4000 **Oral Abstract Session, Fri, 8:00 AM-11:00 AM**

A phase II, multicenter, open-label study of trastuzumab deruxtecan (T-DXd; DS-8201) in patients (pts) with HER2-expressing metastatic colorectal cancer (mCRC): DESTINY-CRC01.

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Background: T-DXd is an antibody-drug conjugate composed of an anti-HER2 antibody, cleavable tetrapeptide-based linker, and topoisomerase I inhibitor payload. Early studies have shown promising activity in advanced HER2-expressing tumors. DESTINY-CRC01 (DS8201-A-J203; NCT03384940) is a phase 2, open-label, multicenter study of T-DXd in pts with HER2-expressing mCRC. **Methods:** Pts with centrally confirmed HER2-expressing, *RAS*–wild type mCRC that progressed on ≥ 2 prior regimens received T-DXd 6.4 mg/kg every 3 weeks (q3w) in 3 cohorts (A: HER2 IHC 3+ or IHC 2+/ISH+; B: IHC 2+/ISH−; C: IHC 1+). The primary endpoint was confirmed objective response rate (ORR) by independent central review in cohort A; secondary endpoints included, disease control rate (DCR; CR + PR + SD), duration of response (DOR), progression-free survival (PFS), overall survival (OS), and ORR in cohorts B and C. **Results:** At data cutoff (Aug 9, 2019), 78 pts (A, 53; B, 7; C, 18) had received T-DXd. Median age was 58.5 y (range, 27-79 y), 52.6% of pts were male, and 89.7% had left colon or rectum cancer; median number of prior regimens was 4 (range, 2-11); all pts had prior irinotecan. Median treatment duration was 3.5 mo (95% CI, 2.1-4.3 mo; cohort A, 4.8 mo [95% CI, 3.9-5.8 mo]); 38.5% of pts remained on T-DXd treatment. The confirmed ORR was 45.3% (24/53 pts; 95% CI, 31.6%-59.6%) in cohort A, including 1 CR and 23 PRs; median DOR was not reached (95% CI, 4.2 mo-NE). The ORR in pts with prior anti-HER2 treatment was 43.8% (7/16 pts; 95% CI, 19.8%-70.1%). The DCR was 83.0% (44/53 pts; 95% CI, 70.2%-91.9%); median PFS was 6.9 mo (95% CI, 4.1 mo-NE); median OS was not reached. No responses were observed in cohorts B or C. Grade ≥ 3 treatment-emergent adverse events (TEAEs) occurred in 61.5% of pts (48/78); the most common (≥10%) were decreased neutrophil count (21.8%) and anemia (14.1%). Seven pts (9.0%) had TEAEs leading to drug discontinuation. Five pts (6.4%) had interstitial lung disease (ILD) adjudicated by an independent committee as related to T-DXd (2 grade 2; 1 grade 3; 2 grade 5 [the only drug-related deaths]). **Conclusions:** Overall, T-DXd 6.4 mg/kg q3w demonstrated remarkable activity in pts with HER2-expressing mCRC refractory to standard therapies, with a safety profile consistent with previous results. ILD is an important risk and requires careful recognition and intervention. Clinical trial information: NCT03384940. Research Sponsor: Daiichi Sankyo Co., Ltd.

4001 **Oral Abstract Session, Fri, 8:00 AM-11:00 AM**

Encorafenib plus cetuximab with or without binimetinib for *BRAF* V600E metastatic colorectal cancer: Updated survival results from a randomized, three-arm, phase III study versus choice of either irinotecan or FOLFIRI plus cetuximab (BEACON CRC).

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Background: BEACON CRC is a randomized, phase 3 study which evaluated the triplet of encorafenib (ENCO) + binimetinib (BINI) + cetuximab (CETUX) and the doublet of ENCO + CETUX vs. investigator's choice of irinotecan + CETUX or FOLFIRI + CETUX in patients (pts) with *BRAF*V600E metastatic colorectal cancer (mCRC) whose disease had progressed after 1-2 prior regimens in the metastatic setting. Primary endpoints were overall survival (OS) and objective response rate (ORR; by blinded central review) for triplet vs control. In a previous interim analysis, triplet and doublet improved OS and ORR versus standard of care. Here we report on an updated analysis. **Methods:** Updated analysis includes 6 months of additional follow-up and response data for all randomized pts. The study is ongoing. **Results:** Pts received triplet (n=224), doublet (n=220), or control (n=221). Median OS was 9.3 months (95% confidence interval [CI]:8.2, 10.8) for triplet and 5.9 months (95% CI:5.1-7.1) for control (hazard ratio [HR] (95% CI): 0.60 (0.47-0.75)). Median OS for doublet was 9.3 months (95% CI: 8.0-11.3) (HR vs. control: 0.61 (0.48-0.77). Confirmed ORR was 26.8% (95% CI: 21.1%-33.1%) for triplet, 19.5% (95% CI: 14.5%-25.4%) for doublet, and 1.8% (95% CI: 0.5%-4.6%) for control. Retrospective subgroup analyses suggested some pts may benefit more from triplet than doublet therapy (Table). Both triplet and doublet showed improved OS compared to control in all subgroups. Adverse events were consistent with prior analysis, with grade ≥3 adverse events in 65.8%, 57.4%, and 64.2% for triplet, doublet and control, respectively. **Conclusions:** The updated analysis of the BEACON CRC study confirmed that encorafenib + cetuximab with or without binimetinib improved OS and ORR in previously treated pts with *BRAF* V600E mCRC compared with standard chemotherapy. Clinical trial information: NCT02928224. Research Sponsor: Pfizer Inc.

OS in select subgroups, triplet vs. doublet.

		Events/Patients	Triplet vs Doublet Medians (months)	HR (95% CI)*
All Patients		265/444	9.3 vs 9.3	0.95 (0.74-1.21)
CRP	**High**	139/174	6.5 vs 5.1	0.76 (0.54, 1.06)
	Normal	120/261	13.8 vs 14.0	1.09 (0.76, 1.56)
ECOG PS	**1**	153/216	8.1 vs 6.1	0.81 (0.59, 1.11)
	0	112/228	10.4 vs 13.9	1.28 (0.88, 1.86)
No. of organs	**3+**	141/214	8.5 vs 6.7	0.69 (0.49, 0.96)
	<=2	124/230	10.0 vs 12.3	1.34 (0.94, 1.91)
Tumor Status	**Partially/Not Resected**	123/188	8.5 vs 8.3	0.80 (0.56, 1.14)
	Resected	142/256	9.5 vs 12.3	1.20 (0.86, 1.68)

*HR<1 favors triplet; HR>1 favors doublet

4002 **Oral Abstract Session, Fri, 8:00 AM-11:00 AM**

First-line FOLFOX plus panitumumab versus 5FU plus panitumumab in RAS-BRAF wild-type metastatic colorectal cancer elderly patients: The PANDA study.

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Background: Data on first-line treatment efficacy in elderly patients are limited. Many analyses adopt a questionable cut-off of 65 years and specific evidence with anti-EGFRs is low. FOLFOX-panitumumab (pan) is an option for RAS wild-type (wt) untreated mCRC patients. Guidelines recommend considering fluoropyrimidine monotherapy as an option for elderly patients, but no randomized studies have ever explored the role of the combination with an anti-EGFR. **Methods:** This is a prospective, open-label, multicenter phase II randomized trial. Unresectable and previously untreated *RAS-BRAF* wt mCRC patients aged ≥70 were randomized to receive FOLFOX-pan (arm A), or 5FU/LV-pan (arm B) for up to 12 cycles followed by pan maintenance until PD. The primary EP was PFS in both arms. Stratification criteria were age (≤75 vs > 75 years), ECOG PS (0–1 vs 2) and geriatric assessment with G8 Score (≤14 vs > 14). In each treatment arm, the null hypothesis for median PFS was set at ≤6 months. Assuming an expected median PFS time ≥9.5 months with both experimental regimens, a sample size of 90 patients in each arm granted to the study a power of 90%, with a type I error rate equal to 5% (1-sided Brookmeyer-Crowley test) for rejecting the null hypothesis. No formal comparison between the two arms was planned. **Results:** From Jul 2016 to Apr 2019 a total of 394 patients were screened, 211 were deemed eligible for inclusion and 185 were randomized (92 arm A and 93 arm B). Main pts' characteristics were (arm A/B): males 66%/61%; median age 77/77y; PS≥1 49%/55%; right colon 23%/21%; G8 > 14 31%/30%. At a median follow up of 20.5 mos, 135 (arm A/B: 64/71) PD events were collected. Median PFS was 9.6 (95% CI 8.8-10.9) in arm A with FOLFOX-pan and 9.1 (95% CI 7.7-9.9) in arm B with 5FU/LV-pan. Response rates were (arm A/B): 65%/57%. Grade 3-4 toxicities were (arm A/B): neutropenia 9.8%/1.1%; diarrhea 16.3%/1.1%; stomatitis 9.8%/4.4%; neurotoxicity 3.3%/0%; fatigue 6.5%/4.4%; skin rash 25%/24.2%, hypomagnesemia 3.3%/7.7%. **Conclusions:** Large prospective randomized studies in molecularly selected elderly mCRC are feasible with multi-center collaborative efforts. Primary EP was met in both treatment arms. 5FU/LV plus panitumumab for up to 12 cycles followed by panitumumab maintenance until PD might be a reasonable option in elderly mCRC patients with RAS/BRAF wt tumors deserving further investigations in phase III trials. Clinical trial information: NCT02904031. Research Sponsor: GONO Group, Pharmaceutical/Biotech Company.

4003 **Oral Abstract Session, Fri, 8:00 AM-11:00 AM**

Celecoxib in addition to standard adjuvant therapy with 5-fluorouracil, leucovorin, oxaliplatin (FOLFOX) in stage III colon cancer: Results from CALGB/SWOG 80702.

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Background: Aspirin and cyclooxygenase-2 (COX-2) inhibitors have been associated with a reduced risk of colorectal polyps and cancer in observational and randomized studies. CALGB/SWOG 80702 tested the effect of celecoxib, a COX-2 inhibitor, on reducing the risk of recurrence in stage III CC. **Methods:** CALGB/SWOG 80702 is a 2x2 randomized controlled phase III trial of 3 v 6 months of adjuvant FOLFOX (data previously reported as part of the IDEA collaboration) with concurrent celecoxib (400 mg daily) v placebo x 3 yrs for patients (pts) with resected stage III CC. The primary endpoint of the trial is disease-free survival (DFS), defined as time from randomization to recurrence or death from any cause. The trial was designed to provide 91% power to detect a hazard ratio (HR) of 0.79 in favor of celecoxib with 2-sided alpha = 0.05 (775 events required); due to slowing accumulation of events 4 years after complete accrual, power was lowered to 85% with same HR and alpha assumptions (696 events required). The DSMB released data on February 24, 2020 at median f/u of 5.6 yrs with 689 DFS events. **Results:** Between June 2010 and November 2015, 2,526 pts were consented and randomized to the trial. Treatment arms were well balanced by patient and tumor prognostic features, as well as low-dose aspirin use. Baseline characteristics included 45% female, 18% non-White, 8% Hispanic, 15% T4, 26% N2. 3-yr DFS for celecoxib was 76.3% v 73.3% for placebo (HR 0.89 [95% CI 0.77-1.04]; P = 0.14). 5-yr overall survival (OS) was 83.9% for celecoxib v 81.7% for placebo (HR 0.87 [95% CI 0.72-1.05]; P = 0.14). When considering the 4 treatment arms separately, 3-yr DFS was 77.0% for 12 months FOLFOX + celecoxib, 74.9% for 12 months FOLFOX + placebo, 75.5% for 6 months FOLFOX + celecoxib, and 71.9% for 6 months FOLFOX + placebo (log rank P = 0.22; P interaction = 0.64). There were no significant differences in grade 3-4 toxicity with celecoxib v placebo. Compliance with protocol celecoxib treatment, defined as 3 yrs of therapy completion or recurrence/death while on treatment, was 58.1% pts on celecoxib and 60.2% pts on placebo. **Conclusions:** The addition of celecoxib to standard chemotherapy did not significantly improve DFS or OS. Clinical trial information: NCT01150045. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

Overall survival (OS) and long-term disease-free survival (DFS) of three versus six months of adjuvant (adj) oxaliplatin and fluoropyrimidine-based therapy for patients (pts) with stage III colon cancer (CC): Final results from the IDEA (International Duration Evaluation of Adj chemotherapy) collaboration.

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Background: In overall population, IDEA pooled analysis did not demonstrate non-inferiority (NI) regarding 3y DFS in pts with stage III CC receiving 3m vs. 6m of adj FOLFOX/CAPOX. However, in pts treated with CAPOX (especially in low-risk pts), 3m of therapy was as effective as 6m. Results of OS and 5y DFS are reported. **Methods:** OS was defined as time from enrollment to death due to all causes. OS NI margin was conservatively set to be Hazard Ratio (HR) = 1.11, which is equivalent to: the maximum acceptable loss of OS efficacy, by shortening treatment to 3m, was half of the OS efficacy gained in MOSAIC trial (i.e., 2.26% absolute reduction in 5y OS rate). Pre-planned sub-group analyses included by regimen and risk group for both OS and 5y DFS. NI was to be declared if the one-sided false discovery rate adjusted (FDRa) NI p-value < 0.025. **Results:** With an overall median survival follow-up of 72 m (range per study, 62 to 84 m), 2584 deaths and 3777 DFS events among 12,835 pts from six trials were observed. Across 6 studies, 39.5% of pts received CAPOX (rate by study, 0% to 75.1%). Overall, the 5y OS rate was 82.4% (3m) and 82.8% (6m), with estimated OS HR of 1.02 (95% confidence interval [CI], 0.95-1.11; FDRa NI p, 0.058) and absolute 5-y OS rate difference of -0.4% (95% CI, -2.1 to 1.3%). Overall, the 5y DFS rate was 69.1% (3m) and 70.8% (6m), with estimated DFS HR of 1.08 (95%CI, 1.01-1.15, FDRa NI p, 0.22). HRs (95% CI) within subgroups see table. **Conclusions:** 5y OS rate reported in IDEA trials was higher than historical rates, regardless of duration of therapy. While overall survival in IDEA did not meet prior statistical assumptions for NI in overall population, the 0.4% difference in 5y OS should be placed in clinical context. OS and 5y DFS results continue to support the use of 3m adjuvant CAPOX for the vast majority of stage III colon cancer pts. This conclusion is strengthened by the substantial reduction of toxicities, inconveniencies and cost associated with shorter treatment duration. Clinical trial information: NCT01150045; 2009-010384-16; NCT00749450; ISRCTN59757862; 2007-003957-10; UMIN000008543; 2007-000354. Research Sponsor: U.S. National Institutes of Health, Other Government Agency.

	OS	Long-term DFS
CAPOX	0.96 (0.85, 1.08)	0.98 (0.88, 1.08)
FOLFOX	1.07 (0.97, 1.18)	1.16 (1.06, 1.26)
Low Risk (T1-3 N1)	0.95 (0.84, 1.08)	1.04 (0.94, 1.14)
High Risk (T4 or N2)	1.08 (0.98, 1.19)	1.12 (1.03, 1.22)

4005 **Oral Abstract Session, Fri, 8:00 AM-11:00 AM**

A randomized phase II/III trial comparing hepatectomy followed by mFOLFOX6 with hepatectomy alone for liver metastasis from colorectal cancer: JCOG0603 study.

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Background: The role of adjuvant chemotherapy after hepatectomy is controversial for liver only metastases from colorectal cancer (LM). Current recommendations for oxaliplatin-containing adjuvant regimen (FOLFOX) for LM are based on extrapolation of the results of the EORTC intergroup trial 40983, which showed that perioperative FOLFOX confirmed a progression-free survival benefit but did not affect overall survival (OS) in LM patients. We conducted a randomized controlled trial to determine if adjuvant modified FOLFOX (mFOLFOX) is superior to hepatectomy alone for LM. **Methods:** Eligible patients aged 20-75 years who had histologically proven colorectal adenocarcinoma with an unlimited number of LM were randomly assigned (1:1) to receive either adjuvant mFOLFOX6 (oxaliplatin 85mg/m^2, l-LV 200 mg/m^2, 5-FU bolus 400 mg/m^2 and 2400mg/m^2 over 48 h), for 12 cycles after surgery (CTX arm), or surgery alone (S alone arm). When treatment compliance after 9 courses of CTX was as high as expected in phase II, the registration was continued in phase III. The primary endpoint of phase III was disease-free survival (DFS), and the secondary endpoints were OS, toxicity, and sites of relapse. The planned sample size was 150 patients (pts) per arm, with a one-sided alpha of 5%, and 80% power detecting a 5y-DFS difference of 12% (25% with S alone vs. 37% with CTX). **Results:** Between Mar. 2007 and Jan. 2019, 300 patients were randomized. 151 pts were allocated to CTX, and 149 pts to S alone. When the third interim analysis of phase III was performed in Dec. 2019, the DSMC recommended the early termination of the trial because a statistically significant difference in terms of DFS but the futility in terms of OS was found. With a median follow-up period of 54 months for disease-free surviving patients, the 3y-DFS was 52.1% (95% CI 43.2 – 60.2) with CTX and 41.5% (33.2 – 49.6) with S alone (hazard ratio 0.63 [0.45 – 0.89], one-sided $p = 0.002 < 0.0163$ for the one-sided alpha level at the interim analysis). However, the 3y-OS was 86.6% (79.2-91.4) with CTX and 92.2% (86.0 – 95.8) with S alone (hazard ratio 1.35 [0.84 – 2.19]). The 5y-OS was 69.5% (59.6-77.5) with CTX and 83.0% (74.5-88.9) with S alone. Median OS after recurrence was 38.4 months in the CTX arm and 87.6 in the S alone arm. **Conclusions:** DFS did not correlate with OS for LM. Postoperative chemotherapy with mFOLFOX6 improves DFS but worsens OS over surgery alone due to more deaths after recurrence in the CTX arm. Adjuvant mFOLFOX is not beneficial to patients after hepatectomy for LM. Clinical trial information: UMIN000000653. Research Sponsor: National Cancer Center Research and Development Fund and Grants-in-Aid for Cancer Research.

