPrint is a gene expression classifier that distinguish patients with low or high risk of disease relapse. It was developed using whole genome expression data and validated in independent validation studies (JCO 2011, Ann Surg 2013). **Methods:** In this study, ColoPrint was validated in stage II (n=96) and III patients (n=95) treated at the MD Anderson Cancer Center. Frozen tissue specimen, clinical parameters and follow-up data (median follow-up 64 months) were available. Stage II patients from this study were pooled with patients from previous studies (n=416) and ColoPrint performance was compared to clinical risk factors described in the NCCN Guidelines 2013. **Results:** In the MDACC patient cohort, ColoPrint classified 56% of stage II and III patients as being at Low Risk. The 3-year Relapse-Free-Survival (RFS) was 90.5% for Low Risk and 78.1% for High Risk patients with a HR of 2.42 (p=0.025). In uni- and multivariate analysis, ColoPrint and stage were the only significant factors to predict outcome. Low Risk ColoPrint patients had a good outcome independent of stage or chemotherapy treatment (91% 3-year RFS for treated patients, 90% for untreated patients) while ColoPrint High Risk patients treated with adjuvant chemotherapy had 3-year RFS of 84%, compared to 70% 3-year RFS in untreated patients (p=0.037). In the pooled stage II dataset, ColoPrint identified 63% of patients as Low Risk with a 3-year RFS of 93% while High Risk patients had a 3-year RFS of 82.3% with a HR of 2.7 (p=0.001). In the univariate analysis, no clinical factor reached statistical significance. Using clinical high risk factors as described in the NCCN guidelines as classification, 56% of patients were classified as low risk with a 3-year RFS of 90.3% while high risk patients had a 3-year RFS of 87.7% with a HR of 0.6 (p=0.63). **Conclusions:** ColoPrint significantly improves prognostic accuracy, thereby facilitating the identification of patients at higher risk who might be considered for additional treatment.

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 (pts).

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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 pts. The aim of the present study was to confirm such preliminary findings in a large cohort of mCRC pts. **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 pts. OS was calculated from date of diagnosis of metastatic disease. Data on response and PFS according to RECIST were collected for *NRAS*mut 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 pts. *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). 18 pts out of 47 *NRAS* mut pts received anti-EGFRs in advanced lines. 8 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 *NRAS*mut pts in advanced lines of treatment (De Roock, 2010; Peeters, 2013; André, 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 pts. 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.

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General Poster Session (Board #10H), Sun, 8:00 AM-11:45 AM

Primary prophylactic granulocyte colony-stimulating factor (GCSF) in Gilbert's disease patients treated with FOLFIRI first line for metastatic colorectal cancer (mCRC): Final results of the FFCD 0604 study.

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Background: Gilbert's disease patients (pts) (homozygous for the UGT1A1*28 allele) have a major risk (>30%) of severe, life-threatening, neutropenia when treated with Irinotecan (IRI). The aim of this study was to demonstrate that, in these pts, treated with IRI 1st line for mCRC, primary prevention with GCSF (lenograstim) reduces under 10% the risk of grade 4 or febrile neutropenia. **Methods:** This is a prospective, multicenter, phase II study of FOLFIRI + bevacizumab 1st line (IRI 180 mg/m² every 2 weeks) and primary prophylactic GCSF (D5 to D11 each course) in mCRC pts with Gilbert's disease. Pre-chemotherapy UGT1A1 genotyping was centralized and standardized using a biological molecular technique applied on DNA blood-extracted lymphocytes. Using a 2-step Fleming design, ($\alpha=5\%$ and $\beta=90\%$), 30 pts had to be included with an interim analysis (IA) planned after 20 pts and 4 months of follow-up. **Results:** Twenty pts from 7 centers were included between 10/2007 and 02/2012 and 19 analysed for the IA. Median pts age was 63 years (range: 45-73), 60% were females, 90% were PS 0 or 1, 80% had a colic primary site and 73% hepatic metastases. The primary site was non-resected in 1/3 of pts. The total number of administered courses of chemotherapy was 229 with a median of 12 per pt (range: 1-40). Among all these courses, 213 were administered with GCSF. IRI was administered as defined by the protocol with a nearly 100% rate of received/theoretical dose. Grade 3 neutropenia rate was 10.5%. No grade 3-4 diarrhea, no grade 4 or febrile neutropenia and no toxic death were observed. No declared SAEs were related to GCSF. In term of best response at 6 months, 7 pts were in complete or partial response and 9 had stable disease. Median progression free survival and overall survival were respectively 8.7 months (4.9; 13.4) and 24.4 months (12.6; ND). **Conclusions:** This study is the first to demonstrate that a pharmacogenetic approach based on a simple genetic test easy to perform can achieve a high rate of safe and performant administration of IRI in high risk mCRC pts. Clinical trial information: NCT00541125.

Second-line chemotherapy (CT) with or without bevacizumab (BV) in metastatic colorectal cancer (mCRC) patients (pts) who progressed to a first-line treatment containing BV: Updated results of the phase III “BEBYP” trial by the Gruppo Oncologico Nord Ovest (GONO).

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Background: Retrospective data suggested that the continuation of BV with second-line CT beyond progression (PD) in pts who received BV in first-line can improve the outcome. Recently, results of the AIO/AMG ML18147 study demonstrated an improved overall survival (OS) by continuing BV beyond PD. **Methods:** This phase III study randomized pts with measurable mCRC treated in first-line with BV plus fluoropyrimidine, FOLFIRI, FOLFOX or FOLFOXIRI, to receive in second-line mFOLFOX6 or FOLFIRI (depending on first-line CT) with or without BV. The primary end-point was progression free survival (PFS). To detect a HR for PFS of 0.70 with an α and β error of 0.05 and 0.20 respectively, the study required 249 events. Assuming an accrual time of 24 months (mos) and a follow up of 12 mos we planned to randomize 262 pts. **Results:** Considering the results of the AIO/AMG ML18147 trial, 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). Pts characteristics were (arm A/arm B): 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%. At a median follow up of 18 mos the study met its primary endpoint by improving PFS in the BV arm. We updated results and at a median follow up of 22 mos the improvement in PFS for the experimental arm was confirmed with a median PFS of 5.2 mos for arm A and 6.7 mos for arm B (HR=0.66; 95% CI 0.49–0.90; unstratified p=0.0072). Subgroup analyses showed a consistent benefit in all subgroups including gender (F: HR=0.63; M: HR=0.72) and first-line PFS (≤ 10 mos: HR=0.57; > 10 mos: HR=0.71). Response rates (RECIST) were 18% and 21% (p=0.71). Toxicity profile was consistent with previously reported data. The OS data are still immature, with 56 events in arm A and 54 in arm B and the median OS is 16.0 mos and 16.5 mos respectively (HR=0.83; 95% CI 0.57-1.22; unstratified p=0.34). **Conclusions:** This study demonstrates an improvement in PFS by continuing BV in second-line in pts who had received CT+BV in first-line. Clinical trial information: NCT00720512.

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General Poster Session (Board #11B), Sun, 8:00 AM-11:45 AM

SPIRITT (study 20060141): A randomized phase II study of FOLFIRI with either panitumumab (pmab) or bevacizumab (bev) as second-line treatment (tx) in patients (pts) with wild-type (WT) *KRAS* metastatic colorectal cancer (mCRC).

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Background: Pmab has demonstrated significant improvement in progression-free survival (PFS) in pts with WT *KRAS* mCRC as 2nd-line tx in a phase III trial comparing pmab + FOLFIRI vs FOLFIRI alone. Here, we describe the results of SPIRITT, a multicenter, randomized phase II study evaluating pmab + FOLFIRI and bev + FOLFIRI in pts with WT *KRAS* mCRC previously treated with a 1st-line bev + oxaliplatin (Ox)-based chemotherapy regimen. **Methods:** Pts were randomized 1:1 to pmab 6.0 mg/kg + FOLFIRI Q2W or to bev 5.0 or 10.0 mg/kg + FOLFIRI Q2W. Eligibility criteria included: WT *KRAS* mCRC, ECOG \leq 1, no prior irinotecan or anti-EGFR tx, and tx failure of prior 1st-line bev + Ox-based therapy (\geq 4 cycles). The primary endpoint was PFS; secondary endpoints included overall survival (OS), objective response rate (ORR), and safety. No formal hypothesis was tested. **Results:** 182 pts with WT *KRAS* mCRC were randomized. All pts received tx. Efficacy results are shown (Table). Worst grade of 3/4 adverse events (AE) occurred in 78% of pts in the pmab + FOLFIRI arm and 65% in the bev + FOLFIRI arm. Grade 5 AEs occurred in 7% of pts in the pmab + FOLFIRI arm and 7% in the bev + FOLFIRI arm. Tx discontinuation due to any AE was 29% in the pmab + FOLFIRI arm and 25% in the bev + FOLFIRI arm. **Conclusions:** In this estimation study of pts with WT *KRAS* mCRC that previously received bev + Ox-based tx, the PFS hazard ratio (HR) was 1.01 (95% CI: 0.68 - 1.50). The OS HR was 1.06 (95% CI: 0.75 - 1.49). The observed ORR was higher in the pmab + FOLFIRI arm. 54% of bev + FOLFIRI pts received subsequent anti-EGFR tx. The safety profile for both arms was similar to previously reported studies. Tx discontinuation rates due to AEs were similar between the arms. Clinical trial information: NCT00418938.

	Pmab + FOLFIRI	Bev + FOLFIRI	HR (95% CI)
N	91	91	
Median PFS,* mos (95% CI)	7.7 (5.7 - 11.8)	9.2 (7.8 - 10.6)	1.01 (0.68 - 1.50)
Median OS, mos (95% CI)	18.0 (13.5 - 21.7)	21.4 (16.5 - 24.6)	1.06 (0.75 - 1.49)
N	87	83	
ORR,* n (%) [95% CI]	28 (32 [23 - 43])	16 (19 [11 - 29])	
Pts receiving therapy after tx phase, n (%)			
Anti-EGFR	24 (26)	49 (54)	
Anti-VEGF	18 (20)	22 (24)	

*Assessments based on blinded central radiology review per modified RECIST 1.0.

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General Poster Session (Board #11C), Sun, 8:00 AM-11:45 AM

Comprehensive analysis of *KRAS* and *NRAS* mutations as predictive biomarkers for single agent panitumumab (pmab) response in a randomized, phase III metastatic colorectal cancer (mCRC) study (20020408).

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Background: An exploratory biomarker analysis of the randomized, phase 3 monotherapy 20020408 study of pmab vs best supportive care (BSC) demonstrated that mutations in *KRAS* exon 3 and *NRAS* exons 2 and 3 appeared to be predictive of pmab response (Peeters et al, 2013). We expanded these results to determine whether mutations in exon 4 of the *KRAS* and *NRAS* genes are predictive for pmab treatment and to determine the treatment effect in the overall wild-type (WT) *KRAS* and *NRAS* population. **Methods:** Using a combination of Next Generation Sequencing, Sanger Sequencing, and WAVE-based SURVEYOR Scan Kits from Transgenomic, archival patient tumors were examined for mutations in *KRAS* and *NRAS* exon 4. These data were combined with previously presented data from *KRAS* and *NRAS* exon 2 and 3 analyses for evaluation of the comprehensive WT *KRAS* and *NRAS* subgroup. **Results:** 9/243 (3.7%) and 2/243 (0.8%) patient tumors with WT *KRAS* exon 2 status harbored a mutation in *KRAS* or *NRAS* exon 4, respectively. One tumor had mutations in both *KRAS* and *NRAS* exon 4. In the pmab arm, patients with WT *KRAS* and WT *NRAS* tumor status had an objective response rate (ORR) of 15% (11/72) whereas patients with mutant (MT) *KRAS* or MT *NRAS* tumor status had an ORR of 1% (1/95; 1 patient with MT *KRAS* exon 4 had a partial response). There were no responses in the BSC arm regardless of the tumor status. In this analysis set, the treatment hazard ratio (HR; pmab:BSC) for progression-free survival (PFS) in the WT *KRAS* and WT *NRAS* subgroup was 0.38 (95% CI: 0.27 - 0.56), and in the MT *KRAS* or MT *NRAS* subgroup was 0.98 (95% CI: 0.73 - 1.31). The original WT *KRAS* exon 2 subgroup PFS HR was 0.45 (95% CI: 0.34 - 0.59) (Amado et al, 2007). **Conclusions:** This exploratory analysis suggests that mutations in *KRAS* and *NRAS* exon 4 occur in a small, but meaningful percentage of patients with mCRC. Extending previous findings from this study in patients with MT *KRAS* and/or MT *NRAS* exon 2 and/or 3 tumors, patients with MT *KRAS* and/or MT *NRAS* exon 4 tumors do not appear to benefit from pmab therapy. Clinical trial information: NCT00113763.