Short-course radiotherapy followed by chemotherapy before TME in locally advanced rectal cancer: The randomized RAPIDO trial.

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Background: Local control in locally advanced rectal cancer (LARC) has improved. However, systemic relapses remain high even with postoperative chemotherapy, possibly due to low compliance. Short-course radiotherapy (SCRT) followed by delayed surgery with, in the waiting period, chemotherapy, may lead to better compliance, downstaging and fewer distant metastases. The main objective of the international multicenter phase III RAPIDO trial is to decrease Disease-related Treatment Failure (DrTF), defined as locoregional failure, distant metastasis, a new primary colon tumor or treatment-related death, by reducing the risk of systemic relapse without compromising local control. **Methods:** MRI-diagnosed LARC patients with either cT4a/b, extramural vascular invasion, cN2, involved mesorectal fascia or enlarged lateral lymph nodes considered to be metastatic were randomly assigned to SCRT (5x5 Gy) with subsequent six cycles of CAPOX or nine cycles of FOLFOX4 followed by total mesorectal excision (TME) (experimental arm) or, capecitabine-based chemoradiotherapy (25-28 x 2.0-1.8 Gy) followed by TME and optional, predefined by hospital policy, postoperative eight cycles of CAPOX or twelve cycles of FOLFOX4 (standard arm). **Results:** Between June 2011 and June 2016, 920 patients were randomized. Pathological complete response rates were 27.7% vs 13.8% (OR 2.40 [1.70 – 3.39]; $p < 0.001$) in the experimental and standard arms, respectively. At three years, cumulative probability of DrTF was 23.7% in the experimental arm and 30.4% in the standard arm (HR 0.76 [0.60 – 0.96]; $p = 0.02$). Probability at three years of distant metastasis and locoregional failure were, in the experimental and standard arms, 19.8% vs 26.6% (HR 0.69 [0.53 – 0.89]; $p = 0.004$) and 8.7% vs 6.0% (HR 1.45 [0.93 – 2.25]; $p = 0.10$), respectively. No differences in DrTF between hospitals with or without policy for postoperative chemotherapy were found ($p = 0.37$). Overall health ($p = 0.192$), quality of life ($p = 0.125$) and low anterior resection syndrome score ($p = 0.136$) were comparable between the two treatment arms. **Conclusions:** A lower rate of DrTF, as a result of a lower rate of distant metastases, in high-risk LARC patients can be achieved with preoperative short-course radiotherapy, followed by chemotherapy and TME than by conventional chemoradiotherapy. In addition, the high pCR rate, achieved with the experimental treatment regimen can contribute to organ preservation. This treatment can be considered as a new standard of care. Clinical trial information: NCT01558921. Research Sponsor: Dutch Cancer Foundation, Swedish Cancer Society, Swedish Research Council, Spanish Ministry of Economy and Competitiveness, Spanish Clinical Research Network and European Regional Development Fund.

4007 **Oral Abstract Session, Fri, 8:00 AM-11:00 AM**

Total neoadjuvant therapy with mFOLFIRINOX versus preoperative chemoradiation in patients with locally advanced rectal cancer: Final results of PRODIGE 23 phase III trial, a UNICANCER GI trial.

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Background: PRODIGE 23 investigated the role of neoadjuvant mFOLFIRINOX before preoperative (preop) chemoradiation (CRT), with TME-surgery and adjuvant chemotherapy (CT) in resectable locally advanced rectal cancer. **Methods:** PRODIGE 23 is a phase III multicenter randomized clinical trial. Eligible pts had cT3 or cT4, M0 rectal adenocarcinomas $<$15 cm from the anal verge, age 18-75 years, and WHO PS $\leq$1. Randomization was stratified by center, T stage, N status, tumor location, and perirectal fat extramural extension. Primary endpoint was 3-yr disease-free survival (DFS). Main secondary endpoints were ypT0N0 rate, overall survival (OS) and metastasis-free survival (MFS). 460 pts were required to observe 136 events to show a gain in 3-year DFS from 75% to 85% (HR=0.56) with a 2-sided α=0.05 and 90% power. HR and 95% CI were estimated by a stratified Cox proportional hazard model. Arm A pts received preop CRT (50 Gy, 2 Gy/fraction [fr]; 25 fr + capecitabine), surgery, then adjuvant CT for 6 months (mos). Arm B pts received 6 cycles of mFOLFIRINOX (oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, irinotecan 180 mg/m^2 D1, and 5-FU 2.4 g/m^2 over 46 h) every 14 days, followed by the same preop CRT, surgery and 3 mos of adjuvant CT. Adjuvant CT consisted of mFOLFOX6 or capecitabine, depending on the centre's choice for all pts. Imaging work-up, operative and pathology reports were centrally reviewed. **Results:** (ITT) Between 6/2012 and 6/2017, 230 and 231 pts were randomly assigned in Arm A/B, respectively by 35 participating centers. Pts characteristics were well balanced. Neoadjuvant mFOLFIRINOX and CRT in both arms were well tolerated. Compliance to CRT and to adjuvant CT was not hampered by neoadjuvant CT. Surgical morbidity did not differ between the 2 arms. The ypT0N0 rate was 11.7 vs 27.5% in Arm A/B ($p<0.001$). Median follow-up was 46.5 mos. 136 DFS events was reported. 3-yr DFS was significantly increased in arm B (HR 0.69, 95% CI 0.49-0.97, p=0.034): 68.5% (CI: 61.9-74.2) vs 75.7% (CI: 69.4-80.8) in arm A/B. The subgroup analysis showed no evidence of heterogeneity of the effect size of treatment on DFS. 3-yr MFS was also significantly higher in arm B: 71.7 in arm A vs 78.8% (HR 0.64, CI 0.44-0.93, $p<0.02$) in arm B. 3-yr OS was 87.7 vs 90.8% (HR 0.65, CI 0.40-1.05, p=0.077) in arm A/B, with 54.2% of the pts with recurrence being alive. **Conclusions:** Neoadjuvant mFOLFIRINOX plus CRT is safe, and significantly increased ypCR rate, DFS and MFS. OS data are not mature. Clinical trial information: NCT01804790. Research Sponsor: FRENCH CANCER INSTITUTE - INCA - PHRC, Other Foundation.

4008 **Oral Abstract Session, Fri, 8:00 AM-11:00 AM**

Preliminary results of the organ preservation of rectal adenocarcinoma (OPRA) trial.

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Background: Organ preservation (OP) with a watch and wait strategy (WW) and total neoadjuvant therapy (TNT) are new treatment paradigms for patients with locally advanced rectal cancer. The safety and efficacy of WW and of TNT have not been studied prospectively. **Methods:** Patients with MRI stage II and III rectal adenocarcinoma were randomized to 4 months of FOLFOX or CAPEOX before (Induction) or after (Consolidation) fluorouracil or capecitabine based chemoradiotherapy (CRT). Patients were re-staged 8-12 weeks after finishing TNT with digital rectal exam, flexible sigmoidoscopy and MRI. Patients with complete or near-complete clinical response were offered WW. Those with incomplete response had total mesorectal excision. The trial was designed so that each arm served as its own single-stage study that discriminates between 3-year disease-free survival (DFS) rates of 75% (historical null) and 85%, with 86% power, and a two-sided type I error of 5%. Secondary objectives included comparing DFS, OP, and distant metastasis-free survival (DMFS) rates between the two arms using the log-rank test. **Results:** Of 324 patients enrolled, 307 (152 I, 155 C) are currently evaluable for the time-to-event analysis as of 2/1/2020. Median follow-up is 2.1 years; 52 DFS events were observed. Patient demographics and tumor characteristics were generally balanced across the two arms. Full compliance with systemic chemotherapy was 82% and 81% for the I- and C-arms, respectively. The median radiation dose was 5400 cGy for both arms. Table shows 3-y DFS, DMFS, and OP rates. **Conclusions:** A WW strategy for patients with locally advanced rectal cancer that achieve a clinical complete response to TNT results in organ preservation for a high proportion of patients without compromising survival. Up-front CRT followed by consolidation chemotherapy resulted in a numerically higher WW rate compared to induction chemotherapy followed by CRT. Clinical trial information: NCT02008656. Research Sponsor: U.S. National Institutes of Health.

3-year rates with 95% CI.

	Induction		Consolidation		p*
DFS	78%	(70%,87%)	77%	(69%,86%)	0.90
DMFS	81%	(74%,90%)	83%	(76%,91%)	0.86
OP	43%	(35%,54%)	58%	(49%,69%)	0.01

*log-rank test

4009 Poster Discussion Session; Displayed in Poster Session (Board #1), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Circulating tumor DNA to detect minimal residual disease, response to adjuvant therapy, and identify patients at high risk of recurrence in patients with stage I-III CRC.

Noelia Tarazona, Tenna V Henriksen, Juan Antonio Carbonell-Asins, Thomas Reinert, Shruti Sharma, Desamparados Roda, Svetlana Shchegrova, Marisol Huerta, Susana Roselló, Derrick Renner, Himanshu Sethi, Bernhard Zimmermann, Alexey Aleshin, Andres Cervantes, Claus Lindbjerg Andersen; Department of Medical Oncology, INCLIVA Biomedical Research Institute, University of Valencia, Instituto de Salud Carlos III, CIBERONC, Valencia, Spain; Department of Molecular and Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark; Department of Medical Oncology & Bioinformatics and Biostatistics Unit, INCLIVA Biomedical Research Institute, University of Valencia, Valencia, Spain, Valencia, Spain; Aarhus University Hospital, Aarhus, Denmark; Natera, Inc., San Carlos, CA; Department of Medical Oncology, INCLIVA Biomedical Research Institute, University of Valencia, Valencia, Spain; Department of Molecular Medicine, Aarhus University Hospital/Skejby, Århus N, Denmark

Background: The clinical utility of tracking circulating tumor DNA (ctDNA) as a non-invasive biomarker for detecting minimal residual disease (MRD) and stratifying patients based on their risk of developing relapse has been well established in colorectal cancer (CRC). This study evaluates the detection and longitudinal monitoring of ctDNA in CRC patients pre- and post-operatively, during and after adjuvant chemotherapy (ACT). **Methods:** The prospective, multicenter cohort study recruited patients (n = 193) diagnosed with resected stage I-III CRC. Plasma samples (n = 1052) were collected at various timepoints with a median follow up of 21.6 months (4.6-38.5 months). Individual tumors and matched germline DNA were whole-exome sequenced and somatic mutations identified. Multiplex PCR assays were designed to 16 tumor-specific single-nucleotide variants to track ctDNA in plasma samples. The study evaluated the relationship between ctDNA status and clinical outcomes including radiologic imaging. Cox regression was used to calculate recurrence-free survival (RFS) in patients stratified by ctDNA status postoperatively and post-ACT. Multivariable analysis was performed with all clinical variables. Best model was selected according to Akaike Information Criterion. **Results:** Pre-operatively ctDNA was detected in 90% (n = 166/185) of the patients. Post-operative ctDNA status prior to ACT was assessed in 152 patients, of which 9.2% (14/152) were identified to be MRD-positive and 78.5% (11/14) eventually relapsed. In contrast, 10.1% (14/138) of MRD-negative cases relapsed (HR: 16.53; 95% CI: 7.19-38.02; $p < 0.001$). Longitudinal ctDNA-positive status, post-ACT (n = 84) and post definitive therapy (n = 139) was associated with a 27.92 HR (95% CI: 9.16-85.11; $p < 0.001$) and a 47.52 HR (95% CI: 17.34-130.3.; $p < 0.001$), respectively. In the multivariable analysis, longitudinal ctDNA status was the only significant prognostic factor associated with RFS (HR: 53.19, 95% CI: 18.87-149.90; $p < 0.001$). Serial ctDNA analysis detected MRD up to a median of 9.08 months (0.56-16.5 months) ahead of radiologic relapse with a sensitivity of 79.1% and specificity of 99%. **Conclusions:** Postoperative ctDNA analyses detect patients with high-risk of recurrence, with near 100% specificity. Early detection of MRD and longitudinal monitoring of ctDNA could guide treatment decisions. Intervention trials to assess the clinical benefit of ctDNA use are underway. Research Sponsor: Natera, Inc., San Carlos, CA.

4010 Poster Discussion Session; Displayed in Poster Session (Board #2), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

A new prognostic and predictive tool to enhance shared decision making in stage III colon cancer.

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Background: Survival outcomes in patients with stage III colon cancer varies widely according to T-N sub-stages. The ability to estimate the benefit of each therapeutic option (surgery alone, fluoropyrimidines alone, oxaliplatin-based doublet for either 3 or 6 months) in each T-N subgroup within stage III, may provide more accurate information helping doctors and patients in the complex shared decision-making process surrounding adjuvant therapy. **Methods:** Theoutcomedata of 12,834 patients with stage III colon cancer enrolled in the IDEA trial served as our database. Patients were categorized in 16 sub-stages, based on the T-N categories. We created a meta-regression model to predict the expected 3-year DFS within each T-N sub-stage and hence the 5-year DFS rates were projected. We then evaluated the efficacy of each therapeutic option in every sub-stage, working backward by subtraction, using an average of the HRs reported in the pertinent trials publication as conversion factor. **Results:** Large differences in 3-year DFS rate were observed among the subgroups, ranging from 95% (T1N1a) to 29% (T4N2b) in the overall population. The contribution to outcome of each therapeutic option in this setting varied widely across sub-stages. According to our model, patients with T1N1a cancers have a projected 5-year DFS of 85% with surgery alone. Adjuvant fluoropyrimidine alone results in 4.2% absolute DFS gain; an additional 1.7% and 0.6% gain is seen with oxaliplatin for 3 and 6 months, respectively. Patients with T4N2b cancers show a 4.7% 5-year DFS with surgery alone, and a 7.1%, 5.0%, 2.1% increase with the aforementioned adjuvant options, respectively. **Conclusions:** The resulting overlay bar graph gives patients and doctors the projected relative benefit of each treatment option and may substantially help the shared decision-making process. Research Sponsor: This research was partly supported by Associazione Italiana per la Ricerca sul Cancro (AIRC) IG 2018; by the National Cancer Institute at the National Institutes of Health [grant number: U10CA180882]; NCA (Institut National du Cancer) and PHRC2009 (Inst.

4011 Poster Discussion Session; Displayed in Poster Session (Board #3), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Impact of high-risk features on disease-free survival (DFS) in patients (pts) with high-risk stage II colon cancer (CC) in ACHIEVE-2 trial as part of the IDEA collaboration.

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Background: The IDEA collaboration for high-risk stage 2 colorectal cancer patients (pts) demonstrated that for CAPOX, 3 months was non-inferior to 6 months treatment, while for FOLFOX, 6 months was superior to 3 months treatment. We investigated the impact of high risk features on disease-free survival (DFS). **Methods:** ACHIEVE-2, one of the 4 IDEA studies (SCOT, TOSCA, ACHIEVE-2, HORG), was an open-label, multicenter randomized trial for high-risk stage II colon cancer. High risk features are defined as one or more: T4, inadequate nodal harvest < 12, poorly differentiated, clinical sign of obstruction and perforation or vascular invasion. The association of high risk features with DFS were measured by Cox regression analyses. **Results:** Between 2014 and 2017, ACHIEVE-2 enrolled 525 pts, out of whom 514 pts were the modified ITT (mITT) population; 432 received CAPOX (84.0%) and 82 did mFOLFOX6 (16.0%). High-risk features included 35.8% of T4, 12.8% of inadequate nodal harvest, 11.5% of poorly differentiated, 19.3% of obstruction, 6.4% of perforation and 87.5% of vascular invasion; 47.3% had one features, 35.2% had two, 14.6% had three, and 2.9% had four or more. With a median follow-up of 36.1 months, 3-year DFS rates were 88% in both arms, with a hazard ratio (HR) of 1.12 (95% CI, 0.67-1.87, p=0.67). In multivariate analysis, T4 (HR 3.77 [2.18-6.53], $p< 0.0001$) and inadequate nodal harvest (HR 2.98 [1.59-5.59], p= 0.0006) remained independent significant negative prognostic factors. The 3-year DFS rates in T4 and Non-T4 diseases were 78% and 94% ($p<0.0001$), while 3-year DFS rate in pts with inadequate and adequate nodal harvest were 77% and 90% (p=0.0059). No interaction was observed between treatment duration and T4 or inadequate nodal harvest. **Conclusions:** Our findings indicated the relative impact of high risk features on DFS varies across factors; T4 and inadequate nodal harvest < 12 were more significant than the others. Our results must be interpreted within the combined analysis as well as within the reproducibility of results across the 4 trials. Clinical trial information: 000013036. Research Sponsor: None.

4012 Poster Discussion Session; Displayed in Poster Session (Board #4), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Improving the AJCC/TNM staging classification for colorectal cancer: The prognostic impact of tumor deposits.

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Background: Identification of tumor deposits (TD) currently plays a limited role in staging for colorectal cancer (CRC) other than for N1c designation. The aim of this study was to determine the prognostic impact, beyond AJCC N1c designation, of TD among primary CRC patients. **Methods:** Patients with stage 1 to 3 primary CRC diagnosed between 2010 and 2015 were identified from the Surveillance, Epidemiology and End Results (SEER) database. Cancer specific survival (CSS) stratified by TDs and nodal status was calculated, and Kaplan-Meier method and multivariable COX proportional hazards regression analyses were performed. **Results:** A total of 74,494 patients with primary CRC were identified. Mean age was 66.4 (SD+/-13.2) years, 36,988 (49.7%) were female and 40,651 (54.6%) were right-sided. TDs were present in 4,481 patients (6.0%) and 26,603 (35.7%) had lymph node metastases. The presence of TDs were significantly associated with adverse tumor characteristics including advanced pathological stage, nodal and metastasis status, higher grade and perineural invasion. Incorporating TDs into each nodal status was independently associated with worse CSS and supported reclassification of nodal status to incorporate TDs following multivariable regression analysis as outlined in the table. Following multivariable regression analysis, the proposed AJCC nodal reclassification incorporating TDs, in combination with tumor stage was a strong predictor of CSS, and also represents a new summary staging. **Conclusions:** TDs are an independent predictor of worse outcome in CRC. The presence of TDs have distinctly different CSS and these data support modification of the current N classification. This study proposes a reclassification of the AJCC system for CRC to incorporate TDs and informs an updated node and summary stage. Research Sponsor: None.

Proposed AJCC Reclassification	Includes current & modification	Adjusted HR (95% CIs)
N0	N0	1.00
N1a	N1a TD-ve	1.90 (1.78-2.05)
N1b	N1b TD-ve, N1c	2.63 (2.48-2.80)
N1c	Removed	-
N2a	N2a TD-ve, N1a-b TD+ve	3.73 (3.50-3.98)
N2b	N2a TD +ve, N2b TD-ve	6.12 (5.73-6.54)
N3	N2b TD+ve	7.91 (6.94-9.01)

4013 Poster Discussion Session; Displayed in Poster Session (Board #5), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

FOxTROT: neoadjuvant FOLFOX chemotherapy with or without panitumumab (Pan) for patients (pts) with locally advanced colon cancer (CC).

Jenny F. Seligmann, FOxTROT Collaborative Group; University of Leeds, Leeds, United Kingdom

Background: FOxTROT has reported marked down-staging, reduced perioperative morbidity and a trend towards fewer recurrences with 6 wks of oxaliplatin-fluoropyrimidine neoadjuvant chemotherapy (NAC) in CC (Seymour, ASCO 2019 abstract 3504). Using updated data, we investigate the contribution of panitumumab (Pan) and tumour markers to efficacy of NAC. **Methods:** 1053 pts with radiologically-staged T3-4, N0-2, M0 CC were randomly allocated (2:1) to either 6 wks of NAC and 18 wks of postoperative adjuvant chemotherapy (AC) or 24 wks of AC. 279 pts with *RAS*-wt tumours were also randomised 1:1 to receive Pan or not with NAC. The primary endpoint was freedom from recurrence or residual disease at 2 years for NAC vs AC, and depth of extramural spread for the Pan randomisation; secondary endpoints include safety, histological downstaging, CC-specific survival and OS. **Results:** Of 699 allocated pre-and-postoperative chemotherapy, 674 (97%) started and 612 (88%) completed NAC. 684/699 (97.8%) pre-and-postoperative and 349/354 (98.6%) control patients underwent tumour resection. There was marked T- and N-down-staging and tumour regression with NAC (all $p<0.001$). There were fewer disease recurrences within 2 years in the NAC than AC group: 15.6% (109/698) vs 19.5% (69/354), RR=0.76 (95%CI 0.56-1.02), P=0.07. Response to NAC was significantly ($p<0.001$) less in MMR-deficient (dMMR) than MMR-proficient (pMMR) tumours: 7%(8/115) vs 23%(128/553) moderate or greater histological tumour regression. Reductions in 2-year recurrence were also seen only in pMMR tumours [RR=0.72 (0.52-1.00), p=0.05], with no apparent benefit in dMMR tumours: RR=0.94 (0.43 to 2.07), p=0.9]. Analyses of panitumumab will be presented. **Conclusions:** Six weeks of NAC for operable CC can be delivered safely, with marked histopathological down-staging, and may result in better disease control at 2 years in pMMR disease. Clinical trial information: 87163246. Research Sponsor: Cancer Research UK, Pharmaceutical/ Biotech Company.

4014 Poster Discussion Session; Displayed in Poster Session (Board #6), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Tailored treatment strategy for locally advanced rectal carcinoma: Five-year results of the French phase II, randomized, multicenter GRECCAR4 trial.

Philippe Rouanet; Institut Régional du Cancer de Montpellier, Montpellier, France

Background: Preoperative radiochemotherapy and total mesorectal excision are the standard-of-care for locally-advanced rectal carcinoma, but some patients are over- or undertreated. Our phase II study assessed the feasibility of tailored radiochemotherapy, based on tumor response to induction high-dose chemotherapy (FOLFIRINOX). **Methods:** We enrolled 206 patients; good responders after chemotherapy (≥75% tumor volume reduction) were randomly assigned to immediate surgery (arm A) or standard radiochemotherapy (Cap 50: 50 Gy and oral capecitabine daily) plus surgery (arm B). Poor responders were randomly assigned to Cap 50 (arm C) or intensive radiochemotherapy (Cap 60 (60 Gy irradiation), arm D) before surgery. **Results:** After induction treatment, 194 patients were classified as good (n=30, 15%) or poor (n=164, 85%) responders, and included in arms A and B (16 and 14 patients) or C and D (113 and 51 patients). The primary objective was obtained: (90% CI) R0 resection rates in the four arms respectively were 100% (74–100), 100% (85–100), 83% (72–91), and 88% (77–95). At 5 years: overall survival 90% (CI: 47.3-98.5), 93.3% (CI: 61.3-99.0), 84.3% (CI: 71.0-91.8), 86.1% (CI: 71.6-93.5); disease-free survival 80% (CI: 40.9-94.6), 89.5% (CI: 64.1-97.3), 72.9% (CI: 58.5-82.9), 72.8% (CI: 57.7-83.2); local recurrence 0, 0, 2.1% (CI: 0.3-13.9), 9.3% (CI: 3.6-23.0); metastasis 20% (CI: 5.4-59.1), 10.5% (CI: 2.7-35.9), 18% (CI: 31.8-94.6), 18.8% (CI: 10.2-33.0). Late morbidity and quality of life evaluations showed no significant difference between arms. **Conclusions:** Tailoring preoperative radiochemotherapy based on induction treatment response is safe and promising. Early tumoral response to induction chemotherapy can discriminate tumor prognosis. Clinical trial information: NCT01333709. Research Sponsor: Grant INCa-DGOS_5506: PHRC-K 2012–112.

4015 Poster Discussion Session; Displayed in Poster Session (Board #7), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

FOLFOXIRI/bevacizumab (bev) versus doublets/bev as initial therapy of unresectable metastatic colorectal cancer (mCRC): A meta-analysis of individual patient data (IPD) from five randomized trials.

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Background: Several randomized trials demonstrated that intensifying the upfront chemotherapy in combination with bev is beneficial for mCRC patients with an increased incidence of some adverse events. All trials had primary endpoints other than OS, and a proper estimation of the magnitude of the OS benefit from FOLFOXIRI/bev versus doublets (FOLFIRI or FOLFOX)/bev is currently lacking. Within each trial, subgroup analyses failed to identify predictors of benefit from the intensified therapy. To test OS with higher power compared to single trials, and to explore interaction of treatment effect with main patients' and disease characteristics, we performed an IPD meta-analysis. **Methods:** IPD were collected from 5 randomized trials: CHARTA (NCT01321957), OLIVIA (NCT00778102), STEAM (NCT01765582, only combined FOLFOXIRI/bev and FOLFOX/bev arms), TRIBE (NCT00719797) and TRIBE2 (NCT02339116). Primary endpoint was OS. Secondary endpoints included PFS, objective response rate (ORR), R0 resection rate, G3/4 adverse events, and subgroup analyses. All statistical analyses were by intention-to-treat, stratified by trial. **Results:** 1697 pts randomized to FOLFOXIRI/bev (N=846) or doublets/bev (N=851) were included. Among pts in the doublets/bev group, 595 (70%) received FOLFOX/bev and 256 (30%) FOLFIRI/bev. At a median follow up of 39.9 mos, pts assigned to FOLFOXIRI/bev reported significantly longer OS than those assigned to doublets/bev (median OS 28.9 vs 24.5 months; HR 0.81 [95%CI 0.72-0.91], $p<0.001$), with no significant heterogeneity among trials ($p=0.39$; $I^2=2\%$). The estimated 5-yr OS was 22.3% vs 10.7% ($p<0.001$). No significant interaction effect between treatment arm and OS was demonstrated in terms of metastatic spread (liver-limited vs. not liver-limited $p=0.665$), primary side ($p=0.656$), and *RAS/BRAF* status ($p=0.337$). Pts assigned to FOLFOXIRI/bev achieved longer PFS (median PFS 12.2 vs 9.9 months; HR 0.74 [95%CI 0.67-0.82], $p<0.001$), higher ORR (64.5% vs 53.6%, $p<0.001$), higher R0 resection rate (16.4% vs 11.8%, $p=0.007$), and experienced higher rates of G3/4 neutropenia ($p<0.001$), febrile neutropenia ($p=0.019$), mucositis ($p=0.024$), nausea ($p=0.016$), and diarrhea ($p<0.001$). **Conclusions:** FOLFOXIRI/bev determines a clinically and statistically significant improvement of mCRC patients' OS vs doublets/bev with a meaningful effect also on 5-yr OS, PFS, ORR and R0 resection rate. No significant heterogeneity among explored subgroups was found. Research Sponsor: None.

4016 Poster Discussion Session; Displayed in Poster Session (Board #8), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Consensus molecular subtypes and CRCassigner classifications in metastatic colorectal cancer (mCRC): Prognostic and predictive impact in the TRIBE2 study.

Beatrice Borelli, Elisa Fontana, Mirella Giordano, Carlotta Antoniotti, Francesca Bergamo, Sabina Murgioni, Filippo Pietrantonio, Federica Morano, Emiliano Tamburini, Alessandra Boccaccino, Daniele Santini, Veronica Conca, Nicoletta Pella, Evaristo Maiello, Clara Ugolini, Gabriella Fontanini, Alfredo Falcone, Gift Nyamundanda, Anguraj Sadanandam, Chiara Cremolini; Department of Translational Research and New Technologies in Medicine and Surgery, Unit of Medical Oncology 2, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy; Division of Molecular Pathology, The Institute of Cancer Research, Sutton, London, United Kingdom; Department of Surgical, Medical, Molecular Pathology and Critical Area, University of Pisa, Pisa, Italy; Unit of Medical Oncology 1, Department of Oncology, Istituto Oncologico Veneto, IRCCS, Padua, Italy; Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Oncology Unit, Ospedale degli Infermi, Rimini, Italy; Department of Medical Oncology, University Campus Bio-Medico, Rome, Italy; Department of Oncology, University and General Hospital, Udine, Italy; Oncology Unit, Foundation IRCSS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy; Unit of Pathological Anatomy, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy; Department of Surgical, Medical, Molecular Pathology, and Critical Area, University of Pisa, Pisa, Italy

Background: The TRIBE2 study (NCT02339116) recently demonstrated the superiority of upfront FOLFOXIRI/bevacizumab (bev) when compared to a pre-planned strategy of doublets/bev in molecularly unselected but mostly (74%) *RAS*/*BRAF* mutant mCRC patients. The Consensus Molecular Subtypes (CMS) and CRCAssigner (CRCA) demonstrated prognostic value in multiple studies, but their predictive role has not been established so far. Given the poor prognosis associated with early stage mesenchymal/stem-like subtypes, we hypothesized that the CMS/CRCA classifiers could predict benefit from the upfront intensified strategy in patients included in the TRIBE2 study. **Methods:** Untreated formalin-fixed paraffin-embedded samples were classified into CMS/CRCA subtypes using a custom nCounter assay (NanoString Technologies). The impact of subtypes on progression free survival (PFS), progression free survival 2 (PFS2, defined as the time from randomization until the second evidence of disease progression) or overall survival (OS) was evaluated in the profiled population. **Results:** 426 and 428 (63%) patients enrolled in the TRIBE2 study were profiled according to CMS and CRCA classifications, respectively. The distribution of CMS/CRCA subtypes differed according to primary tumour site (both $p < 0.001$ for CMS/CRCA) and *RAS*/*BRAF* mutational status (both $p < 0.001$ for CMS/CRCA). Significant associations of both CMS/CRCA classifiers with PFS, PFS2 and OS were demonstrated (Table). The effect of treatment intensification was independent of CMS subtypes (p for interaction for PFS/PFS2/OS: ns). Significant interaction effect between CRCA subtypes and treatment arm was reported in terms of PFS ($p = 0.017$), PFS2 ($p = 0.010$) and OS ($p = 0.008$). The benefit from the intensification of the upfront chemotherapy seemed more relevant in the stem-like (PFS, HR = 0.60; $p = 0.03$) and mixed subtypes (HR = 0.44; $p = 0.002$). **Conclusions:** CMS subtypes have a prognostic role in mCRC independently of *RAS*/*BRAF* status. CRCA classification may help identifying subgroups of patients who may derive a more substantial benefit from upfront FOLFOXIRI/bev. Research Sponsor: GONO Foundation.

	CMS1	CMS2	CMS3	CMS4	Enterocyte	Goblet-like	Inflammatory	Stem-like	Transit-amplifying	Mixed
Median PFS (months)	5.4	12.9	8.3	10.7	10.0	9.9	7.9	14.6	11.2	9.9
P unadj/adj		**0.0001** / **0.01**					**0.04** / 0.36			
Median PFS2 (months)	8.0	19.2	13.7	18.1	15.7	16.0	12.2	24.0	18.1	16.5
P unadj/adj		**0.0004** /0.09					**0.04** / 0.37			
Median OS (months)	8.9	27.0	18.3	26.2	22.3	24.9	19.8	31.3	25.6	21.0
P unadj/adj		**0.0003** / 0.08					**0.02** / 0.55			

4017 Poster Discussion Session; Displayed in Poster Session (Board #9), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

First-line biological agents plus chemotherapy in elderly patients with metastatic colorectal cancer: A retrospective pooled analysis.

Pilar Garcia-Alfonso, Eduardo Diaz-Rubio, Albert Abad, Alfredo Carrato, Bartomeu Massuti, Rosa Rodríguez Alonso, Jose Luis Manzano, Andres J. Muñoz Martín, Gema Durán, Beatriz García de Paredes, Maria Jose Safont Aguilera, Reyes Ferreiro Monteagudo, Eva Martinez de Castro, Encarnación González Flores, Manuel Valladares-Ayerbes, Cristina Gravalos Castro, Vicente Alonso Orduña, Jose María Vieitez, Pilar Escudero, Enrique Aranda; Hospital General Universitario Gregorio Marañón, Madrid, Spain; Hospital Clínico San Carlos, Instituto de Investigación Hospital Clínico San Carlos (IdISSC), University Complutense, Madrid, Spain, CIBERONC, Madrid, Spain; Instituto Catalán de Oncología, Hospital Germans Trias i Pujol, Barcelona, Spain; IRYCIS, CIBERONC, Alcalá University, Hospital Universitario Ramón y Cajal, Madrid, Spain; Alicante University Hospital ISABIAL, Alicante, Spain; IMIBIC, Hospital Universitario Reina Sofía, Córdoba; Universidad de Córdoba, CIBERONC, Instituto de Salud Carlos III, Córdoba, Spain; Instituto Catalán de Oncología, Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain; Hospital General Universitario Gregorio Marañón, Instituto Investigación Sanitaria Gregorio Marañón, Madrid, Spain; Hospital Universitario Regional y Virgen de la Victoria, Málaga, Spain; Hospital Clínico San Carlos, Instituto de Investigación Hospital Clinico San Carlos (IdISSC), CIBERONC, Madrid, Spain; Hospital General Universitario de Valencia, Valencia, Spain; Hospital Universitario Marqués de Valdecilla, Santander, Spain; H. Virgen de las Nieves, Granada, Spain; Complejo Hospitalario Universitario A Coruña, Instituto Investigación Biomédica INIBIC, A Coruña, Spain; Hospital Doce de Octubre, Madrid, Spain; Aragon Institute of Biomedical Research (IISA), Miguel Servet University Hospital, Spanish Cancer Network (RTICC), Instituto de Salud Carlos III, Zaragoza, Spain; Hospital Universitario Central de Asturias, Oviedo, Spain; Department of Medical Oncology, Hospital Clínico Lozano Blesa, Zaragoza, Spain; IMIBIC, Reina Sofía Hospital, University of Córdoba, CIBERONC, Instituto de Salud Carlos III/ Spain, Córdoba, Spain

Background: Biological agents, in combination with chemotherapy, are recommended as first-line treatment of metastatic colorectal cancer (mCRC); however, evidence guiding appropriate management of elderly patients with mCRC is lacking. This study compared the efficacy and safety outcomes in older versus younger patients with mCRC who received first-line biological therapy. **Methods:** This retrospective analysis used pooled data from five Spanish TTD collaborative group studies of adults with advanced CRC who received first-line treatment with bevacizumab, cetuximab or panitumumab, stratified by age ($\geq$65 vs $<$ 65 years). Endpoints included progression-free survival (PFS), overall survival (OS), overall response rate (ORR) and safety. **Results:** In total, 999 patients from five studies were included in the analysis; 480 (48%) were aged $\geq$65 years and 519 (52%) were aged $<$ 65 years; 733 (73.37%) were treated with bevacizumab, 189 (18.92%) received cetuximab and 77 (7.71%) received panitumumab. Median PFS did not significantly differ between patients aged $\geq$65 versus $<$ 65 years (9.9 vs 9.4 months; hazard ratio [HR] 1.01; 95% confidence interval [CI] 0.88–1.17). Median OS was significantly shorter in older versus younger patients (21.3 vs 25.0 months; HR 1.21; 95% CI 1.04–1.41; P = 0.0132). There was no significant difference between older versus younger patients in ORR (59% vs 62%). Older patients experienced more treatment-related grade $\geq$3 adverse events. **Conclusions:** Biological agents are an effective first-line treatment option for elderly patients with mCRC, with comparable efficacy in PFS and ORR to that observed in younger patients and a manageable safety profile. Research Sponsor: Roche Farma SA.

4018 Poster Discussion Session; Displayed in Poster Session (Board #10), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

CodeBreak 100: Activity of AMG 510, a novel small molecule inhibitor of $KRAS^{G12C}$, in patients with advanced colorectal cancer.