Accent-based nomograms (NGs) to predict time to recurrence (TTR) and overall survival (OS) in stage III colon cancer (CC).

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Background: Current prognostic tools and staging systems in CC use relatively few patient (pt) characteristics; including additional covariates may improve prediction. Using the large ACCENT database, we constructed clinically based NGs for OS and TTR in stage III CC that better separate pts into risk groups compared to AJCC v7 staging. **Methods:** 15,936 stage III pts accrued to phase III clinical trials since 1989 were used to construct Cox models for TTR and OS. Variables included age, sex, race, BMI, performance status, tumor grade, tumor stage, ratio of positive lymph nodes to nodes examined, number/location of primary tumors (any multiple versus single left, right, or transverse), and treatment (5FU variations vs. 5FU with oxaliplatin or irinotecan). Missing data (<18%) were imputed, continuous variables modeled with splines, and clinically relevant pairwise interactions included if $p < 0.001$. Final models were internally validated via bootstrapping for corrected calibration and C-indices for survival data. NG-defined risk tertiles were compared to AJCC v7 stage III for observed 3-year (yr) TTR and 5-yr OS for a subset of 7400 pts with complete data. **Results:** All variables were statistically and clinically significant for OS; age and race did not predict TTR. No meaningful interactions existed. NGs for OS and TTR were well calibrated and associated with C-indices of 0.66 and 0.65, respectively, vs. 0.58 and 0.59 for AJCC. NG risk tertiles were better separated than AJCC groups, (3-yr TTR, 5-yr OS below), with fewer mid-risk NG pts. Removing treatment from NGs did not affect performance ($C=0.66$ for OS and 0.65 for TTR). **Conclusions:** The proposed ACCENT NGs are internally valid and have the potential to aid prognostication, decision-making, and patient/physician communication in pts with stage III CC.

	3Y TTR (95% CI)			5Y OS (95% CI)		
	IIIA / Low	IIIB / Mid	IIIC / High	IIIA / Low	IIIB / Mid	IIIC / High
AJCC	0.82 (0.80, 0.84) N = 1336	0.72 (0.70, 0.73) N = 4575	0.47 (0.44, 0.50) N = 1012	0.80 (0.78, 0.83) N = 1336	0.75 (0.74, 0.76) N = 4575	0.51 (0.48, 0.54) N = 1012
Nomo	0.82 (0.80, 0.83) N = 2,891	0.71 (0.67, 0.73) N = 2,184	0.51 (0.49, 0.53) N = 1,848	0.85 (0.84, 0.86) N = 2,863	0.74 (0.72, 0.76) N = 2,185	0.53 (0.51, 0.56) N = 1,875

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General Poster Session (Board #11E), Sun, 8:00 AM-11:45 AM

Randomized, phase II study of bevacizumab with mFOLFOX6 or FOLFOXIRI in patients with initially unresectable liver metastases from colorectal cancer: Resectability and safety in OLIVIA.

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Background: Patients (pts) with unresectable colorectal cancer liver-only metastases (CLMs) may become resectable after downsizing by chemotherapy (CT) and biologic therapy. Although biologics are thought to improve overall response rate (ORR), the optimal combination of a biologic and CT for resectability remains uncertain. **Methods:** This open-label, multinational study randomized pts with unresectable CLMs to bevacizumab (BEV) plus mFOLFOX6 or FOLFOXIRI q2w. Resectability was assessed by interdisciplinary review. Unresectability was defined as ≥ 1 of the following: no possibility of upfront R0/R1 resection of all hepatic lesions, $<30\%$ estimated residual liver after resection, or disease in contact with major vessels of the remnant liver. The primary end point was overall resection rate (R0/R1/R2). **Results:** From 10/2008 to 12/2011, 80 pts were randomized to mFOLFOX6-BEV (n=39) or FOLFOXIRI-BEV (n=41). Pt characteristics were male (46% vs 71%), aged ≥ 60 y (36% vs 63%), ECOG PS of 1 (23% vs 37%), and ≥ 5 target CLMs (49% vs 49%) in the mFOLFOX6-BEV and FOLFOXIRI-BEV arms, respectively. Resection rate, ORR, and progression-free survival (PFS) data are shown (Table). Grade ≥ 3 adverse events (AEs) occurred in 84% and 95% of pts receiving mFOLFOX6-BEV and FOLFOXIRI-BEV, respectively, and included neutropenia (35% vs 48%; febrile, 8% vs 13%) and diarrhea (14% vs 28%). **Conclusions:** The results suggest that FOLFOXIRI-BEV improves resection rates, ORR, and long-term outcomes vs mFOLFOX6-BEV in pts with initially unresectable CLMs. CT- and BEV-related AEs occurred with the expected incidence and were manageable. FOLFOXIRI-BEV should be evaluated further as an effective regimen to downsize CLMs. Clinical trial information: NCT00778102.

Pts, % (95% CI)	mFOLFOX6-BEV n=39	FOLFOXIRI-BEV n=41	Difference	P
Resection rate (R0/1/2)	48.7 (32.4-65.2)	61.0 (44.5-75.8)	12.3 (-11.0-35.5)	.271
Resection rate (R0/1)	33.3 (19.1-50.2)	51.2 (35.1-67.1)	17.9 (-5.0-40.7)	.106
Resection rate (R0)	23.1 (11.1-39.3)	48.8 (32.9-64.9)	25.7 (3.9-47.5)	.017
ORR	61.5 (44.6-76.6)	80.5 (65.1-91.2)	18.9 (-2.1-40.0)	.061
Median PFS (immature, mo (95% CI))	11.6 (8.1-14.2)	21.0 (18.6-31.8)	-	-

Overall survival (OS) analysis from PRIME: Randomized phase III study of panitumumab (pmab) with FOLFOX4 for first-line metastatic colorectal cancer (mCRC).

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Background: The primary and final analyses of PRIME demonstrated that pmab + FOLFOX4 significantly improved progression-free survival (PFS) vs FOLFOX4 alone for first-line treatment of patients (pts) with wild-type (WT) *KRAS* exon 2 mCRC. **Methods:** Pts were randomized 1:1 to pmab 6.0 mg/kg every 2 weeks + FOLFOX4 or FOLFOX4 alone and had no prior chemotherapy for mCRC, ECOG performance status ≤ 2 , and tumor tissue for biomarker testing. The primary endpoint was PFS by central assessment. Secondary endpoints included OS, objective response rate, and safety. *KRAS* exon 2 tumor status was determined by a blinded central lab prior to the primary analysis. This exploratory analysis of updated survival ($>80\%$ OS events) estimated the treatment effect of pmab + FOLFOX4 compared with FOLFOX4 alone on OS by *KRAS* exon 2 status. Previous analyses in pts with WT *KRAS* exon 2 tumor status reported OS with an event rate of 54% of pts in the primary analysis and 68% of pts in the final analysis. **Results:** 1183 pts were randomized and received treatment: 593 pts in the pmab + FOLFOX4 arm and 590 pts in the FOLFOX4 alone arm. The *KRAS* exon 2 ascertainment rate was 93%, consistent with the primary analysis. 535/656 pts (82%) with WT *KRAS* exon 2 mCRC had an OS event at the time of this analysis. Results are shown (Table). **Conclusions:** In this updated analysis, an improvement in OS was observed in pts with WT *KRAS* exon 2 mCRC treated with pmab + FOLFOX4 vs FOLFOX4 alone ($p = 0.03$). Median OS was reduced in pts with mutant (MT) *KRAS* mCRC ($p = 0.16$) and is consistent with previous analyses. Updated efficacy and safety results will be presented. *KRAS* testing is critical to select appropriate pts with mCRC for treatment with pmab. Clinical trial information: NCT00364013.

WT <i>KRAS</i> mCRC (n = 656)	Pmab + FOLFOX4 (n = 325)	FOLFOX4 alone (n = 331)	Hazard ratio (95% CI)	Descriptive p value
Pts who have died (any cause) - n (%)	256 (79)	279 (84)		
Median OS - mos (95% CI)	23.8 (20.0 - 27.7)	19.4 (17.4 - 22.6)	0.83 (0.70 - 0.98)	0.03
MT <i>KRAS</i> mCRC (n = 440)	Pmab + FOLFOX4 (n = 221)	FOLFOX4 alone (n = 219)		
Pts who have died (any cause) - n (%)	193 (87)	195 (89)		
Median OS - mos (95% CI)	15.5 (13.1 - 17.6)	19.2 (16.2 - 21.5)	1.16 (0.94 - 1.41)	0.16

Phase II clinical activity and tolerability of the SMAC-mimetic birinapant (TL32711) plus irinotecan in irinotecan-relapsed/refractory metastatic colorectal cancer.

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Background: Birinapant (B) is a SMAC-mimetic that inhibits IAPs and has potent preclinical anti-tumor synergy combined with TNF α -inducing chemotherapies [i.e irinotecan (I)]. B and I combination is well-tolerated and has encouraging activity in a phase I study. This study tested B+I with an ascending dose strategy (ADS) of B to mitigate Bell's palsy (BP) risk, an unusual and reversible side effect of SMAC mimetics. **Methods:** I at 350mg/m² IV q3weeks was administered with B weekly (2 of 3 weeks). The dose of B was titrated incrementally during Cycle 1: C1D1 at 5.6mg/m² and C1D8 at 11mg/m² for ADS. For Cycle 2 (C2) and ongoing treatment, the B dose was 22mg/m² or 35mg/m², which were the MTD and DLT (BP) dose levels when combined with I from the Ph 1 study. Safety and clinical activity for KRAS mutant (KRAS-MT) and wild-type (KRAS-WT) were assessed in 3 cohorts: (1) at 22mg/m² for CRC KRAS MT; (2) 22mg/m² for CRC KRAS WT; (3) 35mg/m² for CRC KRAS MT. **Results:** 51 patients (pts) with CRC had a median number of 4 prior regimens with 47 refractory/relapsed to irinotecan (92%). Tolerability was comparable to I alone. There were 2 PRs (4%), 27 SD (>2 cycles; 53%, median 4.7 mo), 17 PD (33%), and 5 non-evaluable pts (9%) for an overall clinical benefit (CR+PR+SD) rate of 57%. Median progression-free survival (PFS) was 2.1 months, and 6 mo PFS was 20%. KRAS MT CRC with prior I had a median PFS of 2.9 mo and 6 mo PFS of 25% (n=20). KRAS WT CRC with prior I had a median PFS of 1.4 mo and 6 mo PFS of 17% (n=18). The ADS seemed to reduce BP risk. No BP events occurred among 40 pts (22mg/m² with ADS), compared to 1 of 7 pts (22mg/m² without ADS). In the 35mg/m² cohort, 1 BP event occurred among 12 pts (with ADS), compared to 3 of 6 (35mg/m² without ADS). **Conclusions:** B + I demonstrated clinical benefit in pts refractory/relapsed to irinotecan, with greatest benefit in KRAS MT CRC. The ADS may provide a mitigation strategy for BP risk. Prior studies with I retreatment have showed no benefit in KRAS MT CRC. Comparable CRC pts with best supportive care have 6 mo PFS of 2%. Clinical activity supports the hypothesis for therapeutic synergy of B + I, with I as a TNF α -inducing agent. Further study of this combination is warranted. Clinical trial information: NCT01188499.

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General Poster Session (Board #11H), Sun, 8:00 AM-11:45 AM

Clinical activity, safety, and biomarkers of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic CRC, gastric cancer (GC), SCCHN, or other tumors.