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Background: Kirsten rat sarcoma viral oncogene homolog *(KRAS)* p.G12C mutation is associated with poor prognosis in colorectal cancer (CRC). AMG 510 is a first-in-class small molecule that specifically and irreversibly inhibits $KRAS^{G12C}$ by locking it in the inactive guanosine diphosphate-bound state. In a previous interim analysis of the phase 1, first-in-human trial of AMG 510, we observed a favorable safety profile and preliminary antitumor activity in patients (pts) with advanced solid tumors harboring *KRAS* p.G12C. Here, we present updated data in pts with CRC. **Methods:** Key inclusion criteria were *KRAS* p.G12C mutation identified through molecular testing, measurable disease, and progression on standard therapy. Primary endpoint was safety. Secondary endpoints were objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), as assessed per RECIST 1.1, and overall survival (OS). Oral daily doses of 180, 360, 720, and 960mg were tested in the dose escalation phase, and 960mg dose was selected for the expansion phase. **Results:** As of Jan 8, 2020, 42 pts with CRC (21 female [50%], median age: 57.5 years [range: 33–82]) were enrolled and dosed (25 on 960mg). All pts received prior systemic therapies; 19 pts (45.2%) received $>$ 3 prior lines. Median follow-up was 7.9 months (mos) (range: 4.2–15.9). 13 pts (31.0%) died, and 8 pts (19.0%) remained on treatment (tx). 22 (52.4%) and 8 (19.0%) pts had remained on tx for more than 3 and 6 months, respectively. Progressive disease was the most common reason for tx discontinuation. 20 pts (47.6%) had tx-related adverse events (TRAEs): 18 (42.9%) had grade 2 or lower TRAEs; 2 (4.8%) had grade 3 TRAEs, which were diarrhea (2.4%) and anemia (2.4%). There were no dose-limiting toxicities, fatal TRAEs, or TRAEs leading to tx discontinuation. Overall, ORR and DCR were 7.1% (3/42) and 76.2% (32/42), respectively. At 960mg, ORR and DCR were 12.0% (3/25) and 80.0% (20/25). 3 pts with PR had duration of response of 1.5, 4.2, and 4.3 months, respectively, and their responses were still ongoing at data cutoff. In all pts treated with all doses, median duration of stable disease was 4.2 mos (range: 2.5[+]–11.0). PFS/OS will be reported. **Conclusions:** In pts with heavily pretreated *KRAS* p.G12C mutant CRC, AMG 510 monotherapy was well tolerated, with the majority of pts achieving disease control. Study is ongoing. Clinical trial information: NCT03600883. Research Sponsor: Amgen Inc.

4019 Poster Discussion Session; Displayed in Poster Session (Board #11), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

REGOMUNE: A phase II study of regorafenib plus avelumab in solid tumors—Results of the non-MSI-H metastatic colorectal cancer (mCRC) cohort.

Sophie Cousin, Carine A. Bellera, Jean Philippe Guégan, Carlos A. Gomez-Roca, Jean-Philippe Metges, Antoine Adenis, Simon Pernot, Coralie Cantarel, Michèle Kind, Maud Toulmonde, Kevin Bourcier, Isabelle Soubeyran, Alban Bessede, Antoine Italiano; Department of Medicine, Institut Bergonié, Bordeaux, France; INSERM CIC 14.01 Bordeaux, Clinical Epidemiology Unit, Bordeaux, France; Immusmol, Bordeaux, France; Institut Universitaire du Cancer de Toulouse–Oncopole, Toulouse, France; Centre Hospitalier Regional Universitaire (CHRU) de Brest–Hopital Morvan, Brest, France; Institut du Cancer de Montpellier, Montpellier, France; Institut Bergonié, Bordeaux, France; Institut Bergonié, Department of Imaging, Bordeaux, France; Institut Bergonié, Department of Medical Oncology, Bordeaux, France; Bergonie Institute, Bordeaux, France; ImmuSmol, Bordeaux, France; Early Phase Trials Unit, Institut Bergonié, Bordeaux, France

Background: Regorafenib (R) has been shown to modulate anti-tumor immunity by different mechanisms including reduction of tumor-associated macrophages (TAMs). Synergy between R and anti–PD-1/PD-L1 antibodies has been shown in pre-clinical models. **Methods:** This is a single-arm open-label multicentric phase II trial assessing the efficacy and safety of R (160 mg QD 3weeks/4) + Avelumab (A) (10 mg/kg every 2 weeks) combination in non MSI-H mCRC patients (pts). The primary endpoint was the confirmed objective response rate, based on central review according to RECIST 1.1. Secondary endpoints included: 1-year progression free survival (PFS), 1-year overall survival (OS), and Safety using NCI-CTCAE v5.0. Correlative studies were planned from pts tumor samples obtained at baseline and C2D1. **Results:** Between Nov. 2018 and Oct. 2019, 48 pts were enrolled in 4 centers. Median age was 61.8 (range: 26.3-78.7). Median follow-up was: 7.2 months. Median number of previous treatment lines was: 3 (range: 1-7). 41 (87.2%) pts experienced at least 1 dose modification or treatment interruption. The most common grade 3/4 adverse events were palmar-plantar erythrodysesthesia syndrome (29.8%), hypertension (23.4%) and diarrhea (12.8%). No death was related to the treatment. Among 40 pts who had at least one imaging tumor assessment, 12 (30%) had reduction in tumor burden. Best response was stable disease for 23 pts (57.5%) and progressive disease for 17 pts (42.5%). The median PFS and OS were 3.6 months ($CI_{95\%}$: [1.8 – 5.4]) and 10.8 months ($CI_{95\%}$: [5.9 – NA]) respectively. Baseline tumor samples and paired biopsies were available for 24 and 15 pts respectively. High infiltration by TAMs at baseline was significantly associated with adverse outcome (PFS: 1.9 vs 3.7 months, p=0.045; OS: 4.8 months vs NR, p=0.027). Increased tumor infiltration by CD8+ at C2D1 compared to baseline was significantly associated with better PFS (p=0.011). Combining low TAMs infiltration and low tumor cells to CD8+ T cells distance enabled the identification of a subgroup of pts (n= 6/24, 25%) more likely to benefit from R+A combination: median PFS: 5.3 vs 1.9 months (p=0.037); median OS: NR vs 5.3 months (p=0.02). **Conclusions:** The R+A combination achieved PFS and OS that compared favourably with historical data of R alone in this clinical setting. High-resolution analysis of tumor samples identified a composite score based on TAMs infiltration and tumor cell to CD8+ T cells distance which could be used as a biomarker in further studies investigating this approach in mCRC pts. Clinical trial information: NCT03475953. Research Sponsor: Bayer and Merck.

4020 Poster Discussion Session; Displayed in Poster Session (Board #12), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Pembrolizumab for previously treated advanced anal squamous cell carcinoma: Pooled results from the KEYNOTE-028 and KEYNOTE-158 studies.

Aurelien Marabelle, Philippe Alexandre Cassier, Marwan Fakih, Steven Chuan-Hao Kao, Dorte Nielsen, Antoine Italiano, Tormod Guren, Marloes Van Dongen, Kristen Renee Spencer, Giovanni M. Bariani, Paolo Antonio Ascierto, Armando Santoro, Sandrine Hiret, Patrick Alexander Ott, Sarina Anne Piha-Paul, Chih-Chin Liu, Melanie A. Leiby, Kevin Norwood, Jean-Pierre Delord; Gustave Roussy, Université Paris-Saclay, Villejuif, France; Centre Léon Bérard, Lyon, France; City of Hope National Medical Center, Duarte, CA; Chris O'Brien Lifehouse, Camperdown, NSW, Australia; Herlev Hospital, University of Copenhagen, Copenhagen, Denmark; Early Phase Trials Unit, Institut Bergonié, Bordeaux, France; Oslo University Hospital, Oslo, Norway; Antoni van Leeuwenhoek, Amsterdam, Netherlands; Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; Instituto do Câncer do Estado de São Paulo, Universidade de São Paulo, São Paulo, Brazil; Fondazione IRCCS-Istituto Nazionale dei Tumori, Naples, Italy; Humanitas University, Pieve Emanuele, Italy; Institut de Cancérologie de l'Ouest, Saint-Herblain, France; Dana-Farber Cancer Institute, Boston, MA; Department of Investigational Cancer Therapeutics (Phase I Program), The University of Texas MD Anderson Cancer Center, Houston, TX; Merck & Co., Inc., Kenilworth, NJ; Institut Claudius Regaud IUCT-Oncopole, Toulouse, France

Background: Patients (pts) with anal squamous cell carcinoma (ASCC) have poor outcomes and few treatment options. We report a pooled analysis of pembrolizumab (pembro) antitumor activity and safety in the ASCC cohorts of the multicohort studies KEYNOTE-028 (NCT02054806; phase 1b) and KEYNOTE-158 (NCT02628067; phase 2), providing a robust sample size and longer follow-up. **Methods:** Eligible pts were aged ≥18 y with histologically/cytologically confirmed metastatic/unresectable ASCC, had prior failure of/intolerance to standard therapy or no standard therapy options, measurable disease (RECIST v1.1), ECOG PS 0/1, and a tissue sample evaluable for PD-L1/biomarkers (KEYNOTE-028 required PD-L1 positivity). Baseline PD-L1 expression was assessed using a prototype IHC assay (QualTek) in KEYNOTE-028 and the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies) in KEYNOTE-158. Pts received pembro 10 mg/kg Q2W (KEYNOTE-028) or 200 mg Q3W (KEYNOTE-158) for 2 y or until PD/unacceptable AEs. The primary endpoint in both studies was ORR (per RECIST v1.1). Secondary endpoints were duration of response (DOR), PFS, OS, and safety. **Results:** 137 pts with ASCC were treated in KEYNOTE-028 (n = 25) or KEYNOTE-158 (n = 112) and were included in this analysis (median age, 61 y; 83.2% women; 73.0% had PD-L1–positive tumors). Median follow-up was 11.7 mo; 124 pts (90.5%) had discontinued treatment. ORR (95% CI) was 10.9% (6.3%–17.4%). 8 pts had CR and 7 had PR. ORR (95% CI) by PD-L1 status was 14.0% (7.9%–22.4%) in the PD-L1 positive group and 3.3% (0.1%–17.2%) in the PD-L1 negative group. Among all treated pts, median DOR was not reached (range, 6.0+ to 57.5+ mo). By Kaplan-Meier estimation, 84.6% of responders had a DOR ≥24 mo. Median PFS was 2.1 mo (95% CI, 2.0–2.1) and median OS was 11.7 mo (95% CI, 8.8–14.5). The 12-mo PFS and OS rates were 14.5% and 47.4%. 85 pts (62.0%) had +1 treatment-related AE, 24 pts (17.5%) with grade 3–4 events (no grade 5 events). 32 pts (23.4%) had immune-mediated AEs; 2 pts (1.5%) had infusion related reactions. **Conclusions:** In pts with previously treated advanced ASCC, pembro showed durable antitumor activity, particularly in pts with PD-L1–positive tumors, and manageable toxicity. Clinical trial information: NCT02054806 (KEYNOTE-028), NCT02628067 (KEYNOTE-158). Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

4021 **Poster Session (Board #13), Fri, 8:00 AM-11:00 AM**

Pre- versus postoperative CAPOX plus bevacizumab (CAPOX-Bev) for resectable liver metastases from colorectal cancer (CLM): A randomized phase II/III trial (HiSCO-01).

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Background: The role of neoadjuvant chemotherapy, particularly for those with initially resectable CLM, is controversial. And the optimal regimen and duration to be used in the neoadjuvant setting is not established. We conducted prospective, multicenter, randomized phase II/III study to assess pre-operative 8 cycles of CAPOX-Bev (arm A) plus radical surgery compared with post-operative 8 cycles of CAPOX-Bev (arm B) for patients (pts) with resectable CLM. **Methods:** The primary endpoint in the Phase II was completion rate of protocol treatment (more than 6 cycles of CAPOX-Bev plus R0 surgical resection) and PFS in the Phase III. The secondary endpoints were OS, ORR (arm A), liver damage (arm A), safety. The Phase III part was terminated due to slow enrollment. **Results:** 81 pts were enrolled from 10 centers between November 2010 and November 2017. The full analysis set consisted of 76 pts who started protocol treatment (arm A 37 vs. arm B 39). 76 pts had the following characteristics: median age 66 (27-80), median number of liver metastases 2 (1-14), 69.7% male, 67.1% synchronous and 94.7% primary resected. Completion rate of protocol treatment was 89.2% in arm A and 71.8% in arm B (p = .06). ORR was 63.9%, including 2 pts who had pathologically complete response (5.6%). Only 1 pts in arm A could not undergo surgery due to progression of disease. In the chemotherapy safety population, arm B was associated with more grade 3 neutropenia and grade 3 gastrointestinal disorder than arm A. The most frequent surgical adverse event was biliary fistula, with an incidence of 0% in arm A and 10.3% in arm B (p = .02). No patient died from treatment-related adverse events. The median follow-up time was 40 months. The rate of PFS at 3 years was 32.2% in arm A versus 38.5% in arm B (p = .99). **Conclusions:** Pre-operative 8 cycles of CAPOX-Bev is compatible with radical surgery, but may have no impact on progression-free survival compared with post-operative chemotherapy. Clinical trial information: UMIN000003783. Research Sponsor: None.

4022 **Poster Session (Board #14), Fri, 8:00 AM-11:00 AM**

Impact of empirically eliminating 5-fluorouracil (5-FU) bolus and leucovorin (LV) in patients with metastatic colorectal cancer (mCRC) receiving first-line treatment with mFOLFOX6.

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Background: Systemic chemotherapy with a 5-FU-based regimen, such as mFOLFOX6, is the preferred first line treatment option for mCRC. Due to hematologic toxicities associated with the 5-FU bolus component, providers may choose to eliminate it empirically in patients receiving palliative therapy. This study aimed to assess the impact of empirically eliminating the 5-FU bolus and LV from first line treatment with mFOLFOX6 in mCRC. **Methods:** This was a retrospective chart review of patients ≥ 18 years old with mCRC receiving palliative first line mFOLFOX6 chemotherapy with (bolus) or without (non-bolus) the 5-FU bolus and LV components from January 1, 2015 through August 31, 2019 at Moffitt Cancer Center. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), disease control rate (DCR) defined as partial response and stable disease at first scan, utilization of growth factor support and safety. **Results:** Data analysis cutoff was December 31, 2019, with 61 patients included in the bolus arm and 72 in the non-bolus arm. Median follow-up time was 21.8 months. No difference was found in median PFS (8.12 vs. 6.64 months, p=0.787) or OS (29.36 vs. 21.6 months, p=0.395) between the bolus and non-bolus arms, respectively. Observed DCR at first scan was similar between both arms (47.3% vs. 52.7%, p=0.44). Utilization of growth factor support was significantly higher in the bolus arm (73.7% vs. 26.3%, p=0.012). Fewer grade ≥ 3 treatment-related hematologic adverse events (AE) were seen in the non-bolus arm (37.7% vs. 22.2%, p=0.058) (table). **Conclusions:** This is the only study to date that analyzed the impact of empirically eliminating 5-FU bolus and LV from first line palliative therapy with mFOLFOX6 in mCRC. Results showed no significant difference in median PFS or OS. Despite reduced growth factor utilization, the non-bolus arm demonstrated a favorable safety profile with less treatment-related hematologic grade ≥ 3 AE. The results of this study warrant consideration of empirically eliminating 5-FU bolus and LV from the mFOLFOX6 regimen to avoid additive toxicities without negatively impacting efficacy. Research Sponsor: None.

Hematologic AE grade ≥ 3, n (%)	Bolus (n=61)	Non-bolus (n=72)
Neutropenia	12 (20)	9 (13)
Anemia	12 (20)	8 (11)
Thrombocytopenia	3 (5)	2 (3)

4023 **Poster Session (Board #15), Fri, 8:00 AM-11:00 AM**

Differential association of proton pump inhibitors with efficacy of capecitabine and 5-fluorouracil in metastatic colorectal cancer: A post-hoc analysis from AXEPT phase III trial.

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Background: Proton pump inhibitors (PPIs) reportedly can impair the absorption of oral anticancer agents by potent acid suppression. Concomitant use of a PPI with capecitabine (Cap) was suggested to be associated with poor outcome in gastrointestinal cancers, however, the potential interaction has not been studied yet in a prospective randomized clinical trial comparing Cap with 5-fluorouracil (FU). We analyzed the differential impact of PPI use on Cap and FU using dataset from AXEPT trial, a phase III randomized trial that demonstrated non-inferiority of a modified XELIRI (mXELIRI; Cap plus irinotecan) with FOLFIRI (FU, leucovorin and irinotecan), both either with or without bevacizumab in patients (pts) with metastatic colorectal cancer (mCRC). **Methods:** From the per-protocol set (n = 620), pts with available information on concomitant medications (n = 482) were eligible for this sub-study. PPI use was defined as concomitant exposure of Cap and any PPI for 20% or more of the study period. The treatment-by-PPI-use interaction was examined adjusting to stratification factors including age, sex, country, performance status, number of metastatic sites, previous use of oxaliplatin, and concurrent bevacizumab treatment. **Results:** 49 (10.1%) pts were PPI users. Clinical characteristics were well balanced between the two groups differing in PPI use. In PPI users, the mXELIRI group tended to have poorer OS (hazard ratio [HR], 1.83; 95% confidence interval [CI], 0.96–3.48; p = 0.0644) compared with the FOLFIRI group. In contrast, within PPI non-users, OS of mXELIRI was better than that of FOLFIRI (HR, 0.76; 95% CI, 0.61- 0.95; p = 0.0162). Similarly, a trend of worse PFS with mXELIRI than with FOLFIRI was observed in PPI users (HR, 1.73; 95% CI, 0.94-3.21; p = 0.0798), but not in PPI non-users (HR, 0.90; 95%CI, 0.73 – 1.10; p = 0.2871). Treatment-by-PPI-use interaction was significant for OS (p = 0.0116) and PFS (p = 0.0415). No significant interactions were found between treatment and PPI use in terms of treatment failure, overall response, disease control, and grade 3–4 toxicities. **Conclusions:** There was a significant interaction between PPI use and treatment (Cap vs FU) in terms of OS and PFS in AXEPT dataset. This suggests that PPI use could impair the efficacy of Cap, but not that of FU. PPIs should be used with caution in pts with mCRC taking Cap. Clinical trial information: NCT01996306. Research Sponsor: Chugai Pharmaceutical and Hoffmann-La Roche.

4024 **Poster Session (Board #16), Fri, 8:00 AM-11:00 AM**

Cetuximab/irinotecan/5-FU +/-oxaliplatin or FOLFOXIRI +/- bevacizumab in patients with colorectal cancer and nonresectable liver metastases (AIO CELIM2-study).

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Background: EGFR based combinations and the triplet combination FOLFOXIRI are known to increase response rates compared to doublet combinations. **Methods:** Patients with colorectal cancer and nonresectable liver metastases were enrolled into the trial. RAS wild type patients were randomised to cetuximab/FOLFIRI or cetuximab/FOLFOXIRI, RAS/BRAF mutant patients were randomised to FOLFOXIRI with or without bevacizumab. The primary endpoint was response. Secondary endpoints included progression free and overall survival. The trial was closed early due to poor recruitment. **Results:** Between 2014 and 2018, ninety-two pts were enrolled into the study. 54 wild type pts were randomised into cetuximab based treatment with (28 pts) or without (26 pts) oxaliplatin, 38 RAS/BRAF mutant pts were randomised to receive FOLFOXIRI alone (18 pts) or plus bevacizumab (16 pts). Objective response was achieved in 21/26 pts (81 % [95 CI: 61 – 93 %]) with cet/FOLFIRI, 24/28 pts (86 % [95 CI: 67 – 96 %]) with cet / FOLFOXIRI, 13/1 8 pts (72 % [95 CI: 46 – 90 %]) with FOLFOXIRI and 14/20 pts (70 % [95 CI: 46 – 88 %]) with bev/FOLFOXIRI. Two pts with cet/FOLFOXIRI and one pat with FOLFOXIRI achieved CR according to imaging. The median PFS was 12.7 [95 % CI: 7.2 – 18.2], 15.0 [95 % CI: 11.3 – 18.7], 17.5 [95 % CI: 8.0 – 27.1] and 15.0 [95 % CI: 11.4 – 18.5] months with cet/FOLFIRI, cet/FOLFOXIRI, FOLFOXIRI and bev/FOLFOXIRI. The median overall survival was 42 mo. [95 % CI: 28 – 55], 55 [95 % CI:41 – 68], 28 [95 % CI: 22 – 36] and 44 [95 % CI: 0 – 94] months with cet/FOLFIRI, cet/FOLFOXIRI, FOLFOXIRI and bev/FOLFOXIRI. The frequency of grade $\geq$ 3 toxicity per arm (cet/FOLFIRI, cet/FOLFOXIRI, FOLFOXIRI and bev/FOLFOXIRI) was 29 %, 46 %, 56 %. 45 % for neutropenia/leukopenia, 11 %, 12 %, 28 %, 25 % for diarrhea and 29 %, 19 %, 6 % and 5 % for skin toxicities. **Conclusions:** High response rates were observed in patients with colorectal liver metastases with all regimens. The numerically highest response rate was observed in RAS wild type patients treated with cetuximab/FOLFOXIRI. Clinical trial information: NCT01802645. Research Sponsor: Merck-Serono.

4025 **Poster Session (Board #17), Fri, 8:00 AM-11:00 AM**

Skeletal muscle loss under chemotherapy and its association with survival and systemic treatment toxicity in metastatic colorectal cancer: An AGEO prospective multicenter study.

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Background: We showed in a previous work that "Patient Generated-Subjective Global Assessment" (PG-SGA) was independently associated with survival and treatment toxicities in non-pretreated metastatic colorectal cancer (mCRC) patients. We have evaluated here if muscle mass in these patients can provide useful additional information for clinical practice. The objective of the present work was to evaluate the association between baseline sarcopenia, and the variation of the Skeletal Muscle Index (SMI) under treatment with survival and chemotherapy-related toxicities in our population of non-pretreated mCRC patients. **Methods:** This prospective multicenter observational study enrolled non-pretreated mCRC patients. Measurement of SMI was performed on routine CT scan at day 0 (D0) and day 60 (D60). PG-SGA score and other nutritional factors were collected at D0. Progression-free survival (PFS) and overall survival (OS) were calculated from treatment start. Treatment related toxicities were registered according to the NCI CTCAE v4.0. **Results:** 149 patients were included in eight French centers from 7/2013 to 11/2016. Sarcopenia at baseline was not significantly associated with survival outcomes or chemotherapy-related toxicities. The best cut-point value of SMI variation (between D0 and D60) for OS prediction obtained with a log-rank maximisation method was -14%. The decrease in SMI $>$ 14%, with a median follow-up of 23 months, was significantly associated with shorter PFS (6 vs 9 mo; HR 1.8, 95%CI 1.1-3.1, p = 0.02) and OS (8.5 vs 26 mo; HR 2.4, 95%CI 1.3-4.4, p = 0.004), independently of hypoalbuminemia and malnutrition defined by PG-SGA, in multivariate analysis. 40% of patients with a SMI decrease $>$ 14%, and 22% of patients with a SMI increase or stable or decrease $<$ 14% developed grade $\geq$ 2 clinical toxicities (OR 3.0, 95%CI 1.2-7.7, p = 0.02), but the difference was not statistically significant in multivariate analysis (OR 2.3. 95%CI 0.8-6.7, p = 0.1). **Conclusions:** To our knowledge, this study is the first study assessing the association of skeletal muscle loss with survival and treatment toxicities in patients with mCRC prospectively. In our population of non pre-treated mCRC patients, baseline sarcopenia was not associated with poor survival outcomes, but the decrease in SMI $>$ 14% during the first two months of treatment was significantly associated with decreased PFS and OS, independently of other prognostic and nutritional factors. Research Sponsor: Nutricia.

4026 **Poster Session (Board #18), Fri, 8:00 AM-11:00 AM**

High amphiregulin mRNA expression is a strong prognostic biomarker with response to cetuximab in FIRE-1, CIOX, and FIRE-3.

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Background: Amphiregulin (*AREG*) and epiregulin (*EREG*) were discussed as biomarkers for treatment of metastatic colorectal cancer (mCRC). Data from randomized controlled trials (RCT) are limited. **Methods:** *AREG* and *EREG* mRNA expression by RTqPCR in relation to housekeeping genes were available from 688 patients of three RCT (FIRE-1, n = 192, FUFIRI vs. mIrOx; CIOX, n = 113, cetuximab + CAPIRI/CAPOX; FIRE-3, n = 383, FOLFIRI+cetuximab/bevacizumab) and were normalized to their respective range of each trial with median and 3rd quartile as threshold values. Kaplan-Meier estimated overall survival (OS) and progression-free survival (PFS). Cox regression analysis calculated hazard ratio (HR) and 95% confidence interval (95% CI). Overall response rate (ORR) was compared by chi square test. **Results:** Across all trials, high *AREG* mRNA expression appeared as strong prognostic biomarker for OS, PFS and ORR for all threshold values. In *RAS* wildtype patients, high *AREG* expression was associated with better OS and PFS for cetuximab but not bevacizumab treatment. (Table) No effects were seen for epiregulin when all trials were analysed together. **Conclusions:** High *AREG* mRNA expression appeared as strong prognostic biomarker in mCRC. Positive predictive information might exist for cetuximab treatment. Research Sponsor: None.

Outcome according to AREG mRNA expression in FIRE-1, CIOX, FIRE-3.

	< median	> median	< 3rd quartile	> 3rd quartile
All patients				
n FIRE-1	103	89	152	42
n CIOX	60	53	86	27
n FIRE-3	181	202	279	104
OS, months	21.5	26.2	22.6	28.6
HR [95% CI], p	0.80 [0.68 – 0.94] p = 0.007		0.76 [0.63 – 0.92] p = 0.005	
PFS, months	8.1	10.0	8.9	10.6
HR [95% CI], p	0.74 [0.63 – 0.86] p = 0.001		0.79 [0.68 – 0.94] p = 0.009	
ORR, %	51.6	63.1	52.6	71.5
P (Chi sq.)	0.004		< 0.0001	
RAS WT & bevacizumab treated patients				
n FIRE-3	66	68	99	35
OS, months	23.8	27.5	23.8	28.6
HR [95% CI], p	0.93 [0.65 – 1.33] p = 0.71		0.96 [0.65 – 1.43] p = 0.85	
PFS, months	10.3	11.3	10.7	11.5
HR [95% CI], p	0.92 [0.65 – 1.30] p = 0.63		1.03 [0.70 – 1.53] p = 0.87	
RAS WT & cetuximab treated patients				
n CIOX	34	32	47	19
n FIRE-3	51	70	76	45
OS, months	23.5	36.6	24.5	37.1
HR [95% CI], p	0.60 [0.43 – 0.63] p = 0.002		0.61 [0.43 – 0.87] p = 0.006	
PFS, months	7.8	10.6	8.6	11.2
HR [95% CI], p	0.66 [0.49 – 0.88] p = 0.006		0.77 [0.56 – 1.05] p = 0.10	

4027 **Poster Session (Board #19), Fri, 8:00 AM-11:00 AM**

Prognostic characteristics of patients with benign mesenteric lymph node enlargement after surgical resection for colorectal cancer.

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Background: Patients with lymph node metastasis of colorectal cancer (CRC) have a greater risk of recurrence. However, the characteristics of benign mesenteric lymph node enlargement (BLNE) are not well documented. The aim of this study is to assess clinical and prognostic significance of BLNE in patients with CRC. **Methods:** 601 patients who underwent surgery for stage 0, I, II CRC from January 2010 to April 2014 were included and separated into two groups by presence of BLNE. Univariate and multivariate analyses were constructed to demonstrate prognostic factors between BLNE group (n = 275) and control group (n = 326). **Results:** The risk of recurrence in BLNE group after curative resection was significantly lower than control group, with the 1-, 3-, and 5-year disease-free survival rates being 98.2, 91.6, and 86.9 %, in BLNE group and 95.7, 86.2, and 78.2 %, in control group respectively (p = 0.004). The mortality in BLNE group was lower compared with non BLNE group (mean overall survival: 95.7 $\pm$ 1.2 vs. 89.5 $\pm$ 1.4 months, p = 0.001). Patients of BLNE group also had a higher percentage of younger age, family tumor history, left sided tumors and tumor size $\geq$4cm. Adjusted Cox regression showed BLNE was an independent prognostic factor for both disease free survival and overall survival (*P*= 0.003 and 0.001). **Conclusions:** The study indicates that BLNE can be a useful positive factor in predicting recurrence and long-term survival concerning CRC patients. This conclusion offers a new viewpoint about CRC genesis and progression. Research Sponsor: None.

4028 **Poster Session (Board #20), Fri, 8:00 AM-11:00 AM**

Fruquintinib combination with sintilimab in refractory metastatic colorectal cancer patients in China.

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Background: Fruquintinib, a vascular endothelial growth factor receptor (VEGFR) inhibitor, is a new anti-cancer targeting drug independently developed in China for refractory metastatic colorectal cancer (mCRC). Because Regorafenib combined with nivolumab has a promising future in patients with refractory mCRC, we aim to evaluate the efficiency of combination of Fruquintinib with Sintilimab (a highly selective, fully human monoclonal antibody PD-1 mAb) in these patients. **Methods:** Fifty-two patients with refractory mCRC were given fruquintinib (3mg orally, once daily for 3 weeks, followed by 1 weeks off in 4 weeks cycles) and sintilimab (200mg intravenously, once every 3 weeks). Before treatment, peripheral blood samples were collected and next-generation sequencing was performed to detect the gene profile of patients. **Results:** The ORR was 15.38% (8/52), DCR was 57.6% (30/52), and mPFS was 108 days. The patients was divided into two groups according to their PFS: PFS $\geq$ 90 days and PFS $<$90 days. PFS was significantly worse in patients with the following mutations: AMER1 (p=0.0073), DNMT3A (p=0.0075), ETV5 (p=0.012), EWSR1 (p=0.016), FANCA (p=0.019), IKBKE (p=0.0073), NOTCH1 (p=0.015), STAG2 (p=0.012) and TCF7L2 (p=0.0073). It was also significantly worse in the patients had the abnormalities of complexity and coagulation cascades ($p = 0.026$) and pancreatic cancer pathway (p = 0.0098). **Conclusions:** Fruquintinib combined with Sintilimab seemed not resulted in a significant increase in ORR, DCR and OS in refractory mCRC. Certain mutational genes and abnormal pathway caused by some frameshift mutations may affect the efficacy. It is suggested that targeting these mutational genes and signaling pathway may be helpful to improve the efficacy of Fruquintinib combination with Sintilimab. Research Sponsor: None.

4029 **Poster Session (Board #21), Fri, 8:00 AM-11:00 AM**

Sex differences in efficacy and toxicity of first-line treatment of metastatic colorectal cancer (CRC): An analysis of 18,399 patients in the ARCAD database.

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Background: The clearance of 5-FU differs significantly between men (M) and women (W). Adjuvant chemotherapy (CT) for CRC has a higher toxicity in W. The impact of sex on efficacy and toxicity in first-line trials of metastatic CRC (mCRC) is unknown. **Methods:** We analyzed patient (pt) and tumor characteristics, toxicities (nausea (AE1), vomiting (AE2), diarrhea, neutropenia (AE3)) and efficacy (overall survival (OS), progression-free survival (PFS)) according to sex in the following treatment groups: A: CT alone, B: CT + bevacizumab, C: CT + EGFR-antibodies, with subgroup analyses in the CT alone group for single-agent, doublets and triplets, as well as irinotecan- and oxaliplatin-based regimens. Pts from trials with treatments still used today and all relevant data available were eligible. OS and PFS were assessed using Kaplan-Meier and Cox models adjusted for primary tumor location and performance status (PS). **Results:** We included 28 trials with 18.399 pts (11.352 M and 7.047 W). W were younger (61 vs. 63 years), had more often a PS of 1 (49 vs 45%), BRAF mutations (10 vs. 7%), right-sided tumors (42 vs. 35%) and less often rectal tumors (26 vs. 32%). Significant differences in toxicity are reported in table. Rates of diarrhea were similar. There was no sex disparity in OS in the predefined subgroups except for pts receiving triplets where OS was better in M (HR_{adj}=1.39 (1.05 - 1.85)). Median (interquartile range) OS in months for M and W was 16.7 (9.2-27.4) and 16.2 (8.9-27.2) in group 1, 21.9 (12.7-37.5) and 22.3 (12.9 – 39.0) in group 2, and 26.8 (14.6-45.3) and 24.8 (12.3-49.2) in group 3. HRs_{adj} (W vs M) (95% CI), *p* values for OS were 1.02 (0.96-1.09), .557, 0.92 (0.83-1.03), .142, 0.99 (0.85-1.14), .866. **Conclusions:** M and W with mCRC differ significantly regarding patient and tumor characteristics. The significant higher toxicity in W does not translate in a higher treatment efficacy. Apart from known sex differences in pharmacokinetics of 5-FU, differences in pharmacodynamics must be postulated. Research Sponsor: Fondation ARCAD.

	Toxicity Gr 1-4 n (%)		Toxicity Gr 3-4 n (%)	
CT alone	**M**	**W**	**M**	**W**
AE	1745 (62.2)	1098 (70.3)	157 (5.6)	130 (8.3)
AE 2	1149 (39.3)	802 (48.8)	154 (5.3)	120 (7.3)
AE 3	1519 (48.1)	993 (54.8)	607 (19.2)	506 (27.9)
CT + bev				
AE 1	1237 (58.9)	1037 (73.6)	77 (3.7)	96 (6.8)
AE 2	782 (37.3)	728 (51.6)	99 (4.7)	96 (6.8)
AE 3	536 (29.8)	455 (37.7)	282 (15.7)	290 (24.0)
CT + anti-EGFR antibodies				
AE 1	941 (59.4)	627 (71.6)	77 (4.9)	63 (7.2)
AE 1	618 (29.1	509 (42.1)	63 (3.0)	63 (7.2)
AE 3	1080 (50.6)	754 (62.3)	439 (20.6)	428 (35.4)

4030 **Poster Session (Board #22), Fri, 8:00 AM-11:00 AM**

Real-world outcomes of patients with BRAF-mutated mCRC treated in the United States.

Matthew Braithwaite, Christopher Duane Nevala-Plagemann, Kelsey Baron, Benjamin Haaland, Lisa M. Pappas, Ignacio Garrido-Laguna; University of Utah, Salt Lake City, UT; Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; Division of Internal Medicine, Intermountain Medical Center, Murray, UT; Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT

Background: BRAF mutations portend a poor prognosis in metastatic colorectal cancer (mCRC). Recent trials have hypothesized that using more aggressive triplet-based chemotherapy regimens such as FOLFOXIRI in the frontline setting may improve outcomes in this patient population. In this study, we utilized real-world data to assess whether FOLFOXIRI is being used in the United States (US) and compared survival outcomes in BRAF mutated (BRAFmt) mCRC stratified by first line (1L) therapy. **Methods:** The nationwide Flatiron Health EHR-derived de-identified database was reviewed for patients diagnosed with mCRC between 2013 and 2018. Patients who had documented BRAF mutation testing and received a standard 1L therapy were included for analysis. Patients who did not have a visit or medication order within 90 days of metastatic diagnosis were excluded to ensure patients were engaged with care at the data-providing institution. Kaplan-Meier and Cox proportional hazard modeling were used to compare survival outcomes stratified by BRAF mutation status and 1L therapy received. **Results:** A total of 4,454 patients with documented BRAF mutational status were included, of which 3,988 (89.5%) were BRAF wild type (BRAFwt) and 466 (10.5%) were BRAFmt. Median OS was 15.4 months (mo) in the BRAFmt group compared to 28.1 mo in the BRAFwt group (HR 0.48, 95% CI 0.41- 0.56, $p < 0.001$). Only 3% (n = 16) of BRAFmt patients received 1L FOLFOXIRI +/- bevacizumab with a median OS of 13.8 mo compared to 15.5 mo in patients receiving a chemotherapy doublet (FOLFOX, CAPEOX, or FOLFIRI) +/- bevacizumab (95% CI 4.9 – not reached vs 14.3 – 19.0, p = 0.38). In BRAFmt patients, multivariate analysis (MVA) did not detect a significant improvement in OS with the use of FOLFIRI plus bevacizumab (HR 0.88, 95% CI 0.50-1.56, p = 0.67) or FOLFOX/CAPEOX plus bevacizumab (HR 0.89, 95% CI 0.59 – 1.34, p = 0.58) when compared to chemotherapy doublet alone. A MVA comparing 1L therapies in the BRAFwt group did not detect a significant improvement in OS with bevacizumab plus chemotherapy doublet compared to chemotherapy doublet alone. When stratified by 1L treatment regimen, similar proportions of BRAFmt patients received second line therapy. **Conclusions:** This analysis of real-world data confirms the negative prognostic impact of BRAF mutations in mCRC and suggests that FOLFOXIRI has not been widely adopted in the management of these patients in the US. We were unable to demonstrate any significant difference in OS of patients with BRAFmt mCRC based on type of 1L therapy received. Research Sponsor: None.