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Background: PD-L1 has been reported to be expressed broadly in human cancer and can lead to inhibition of anti-tumor T-cell responses. MPDL3280A, a human monoclonal antibody containing an engineered Fc-domain designed to optimize efficacy and safety, targets PD-L1, blocking PD-L1 from binding its receptors, including PD-1 and B7.1. Pts with a broad range of tumors were examined in an expansion study with MPDL3280A. **Methods:** Pts with locally advanced or metastatic tumors received MPDL3280A administered IV q3w. Pts were treated for up to 1 y. Response was assessed by RECIST v1.1. **Results:** As of Jan 10, 2013, 20 pts with tumor types other than NSCLC, RCC and mM were evaluable for safety and treated at doses of 0.01-20 mg/kg (≤ 1 [n=3], 3 [n=1], 10 [n=3] and 20 mg/kg [n=13]). Median pt age was 67 y (range 26-80 y), 100% were PS 0-1, 90% had prior surgery and 45% had prior radiotherapy. 95% of pts received prior systemic therapy. Pts received MPDL3280A treatment for a median of 96 days (range 22-330). The incidence of all G3/4 AEs, regardless of attribution, was 50%. No G3-5 pneumonitis or diarrhea was reported. Confirmed RECIST responses were observed in several tumor types, including CRC, GC and SCCHN. Additionally, antitumor activity (tumor shrinkage that has not yet met criteria for a RECIST response) has been observed in sarcoma and lymphoma. Analysis of biomarker data from archival tumors revealed that all pts reported to have RECIST response had baseline tumors that were PD-L1 positive. Updated data will be presented. **Conclusions:** Treatment with MPDL3280A was well tolerated, with no pneumonitis-related deaths. Rapid responses were observed in pts with CRC, GC and SCCHN. PD-L1 tumor status appears to correlate with responses to MPDL3280A. These data suggest that PD-L1 is a conserved mechanism for mediating tumor immune escape across a range of tumor types. MPDL3280A may be broadly active as anti-cancer therapy in PD-L1-expressing tumors, supporting further investigation. Clinical trial information: NCT01375842.

3623

General Poster Session (Board #12A), Sun, 8:00 AM-11:45 AM

Discovering new targeted therapies for BRAF mutant-like colorectal cancers.

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Background: Approximately 10% of colorectal cancers (CRCs) harbor a BRAF mutation (BRAFM). Patients with BRAFM tumors have poor prognosis and are a therapeutic challenge. A BRAFM gene expression signature has been communicated (Popovici et al, JCO 2012), which can identify BRAFM tumors as well as BRAF wild-type tumors that display a similar expression pattern. Collectively, these tumors are termed BRAFM-like. Our goal was to validate this signature using next-generation sequencing and to discover novel therapies for BRAFM-like CRCs using a systems biology approach. **Methods:** We developed a semi-automated workflow that integrates publicly available tools named the *Cancer In-silico Drug Discovery* (CIDD). To validate the BRAFM-like signature, we used CIDD to analyze the CRC dataset from the The Cancer Genome Atlas Network (TCGA). Samples were stratified on BRAFM status using exome-sequencing, and expression profiles were inferred from RNA-sequencing. We matched expression profiles with drug-induced signatures inferred from the Connectivity Map (CMap) – a systems biology tool that contains expression data of cell lines treated with 1,500 compounds. CIDD statistically ranks candidate compounds and annotates them to pathways using public databases. **Results:** When applied to TCGA RNA-sequencing data, a classifier based on the BRAFM-like signature resulted in 93.3% sensitivity and 83.5% specificity for detecting BRAFM samples. When applied to Agilent gene expression data, this resulted in 80% sensitivity and 91.1% specificity. 41% of KRAS-mutated samples and 14% of double wild-type samples were predicted to be BRAFM-like. 100% of MSI-high and 18% of MSS samples were predicted to be BRAFM-like. Compounds near the top of our drug rankings include Gefitinib and MG-262 a proteasome inhibitor. **Conclusions:** We have validated the BRAFM-like signature using RNA-sequencing and Agilent expression data from the TCGA, and showed a high degree of robustness across technologies. We have identified EGFR and proteasome inhibitors as potential compounds to target BRAFM-like CRCs.

Predicting overall survival (OS) in patients (pts) with metastatic colorectal cancer (mCRC) treated with chemotherapy (CT): The British Columbia Cancer Agency (BCCA) mCRC score.

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Background: The prognosis of individual pts with mCRC can be highly variable. Our objective was to develop a scoring system to improve the prognostication of mCRC pts at baseline assessment. We also further explored the impact of palliative resection (PR) of the primary tumor on OS. **Methods:** Pts diagnosed with mCRC from 2006 to 2008, referred to 1 of 5 regional cancer centers in British Columbia were retrospectively reviewed. Pts with prior early stage CRC who relapsed with mCRC were excluded. Multivariate stepwise selection was performed using significant variables from univariate analysis. Patients were assigned a composite risk score (range 0-15) based on their baseline variables, and then separated into quartiles for OS using cut-point analysis and Kaplan Meier methods. A secondary propensity score matched analysis was performed to obtain hazard ratios (HR) for death in order to control for baseline differences between pts who underwent PR and those who did not. **Results:** A total of 505 mCRC pts were included: median age 63 (range 22-86), 58% male, 75% ECOG 0-1, 58% colon primary, 34% >1 metastatic site, and 46% smokers. In this cohort, 81% of the population underwent PR. ECOG 2-3, no primary resection, colon primary, >1 metastatic site, CEA level >4 ng/ml, male gender, and smoker were significant in the multivariate model and subsequently assigned a score. Median OS varied significantly depending on the composite risk score (table). After ECOG PS, PR of the primary was the second strongest prognostic factor (HR 2.3, 95%CI 1.6-3.3). To further explore this, a propensity score matched analysis was performed adjusting for age, gender, ECOG and receipt of chemotherapy. Prognosis continued to be more favorable in the PR group with a median OS of 17 vs. 7.9 months (HR 0.66, 95% CI 0.50-0.86, p=0.0019). **Conclusions:** In this population based analysis, the BCCA mCRC score was a simple and effective method to improve prognostication for mCRC pts. PR of the primary was associated with significantly longer OS.

Score	N	Median OS (months)	HR [95% CI]
0-3	181	33.6	1.0
4-5	136	25.9	1.47 [1.03-2.11]
6-8	117	17.1	2.31 [1.64-3.25]
9-15	71	10.4	5.92 [4.0-8.7]
P value			<0.01

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General Poster Session (Board #12C), Sun, 8:00 AM-11:45 AM

Phase I dose escalation of the oral histone deacetylase inhibitor (HDACi) resminostat in combination with FOLFIRI in colorectal cancer (CRC) patients: The SHORE trial.

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Background: Resminostat is a novel oral HDAC inhibitor with broad activity in various cancer models. In CRC models, resminostat revealed synergistic effects with 5-FU and irinotecan/SN-38, indicating its (re-)sensitization potential when applied in combination therapy. Furthermore, resminostat downregulates thymidylate synthase, involved in drug resistance to 5-FU and effectively inhibits HDAC2, one of the target enzymes believed to critically support development of CRC. The phase I/II SHORE trial investigates resminostat in combination with FOLFIRI in patients previously treated with 5-FU. **Methods:** Patients (pts) with advanced CRC having previously received 5-FU alone or in combination with other agents who were scheduled for FOLFIRI in second or later treatment lines were included. The phase I comprised an open-label, inter-patient, '3+3' dose escalation design with increasing doses of resminostat combined with standard FOLFIRI. Pts received resminostat on 5 consecutive days, followed by a 9-day drug free period ('5+9' scheme, i.e. 14-day cycles). On days 3 and 4 of each cycle (C), FOLFIRI was administered. Primary objective of the Phase I part was to determine safety and tolerability, the maximum tolerated dose and pharmacokinetics of the combination. **Results:** 17 pts (median age 61 yrs; 12 males; 11 ECOG 0; 6 ECOG 1; median therapy line 2 [2-6]) were enrolled in 4 dose levels of resminostat 200, 400, 600 mg QD (3 pts each) and 400 mg BID (6 pts) plus FOLFIRI. Two pts discontinued in C1 and were replaced. No DLT occurred. AEs consisted mainly of GI symptoms of mild and moderate intensity (nausea, vomiting and diarrhea) leading to decreased electrolyte plasma levels in some pts. In the highest dose level tested (400 mg BID) hematological toxicity, mainly neutropenia up to grade 4, was observed leading to dose reductions in 3 pts in C3 and C7. No objective responses were reported, however some pts showed SD for prolonged time (up to 32 w). Results of the completed phase I part will be reported. **Conclusions:** The combination of resminostat with standard FOLFIRI was safe and well tolerated warranting continuation into the Phase II part of the study. Clinical trial information: NCT01277406.

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General Poster Session (Board #12D), Sun, 8:00 AM-11:45 AM

Effect of EGFR inhibition on HER3/PI3K activation by feedback induction of ErbB heterodimers in cetuximab-sensitive colon cancer cells.

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Background: Although cetuximab treatment has been successful for the treatment of KRAS wild-type colorectal cancers, complete remissions are rarely seen in patients, leading ultimately to resistance. We hypothesized that in cetuximab-sensitive patients, the ErbB network is insufficiently targeted since network plasticity may occur. **Methods:** We have used EGFR-sensitive colorectal cancer cells and investigated ErbB network activity and adaptations by RTK arrays, western blot, and Collaborative Enzyme Enhance Reactive immunoassay (CEER). These were complemented by ErbB heterodimerization (HER2:3, HER1:2, HER1:3, HER3:PI3K) assays using CEER. Effects on cell survival were measured using colony formation assay. In addition to the EGFR sensitive cell line, 200 clinical colorectal cancer (CRC) samples were profiled utilizing CEER for RTKs, downstream signaling, and heterodimerization. **Results:** EGFR and downstream signaling proteins AKT, ERK, and RSK were potently inhibited by cetuximab or gefitinib at 24h of treatment in EGFR sensitive colorectal cancer cell line. At 24h of treatment, we observed approximately 2 folds increase in total HER2 and HER3 protein levels, 2.7 folds in phosphorylated HER3, and 5.4 folds in HER2:HER3 heterodimer formation. Concurrently, increased in ErbB heterodimer formation was accompanied by 5 folds increase in PI3K binding to HER3, resulting in enhanced HER3 signaling, with increase in AKT, ERK, and RSK. Co-treatment of these cells with cetuximab and HER2 inhibitor Trastuzumab or by treatment with lapatinib blocked the induction of HER2:HER3 heterodimer, HER3 phosphorylation, and PI3K binding to HER3. In 30% of the 200 clinical colorectal cancer samples profiled, we observed an increased in phosphorylated HER3, formation of HER2:HER3 and HER3:PI3K heterodimers along with HER1 activation (KRAS WT). **Conclusions:** Combination of HER2 inhibitor with an EGFR inhibitor could potentially increase the therapeutic index in cetuximab sensitive patients, and suppress activation of feedback mechanisms upon EGFR inhibition. Current findings suggest that CRC patients with similar profile would benefit from these combination therapies.

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General Poster Session (Board #12E), Sun, 8:00 AM-11:45 AM

Cost implications of reactive versus prospective testing for dihydropyrimidine dehydrogenase (DPD) deficiency in patients with colorectal cancer.