4031 **Poster Session (Board #23), Fri, 8:00 AM-11:00 AM**

Results from the safety lead-in for a phase II study of pembrolizumab in combination with binimetinib and bevacizumab in patients with refractory metastatic colorectal cancer (mCRC).

Christopher Hanyoung Lieu, Sarah Lindsey Davis, Stephen Leong, Alexis Diane Leal, Patrick Jud Blatchford, Gurprataap Singh Sandhu, William T. Purcell, Sunnie S. Kim, Zoe Van De Voorde, Rachel Telles, Anne Martin, Tiffany Cull, Meredith Waring, Colin Reed, Chimmoua Lee, Amanda Siedem, Matthew R Lee, Todd Pitts, S. Gail Eckhardt, Wells A. Messersmith; University of Colorado Comprehensive Cancer Center, Aurora, CO; University of Colorado Cancer Center, Denver, CO; Division of Medical Oncology, Department of Medicine, University of Colorado School of Medicine, Aurora, CO; University of Colorado Denver, Denver, CO; University of Pittsburgh Medical Center, Pittsburgh, PA; Georgetown Lombardi Comprehensive Cancer Center, Washington, DC; University of Colorado, Aurora, CO; University of Colorado School of Medicine, Aurora, CO; University of Texas Dell Medical School, Austin, TX

Background: The majority of pts with mCRC have microsatellite stable (MSS) tumors with minimal response to PD-L1/PD-1 blockade. MEK inhibition and VEGF inhibition have immunomodulatory effects (upregulation of tumor major histocompatibility complex-I expression, enhanced T-cell infiltration, reduced MDSCs and Tregs in tumors) supporting clinical evaluation of combined MEKi (B), anti–PD-1 (P), and anti-VEGF (BV) in pts with mCRC. We hypothesize that the combination of binimetinib, pembrolizumab, and bevacizumab (BPBV) will result in greater clinical benefit than pembrolizumab alone. **Methods:** Patients with chemotherapy-refractory mCRC were evaluated (20 planned in the safety lead-in and 50 planned for total accrual). B was dosed at 45mg PO BID, P was administered at 200mg IV Q21 days, and BV was administered at 7.5mg/kg IV Q21 days. Primary objectives were safety, tolerability, and investigator-assessed ORR by RECIST 1.1. Clinical benefit rate (CR+PR+SD) and progression-free survival were secondary endpoints. Descriptive statistics were used to summarize safety and clinical activity. **Results:** As of January 9, 2020, 21 pts (10 KRAS/NRASmt, 11 RASwt, 21 MSS) were enrolled into the safety lead-in and were evaluable. The median number of prior therapies was 6. The BPBV combination was tolerable. Treatment-related Gr 1-2 and Gr 3-4 AEs occurred at 60% and 38%, respectively. The most frequent related Gr 3-4 AEs were aceniform rash, diarrhea, and hypertension (19%, 14%, 14% respectively). No treatment-related Gr 5 AEs occurred. A total of 17 patients were evaluable for response. Confirmed PR was observed in 2 pts (12%). SD was noted in 14 patients (82%) leading to a clinical benefit rate of 94%. 1 patient had PD as the best response to treatment. Median PFS was 6.4 months (95% CI 4.2-8.9). Molecular determinants, immune biomarkers, and updated tumor assessments of response will be presented. **Conclusions:** B + P + BV demonstrated a tolerable safety profile and improvements in ORR and clinical benefit rate compared to those reported with SOC in heavily pretreated pts with mCRC. Objective responses observed in pts were durable, suggesting benefit of this novel combination in a patient population refractory to immune therapies. Clinical trial information: NCT03475004. Research Sponsor: Merck, U.S. National Institutes of Health.

4032 **Poster Session (Board #24), Fri, 8:00 AM-11:00 AM**

Pembrolizumab monotherapy for patients with advanced MSI-H colorectal cancer: Longer-term follow-up of the phase II, KEYNOTE-164 study.

Luis A. Diaz, Dung T. Le, Tae Won Kim, Eric Van Cutsem, Ravit Geva, Dirk Jaeger, Hiroki Hara, Matthew E. Burge, Bert H. O'Neil, Petr Kavan, Takayuki Yoshino, Rosine Guimbaud, Hiroya Taniguchi, Elena Elez, Salah-Eddin Al-Batran, Patrick M Boland, Yi Cui, Carlos Alberto Mayo, Patricia Marinello, Thierry Andre; Memorial Sloan Kettering Cancer Center, New York, NY; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; University Hospitals Gasthuisberg Leuven, KU Leuven, Leuven, Belgium; Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; Department of Medical Oncology, National Center for Tumor Diseases, Heidelberg University Hospital, Heidelberg, Germany; Saitama Cancer Center, Saitama, Saitama Prefecture, Japan; Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia; Indiana University Simon Cancer Center, Indianapolis, IN; McGill University, Montréal, QC, Canada; National Cancer Center Hospital East, Kashiwa, Japan; Centre Hospitalier Rangueil, Toulouse, France; Medical Oncology Department, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Institute of Clinical Research (IKF) at Krankenhaus Nordwest, UCT-University Cancer Center, Frankfurt, Germany; Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; MSD China, Beijing, China; Merck & Co., Inc., Kenilworth, NJ; Sorbonne University and Saint-Antoine Hospital, Paris, France

Background: Pembrolizumab provides effective antitumor immunity and durable responses in patients (pts) with advanced, colorectal cancer (CRC) with microsatellite instability-high (MSI-H) tumors. We present data on antitumor immunity with pembrolizumab in pts from the phase 2, KEYNOTE-164 study who had approximately 3 years of follow-up, and in pts re-treated after disease progression. **Methods:** KEYNOTE-164 enrolled pts with metastatic MSI-H CRC, MSI-H status confirmed locally by IHC or PCR, and $\geq$2 (cohort A) or $\geq$1 (cohort B) prior lines of therapy (fluoropyrimidine, oxaliplatin, irinotecan, or anti VEGF/EGFR). Eligible pts received pembrolizumab 200 mg Q3W for 2y (35 administrations) or until progression, unacceptable toxicity, or withdrawal. Pts who stopped pembro due to a confirmed CR or after completing 2y of treatment and who progressed after stopping were eligible for re-treatment with up to 17 administrations in the second-course phase, at investigator discretion. Tumor response was assessed Q9W per RECIST v1.1 by independent review. The primary endpoint was ORR. Secondary endpoints included DOR, PFS, OS, and safety. The data cutoff date was Sep 9, 2019. **Results:** At data cutoff, the median follow-up was 31.4 mo (range, 0.2-47.8) for 61 pts in cohort A and 36.1 mo (0.1-39.3) for 63 pts in cohort B. ORR was 32.8% (3CR, 17PR; 95% CI% 21.3-46.0) for cohort A and 34.9% (8CR, 14PR; 95% CI 23.3-48.0) in cohort B. Median DOR was not reached (NR [range, 6.2-41.3+]) and not reached (range, 3.9+ to 37.1+), respectively. Fifteen pts in cohort A and 17 in cohort B had ongoing responses at data cutoff. Median PFS was 2.3 mo (95% CI 2.1-8.1) with 3-yr PFS rate of 31% in cohort A and was 4.1 mo (2.1-18.9) with 3-yr PFS rate of 34% in cohort B. Median OS was 31.4 mo (21.4-NR) with 3-yr OS rate of 49% in cohort A and was not reached (19.2-NR) with 3-yr OS rate of 52% in cohort B. Nine pts (6 in cohort A, 3 in cohort B) had a second course of treatment. The best response in second course was PR in 1 patient each in cohort A and B. Grade 3-4 drug-related adverse events occurred in 10 (16%) pts in cohort A and 8 (13%) pts in cohort B. No grade 5 drug-related events occurred. **Conclusions:** After approximately 3 y of follow-up, pembrolizumab continues to provide effective long-term antitumor immunity with durable responses, with small numbers of drug-related adverse events and no drug-related deaths in pts with advanced, MSI-H CRC. Clinical trial information: NCT02460198. Research Sponsor: Merck & Co., Inc.

4034 **Poster Session (Board #26), Fri, 8:00 AM-11:00 AM**

Outcomes and prognostic factors of patients (pts) with metastatic colorectal cancer (mCRC) who underwent pulmonary metastasectomy (PM) with curative intent.

Gustavo Cartaxo de Lima Gössling, Fernando de Souza Pereira, Rafaela Kathrine da Silva, Leonardo de Brittes Andrade, Nicolas Peruzzo, Maurício Guidi Saueressig, Márcio Fernandes Chedid, Gilberto Schwartsmann, Aparna Raj Parikh; Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil; Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil; Massachusetts General Hospital, Boston, MA

Background: Indications for PM in pts with mCRC are often based on the presence of favorable prognostic factors. We aimed to analyze the prognostic factors and outcomes of pts treated with PM for mCRC. **Methods:** We retrospectively identified pts with mCRC who underwent PM with curative intent between Jan 1985 and Dec 2019 at Hospital de Clínicas de Porto Alegre. Demographics, clinico-pathological features and previously described prognostic factors were collected. Univariate Cox regression was performed and followed by Kaplan-Meier (KM) curves with log-rank test when significant. **Results:** Fifty-eight pts underwent PM. Demographics are described in Table. Wedge resection was performed in 87.9% and margins were negative in 89.1%. Mean number of lesions was 2.4 ± 1.7, with the largest measuring 1.7 ± 0.9 cm. Two or more resections were performed in 36.2%, nodal sampling in 27.3%, and nodal disease was found in 5.2%.Thirty-day readmission rate was 5.2%. One pt had a Clavien-Dindo grade IIIb complication. RAS/RAF/MMR and CK20/CDX2 were available for 13.8% and 58.6% of the sample. Median PFS 14 months (m) (95% CI 10.4 - 17.5), median OS 58 m (95% CI 33.5 - 82.4) and 5-year survival 49.8%. Unfavorable prognostic factors for OS included disease-free interval (DFI) $<$ 24 m (40 m, 95% CI 31.8 - 48.1 vs 85 m, 95% CI 75.7 -96.2; P $<$ 0.005), synchronous presentation (33 m, 95% CI 23.9 - 42.0 vs 77 m, 95% CI 50.7 - 103.2; P $<$ 0.001), largest lesion size $\geq$ 2cm (37 m, 95% CI 22.9 - 51.0 m vs 81 m, 95% CI - 33.7 - 128.2, P = 0.019) and lack of CK20 expression (19 m, 95% CI 12.1 - 27.2 vs. 83 m, 95% CI 46.9 - 119.0; P $<$ 0.001). More than one lesion at presentation was prognostic for PFS (11 m, 95% CI 7.6 - 14.3 vs 23 m, 95% CI 0.1 - 59.2; P = 0.003) but not OS (P = 0.11). Grade was significant at Cox regression but showed no effect in further analysis. Neither CEA at baseline or relapse, resection margins, Charlson comorbidity index (CCI) or adjuvant chemotherapy were prognostic. **Conclusions:** Our results suggest a benefit for select pts and PM. Lack of CK20 expression may be associated with more aggressive disease and shorter OS. Additional molecular prognostic factors after PM should be further explored. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

Demographics.	
Age (years, median ± SD)	**64 ± 8.3**
Sex (men, %)	55.2%
Primary site (rectum, %)	56.9%
Laterality (left, %)	89.7%
CEA at diagnosis (median ± SD)	27.9 ± 81.2
Stage*:	
I	3,5%
II	28.1%
III	49.2%
IV	19.2%
DFI (months, median ± SD)	17.7. ± 17.5
CEA at relapse (median ± SD)	6.4 ± 15.1
Synchronous resectable liver disease (%)	25.9%
CCI (relapse)	
0-1	25.9%
2-3	55.2%
≥ 4	18.9%

*1 missing

4035 **Poster Session (Board #27), Fri, 8:00 AM-11:00 AM**

Genomic aberration of chromatin regulatory BAF complex as predictive biomarker for immunotherapy in gastrointestinal adenocarcinoma.

Changsong QI, Sai Ge, Zhi Peng, Xiaotian Zhang, Yu Xu, Guoqiang Wang, Yuezong Bai, Lin Shen; Department of Gastrointestinal Oncology, Beijing Cancer Hospital, Beijing, China; GI Oncology Department, Beijing Cancer Hospital, Beijing, China; Department of Gastrointestinal Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing, China; The Medical Department, 3D Medicines Inc., Shanghai, China; Department of Gastrointestinal Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital & Institute, Beijing, China

Background: SNF/SWI, a large ATP-dependent chromatin remodeling complex, is required for transcriptional activation of genes normally repressed by chromatin, and critical to tumor initiation and progression. Here, we analyzed the predictive utility of the mutations of the SNF/SWI members involved in BAF and PBAF complexes, and sought to explore the potential mechanisms. **Methods:** Clinical, genomic, transcriptional, and immunohistochemical data from immunotherapeutic cohort (MSKCC, n=185), Cancer Cell Line Encyclopedia (CCLE, n=92), The Cancer Genome Atlas (TCGA, n=925), and 3D Medicines database (3DMed, n=1812) were analyzed to explore the predictive effect of genomic aberration of BAF complex on the benefit from immunotherapy in patients with gastrointestinal adenocarcinoma. **Results:** In the MSKCC cohort involving 185 patients with gastrointestinal adenocarcinoma, the mutation of any member involved in BAF complex (*ARID1A*, *ARID1B*, *SMARCA4*, *SMARCB1*, and *SMARCD1*) was significantly associated with prolonged OS of ICI treatment (HR 0.53, 95%CI 0.31-0.90, P=0.019), instead of the mutations of PBAF members including *PBRM1* and *ARID2*. In addition, BAF mutation was not linked with better prognosis in TCGA database, indicating its predictive, not prognostic efficacy of immunotherapy. BAF-mutated samples exhibited higher tumour mutational burden (TMB, P<0.05, Table), and increased mRNA expression of immune-related genes including chemokines and granzyme A. In the 3DMed cohort where tumour samples received both genomic sequencing and PD-L1 immunohistochemical staining, BAF mutation was associated with higher PD-L1 positive rate in tumour cells (P<0.05, Table). **Conclusions:** Genomic aberration of members in chromatin regulatory BAF complex may serve as a predictive, not prognostic biomarker of ICI benefit in patients with gastrointestinal adenocarcinoma, partially underlying the mechanisms including higher mutational burden, transcription of immune-related genes, and protein-level PD-L1 expression. Research Sponsor: Beijing Cancer Hospital.

			Mutational count						
Database	Tumour site	n	BAF-mutant (median)			BAF-wildtype (median)			P value
CCLE	GC	36	680			324			<0.001
	CRC	56	584			117			<0.001
TCGA	GC	532	247.5			91			<0.001
	CRC	393	469.5			98			<0.001
Mutational burden									
3DMed	GC	679	8.07			5.65			<0.001
	CRC	1133	11.12			7.26			<0.001
MSKCC	GC	75	7.02			5.27			0.026
	CRC	110	6.14			59.79			<0.001
PD-L1 expression									
Database	Tumour site	n	BAF-mutant			BAF-wildtype			P value
			TPS≥10	TPS≥1	TPS<1	TPS≥10	TPS≥1	TPS<1	
3DMed	GC	679	23	37	137	30	83	369	0.040
	CRC	1133	24	42	157	37	119	754	<0.001

4036 **Poster Session (Board #28), Fri, 8:00 AM-11:00 AM**

Trifluridine/tipiracil or regorafenib in refractory metastatic colorectal cancer patients: An AGEO prospective "real life" study.

Clélia Coutzac, Isabelle Trouilloud, Pascal Artru, Julie Henriques, Thérese Masson, Christelle De La Fouchardiere, Solene Doat, Olivier Bouché, Romain Coriat, Angelique Saint, Valérie Moulin, Dewi Vernerey, David Tougeron, Julien Taieb; Centre Léon Bérard, Lyon, France; Hopital Saint Antoine, Paris, France; Private Hospital Jean Mermoz, Lyon, France; Methodology and Quality of Life in Oncology Unit, Besançon University Hospital, Besançon, France; Département d'Oncologie Médicale CHU Poitiers, Poitiers, France; Leon Berard Cancer Centre, Lyon, France; University Hospital Pitie Salpetriere APHP, Paris, France; CHU Robert Debré, Reims, France; Cochin University Hospital, Paris, France; Centre Antoine-Lacassagne, Nice, France; CH La Rochelle, La Rochelle, France; Department of Gastroenterology, Poitiers University Hospital, Poitiers, France; Hôpital Européen Georges Pompidou, Paris, France

Background: Regorafenib (R) and trifluridine/tipiracil (T) have proved their efficacy in patients (pts) with metastatic colorectal cancer (mCRC) refractory to standard chemotherapy and targeted therapies. However, it remains unclear which drug should be administered first. **Methods:** This observational study was prospectively conducted in 13 centers between 6/2017 and 9/2019 in France. All consecutive pts with chemoresistant mCRC and receiving T and/or R were eligible. The aim of this study was to describe efficacy and tolerability of T and/or R. Overall survival (OS) and progression-free survival (PFS) of pts receiving T then R (T/R) and the opposite sequence (R/T) were also assessed. **Results:** A total of 237 pts (25% R and 75% T) were enrolled (109 male, median age: 67 years (32-91), mean previous lines of treatment: 2.5 (1-7)). Baseline ECOG PS was 0-1 in 77% of pts. As compared to R pts, T pts were significantly older (68 years vs 63; $p = 0.033$) and with > 3 metastatic sites (44% vs 30%, $p = 0.018$). Median OS were 6.6 and 6.2. months in the T and R group, respectively (NS). Median PFS were 2.4 and 2.1 months in the T and R group, respectively (NS). After matching 46 paired pts according to primary tumor resection, age and number of metastatic sites, a trend to a longer OS (9.5 vs 6.8 months; $p = 0.17$) and a significantly longer PFS (2.8 vs 2 months; $p = 0.048$) were observed in the T group. Among the overall population, 24% of pts received R/T or T/R sequence. Median OS from first treatment were 10.7 months in the R/T group and 9.8 months in the T/R (NS). Treatment sequence was not an independent prognostic factor for OS or PFS in multivariable analysis. Tolerability profiles were similar to previously published data, but dose reductions were more frequent in the R group (44 vs 27%, $p = 0.008$). **Conclusions:** Efficacy and safety results in this real life prospective study are in line with those published phase III trials. Both treatments seem similar in term of efficacy favoring T for clinical use as shown by the higher number of patients receiving this drug. Research Sponsor: None.

4038 **Poster Session (Board #30), Fri, 8:00 AM-11:00 AM**

FOLFIRI versus irinotecan monodrug as second-line treatment in metastatic colorectal cancer patients: An open, multicenter, prospective, randomized controlled phase III clinical study.

Weijian Guo, Xiaowei Zhang, Yusheng Wang, Wen Zhang, Xin Liu, Wei Shen, Yifu He, Xiaodong Zhu, Zhiyu Chen, Hong Qiang Wang, Mingzhu Huang, Zhe Zhang, Xiaoying Zhao, Lixin Qiu, Chenchen Wang, Xuedan Sheng; Shanghai Medical College, Fudan University Shanghai Cancer Center, Shanghai, China; Department of Medical Oncology, Fudan University Shanghai Cancer Center; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China; Shanxi Tumor Hospital, Taiyuan, China; Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China; Department of Oncology, Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China; Anhui Provincial Cancer Hospital, Hefei, China; Fudan University Shanghai Cancer Center, Shanghai, China; Department of Oncology, Zhejiang province Zhoushan hospital, Zhoushan, 316000, China, Zhoushan, China; Department of Medical Oncology, Fudan University Shanghai Cancer Center, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China; Department of Medical Oncology, Fudan University Shanghai Cancer Center; Department of Oncology, Shanghai Medical College, Fudan University, Shangai, China; Department of Medical Oncology, Fudan University Shanghai Cancer Center, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China, Shanghai, China

Background: The most commonly used treatment methods for metastatic colorectal cancer (mCRC)are systemic chemotherapy, molecular targeted therapy and local treatment. The main chemotherapy drugs for mCRC include Irinotecan, Oxaliplatin and 5-Fu. V308 Research shows that FOLFOX and FOLFIRI can be standard first or second-line of each other in the treatment of metastatic colorectal cancer. However if the first-line treatment regimen containing 5-FU fails, whether it is necessary to re-challenge 5-FU when Irinotecan is applied in the second line is unknown. There is no head-to-head comparative study to answer whether the FOLFIRI regimen is better than the Irinotecan monodrug. Therefore, it is necessary to carry out a comparative study of FOLFIRI Versus Irinotecan monodrug to observe whether adding 5-Fu on the basis of Irinotecan can improve the therapeutic effect. **Methods:** This was a randomized phase III trial. Patients from 5 centers in China with metastatic colorectal adenocarcinoma, for whom first-line of chemotherapy including oxaliplatin combined with fluorouracil drugs (combined or not combined with targeted therapy) had failed, were enrolled. 172 patients with mCRC were randomly treated with FOLFIRI or Irinotecan monodrug were included in this study. FOLFIRI group: Irinotecan 180mg/m^2; Lecovorin 400mg/m^2; 5-Fu 400mg/m^2; 5-Fu 2400mg/m^2 CIV 46h. Irinotecan monodrug group 180mg/m^2, The regimen was repeated every 2 weeks. The primary endpoint is PFS, and this clinical trail is a superiority trial. **Results:** ITT (Intention-To-Treat) analysis: Among 172 patients, 10 had PR, 93 had SD, and 63 had PD, 6 patients have not received efficacy evaluation yet. The ORR was 5.68% VS. 5.95%, and the DCR was 61.36% and 54.76% in FOLFIRI group and Irinotecan monodrug group, respectively. Adverse reactions included neutropenia, stomatitis, diarrhea, fatigue, abnormal liver enzymes, pyrexia, arrhythmia, nausea and most of these were grade 1-2. The dose reduction rate induced by drug tocixity of was 13.64% and 7.14% in FOLFIRI group and Irinotecan monodrug group, respectively. **Conclusions:** These data show that Irinotecan monodrug has the similar ORR and DCR with FOLFIRI regimen in second-line treatment of mCRC. Irinotecan monodrug has lower adverse effect. Clinical trial information: NCT02935764. Research Sponsor: None.

4039 **Poster Session (Board #31), Fri, 8:00 AM-11:00 AM**

Encorafenib plus cetuximab with or without binimetinib for *BRAF* V600E-mutant metastatic colorectal cancer: Quality-of-life results from a randomized, three-arm, phase III study versus the choice of either irinotecan or FOLFIRI plus cetuximab (BEACON CRC).

Scott Kopetz, Axel Grothey, Eric Van Cutsem, Rona Yaeger, Harpreet Singh Wasan, Takayuki Yoshino, Jayesh Desai, Fortunato Ciardiello, Fotios Loupakis, Yong Sang Hong, Neeltje Steeghs, Tormod Kyrre Guren, Hendrik-Tobias Arkenau, Pilar Garcia-Alfonso, Ashwin Gollerkeri, Kati Maharry, Janna Christy-Bittel, Christopher Hunt Keir, Michael D Pickard, Josep Tabernero; The University of Texas MD Anderson Cancer Center, Houston, TX; West Cancer Center, Germantown, TN; University Hospitals Gasthuisberg Leuven, KU Leuven, Leuven, Belgium; Memorial Sloan Kettering Cancer Center, New York, NY; Hammersmith Hospital, Imperial College Health Care Trust, London, United Kingdom; National Cancer Center Hospital East, Kashiwa, Japan; Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; University of Campania, Naples, Italy; Istituto Toscano Tumori, Pisa, Italy; Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Netherlands Cancer Institute, Amsterdam, Netherlands; Department of Oncology, Oslo University Hospital, Oslo, Norway; Sarah Cannon Research Institute UK Limited, London, United Kingdom; Hospital General Universitario Gregorio Marañón, Madrid, Spain; Pfizer Inc, Cambridge, MA; Pfizer Inc., Boulder, CO; Pfizer Inc, New York, NY; Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

Background: In the BEACON CRC study, the triplet regimen of encorafenib (ENCO) + binimetinib (BINI) + cetuximab (CETUX) significantly improved overall survival (OS, HR:0.52, $P < 0.0001$) and objective response rates (ORR, 26% vs 2%, $P < 0.0001$) in patients (pts) with *BRAF*V600E metastatic colorectal cancer (mCRC) compared with current standard of care. This analysis focuses on the patient-reported quality of life (QOL) assessments from this study. **Methods:** The BEACON CRC study was a randomized, open-label, 3-arm, phase 3 global study which evaluated triplet (ENCO+BINI+CETUX) or doublet (ENCO+CETUX) vs. investigator's choice of irinotecan + CETUX or FOLFIRI + CETUX in pts with *BRAF*V600E mCRC. QOL assessments (secondary endpoints in the trial) included the EORTC QOL Questionnaire (QLQ C30), Functional Assessment of Cancer Therapy Colon Cancer (FACT C), EuroQol 5D 5L, and Patient Global Impression of Change (PGIC). The primary assessment for the QOL variables was the time to definitive 10% deterioration. The study is ongoing. **Results:** 665 pts were randomly assigned to receive either triplet (n = 224), doublet (n = 220), or control (n = 221). Reduction in the risk of QOL deterioration was an estimated 45% (HR 0.55, 95% CI: 0.43, 0.70) and 52% (HR 0., 9485% CI: 0.38, 0.62) in EORTC QLQ C30 and FACT C assessments, respectively, in favor of the triplet regimen over control. For the doublet vs. control, reduction in risk of QOL deterioration was an estimated 46% (HR 0.54, 95% CI: 0.43, 0.69) and 54% (HR 0.46, 95% CI: 0.36, 0.59) in EORTC QLQ C30 and FACT C, respectively in favor of the doublet. Similar results were observed in EuroQol 5D 5L and PGIC assessments. There were no overall differences in QOL between triplet and doublet across the 4 instruments. **Conclusions:** In BEACON CRC, triplet and doublet demonstrated substantial improvement in patient-reported QOL assessments over the current standard of care in pts with *BRAF*V600E-mutant metastatic CRC whose disease had progressed after 1 or 2 prior regimens. Clinical trial information: NCT02928224. Research Sponsor: Pfizer Inc.

Nivolumab (NIVO) + low-dose ipilimumab (IPI) as first-line (1L) therapy in microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): Two-year clinical update.

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Background: In the phase 2 CheckMate 142 trial, NIVO + low-dose IPI had robust, durable clinical benefit and was well tolerated as 1L therapy for MSI-H/dMMR mCRC (median follow-up 13.8 months [mo; range, 9–19]; Lenz et al. *Ann Oncol* 2018;29:LBA18). Longer follow-up is presented here. **Methods:** Patients (pts) with MSI-H/dMMR mCRC and no prior treatment for metastatic disease received NIVO 3 mg/kg Q2W + low-dose IPI 1 mg/kg Q6W until disease progression or discontinuation. The primary endpoint was investigator-assessed (INV) objective response rate (ORR) per RECIST v1.1. **Results:** In 45 pts with median follow-up of 29.0 mo, ORR (95% CI) increased to 69% (53–82) (Table) from 60% (44.3–74.3); complete response (CR) rate increased to 13% from 7%. The concordance rate of INV and blinded independent central review was 89%. Median duration of response (DOR) was not reached (Table). Median progression-free survival (PFS) and overall survival (OS) were not reached, and 24-mo rates were 74% and 79%, respectively (Table). Nineteen pts discontinued study treatment without subsequent therapy. An analysis of tumor response post discontinuation will be presented. Ten (22%) pts had grade 3–4 treatment-related adverse events (TRAEs); 3 (7%) had grade 3–4 TRAEs leading to discontinuation. **Conclusions:** NIVO + low-dose IPI continued to show robust, durable clinical benefit with a deepening of response, and was well tolerated with no new safety signals identified with longer follow-up. NIVO + low-dose IPI may represent a new 1L therapy option for pts with MSI-H/dMMR mCRC. Clinical trial information: NTC02060188. Research Sponsor: Bristol-Myers Squibb.

Efficacy (INV)[a].

	NIVO + low-dose IPI (N = 45)
ORR,[b] n (%) [95% CI]	31 (69) [53–82]
Best overall response, n (%)	
CR	6 (13)
PR	25 (56)
SD	7 (16)
PD	6 (13)
Not determined	1 (2)
Disease control rate,[c] n (%) [95% CI]	38 (84) [70.5–93.5]
Median time to response (range), mo	2.7 (1.2–27.7)
Median DOR (range), mo	NR (1.4+ to 29.0+)
Median PFS, mo (95% CI)	NR (NE)
24-mo rate, % (95% CI)	74 (57.2–84.5)
Median OS, mo (95% CI)	NR (NE)
24-mo rate, % (95% CI)	79 (64–89)

[a]Median follow-up = time on study from first dose to data cutoff (29.0 mo [range, 24.2–33.7]).
[b]Pts with CR or PR divided by number of treated pts.
[c]Pts with CR, PR, or SD for ≥ 12 weeks divided by number of treated pts.
NE, not estimable; NR, not reached; PD, progressive disease; PR, partial response; SD, stable disease.

4041 **Poster Session (Board #33), Fri, 8:00 AM-11:00 AM**

Metastases resection in colorectal cancer patients with mutation in oncogene BRAF or tumors located on the right side: Experience at the HGUGM.

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Background: Approximately 25% of patients with colorectal cancer (CRC) debut with metastatic disease. In addition, 25-35% of patients with localized disease at diagnosis develop metastatic lesions during the evolution of their disease. Consequently, approximately 50-60% of patients with CRC will present metastatic lesions at some point in their lives. Metastasis resection has improved the prognosis of these patients, achieving overall survival (OS) that exceed 40 months. However, there are doubts about the benefit of this approach in patients with mutations in oncogene BRAF or tumors located on the right-side, due their poor prognosis. The aim of the study is to analyze the impact of metastases resection on OS of these populations. **Methods:** We conducted a retrospective analysis of patients with mCRC attended in the Medical Oncology Department of the Hospital General Universitario Gregorio Marañón (Spain) between January 2010 and 2018. **Results:** 487 patients were identified and included in the analysis. Median age was 71 years (62-81). Most patients were males (62.4%). 55.2% had metastatic lesions at diagnosis. Most patients had ECOG 0-1 at diagnosis of metastatic disease (91.0%). 8.9% of patients had BRAF mutations (n = 21) and 31.8% of patients had primary tumors located on the right-side (n = 152). 474 patients received first-line chemotherapy (97.3%). OS of the entire cohort was 29.67 months; 30.69 months in BRAF mutated patients vs 35.89 in wild-type patients ($p = 0.161$); 25.29 months in right-side tumors vs 31.02 in left-side tumors ($p = 0.044$). 306 patients (62.8%) underwent metastases resection. Most common location was liver (51.4%). 147 patients (30.2%) underwent a second metastases resection. Mean number of metastases surgeries was 1.35 (+/-1.40). OS since metastases resection was 24.83 months in BRAF mutated patients vs 41.55 months in wild-type patients ($p = 0.020$). According to location, it was 35.49 months in right-side tumors vs 43.78 months in left-side tumors ($p = 0.106$). In BRAF mutated patients, OS was 38.19 months in patients underwent metastases resection vs 18.52 months in non-surgical patients ($p = 0.043$); 41.51 months vs 16.18 months respectively in patients with tumors located on the right-side ($p < 0.001$). **Conclusions:** Metastases resection has a positive impact on overall survival of patients with mutations in oncogene BRAF or right-side tumors, even though their prognosis is still poor compared to patients without these alterations. Research Sponsor: None.

4042 **Poster Session (Board #34), Fri, 8:00 AM-11:00 AM**

Rectal cancer in young patients: Clinicoepidemiologic profile and treatment outcomes.

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Background: Colorectal cancers are 3rd most common cause of cancer globally however studies of rectal cancers alone in younger patients are scarce. Rectal cancers in Asian patients present at a younger age and has an aggressive tumor biology. This study looks at rectal cancer in young patients, ≤30 years old, with the aim to report clinico-epidemiologic profile and treatment outcomes in this subgroup. **Methods:** Retrospective analysis was conducted at a tertiary care centre. Of total 845 rectal cancer patients between 2012-2017, 103 patients of young rectal cancers were enrolled. Kaplan Meier method was used for survival analysis and cox regression analysis was done to identify factors affecting survival. **Results:** Young rectal cancer patients constituted 12.2% of the total rectal cancer patients. Male: Female ratio was 2.3:1 and the mean age was 24.7 ± 3.9 years. Around 73.8 % patients had locoregional disease (stage I/II/III) at presentation.CEA levels were elevated in 36.9% of patients, while most common histology was signet ring cell histology which was present in 51.5% of patients. Of 76 patients with locoregional disease, 75% received neoadjuvant chemoradiotherapy, 7.9% received neoadjuvant chemotherapy alone while 3.9% received neoadjuvant radiotherapy alone. Of 76 patients with locoregional disease, 55 patients underwent surgery of which 53.9% underwent low anterior resection while 18.4% underwent abdomino-perineal resection. Pathologic CR rates were seen in 13.3%, while recurrences were seen in 55.4% of non-metastatic patients. Overall 5-year survival for the whole study group was 19.5%, while 1-year PFS and 3-year DFS for metastatic and non-metastatic disease were 5% and 43.8% respectively. On regression analysis elevated CEA levels and not achieving a pathologic CR (pCR) with neoadjuvant therapy had a trend towards worse overall survival (HR 2, 95% CI 1-4, p = 0.063), (HR 4.7, 95% CI 0.64-35.1, p = 0.125) respectively. **Conclusions:** Rectal cancers in Asia present at younger age and this younger population is associated with advanced stage, increased CEA at presentation, aggressive histology and poor survival. CEA raise and not achieving pCR were associated with trend towards worse survival. Research Sponsor: None.

4043 **Poster Session (Board #35), Fri, 8:00 AM-11:00 AM**

Recurrence after surgery for concurrent metastatic colorectal cancer: The perspective of bioinformatics and machine learning.

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Background: Recurrence of concurrent metastatic colorectal cancers (mCRCs) after surgery is still a challenge. But mCRCs' outcomes are heterogeneous, and no clinicopathological methods can predict its recurrence and guide postoperative treatment from an intrinsic cell activities and extrinsic immune microenvironment perspective. We aimed to identify such gene models. **Methods:** Gene expression analysis on CRCs. Based on metastasis-related genes, a metastatic evaluation model (MEM) was developed, dividing mCRCs into high and low recurrence risk clusters. Machine learning tested MEM's importance to predict recurrence. Further investigating MEM's two clusters made an immune prognostic model (IPM) with immune genes differentially expressed between MEM clusters. The predictive performance of MEM and IPM on prognosis was comprehensively analyzed and validated. The mechanism of IPM on the immune microenvironment and response to immuno/chemotherapy was analyzed extensively. **Results:** RNA data of 998 CRCs were analyzed. High postoperative recurrence risk in mCRCs was owing to immune response's down-regulation, which was influenced by 3 MEM genes (*BAMBI, F13A1, LCN2*) and their related 3 IPM genes (*SLIT2, CDKN2A, CLU*). MEM and IPM were developed and validated on 239 mCRCs to differentiate a low and high recurrence risk (AUCs $>$ 0.7). Functional enrichment analysis showed immune response and immune system diseases pathway represented the major function and pathway related to IPM gene. IPM high-risk group (IPM-high) had higher fractions of Tregs (P= 0.04), lower fractions of resisting memory CD4+ T cells (P= 0.02) than IPM-low. And stroma and immune cells in IPM-high samples were scant (P= 0.0002, 0.001, respectively). In IPM-high, MHC class II molecules all down-expressed, and DNA methylation disordered. TIDE algorithm and GDSC analysis discovered IPM-low was more promising to respond to both anti-CTLA4 therapy (P= 0.005) and common FDA targeted drugs ($P<$ 0.05), while IPM-high had nonresponse to both of them. But anti-CDKN2A agent with activation of MHC class II response might reverse the dilemma of this refractory mCRCs subgroup. **Conclusions:** Postoperative recurrence of mCRC is strongly related to immune microenvironment. Our two relative gene models could identify subgroups of mCRC with different recurrence risk, and stratify mCRCs sensitive to immune/chemotherapy, even highlight the ignored importance of MHC class II molecules on immunotherapy in mCRCs for the first time. Research Sponsor: Capital's Funds for Health Improvement and Research [grant number 2018-1-4021].