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Background: DPD is an enzyme encoded by the *DPYD* gene involved in the metabolism of the chemotherapy drug 5-fluorouracil (5FU) and the oral 5FU prodrug capecitabine. Patients (pts) with *DPYD* mutations are at risk of severe toxicities from standard dose 5FU, although they may safely receive lower dose therapy with careful monitoring and dose escalation. **Methods:** In this retrospective study we identified all pts starting 5FU-based chemotherapy for colorectal cancer (CRC) at our institution between Jan 1 2010 and Dec 31 2012. During this time DPD testing was usually performed in a reactive manner, typically for pts experiencing severe toxicities. We reviewed the charts of pts who tested positive for *DPYD* mutations and assessed the financial implications of their hospitalizations with toxicity. These costs were compared to the costs which would have incurred if all pts starting such therapy had been proactively tested. **Results:** A total of 134 pts started first-line 5FU-based chemotherapy for CRC over the study period, 66 in the adjuvant setting and 68 for metastatic disease. 31 pts had *DPYD* mutation testing performed. 6 tests (19% of those tested, 4.5% of the total population) revealed heterozygote *DPYD* mutations. 5 pts had already experienced severe treatment-related toxicity resulting in cessation of therapy, while one was tested prospectively and received chemotherapy with dose reduction *ab initio*. The total cost related to hospitalization with toxicity for these 5 pts was €155,083. At €177 per test, the cost to prospectively test all pts starting first-line 5FU-based therapy over the time period would have been €23,718 representing a saving of €131,365 through avoiding these admissions alone. 4 pts who tested positive for *DPYD* mutations were receiving adjuvant therapy and none restarted therapy following severe toxicity early in their therapy. 2 pts subsequently relapsed with metastatic disease. **Conclusions:** Prospective testing for *DPYD* mutations in pts with CRC starting 5FU-based therapy for the first time represents a considerable cost-saving opportunity, in addition to potentially avoiding prolonged hospitalization and morbidity for a sizeable minority of pts.

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General Poster Session (Board #12F), Sun, 8:00 AM-11:45 AM

TFAP2E methylation status and prognosis of patients with radically resected colorectal cancer.

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Background: Transcription factor AP-2 ϵ , a member of the AP-2 family has extensively studied in many cancers. Recently, it has been suggested that the gene encoding AP-2 ϵ (TFAP2E) is involved in the development of colorectal cancer (CRC) and is also associated with clinical outcomes of the patients with CRCs. Therefore, we have investigated the clinical significance of TFAP2E in CRC patients who underwent curative resections. **Methods:** A single-institution cohort of 248 patients with curatively resected, stage I/II/III CRCs between March and December, 2004 were included, and the analyses were performed in 193 patients whose tumors were available for TFAP2E methylation status. **Results:** One hundred twelve patients (58%) showed TFAP2E hypermethylation, which was significantly more common in CRCs with distal location, low pathologic T stage (T1/T2) and stage I. After a median follow-up duration of 86.3 months, the patients with TFAP2E hypermethylation had a trend for better survival outcome in terms of relapse-free survival (RFS) and overall survival (OS) (TFAP2E hypermethylation vs. hypomethylation; 5-year RFS rate 90% vs. 80%, $p=0.063$; 6-year OS rate 88% vs. 80%, $p=0.083$). Multivariate analysis showed pathologic nodal stage and TFAP2E methylation status were independent prognostic factors affecting both RFS and OS, which also remained significant factors in the subgroup analysis including 154 patients with stage II/III CRCs who had received adjuvant chemotherapy. **Conclusions:** TFAP2E hypermethylation was associated with better clinical outcome and may be considered as an independent prognostic factor in the patients with curatively resected CRC.

Prognostic biomarkers in a series of stage II colon cancer.

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Background: Different clinico-pathological factors are used to define a group of patients with high-risk stage II colon cancer (CC) that may benefit of adjuvant treatment. Moreover, several molecular markers, such as microsatellite instability (MSI) and *BRAF*, have been widely investigated as prognostic factors. Recently a high stroma component (EMT+ subtypes) has also been associated with poor outcome. The aim of the study is to analyze the prognostic value of MSI, *BRAF* and tumor-stroma ratio in a prospective series of stage II CC patients. **Methods:** FFPE tissue from 432 stage II CC patients operated at Hospital Universitari de Bellvitge (1996 - 2006) were included in the study. MSI status was assessed by the analysis of 5 mononucleotide repeat markers (BAT-25, BAT-26, NR-21, NR-24 and MONO-27). *BRAF* V600E mutation was analyzed by single strand conformation polymorphism technique. Tumor-stroma ratio was analyzed by immunohistochemistry. Associations between molecular factors and clinical features were assessed by Chi-Squared (X^2) tests. A Cox regression model was used to evaluate the Relapse Free (RFS) and the Colon Cancer specific Survival. **Results:** MSI status could be determined in 350 patients. 48 (14%) had MSI high (MSI-H) tumor. *BRAF* status could be assessed in 380 cases. 58 (15%) cases were *BRAF* mutated. Tumor-stroma ratio was analyzed in 407 tumor samples. 176 (43%) tumors had more than 50% intra-tumor stroma and were classified as stroma-high. MSI-H tumors were significantly located in right colon (X^2 p-value = 1.03e-5), were poorly differentiated (X^2 p-value = 0.003) and had more than 12 lymph nodes resected (X^2 p-value = 0.037). MSI-H tumors were associated with *BRAF* mutation (X^2 p-value = 0.02) and stroma-low (X^2 p-value = 0.0005). When a molecular prognostic risk classification was performed, patients with MSI-H /stroma-low suggested a low risk of relapse comparing to MSI-H/stroma-high, microsatellite stable (MSS)/stroma-low and MSS/stroma-high patients (HR = 3.15; 95 CI, 0.76 – 13.1, p-value = 0.0602). **Conclusions:** MSI-H tumors have *BRAF* mutation as well as low intra-tumor stroma. Our results suggest that tumor-stroma ratio can explain differential prognosis in MSI-H stage II tumors.

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General Poster Session (Board #12H), Sun, 8:00 AM-11:45 AM

Quantitative analysis of the impact of deepness of response on post-progression survival time following first-line treatment in patients with mCRC.

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Background: The extent of tumor shrinkage in patients (pts) receiving chemotherapy with or without monoclonal antibodies is prognostic for PFS and OS. The 'Deepness of response (DpR)' concept aims to relate tumor shrinkage to post-progression survival (PPS). If tumor shrinkage occurs, DpR is the percentage of shrinkage observed at the nadir compared with baseline. DpR is 0 for no change and negative if the tumor load increases. Longest diameter (LD) based on RECIST or a calculated tumor volume (ASCO GI 2012 #635) can be used to quantify the tumor load. A joint model was presented (ASCO GI 2012 #580, ASCO 2012 #3603) which allows the prediction of a pt PPS time based on DpR. **Methods:** Based on data from the randomized CRYSTAL and OPUS trials, 4 treatment regimens (FOLFIRI +/- cetuximab and FOLFOX4 +/- cetuximab) were studied. A joint model was used to quantify individual changes in tumor size over time and to relate these changes to PFS and OS. Relationships between baseline tumor load and DpR and PPS were studied. A Spearman correlation was used to study the relationship between DpR and PPS for *KRAS* wild-type (wt) pts with progressive disease. **Results:** Results are reported using LD-based measures for 841 pts with *KRAS* wt tumors and imaging data. The 348 pts treated with FOLFIRI alone had a median DpR of 33.3% (interquartile range [IR]: 8.0%, 58.0%) while the 315 pts treated with FOLFIRI + cetuximab had a significantly higher median DpR of 50.9% (IR: 18.4%, 78.6%), $p < 0.0001$. The 96 pts treated with FOLFOX4 alone had a median DpR of 30.7% (IR: 4.0%, 55.9%) and the 82 pts treated with FOLFOX4 + cetuximab had a significantly higher median DpR of 57.9% (IR: 24.0%, 92.9%), $p = 0.0008$. Correlation between DpR and PPS for pts with documented progression is statistically significant in each treatment group for both LD-based and volume-based measurements ($p < 0.0001$ for the CRYSTAL study and $p < 0.005$ for the OPUS study). **Conclusions:** Our results emphasize the value of DpR as a new efficacy outcome measure for clinical trials. The tumor-shrinking capacity of cetuximab was shown to be associated with its ability to prolong PPS.

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General Poster Session (Board #13A), Sun, 8:00 AM-11:45 AM

Analysis of *KRAS*/*NRAS* mutations in PEAK: A randomized phase II study of FOLFOX6 plus panitumumab (pmab) or bevacizumab (bev) as first-line treatment (tx) for wild-type (WT) *KRAS* (exon 2) metastatic colorectal cancer (mCRC).

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Background: PEAK estimated the tx effect of FOLFOX6 with pmab or bev in 1st-line WT *KRAS* mCRC. The PRIME study showed significantly improved progression free survival (PFS) and overall survival (OS) with pmab + FOLFOX vs FOLFOX in pts with WT *RAS* (*KRAS*/*NRAS* exons 2, 3, 4) mCRC in a prospective-retrospective analysis (unpublished data). **Methods:** This prospective-retrospective analysis of PEAK was designed to assess the effect of pmab + FOLFOX6 or bev + FOLFOX6 on PFS (primary endpoint) and OS in WT *RAS* (*KRAS*/*NRAS* exons 2, 3, 4) mCRC. Pts were required to have WT *KRAS* exon 2 tumors. Bidirectional Sanger sequencing and Transgenomic SURVEYOR/WAVE analysis were independently conducted to detect mutations in *KRAS* exon 3 (codons 59/61), exon 4 (codons 117/146); *NRAS* exon 2 (codons 12/13), exon 3 (codons 59/61), exon 4 (codons 117/146); *BRAF* exon 15 (codon 600) in banked specimens. **Results:** 285 WT *KRAS* (exon 2) mCRC patients (pts) were randomized, 278 received tx. The current *RAS* ascertainment rate is 75%. Tx HRs (pmab:bev) for pts with WT *RAS* were 0.63 (95% CI, 0.43-0.94; p = 0.02) for PFS and 0.55 (95% CI, 0.30-1.01; p = 0.06) for OS (Table). The incidence of worst grade 3-5 adverse events was consistent with the primary analysis. Updated OS and *BRAF* results will be presented. **Conclusions:** In this 1st-line estimation study in WT *RAS* mCRC, PFS and OS HR favored pmab + FOLFOX6 relative to bev + FOLFOX6, suggesting that activating *RAS* mutations appear to be predictive for pmab tx effect. The safety profile for both arms was consistent with previously reported studies. Clinical trial information: NCT00819780.

	Pmab + FOLFOX6	Bev + FOLFOX6	HR ^c (95% CI)	Descriptive p value
WT <i>RAS</i> ^a , n	80	80		
Median PFS - mos (95% CI)	13.1 (10.7 - 15.1)	9.5 (7.9 - 12.7)	0.63 (0.43 - 0.94)	0.02
Median OS - mos (95% CI)	NR ^d (28.8 - NR ^d)	29.0 (24.3 - NR ^d)	0.55 (0.30 - 1.01)	0.06
WT <i>KRAS</i> -2, Mutant <i>RAS</i> ^b , n	24	23		
Median PFS - mos (95% CI)	7.8 (6.5 - 9.8)	8.9 (7.3 - 12.0)	1.31 (0.66 - 2.59)	0.44
Median OS - mos (95% CI)	NR ^d (13.0 - NR ^d)	21.6 (13.9 - 25.4)	0.72 (0.28 - 1.83)	0.50

^a WT in *KRAS* and *NRAS* (exons 2, 3, 4). ^b WT *KRAS* (exon 2) and Mutant *KRAS* (exons 3 or 4) or Mutant *NRAS* (exons 2, 3, or 4). ^c Stratified Cox proportional hazards model. ^d Not reached.

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General Poster Session (Board #13B), Sun, 8:00 AM-11:45 AM

Clinicopathologic features of KRAS-mutated colorectal tumors vary by site of mutation.

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Background: KRAS mutations in codons 12 and 13 are present in approximately 40% of all colon cancers and predict a lack of response to monoclonal antibodies to the EGFR among patients with metastatic disease. Activating mutations in codons 61 and 146 occur less frequently, and the clinicopathologic features of this subpopulation of KRAS-mutant colorectal tumors have not been clearly defined. **Methods:** Records of patients treated at MD Anderson Cancer Center between December 2000 and August 2012 for metastatic colorectal cancer whose tumors underwent testing for a KRAS mutation were reviewed for clinical characteristics, concurrent mutations, and survival outcomes. Associations between mutation status and clinic features were measured by calculation of odds ratios, and survival was estimated according to the Kaplan-Meier method. **Results:** Among the 487 records reviewed, 225 KRAS 12/13 mutations (47.2%) and 14 KRAS 61/146 mutations (2.9%) were detected. Liver metastases were less common for patients with KRAS 61/146 mutations than for patients with KRAS 12/13 mutations (OR 0.26, p-value=0.02). No difference in lung metastases was identified for KRAS 61/146 mutated patients when compared to those with KRAS wild-type tumors (OR=2.1, p-value=0.26), even though lung metastases were more common for patients with KRAS 12/13 mutations (OR 2.86, p-value=0.001). There was no association between the presence of a KRAS 61/146 mutation and gender, stage at presentation, site of primary tumor, body mass index, tobacco history, or concurrent PIK3CA mutation. Whereas a worse survival difference from the time of metastasis detection was noted for KRAS 12/13 patients when compared to those with KRAS wild-type tumors (HR 1.74, p-value= 0.002), patients with KRAS 61/146 mutations demonstrated no change in survival outcome (HR 1.10, p-value=0.87). **Conclusions:** Patients with KRAS 61/146 mutations have different patterns of metastases compared to KRAS 12/13, but do not appear to share the poor prognosis associated with the more common KRAS 12/13. These results suggest that clinical phenotypes for patients afflicted with colorectal cancer may differ based on the specific codon mutated within the KRAS oncogene.

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General Poster Session (Board #13C), Sun, 8:00 AM-11:45 AM

A phase I study of sorafenib with FOLFIRI as first-line therapy for metastatic colorectal cancer (mCRC): Safety and efficacy results.

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Background: Phase I dose escalation to a maximum planned dose (MPD) to determine dose-limiting toxicities (DLTs), maximum tolerated dose (MTD), recommended-phase-II-dose (RP2D) and preliminary efficacy of sorafenib and FOLFIRI (irinotecan reduced-dose) in metastatic colorectal cancer (mCRC) patients. **Methods:** Starting doses: irinotecan 80 mg/m² iv d1, sorafenib 400 mg po twice daily (bid, continuous), starting day 2. Escalations based on toxicity observed at the previous dose level (DL) up to: irinotecan 100 mg/m² and sorafenib 800 mg bid. DLT was evaluated within the 1st study cycle (1 cycle = 2 FOLFIRI treatments). **Results:** 5 cohorts were concluded. All 16 ECOG PS 0-1 patients (9/7 men/women; 2/14 rectal/colon) with median age of 64, discontinued study: 10 (62%) disease progression, 4 (25%) toxicity, 1 curative surgery, 1 comorbidities. The dose levels of irinotecan (mg/m², day1) and sorafenib (mg/day, bid, day 2-28) studied were DL1-80/400, DL2-80/600, DL3-90/600, DL4-100/600 and DL5-100/800, repeated every 4 weeks, 3 patients/DL. No DLT was observed. The MTD was not reached at the MPD (DL5). The most common ≥Gr2 treatment related adverse events (AEs) were: neutropenia 81%, HFS 69%, leucopenia 50%, fatigue 38%, anemia 31%, constipation 31%, nausea/vomiting 31%, mucositis 31%, diarrhea 25%, hypophosphatemia 25%. The most severe treatment related AEs were: Gr4: neutropenia 2 (12.5%); pulmonary embolism 1 (6%); Gr3: HFS 9 (56%), neutropenia 3 (19%), leucopenia 3 (19%), hypophosphatemia 3 (19%). Objective response rate was 56% (9 of 16 patients, 95%CI; 33-77%). Response duration was 13 months (95%CI; 5-17). Median progression-free survival and overall survival were 11 months (95%CI; 6-17) and 25 months (95%CI; 15-34), respectively. **Conclusions:** Combination therapy with S and modified FOLFIRI in these patients is well tolerated and demonstrates clinical efficacy at the MPD. The MTD was not reached at the MPD. Future research of this combination is warranted. Supported by Bayer Healthcare Pharmaceuticals. Clinical trial information: NCT00780169.

Ultra-deep amplicon sequencing to identify actionable mutations in matched plasma/tumor specimens from 44 patients with colorectal cancer of UICC stage III and IV.

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Background: Circulating cell-free DNA (cf-DNA) isolated from plasma samples of cancer patients (pts) is a promising source for noninvasive examination of tumor-specific mutation patterns. We examined the efficiency of ultra-deep amplicon sequencing (UDAS) of cf-DNA isolated from plasma and tumor DNA isolated from matched primary tumor tissue of pts with colorectal cancer (CRC). **Methods:** Blood was drawn prior to surgery from 44 pts: 20 male, 24 female; 44-79 years of age (median: 67.5); 11 stage III, 33 stage IV; 36 colon, 8 rectum tumors; no neo-adjuvant therapy. Cf-DNA was isolated from 2 ml of EDTA plasma. UDAS was applied to 72 DNA samples (44 plasma, 28 matched snap-frozen primary tumors) using the MiSeq platform (Illumina). A panel of 49 highly multiplexed amplicons was designed (Life Technologies) representing 9 cancer genes frequently mutated in CRC. For 16 primary tumors the mutation profile was determined using the TruSeq Amplicon Cancer Panel (Illumina). **Results:** Median cf-DNA yield was 310 ng / 2 ml plasma (1ng – 6.600 ng). There was no significant relation between cf-DNA yield and any clinical characteristic. Median amplicon coverage was 20.162 reads per bp (2.913 - 115.782). 33/49 amplicons (67%) had a coverage of > 10.000 reads. Altogether 61 high quality COSMIC-cited mutations were confirmed in plasma of 29/44 (66%) pts: 24/33 (73%) pts in stage IV, 5/11 (45%) pts in stage III. Confirmed mutations are: APC-17; BRAF-2, FBXW7-1, KRAS-15, NRAS-1, PIK3CA-4, SMAD4-2, and TP53-19 mutations. No high quality mutations were found in CTNNB1 and HRAS. Moreover two pts exhibited four high quality plasma mutations which were not detected in the matched primary tumor: APC (R216X), KRAS (Q61K), and SMAD4 (D355E); PIK3CA (E545K). **Conclusions:** Ultra deep amplicon sequencing is suitable to detect mutations in plasma samples of CRC pts with a high concordance to matched primary tumors. The concordance rate can be further increased by extending the spectrum of analyzed mutations or by the enrichment of cf-DNA tumor copies. This method could be applied to detect and monitor metastasis thus opening a new paradigm for the selection of pts for targeted therapies.

Minor response rate to predict patient survival.

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Background: RECIST is widely used to evaluate anticancer therapy efficacy, yet its response cutoff values have not been proven biologically or measurement-error relevant. Our previous study showed that the variability in measuring relative change in total tumor burden (TTB%) was +/-10% in metastatic colorectal cancer (mCRC). Our study investigated the impact of a finer gradation of response categories in predicting survival. **Methods:** 468 patients enrolled in a phase II/III clinical trial evaluating a systemic therapy in mCRC were analyzed. TTB on baseline and 6-week (+/- 3-wk) scans were obtained per RECIST 1.0. Overall survival (OS) was defined from the start of treatment and the date of the scan using the landmark method. The TTB% was summarized using RECIST category and a finer gradation that included cut-offs established in our variability study (<-30%, -30% - -10%, -10% - 10%, 10% - 20%, >20%). The OS and TTB% correlation was evaluated by the Kaplan Meier method and Cox regression. The discriminatory powers of the response summaries were examined using Harrel's c statistics and concordance probability. **Results:** Out of the 468 patients, 141 died. The median survival time for patients with a TTB% at 6 weeks of [-30%, -10%] (n=116), [-10%, 10%] (n=171), [10%, 20%] (n=43), >20% (n=62) were 417, 287, 223 and 172 days, respectively. Among those with a change of < -30% (n=76), over half of patients were still alive. The hazard ratio for OS compared to those with a change of <-30% are listed in the Table. The inclusion of additional categories increased both Harrel's c-statistic (0.69 vs 0.73) and concordance probability (0.63 vs 0.69). Combining the [-10%, 10%] and the [10%, 20%] categories yielded very similar statistics compared to having all 5 categories. Both definitions of OS yielded consistent results. **Conclusions:** Evidence suggests that, in the context of this study, the minor change category of [-30%, -10%] at 6-wk correlates with longer survival compared to the change category of [-10%, 20%], suggesting a possible re-evaluation of conventional response cut-off values.

Relative change at 6 week	Hazard ratio	95% Confidence Interval	P
-30% to -10%	1.91	(0.98, 3.74)	0.057
-10% to 10%	5.37	(2.91, 9.92)	<0.001
10% to 20%	4.69	(2.04, 10.74)	<0.001
>20%	12.60	(6.57, 24.15)	<0.001

Regorafenib (REG) in progressive metastatic colorectal cancer (mCRC): Analysis of age subgroups in the phase III CORRECT trial.

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Background: In the CORRECT phase III trial, the multikinase inhibitor REG demonstrated significant improvement in overall survival (OS) and progression-free survival vs placebo (Pla) in patients (pts) with mCRC whose disease progressed on other standard therapies. The most frequent REG-related grade ≥ 3 adverse events (AEs) of interest were hand-foot skin reaction (HFSR), fatigue, diarrhea, hypertension, and rash/desquamation. We explored whether the impact of REG in pts aged ≥ 65 years differed from that in younger patients. **Methods:** Pts with mCRC progressing following all other available therapies were randomized 2:1 to receive REG 160 mg once daily (n=505) or Pla (n=255) for the first 3 weeks of each 4-week cycle. The dose could be modified to manage AEs. The primary endpoint was OS. We report efficacy, safety, and dosing data from REG recipients by age. **Results:** The REG treatment group included 309 pts <65 years (307 evaluable for safety) and 196 pts ≥ 65 years (193 evaluable for safety). The OS hazard ratio (REG/Pla) was 0.72 (95% confidence interval [CI] 0.56–0.91) in pts <65 years and 0.86 (95% CI 0.61–1.19) in pts ≥ 65 years (interaction p-value = 0.405). Median OS was 6.7 vs 5 months for REG vs Pla in pts <65 years, and 6.0 vs 5.6 months, respectively, in pts ≥ 65 years. Most pts experienced drug-related AEs (<65 years: 93.8%; ≥ 65 years: 91.7%). The rates of grade ≥ 3 REG-related AEs of interest and dose modifications are shown in the Table. In pts <65 years vs ≥ 65 years, median (interquartile range [IQR]) duration of REG was 7.6 weeks (6.6–15.4) vs 7.1 weeks (5.1–17.2), median (IQR) daily REG dose was 160.0 mg (134.6–160.0) vs 160.0 mg (137.5–160.0), and median (IQR) proportion of planned REG dose was 83.3% (65.7–100.0) vs 78.6% (66.7–100.0), respectively. **Conclusions:** In the CORRECT trial, REG demonstrated an OS benefit in pts <65 years and ≥ 65 years. Safety and tolerability of REG appeared to be similar in both age subgroups. Clinical trial information: NCT01103323.

Grade ≥ 3 AEs, %	<65 years (n=307)	65–74 years (n=155)	≥ 75 years (n=38)
Any	52	57	66
HFSR	19	12	18
Fatigue	9	8	16
Hypertension	5	12	11
Diarrhea	7	7	11
Rash/desquamation	5	8	3
Pts with dose modifications, %			
Any	76	73	84
Reduction	27	31	9
Interruption	94	100	100

Time profile of adverse events (AEs) from regorafenib (REG) treatment for metastatic colorectal cancer (mCRC) in the phase III CORRECT study.

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Background: In the CORRECT phase III trial, the multikinase inhibitor REG demonstrated significant improvement in overall survival and progression-free survival vs placebo (P) in patients with mCRC whose disease had progressed on other standard therapies. The most frequent grade 3 AEs were hand-foot skin reaction (HFSR), fatigue, diarrhea, hypertension, and rash. We examined when these AEs first occurred and what impact they had on REG dosing. **Methods:** Adults with mCRC progressing after all standard therapies were randomized to receive REG 160 mg (n=505) or P (n=255) orally once daily for the first 3 weeks of each 4-week cycle. AEs were managed with dose modifications (reduction and interruption) according to the protocol. **Results:** The safety population comprised 753 pts (REG n=500, P n=253). The mean \pm SD treatment duration was 12.1 \pm 9.7 weeks for REG and 7.8 \pm 5.2 weeks for P. Treatment-emergent AEs occurred in 99.6% of REG pts and 96.8% of P pts. AEs occurring in $\geq 10\%$ more REG than P pts were fatigue, HFSR, anorexia, diarrhea, weight loss, voice changes, hypertension, rash/desquamation, oral mucositis, fever, hyperbilirubinemia, and low platelet count. The incidence of grade ≥ 3 HFSR, fatigue, hypertension, and rash/desquamation typically peaked in cycle 1 and tapered to a relatively stable lower incidence over later cycles, while the incidence of diarrhea remained relatively constant throughout the study; median time to first occurrence and worst grade of these AEs is shown in the table. AEs led to dose modifications in 66.6% of REG pts and 22.5% of P pts. **Conclusions:** The most common AEs in the REG group typically occurred early during treatment. Close early monitoring of AEs and proper management by dose modification is recommended. Clinical trial information: NCT01103323.

AE	REG (n=500)			P (n=253)		
	Pts affected, %	Time to AE, days*		Pts affected, %	Time to AE, days*	
		First occurrence	Worst grade		First occurrence	Worst grade
Diarrhea	43	23.5 (12-50)	31.5 (15-71)	17	29 (11-50)	29 (13-50)
Fatigue	63	15 (8-29)	20 (11.5-56)	46	18 (11-29)	29 (15-43)
HFSR	47	15 (11-35)	22 (13-51)	8	16 (8-42)	16 (8-42)
Hypertension	30	14 (8-29)	15 (8-34)	8	20 (14.5-33)	20 (14.5-33)
Rash	29	15 (11-21)	15 (11-23)	5	15 (12-27)	15 (12-27)

* Median (interquartile range).

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General Poster Session (Board #13H), Sun, 8:00 AM-11:45 AM

Randomized phase III clinical study comparing postoperative UFT/LV,UFT+LV/UFT and UFT+LV+PSK/UFT+PSK as adjuvant therapy for curatively resected stage III colorectal cancer HGCSG-CAD study.

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Background: Study showed that the oral anticancer agent UFT/LV is useful as postoperative adjuvant chemotherapy for stage III colorectal cancer. PSK, a protein-bound polysaccharide extracted from the mycelia of *Coriolus versicolor*, is an immunomodulator widely used in gastric, colorectal and lung cancers. **Methods:** Patients aged 20-80 years with stage III colorectal cancer registered in 35 facilities were randomized to: group A (UFT/LV 28 days/5 weeks for 6 months); group B (UFT+LV 28 days/5 weeks for 6 months, then UFT for 12 months); and group C (UFT+LV+PSK 28 days/5 weeks for 6 months, then UFT+PSK for 12 months). Treatment was started within 6 months after curative resection. Outcome measures were relapse-free survival (RFS), overall survival (OS), incidence and severity of adverse events, and QOL. **Results:** Of 342 patients registered, 340 eligible patients were analyzed (84 in group A, 85 in group B, and 171 in group C). At baseline, variation in QOL score was observed but histopathological parameters were not different among 3 groups. Median observation period was 36 months. 3-year RFS was 73.8%, 77.6% and 73.9% in groups A, B, and C [A vs C: hazard ratio (HR) 0.960, 95% confidence interval (CI) 0.575-1.601; B vs C: HR 0.837, CI 0.488-1.433; A vs B: HR 1.151, CI 0.623-2.126]. 3-year OS was 95.2%, 91.8% and 89.9% in groups A, B, and C (A vs C: HR 0.460, CI 0.155-1.367; B vs C: HR 0.814, CI 0.338-1.963 A vs B: HR 0.570, CI 0.167-1.947). Adverse events \geq grade 3 included gastrointestinal symptoms and general status. There was no treatment-related death. Excluding high fatigue score in QOL scale that showed pretreatment variation, stratification analysis showed interaction between family score and group, and efficacy was suggested especially in group C with high score (3-yr RFS: 66.7%, 68.2% and 88.1% in groups A, B, and C. A vs C: HR 3.289, CI 0.951-11.375, B vs C: HR 3.070, CI 0.973-9.685, A vs B: HR 1.084, CI 0.344-3.417). **Conclusions:** A significant difference in primary endpoint was not detected. Variation in QOL at treatment initiation probably greatly affected outcome. Clinical trial information: NCT00209742.

Guanylyl cyclase C (GCC) expression in lymph nodes (LNs) as a determinant of recurrence in stage II colon cancer (CC) patients (pts).

Daniel J. Sargent, Qian Shi, Sharlene Gill, Christophe Louvet, Richard Bernard Everson, Udo Kellner, Thomas E. Clancy, J. Marc Pipas, Murray B. Resnick, Michael O. Meyers, David Huntsman, Pierre Validire, Umar Farooq, Emily S Pavey, Jean-Francois Haince, Guillaume Beaudry, Yves Fradet; Mayo Clinic, Rochester, MN; British Columbia Cancer Agency, Vancouver, BC, Canada; Department of Oncology, Institut Mutualiste Montsouris, Paris, France; University of Connecticut Health Center, Farmington, CT; Johannes Wessling Klinikum Minden, Minden, Germany; Brigham and Women's Hospital/Dana-Farber Cancer Institute, Boston, MA; Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center, Lebanon, NH; Rhode Island Hospital; Brown University, Providence, RI; Division of Surgical Oncology and Endocrine Surgery, University of North Carolina School of Medicine, Chapel Hill, NC; Department of Pathology, Institut Mutualiste Montsouris, Paris, France; DiagnoCure Inc., Quebec, QC, Canada

Background: The first phase of the multi-center prospectively specified retrospective study Validating Indicators To Associate Recurrence (VITAR), assessing the relationship between GCC gene expression in formalin fixed (FFPE) LNs and time to recurrence (TTR) in stage II CC pts not treated with adjuvant chemotherapy (Sargent, *Annals Surg Onc* 2011), showed promising initial results. Here we report a validation set of 463 new stage II CC pts. **Methods:** GCC mRNA was quantified by RT-qPCR using FFPE LNs from untreated T3N0 CC pts diagnosed from 1999-2008 with at least 12 LNs examined, blinded to clinical outcomes. Patients were classified by GCC LN ratio (LNR) (high risk: $LNR > 0.1$; low risk: $LNR \leq 0.1$), with LNR defined as ratio of GCC positive to GCC informative LNs. Cox regression models tested the relationship between GCC and the primary endpoint of TTR, adjusted for age, tumor grade, number of LN examined pathologically, and lymphovascular invasion. Mismatch repair (MMR) status was also assessed. All primary analyses and cut-points were pre-specified. **Results:** 46pts (10%) recurred (rec), median follow-up was 65 months, median LNs examined was 20, and 42% (195/463) were classified high risk. Overall, TTR was not significantly associated with binary GCC LNR risk class ($HR=1.47$, $p=.208$) or DFS ($HR=1.39$, $p=.097$). One site's ($n=97$) tissue grossing method precluded appropriate LN assessment with existing GCC qualification methods. Excluding this site resulted in a TTR $HR=1.91$, $p=0.051$ (multivariate). In a *post-hoc* analysis excluding this site and using a 3-level GCC risk group of high ($LNR > 0.20$), intermediate ($0.10 < LNR < 0.20$) and low ($LNR < 0.10$), high risk group pts had a 5-yr rec risk of 22% versus 8% in low risk ($HR 2.72$, $p=0.006$). MMR status was not significantly associated with TTR (multivariate $p=0.30$). **Conclusions:** GCC status is a promising prognostic factor in appropriately staged stage II CC pts not treated with adjuvant therapy independent of traditional histopathology risk factors, but GCC determination must be performed with methodology adapted to the tissue procurement and fixation technique. Outcome associations were strengthened when considering a 3-level GCC categorization.

3640

General Poster Session (Board #14B), Sun, 8:00 AM-11:45 AM

Real-world comparative economics of a 12-gene assay for prognosis in stage II colon cancer.

Tiffany Yu, Steven R. Alberts, Robert J. Behrens, Lindsay A. Renfro, Geetika Srivastava, Gamini S. Soori, Shaker R. Dakhil, Rex B. Mowat, J. Phillip Kuebler, George P. Kim, Mirosław Mazurczak, John C. Hornberger; Cedar Associates, LLC, Menlo Park, CA; Mayo Clinic, Rochester, MN; Mayo Clinic, Des Moines, IA; Missouri Valley Cancer Consortium, Omaha, NE; Cancer Center of Kansas, Wichita, KS; Toledo Community Hospital Oncology Program CCOP, Toledo, OH; Columbia Oncology Associates, Columbus, OH; Mayo Clinic, Jacksonville, FL; Sanford Cancer Center, Sioux Falls, SD; Cedar Associates LLC/Stanford School of Medicine, Menlo Park, CA

Background: Prior economic analysis of a 12-gene assay (Oncotype DX), compared with patterns of care reported in the NCCN database of patients with stage II, T3, DNA mismatch repair proficient (MMR-P) colon cancer, predicted that the assay would save medical costs and improve patient well-being (Hornberger et al. Value Health 2012). This study assessed the validity of those findings with actual adjuvant chemotherapy (aCT) recommendations. **Methods:** Outcomes and costs were estimated for patients with stage II, T3, MMR-P colon cancer using a Markov model. A study of 141 patients from 17 sites in the Mayo Clinic Cancer Research Consortium collected data on aCT recommended before and after knowledge of the 12-gene assay results (Srivastava et al. abstract). Quality-adjusted life years (QALY) and medical resource use after recurrence were computed using guideline-validated state-transition probability estimation methods. Risk of progression and incidence of adverse events with different aCT regimens were based on published literature. Drug and administration costs for aCT were obtained from 2012 Medicare fee schedules. One-way sensitivity analyses were conducted to evaluate parameter influence on economic impact. **Results:** After receiving the 12-gene assay results, physician recommendations in favor of aCT decreased 22% (95% CI 11%-32%; McNemar test $p < 0.001$) from 73 (52%) to 42 (30%) patients. Oxaliplatin aCT and 5-FU monotherapy recommendations each declined 11%. Average aCT costs decreased \$3,228 for drugs, \$750 for administration, and \$3,168 for adverse events management. Overall, average total direct medical costs decreased \$1,683. The net effect on average patient well-being was a gain of 0.102 QALYs. Total change in medical costs is most influenced by the cost of death due to colon cancer, time-preference discount rate, and the change in aCT recommendations. Savings are expected to persist even if the cost of oxaliplatin dropped by >75% due to generic substitution. **Conclusions:** The 12-gene assay has been shown to alter aCT recommendations for patients with stage II, T3, MMR-P colon cancer. This study provides real-world confirmation that these aCT changes reduce direct medical costs and improve patient well-being.

3641

General Poster Session (Board #14C), Sun, 8:00 AM-11:45 AM

Gain of ALK gene copy number to predict lack of response to anti-EGFR treatment in advanced chemorefractory colorectal cancer (CRC) with KRAS/NRAS/BRAF/PI3KCA wild-type status.

Filippo Pietrantonio, Anna Tessari, Rosalba Miceli, Pamela Biondani, Federica Perrone, Adele Testi, Elena Tamborini, Giuseppe Pelosi, Luigi Mariani, Giuseppe Fanetti, Arpine Gevorgyan, Ilaria Bossi, Maria Di Bartolomeo, Filippo G. De Braud; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Laboratory of Experimental Molecular Pathology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; 5 Unit of Clinical Epidemiology and Trial Organization, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Background: KRAS, BRAF, NRAS and exon 20 PIK3CA quadruple wild-type CRC is associated with 41.2% response rate to anti-EGFR treatments. Even in molecular characterized patients, there is still a subset of non responders. The identification of additional predictive biomarkers is an unmet clinical need for treatment personalization. Alterations of ALK oncoprotein may interfere with the biological activity of EGFR through cross-talk of downstream signalling pathways. **Methods:** This retrospective analysis aimed to investigate the correlation between ALK gene copy number (GCN), assessed by fluorescence in situ hybridization (FISH), and clinical outcome in KRAS/NRAS/BRAF/PI3KCA wild-type chemorefractory advanced CRC patients receiving cetuximab or panitumumab. FISH was performed with break-apart ALK (2p23) probes and gain of ALK GCN was defined as a mean of 3 to 5 signals in $\geq 10\%$ of cells and amplification as ≥ 6 signals. Association of ALK status with RECIST response was performed by Fisher's exact test. **Results:** Forty-one patients were identified, of whom 17 (41%) were ALK GCN positive, whereas the remaining 24 cases (59%) were ALK GCN negative. No ALK translocations were detected. Overall response rate was 19/41 (46%). We observed a partial response in 3/17 patients with ALK GCN positive versus 16/24 patients with ALK GCN negative (18% versus 67%, respectively; $P=0.0036$). Kaplan-meier curves for comparison of median progression-free and overall survival, as well as correlation with ALK expression by immunohistochemistry, will be presented at the Meeting exploring the whole National Cancer Institute data-set. **Conclusions:** In this study population with KRAS/NRAS/BRAF/PI3KCA wild-type tumors, the response rate greater than 40% is in line with literature data. ALK GCN may be a biomarker for clinical outcome prediction in advanced chemorefractory CRC patients treated with cetuximab or panitumumab.

3642

General Poster Session (Board #14D), Sun, 8:00 AM-11:45 AM

Bevacizumab before cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal carcinomatosis of colorectal origin: Analysis of early postoperative complication rate and long term follow-up.

Clarisse Eveno, Guillaume Passot, Diane Goéré, Philippe Soyer, Etienne Gayat, Olivier Glehen, Dominique Elias, Marc Pocard; Hopital Lariboisiere, Paris, France; Centre Hospitalo-Universitaire Lyon Sud, Lyon, France; Institut Gustave Roussy, Villejuif, France; Radiology Department, Lariboisiere Hospital, Paris, France

Background: Patients with stage IV colorectal cancer and peritoneal carcinomatosis are increasingly treated with curative intent and perioperative systemic chemotherapy combined with targeted therapy. The aim of the study was to analyze the potential impact of bevacizumab on early morbidity and survival after cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with peritoneal carcinomatosis of colorectal origin. **Methods:** From 2004 to 2010, in three referral centers, 182 patients with colorectal carcinomatosis were treated with complete cytoreduction followed by HIPEC after either preoperative systemic chemotherapy alone or in combination with bevacizumab. Because there was no control on treatment allocation, propensity score methods were used to control this bias. **Results:** The median time from discontinuation of bevacizumab to HIPEC was 7 weeks (range, 6-10). Major morbidity was greater in the Beva group (34 vs. 19%, $p=0.020$). Nine patients died postoperatively: 5 (6.2%) in the Beva group ($n=80$) and 4 (3.9%) in the group treated with chemotherapy alone ($n=102$) ($p=NS$). The rate of digestive fistulas was greater in the Beva group, although not significant (18 vs. 10%, $p=NS$). After matching, the effect of Bevacizumab on major morbidity (including death) was found to be significant (OR = 2.28, 95% CI; 1.05 - 4.95) ($p=0.04$). No difference in median of overall and disease free survival was found between the two groups (12 and 36 month in Beva group vs. 14.3 and 49 month in the control group, $p=NS$). **Conclusions:** Administration of bevacizumab before surgery with complete cytoreduction followed by HIPEC for colorectal carcinomatosis is associated with 2-fold increased morbidity. The oncologic benefit of bevacizumab before HIPEC remains to be evaluated with prospective randomized study.

Maintenance with the TLR-9 agonist MGN1703 versus placebo in patients with advanced colorectal carcinoma (mCRC): A randomized phase II trial (IMPACT).

Jorge Riera-Knorrenschild, Hans-Joachim Schmoll, Dirk Arnold, Hendrik Kroening, Frank Mayer, Dieter Nitsche, Reinhard Ziehermayr, Werner Scheithauer, Johannes Andel, Christian Meisel, Manuel Schmidt, Burghardt Wittig; Universitätsklinikum Giessen und Marburg, Marburg, Germany; Martin Luther University Halle-Wittenberg, Halle, Germany; Tumor Biology Center, Freiburg, Germany; Schwerpunktpraxis für Hämatologie und Onkologie, Magdeburg, Germany; University Hospital, Medical Center II, Tuebingen, Germany; Barmherziger Schwestern Linz, Linz, Austria; Academic Teaching Hospital, Elisabethinen, Linz, Austria; Medical University of Vienna, Vienna, Austria; Landeskrankenhaus Steyr, Steyr, Austria; Charité-Universitätsmedizin Berlin, Campus Virchow-Klinikum, Berlin, Germany; Mologen AG, Berlin, Germany; Foundation Institute Molecular Biology and Bioinformatics, Freie Universität Berlin, Berlin, Germany

Background: Standard induction chemotherapy for mCRC is often discontinued in patients responding to the treatment. MGN1703, a synthetic DNA-based immunomodulator, acts as TLR-9 agonist. This trial has been conducted to assess clinical efficacy, safety, and immunogenicity of MGN1703 as maintenance therapy vs placebo. **Methods:** The IMPACT trial is an international, multicenter, randomized (2:1) double-blind placebo-controlled phase 2 trial in mCRC patients with disease control (CR, PR, SD) after 4.5 to 6 months of 1st-line induction chemotherapy with FOLFOX/XELOX or FOLFIRI +/- bevacizumab. **Results:** 59 patients have been randomized (43 MGN1703, 16 placebo). Median PFS from start of maintenance was not different with 2.8 vs 2.7 months, however the HR was 0.56 (CI 95%: 0.29-1.08; p=0.069) in favor of MGN1703, due to a small favorable subgroup with long-term PFS (20% vs 0% at 9 months; p=0.006). Total PFS from beginning of induction chemotherapy including maintenance was significantly improved: HR 0.49 (CI 95%: 0.25-0.94), p=0.029. After a median follow-up of 13 months 66% of patients are still alive (67% vs 62%), therefore survival data are still preliminary (HR 0.79; CI 95%: 0.3-2.1) and will be mature at the meeting. Activation of cellular immune function as indicated by significant increase of CD14⁺CD169⁺ monocytes was observed in all but one of the MGN1703 treated patients, while absent in all placebo patients. Treatment was well tolerated: 46.5% vs 31.3% of patients (MGN1703 vs placebo) had any drug-related adverse events (AE) and 20.9% vs 18.8% had AE with grade 3 or 4 (including hypertension, ileus, sepsis, sensory polyneuropathy, nausea/vomiting for MGN1703 and pain, popular exanthema for placebo). **Conclusions:** MGN1703 maintenance seems to prolong PFS in a subgroup of patients with disease control after induction chemotherapy vs placebo, and is associated with relative mild toxicity. This is an early signal in a selected and very limited patient population which supports further investigation. Predictive biomarkers are under evaluation to identify a potential subgroup which might have benefit from this TLR-9 MGN1703 maintenance. Clinical trial information: NCT01208194.

3644

General Poster Session (Board #14F), Sun, 8:00 AM-11:45 AM

Association of aspirin use with improved 5-year survival in colorectal cancer patients with PIK3CA mutation.

Nishi Kothari, Timothy Joseph Yeatman, Kate Fisher, Michael J. Schell, Richard D. Kim; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; Biostatistics Department, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

Background: Recent work has shown an association between longer survival and aspirin use in colorectal cancer (CRC) patients with mutated PIK3CA. It has been hypothesized that this survival advantage could occur via blocking the PI3K pathway and allowing apoptosis of mutated cancer cells. The goal of this work is to examine the use of aspirin and outcome in CRC patients with PI3KCA mutation. **Methods:** PIK3CA mutation status was assessed in paraffin-embedded tumor samples from 471 CRC patients between 1998-2010. PIK3CA mutation was assessed by exome sequencing using an Illumina Next Generation (NGS) platform with 50-100X coverage on all patients. The BWA/GATK pipeline was used to identify variants and indels. Because matched normal samples were not available for comparison to identify somatic mutations, filtering of normal variants was performed using 1000 Genomes. The usage of aspirin was collected retrospectively with electronic chart review. **Results:** Out of 471 patients, 73 were found to have unique PIK3CA mutations by NGS (15.4%). The most common mutations were found at codon 9 (38%) and codon 20 (21%). Patients had a median follow up of 47 months. Initial stage at diagnosis for PIK3CA mutants were as follows: 11 pts were stage I, 31 pts were stage II, 24 pts were stage III and 16 patients were stage IV. Of patients who died, those taking ASA had a 5% cancer related mortality compared to 23% cancer related mortality in non-ASA users. In contrast, the non-cancer related mortality was 25% in ASA users and only 8% in non-ASA users. Cancer specific rates for five year survival were 90% in the ASA group and 57% in the non-ASA group for all stages. In stage IV patients, there was 80% five year survival in the ASA users and 32% in the non-ASA group. **Conclusions:** There was a trend toward improvement in five year survival for colorectal cancer patients with PIK3CA mutations who used ASA. This trend persisted even in stage IV patients. Notably, non-cancer related deaths were higher in the ASA users, most likely secondary to medical comorbidities that necessitated ASA use. As follow up continues and this data set matures, future work will focus on validating these preliminary results and relating specific PIK3CA mutations to ASA response.

TPS3645

General Poster Session (Board #14G), Sun, 8:00 AM-11:45 AM

FOCUS4: A prospective molecularly stratified, adaptive multicenter program of randomized controlled trials for patients with colorectal cancer (CRC).

Kai-Keen Shiu, Tim Maughan, Richard H. Wilson, Richard A. Adams, Cheryl Pugh, Louise Brown, David Fisher, Harpreet Wasan, Gary William Middleton, William P. Steward, Richard S. Kaplan; Medical Research Council Clinical Trials Unit, London, United Kingdom; Gray Institute for Radiation Oncology and Biology, University of Oxford, Oxford, United Kingdom; Queen's University Belfast, Belfast, United Kingdom; Velindre Hospital, Cardiff, United Kingdom; Clinical Trials Unit, Medical Research Council, London, United Kingdom; Hammersmith Hospital, Imperial College Healthcare Trust, London, United Kingdom; University of Birmingham, Birmingham, United Kingdom; Leicester Royal Infirmary, Leicester, United Kingdom

Background: Targeted therapies based on somatic gene mutations or activated pathways have inhibited progression of some cancers. However, although various targets are identifiable in CRC, *KRAS* mutation is currently the only validated predictive biomarker for selection of a targeted therapy. FOCUS4 is a rolling phase II-III trial for testing in a staged way both the utility of molecular stratification and the efficacy of novel agents in subpopulations of mCRC patients. It is also a trial of a new strategy for testing stratified approaches to therapy in any biologically complex tumour type using a Multi-Arm, Multi-Stage design. **Methods:** The study population consists of subjects with newly diagnosed inoperable mCRC. Subjects receive first-line chemotherapy for 16 weeks. During this time the tumour is tested for *BRAF/PIK3CA/KRAS/NRAS* mutations and PTEN loss. Subjects with responding or stable disease on CT, who would normally be candidates for a treatment break, are then randomised to four coherent biomarker-based subgroups: FOCUS4-A: *BRAF* mutant, FOCUS4-B: *PIK3CA* mutant or complete loss of PTEN on IHC, FOCUS4-C: *KRAS* or *NRAS* mutant, FOCUS4-D: All wild type (no mutations of *BRAF, PIK3CA, KRAS* or *NRAS*). For each subgroup, a relevant novel agent or combination is to be tested in an adaptive double-blind placebo controlled randomised trial design with multiple interim analyses for early termination if there is no strong evidence of worthwhile activity. There will also be a 5th subgroup FOCUS4-N testing maintenance capecitabine for unclassifiable tumours or for patients whose marker defined cohort is temporarily suspended. The primary endpoint is progression free survival. Promising results in any biomarker defined cohort will then be tested for response in cohorts without the biomarker. Within the overall trial, biomarker developments can be accommodated with changes in the distribution of the cohorts or testing of new targeted agents. Enrolment will commence in May 2013. Upto 3400 patients will be registered over a 4-5 year period depending on which cohorts pass their staged interim analyses and proceed to later stages, including an overall survival endpoint. Clinical trial information: 2012-005111-12.

TPS3646

General Poster Session (Board #14H), Sun, 8:00 AM-11:45 AM

MLN0264, an investigational, first-in-class antibody-drug conjugate (ADC) targeting guanylyl cyclase C (GCC): Phase I, first-in-human study in patients (pts) with advanced gastrointestinal (GI) malignancies expressing GCC.

Khaldoun Almhanna, Wells A. Messersmith, Jordi Rodon Ahnert, Cristina Cruz, David P. Ryan, JungAh Jung, Adedigbo Fasanmade, Tim Wyant, Thea Kalebic; Moffitt Cancer Center, Tampa, FL; University of Colorado Cancer Center, Aurora, CO; Vall d'Hebron Institute of Oncology, Barcelona, Spain; Institut Català d'Oncologia, Barcelona, Spain; Massachusetts General Hospital, Boston, MA; Millennium Pharmaceuticals, Inc., Cambridge, MA

Background: MLN0264, an investigational ADC that targets GCC, consists of a fully human monoclonal antibody conjugated to the cytotoxic microtubule disrupting agent monomethyl auristatin E (MMAE) via a protease-cleavable linker. MMAE and the linker technology are licensed from Seattle Genetics. GCC is a cell surface protein expressed by normal intestinal epithelial cells, ~95% of metastatic colorectal cancer (mCRC), and subsets of gastric and pancreatic cancers. In normal tissue, GCC is expressed on the apical side of epithelial cell tight junctions; therefore, systemically delivered GCC-targeting agents are expected to be preferentially delivered to tumor tissue in which cell polarity is disrupted. MLN0264 has demonstrated antitumor activity in mouse xenograft models of GCC-expressing tumors (Veiby et al. EORTC-NCI-AACR, 2012), supporting the scientific rationale for this first-in-human study. **Methods:** This study (NCT01577758) was designed to evaluate MLN0264 in ~60 adult pts with GI malignancies expressing GCC ($\geq 1+$), measurable disease by RECIST, and ECOG PS 0/1. This study is being conducted at 4 centers in the US and EU and is estimated to last ~36–42 months. Pts receive IV MLN0264 on day 1 of 21-day cycles for up to 17 cycles or until disease progression/unacceptable MLN0264-related toxicity. Dose escalation is proceeding via an adaptive Bayesian continual reassessment model approach based on dose-limiting toxicities in cycle 1. Following determination of the maximum tolerated dose (MTD), up to 14 pts each will be enrolled to mCRC and gastric carcinoma expansion groups to further characterize the safety, tolerability, and pharmacokinetics (PK) of MLN0264 and evaluate its clinical activity. The primary objectives are to evaluate the safety and tolerability, determine the MTD, and describe the PK of IV MLN0264. Secondary objectives are to evaluate the antitumor activity and immunogenicity of MLN0264. An exploratory objective is to examine the relationship between levels of GCC protein expression in tumor tissue and clinical response. Enrollment as of Jan 2013 was 12 pts. Clinical trial information: NCT01577758.

TPS3647

General Poster Session (Board #15A), Sun, 8:00 AM-11:45 AM

A phase III study of the impact of a physical activity program on disease-free survival in patients with high-risk stage II or stage III colon cancer: A randomized controlled trial (NCIC CTG CO.21).

Christopher M. Booth, Kerry S. Courneya, Janette L. Vardy, Derek J. Jonker, Sharlene Gill, Michael Brundage, Hidde van der Ploeg, Haryana M. Dhillon, Patti O'Brien, Emma Goddard, Michael N. Pollak, Christine Friedenreich, Dongsheng Tu, Rebecca Wong, Ralph M. Meyer; Queen's University Cancer Research Institute, Kingston, ON, Canada; University of Alberta, Edmonton, AB, Canada; University of Sydney, Sydney, Australia; The Ottawa Hospital Cancer Center, Ottawa, ON, Canada; British Columbia Cancer Agency, Vancouver, BC, Canada; Queen's University, Kingston, ON, Canada; VU University Medical Center, Amsterdam, Netherlands; NCIC Clinical Trials Group, Kingston, ON, Canada; Lady Davis Institute for Medical Research, Jewish General Hospital, McGill University, Montreal, QC, Canada; Alberta Health Services Cancer Center, Calgary, AB, Canada; Princess Margaret Hospital, Radiation Medicine Program, Ontario Cancer Institute, Toronto, ON, Canada; NCIC Clinical Trials Group, Queen's University, Kingston, ON, Canada

Background: Observational data indicate that physical activity (PA) is strongly associated with colon-cancer specific survival. NCIC CTG CO.21 (CHALLENGE) is designed to determine the effects of a structured PA intervention on disease-control outcomes for survivors of high-risk stage II or III colon cancer who have completed adjuvant chemotherapy within the previous 2-6 months. **Methods:** Phase III randomized controlled trial. Target sample size of 962 patients is powered to detect a Hazard Ratio of 0.75 for disease-free survival (DFS). Trial participants will be stratified by centre, disease stage, body mass index, and performance status, and will be randomly assigned to a structured, individualized PA intervention or to general health education materials. The PA intervention will consist of a behavioural support program and supervised PA sessions delivered over a 3-year period, beginning with regular face-to-face sessions and tapering to less frequent face-to-face or telephone sessions. The goal of the PA program is to increase weekly PA by 10 MET hours/week. The PA program is delivered by physical activity consultants trained in exercise physiology and behavior change. **Outcomes:** The primary endpoint is DFS. Important secondary endpoints include multiple patient-reported outcomes (including those that address fatigue), objective physical functioning, biologic correlative markers (including assessment of the insulin pathway), and an economic analysis. **Current Enrollment:** The study is open at 19 centers in Canada and 20 centers in Australia. **Accrual as of February 4, 2013** includes 212 registered and 184 randomized patients. **Summary:** Cancer survivors and cancer care professionals are interested in the potential role of PA to improve multiple disease-related outcomes, but a randomized controlled trial is needed to provide compelling evidence to justify changes in health care policies and practice. Clinical trial information: NCT00819208.

TPS3648

General Poster Session (Board #15B), Sun, 8:00 AM-11:45 AM

Dual anti-HER2 treatment of patients with HER2-positive metastatic colorectal cancer: The HERACLES trial (HER2 Amplification for Colo-rectal Cancer Enhanced Stratification).

Silvia Marsoni, Andrea Bertotti, Andrea Sartore-Bianchi, Francesco Leone, Sara Lonardi, Fortunato Ciardiello, Carmine Pinto, Massimo Aglietta, Vittorina Zagonel, Marcello Gambacorta, Walter Franco Grigioni, Massimo Rugge, Mauro Risio, Cosimo Martino, Emanuele Valtorta, Alberto Bardelli, Livio Trusolino, Paolo M. Comoglio, Salvatore Siena; Clinical Trial Coordination Unit - IRCC Institute for Cancer Research and Treatment at Candiolo, Candiolo, Italy; Laboratory of Molecular Pharmacology - IRCC Institute for Cancer Research and Treatment at Candiolo, Candiolo, Italy; Ospedale Niguarda Ca' Granda, Milan, Italy; Division of Medical Oncology - IRCC Institute for Cancer Research and Treatment at Candiolo, Candiolo, Italy; Medical Oncology 1, Istituto Oncologico Veneto IOV - IRCCS, Padova, Italy; Second University of Naples, Naples, Italy; Medical Oncology Unit, S. Orsola-Malpighi Hospital, Bologna, Italy; Oncology 1, IOV - IRCCS, Padova, Italy; S.C. Anatomia Istologia Patologica e Citogenetica - Ospedale Niguarda Ca' Granda, Milan, Italy; Università di Bologna, Bologna, Italy; Second Unit of Pathology, Padova Teaching Hospital, Padova, Italy; Unit of Pathology, Institute for Cancer Research and Treatment, Candiolo, Italy; Laboratory of Molecular Genetics - IRCC Institute for Cancer Research and Treatment at Candiolo, Candiolo, Italy; Scientific Direction - IRCC Institute for Cancer Research and Treatment at Candiolo, Candiolo, Italy; Azienda Ospedaliera Niguarda Ca' Granda, Milano, Italy

Background: We identified HER2 amplification as a potential onco-driver and marker of de novo resistance to anti-EGFR therapy in mCRC PTS for which other known genetic alterations conferring resistance to anti EGFR antibodies were excluded. Exploiting direct transfer xenografts of mCRC surgical samples in mice (xenoPTS), we conducted a multi-arm study in HER2-amplified xenoPTS showing that combinations of lapatinib (L) and trastuzumab (T), or L and pertuzumab (P) induced long-lasting tumor regressions while monotherapy with L led to stabilization and either monotherapy with T or P were ineffective (Bertotti et al. Cancer Discov 2011). The combination of P+T has a strong rationale for treatment of HER2-amplified mCRC, since combining the two agents is synergic in HER2+ breast cancers failing T (Baselga et al. JCO 2010), suggesting a cooperative mechanism of inhibition. On these findings we designed the HERACLES trial. **Methods:** HERACLES is an independent Phase II, 2-sequential cohort trial, assessing the response rate (RR) of T combined with either L (Cohort A) or P (Cohort B), in m CRC PTS harbouring an amplified HER2 tumor (SISH). Endpoints are RR and PFS. For each cohort sample size was calculated according to the Fleming & Hern 1- stage design under identical assumptions: $H_0 = RR\ 10\%$, $H_1 = RR\ 30\%$. With a $\alpha = 0.05$, power = 0.85, 27 patient are required in each cohort (54 patients overall). A or B will be considered positive if ≥ 6 responses/27 PTS are observed. Detection and quantitation of genetic alterations in circulating tumor DNA (liquid biopsy) and Her2 ECD in plasma as potential markers of secondary resistance will be done q14 days until relapse. Eligibility: CRC histology with KRAS WT, HER2 IHC 3+ $\geq 50\%$ cells, prior treatment with fluoropyrimidines, oxaliplatin, irinotecan, anti EGFR moABs based regimens \pm Bevacizumab; measurable disease (RECIST v1.0), ECOG PS ≤ 1 , adequate organ function. Response is assessed q8w. Treatment: L 1000 mg daily po + T 4 mg/kg iv load, then 2 mg/kg iv weekly. Enrollment: since trial start (8/12/12) 198 PTS have been HER2 screened, 10 found positive and 7 are in treatment. EudraCT number : 2012-002128-33. Clinical trial information: 2012-002128-33.

TPS3649

General Poster Session (Board #15C), Sun, 8:00 AM-11:45 AM

ICE CREAM: Irinotecan cetuximab evaluation and the cetuximab response evaluation among patients with G13D mutation.

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Background: Patients with metastatic colorectal cancer (mCRC) whose disease has progressed despite oxaliplatin and irinotecan containing regimens may benefit from the use of EGFR-inhibiting monoclonal antibodies if the tumor contains no mutations in the *KRAS* gene (i.e. WT). However, it is unknown whether antibodies used in this setting, such as cetuximab, are more efficacious alone or in combination with irinotecan, as suggested by the BOND study which did not select for *KRAS* status. This international trial will also evaluate prospectively the activity of cetuximab in the subgroup of patients with mCRC with a specific *KRAS* mutation in codon G13D. In selected retrospective analyses, tumors bearing this mutation appear to derive similar response from cetuximab as WT. Trials involving small molecular subsets (in this case approx. 5% of patients with mCRC, or 18% of patients with *KRAS* mutations) will provide framework for future collaborations. **Methods:** This randomised phase II study of cetuximab +/- irinotecan will recruit patients with metastatic colorectal cancer (mCRC) with either *KRAS* WT (n=50) or G13D mutation (n=50) over 2 years from sites in Australia (12), and three international sites (G13D mutations only): Spain (1), England (1), and Italy (1). The trial will prospectively select the *KRAS* WT arm for the "quadruple WT" genotype (no mutations also in *BRAF*, *NRAS*, *PIK3CA* exon20). Primary objective is 6 month progression free survival. Secondary objectives are response rate, overall survival, quality of life, and translational research including markers that may predict response such as amphiregulin and epiregulin determined by immunohistochemistry. Eligibility: Patients with histologically confirmed CRC with either "quadruple WT" genotype or *KRAS* G13D mutation; unresectable metastatic disease; measurable or evaluable disease; ECOG 0-2; life expectancy at least 12 weeks, and disease progression, or intolerance of thymidylate synthase inhibitor and irinotecan and oxaliplatin containing regimens. Status: Opened to accrual November 2012, at 31 Jan 2013 3/100 patients have been enrolled, all with G13D mutations. Clinical trial information: ACTRN12612000901808.