4044 **Poster Session (Board #36), Fri, 8:00 AM-11:00 AM**

TAS-116, an oral HSP90 inhibitor, in combination with nivolumab in patients with colorectal cancer and other solid tumors: An open-label, dose-finding, and expansion phase Ib trial (EPOC1704).

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Background: Regulatory T cells (Tregs) potentially induce the resistance of anti-PD1/PD-L1 inhibitors (A-PD1). TAS-116, a novel HSP90 inhibitor, enhanced antitumor immunity via reducing Tregs *in vitro* and *in vivo*. Combination of TAS-116 plus A-PD1 showed a superior tumor growth suppression compared with either treatment alone *in vivo*. Based on the above, we investigated safety and efficacy of TAS-116 in combination with nivolumab in patients with solid tumors. **Methods:** Enrolled patients received TAS-116 plus nivolumab in a dose-finding part to estimate the maximum tolerated dose and the recommended phase 2 dose (RP2D). Additional patients were enrolled in a dose-expansion part. TAS-116 monotherapy (orally once daily, 80mg on level 1, 120mg on level 2, and 160mg on level 3) was administrated for 2 weeks followed by the combination with nivolumab (intravenously every 2 weeks, 3 mg/kg). The primary endpoint was dose-limiting toxicities (DLTs) during the first cycle (4 weeks). PD-L1 combined positive score (CPS) and tumor mutation burden (TMB) were assessed. We also conducted biomarker research using paired samples from repeated tumor biopsies and blood collections. **Results:** A total of 44 patients with colorectal cancer (CRC, n = 29), gastric cancer (GC, n = 8), sarcoma (n = 5), non-small cell lung cancer (NSCLC, n = 1) and melanoma (n = 1) after standard of cares were enrolled. One patient had MSI-H CRC, but all other patients had MSS tumors. No DLTs were observed at all levels and TAS-116 160 mg was determined as RP2D. The common grade 3 or worse treatment-related adverse included AST/ALT increased (7%), creatinine increased (5%) and platelet count decreased (5%). Objective tumor response was observed in 6 patients including 4 MSS CRC, 1 MSI-H CRC and 1 sarcoma, resulting in objective response rate (ORR) of 16% in MSS CRC without prior A-PD-1. PD-L1 CPS and TMB could be evaluated in 18 and 17 MSS CRC without prior A-PD-1, respectively. ORR was 27% in patients with CPS $\geq$1 and 0% in patients with CPS $<$ 1. ORR was 33% with TMB-high (median as the cut-off) and 12% with TMB-low. Analysis of tumor-infiltrating lymphocytes before treatment and after TAS-116 monotherapy demonstrated reduction of FoxP3^{hi}CD45RA^{-}Tregs fraction in the tumor microenvironment. **Conclusions:** The combination of TAS-116 160mg plus nivolumab had manageable safety profiles and anti-tumor activity especially for MSS CRC patients, which warrants further investigations in a large cohort. Clinical trial information: UMIN000032801. Research Sponsor: Taiho, Ono.

4045 **Poster Session (Board #37), Fri, 8:00 AM-11:00 AM**

Inpatient outcomes and predictors of mortality in patients with gastrointestinal malignancies presenting with sepsis: A nationwide analysis.

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Background: Sepsis is a frequent cause of morbidity and mortality in patients with malignancy. However, there is paucity of literature on mortality, hospital charges and overall healthcare utilization among patients with GI malignancy, which we hope to characterize in this study. **Methods:** We queried retrospective data from the Nationwide Inpatient Sample (NIS) database for the year 2016. Sepsis (Dx1) was identified using ICD-10 code as primary diagnosis in patients with known GI malignancies (Dx2). Univariate and multivariate Poisson regression analysis was done to study outcomes. Propensity score matching was done to minimize confounding factors. Primary outcome was inpatient mortality. Secondary outcomes were Length of Stay (LOS), Total Charge (TOTCHG) and ICU admission. **Results:** A total of 43,240 patients with GI malignancy were admitted in 2016 with sepsis. Two most common GI malignancies admitted with sepsis were colorectal (35%) and hepato-cellular cancer (HCC) (28.2%). Overall mortality in GI cancer was 19.8% vs 10.2% in all cancers ($p<0.01$). There was male (59%) and Caucasian (63%) preponderance. Out of all hospital admissions for GI malignancy, 41.4% were secondary to sepsis. E. coli (31%) infection and gram-negative bacteremia (15%) were the most common causes of sepsis. Sepsis with GI malignancy was associated with length of stay of 7.4 days vs 5.4 days (coef 2.44, 95% CI 2.3-6.7 p=0.04) and a mean hospital charge of $88,728 vs $ 54, 668 (coef 34,140, 95% CI 44,264-90,646, $p<0.01$) as compared to without sepsis. After adjusting for demographic and patient related variables, independent predictors of mortality were old age, uninsured, African Americans, septic shock requiring pressor support, AKI, inpatient hemodialysis, metabolic encephalopathy and acute respiratory failure. **Conclusions:** Sepsis poses a substantial healthcare burden in patients with GI malignancy and is a major cause of mortality. Early antibiotic treatment is necessary for sepsis control in patients with GI malignancy. Research Sponsor: None.

Multivariate analysis for mortality in patients with GI malignancy admitted with sepsis.

Predictor	Adjusted HR (95% CI)	P-value
Colorectal cancer	Reference	
Esophageal	1.40 (1.13-1.74)	***0.02**
Gastric	1.31 (1.03-1.66)	***0.03**
HCC	1.49 (1.27-1.74)	***<0.01**
Age > 70	1.74 (1.56 – 1.89)	***<0.01**
Uninsured	2.06 (1.56-2.72)	***<0.01**
Encephalopathy	2.54 (1.61- 4.02)	***<0.01**
ICU admission	5.42 (4.61-6.37)	***<0.01**
AKI requiring HD	6.33(5.17-7.74)	***<0.01**

*P value less than <0.05 was considered statistically significant

4046 **Poster Session (Board #38), Fri, 8:00 AM-11:00 AM**

Pembrolizumab (Pem) in combination with stereotactic body radiotherapy (SBRT) for resectable liver oligometastatic MSS/MMR proficient colorectal cancer (CRC).

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Background: SBRT is used to treat liver metastatic CRC, causing an increase in immunogenic antigen release and influx of responding immune cells. We hypothesize that radiation enhances the immunogenicity of MSS CRC and potentiates the effectiveness of PD-1 blockade. This phase Ib study examines the safety and efficacy of the sequential combination of SBRT and Pem in patients (pts) undergoing resection of their disease. **Methods:** Eligibility criteria include MSS CRC with resectable liver-confined metastatic disease. Prior surgery and systemic chemotherapy are allowed. Subjects receive sequential SBRT and cycle 1 of Pem prior to operative management and adjuvant Pem. The primary objectives are to determine the safety/tolerability of this regimen and the recurrence free survival (RFS) at 1 year following clearance of metastatic disease. Correlative studies examined tumor infiltrating CD8+ T lymphocytes (TILs) and the accumulation and proteolysis of versican (VCAN), an immunoregulatory tumor matrix proteoglycan. Proteolysis of VCAN results in the release of an immunostimulatory fragment, versikine. Cancers with low VCAN and high versikine (VCAN proteolysis predominant (VPP)) are hypothesized to respond better to immunotherapies. **Results:** 15 pts (median age 58.2 [range 38-69]) have been enrolled. All pts had prior FOLFOX. SBRT median dose was 50 Gy (40-60 Gy) to a single lesion targeted in all pts. No DLTs were observed. AEs included one case of biliary tract injury and biloma, not related to immunotherapy. No grade 3/4 immunotherapy-related AEs have occurred. 10 pts have completed a minimum follow-up of 1 year post resection. In the intention to treat analysis, the 1 year RFS was 70% (historic control 50%). 2 of 3 pts with BRAF V600E mutations have had early recurrences. 2 pts had VCAN high tumors and both recurred prior to 1 year. 4 pts had VPP cancers and all were recurrence free at 1 year. TILs in the radiated lesions were $>$ 2 times as abundant as in the pre-treatment (tx) tissue for 50% of pts. 3 of 4 pts who had non-radiated lesions available for analysis had TILs $>$ 2 times pre-tx in the non-radiated lesions indicating a potential abscopal effect. **Conclusions:** The combination of SBRT with Pem and surgical resection is well tolerated with no signal of increased immunotherapy-related toxicity and preliminary evidence of potential enhanced efficacy. Clinical trial information: NCT02837263. Research Sponsor: Merck.

4047 **Poster Session (Board #39), Fri, 8:00 AM-11:00 AM**

Clinical and pathologic factors associated with survival in BRAFV600E colorectal cancers.

Van K. Morris, Bryan K. Kee, Michael J. Overman, David R. Fogelman, Arvind Dasari, Kanwal Pratap Singh Raghav, Imad Shureiqi, Benny Johnson, Christine Megerdichian Parseghian, Robert A. Wolff, Cathy Eng, Naveen Garg, Scott Kopetz; The University of Texas MD Anderson Cancer Center, Houston, TX; Mayo Clinic Cancer Center, Rochester, MN

Background: $BRAF^{V600E}$ mutations occur in fewer than 10% of all patients (pts) with metastatic colorectal cancer (mCRC) and arise from sessile serrated adenomas. Despite efficacy with targeted therapies against MAPK signaling and with immunotherapies in this population, survival outcomes for pts with $BRAF^{V600E}$ mCRC in general are poor. Characteristics distinguishing pts with $BRAF^{V600E}$ mCRC with favorable versus unfavorable outcomes have not been well annotated. **Methods:** Records of 188 pts with $BRAF^{V600E}$ mCRC evaluated at MD Anderson Cancer Center between 3/2010-1/2020 were reviewed. Pts with the shortest and longest metastatic survival (N = 25 for each group) were compared. Associations between prognostic group and clinical/pathologic features were measured by odds ratio and for median survival by log-rank testing. **Results:** Median metastatic survival differed between the 2 $BRAF^{V600E}$ mCRC populations (8.6 vs 84 months, $p < .0001$). Pts with poor survival more commonly had primary tumors arising from the hepatic flexure/proximal transverse colon (44% vs 16%, p = .04) and more frequent hepatic involvement (75% vs 28%, p = .001). Pts with favorable survival were more likely to develop metachronous metastases (52% vs 16%, p = .01), have fewer distant organ involvement (median 1 vs 2, p = .02), and undergo definitive locoregional therapy to metastatic disease (44% vs 0%, p = .01). Microsatellite instability (36% vs 4%, p = .008) and a history of tobacco use (44% vs 16%, p = .04) were associated with a favorable prognosis. Durable responses to MAPK-targeted therapies (5/25) and immunotherapy (3/25) were noted in the favorable group. **Conclusions:** Pts with $BRAF^{V600E}$ mCRC can achieve excellent long-term survival which belies conventional context and is driven by locoregional and systemic treatment options alike. Anatomic localization of the primary tumor and prior exposures may highlight environmental influences on tumor biology which account for the clinical heterogeneity of pts with $BRAF^{V600E}$ mCRC. Research Sponsor: None.

4048 **Poster Session (Board #40), Fri, 8:00 AM-11:00 AM**

Evaluation of safety, immunogenicity, and preliminary efficacy of PolyPEPI1018 off-the-shelf vaccine with fluoropyrimidine/bevacizumab maintenance therapy in metastatic colorectal cancer (mCRC) patients.

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Background: PolyPEPI1018 is an off-the-shelf, multi-peptide vaccine containing 12 immunogenic epitopes derived from 7 cancer testis antigens (CTAs) frequently expressed in patients with CRC. Here we report the final results of the phase I study of PolyPEPI1018 vaccine as an add-on to maintenance therapy in mCRC patients. **Methods:** 11 patients with MSS mCRC were vaccinated with PolyPEPI1018 just after the transition to maintenance therapy with fluoropyrimidine/bevacizumab after first-line combo chemotherapy and bevacizumab. Part A: n = 5, single dose; Part B: n = 6, 3 doses, Q12W. Primary endpoint was safety. Immunomonitoring was performed at both blood and tumor levels, as well as prospectively predicted. **Results:** The vaccine was well tolerated; most common side effects were transient skin reactions. No vaccine-related SAE occurred. Pre-existing immune responses were boosted by the vaccine for 7/10 patients. *De novo* responses were also induced, overall, 80% of patients had CD8+ T cell responses against at least 3 CTAs. The magnitude of immune responses as well as the density and the ratio of CD8+/CD3+ tumor infiltrating T cells increased with multiple vaccine doses. Three patients had objective tumor response according to RECIST v1.1: one of them in the single dose group and two of them in the 3 doses group. Both patients in the 3 doses group qualified for curative surgery. One of them had no viable tumor cells in his primary tumor at the time of surgery. Post-trial follow-up revealed PFS of at least 12 months for 3 patients. mPFS was longer for patients receiving multiple doses (9.9 months) compared to single dose (6.1 months). Both measured and predicted multiantigenic immune responses tend to correlate with PFS and tumor volume reduction. **Conclusions:** PolyPEPI1018 was effective in restoring immunological responses to CTAs in patients' with spontaneous immunity against. Treatment with PolyPEPI1018 vaccine and maintenance therapy was safe and demonstrated evidence of early clinical activity in MSS mCRC tumors. Data support further randomized trials with PolyPEPI1018. Clinical trial information: NCT03391232. Research Sponsor: Treos Bio.

4049 **Poster Session (Board #41), Fri, 8:00 AM-11:00 AM**

Sequencing of treatment matters in synchronous liver or lung only metastatic colon cancer.

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Background: Per SEER database, approximately 21% of patients have synchronous metastatic disease at presentation with a median 5 year survival of 14%. Liver is by far the most common site of metastatic disease followed by lung. Metastatectomy of appropriate lesions have achieved a 5 year survival ranged between 40%-70% depending on the extent of the metastasis. For liver or lung only metastatic disease, practice varies from surgery followed by adjuvant chemotherapy to perioperative chemotherapy. Benefit of one approach versus the other has not been demonstrated. We decided to study this using the National Cancer Database (NCDB) database available from the 2010-2015 period. **Methods:** Adults $>$ 20 years with primary colon cancer (excluding rectal and recto sigmoid junction) with single organ metastatic disease to liver and/or lung at diagnosis were identified. All patients had received surgery to the primary site, resection of the distant site and chemotherapy in the neoadjuvant setting (NAC) or adjuvant setting (AC) within 1 year of diagnosis. Histology except for adenocarcinoma and variants were excluded. Patients who died within 90 days of surgery were excluded. Descriptive analysis, Kaplan-Meier plots, Log-Rank tests for univariate and proportional hazards models for multivariate survival analyses were performed. To reduce biases, a sensitive analysis was also performed based on the intention to treat principle by including additional surgery only and chemotherapy only cases. **Results:** A total of 3175 colon cancer patients with liver or lung only metastatic disease were identified. 2487 (78%) had AC and 688 (22%) had NAC. Approximately 54% were males with 90% less than 75 years of age. More patients had private insurance and were treated in academic centers in the NC group (62 Vs 51%) and (58 Vs 42%) respectively. Both groups had similar Charlson comorbidity index. NC approach had better OS with HR of 0.75 (CI 0.65-0.85; $p < 0.0001$) on univariate analysis and 0.86 (0.74-0.98; $P < 0.0281$) on multivariate analysis. On multivariate analysis, age group $>$ 75 years, black race, treatment outside academic research program had worse survival ($p < 0.0001$, 0.0139, 0.0001) respectively. The sensitive analysis showed the similar effects. **Conclusions:** Within the limitations of database review, our analysis suggests survival advantage of neoadjuvant chemotherapy approach over surgery first. Research Sponsor: None.

4050 **Poster Session (Board #42), Fri, 8:00 AM-11:00 AM**

Prognostic effect of specific *RAS/BRAF* mutations in patients (pts) with metastatic colorectal cancer (mCRC).

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Background: Somatic mutations in *KRAS, HRAS, NRAS* (extended *RAS*) and *BRAF* have prognostic and predictive impact in pts with mCRC. We analyzed the prognostic impact of specific somatic mutations in extended *RAS* and *BRAF*. **Methods:** We retrospectively reviewed the electronic medical records of pts with mCRC at our institution who underwent comprehensive genomic profiling (CGP) utilizing the Foundation One assay. DNA was extracted from clinical specimens and CGP was performed on hybrid-capture, adaptor ligation-based libraries for up to 315 genes plus 47 introns from 19 genes frequently rearranged in cancer. BRAF mutations were classified as class I, II and III according to accepted nomenclature. Fisher's exact test and Kaplan Meier estimates were used for statistical analyses. This project was approved by the Medical College of Wisconsin Institutional Review Board. **Results:** 273 pts were identified - median age at diagnosis was 57, 48% were male. Somatic mutations in extended RAS were found in 138 (50%) pts, majority being mutations in *KRAS* (46%). Among pts with *KRAS* mutations, codon 12, 13, 61 and 146 mutations accounted for 73%, 11%, 4% and 6% respectively while *KRAS* G12C mutations accounted for 9%. *BRAF* mutations were detected in 22 (8%) pts - *BRAF* V600E and non–V600E mutations accounting for 4.4% and 3.6% respectively. Among pts with BRAF mutations, 17 (77%) were kinase domain mutations, 16 of which could be further classified as class I (12/16), II (1/16) and III (3/16). Median overall survival (mOS) for the entire cohort was 26.4 months (mo). *KRAS* mutated pts had a mOS of 25.8 mo; pts with *KRAS* G12C mutation had a mOS of 23 mo compared to 27.1 mo for pts with other *KRAS* mutations ($p < 0.001$).Pts with *BRAF* mutation had a mOS of 26.2 mo; pts with *BRAF* V600E mutation had a mOS of 14.1 mo compared to 30.6 mo for pts with *BRAF* non-V600E mutations ($p = 0.1$). **Conclusions:** The poor prognosis of pts with *KRAS* G12C and *BRAF* V600E mutations compared to pts with other *KRAS* and *BRAF* mutations merit further biologic characterization with functional assays. Individualized therapeutic strategies must be conceptualized for mCRC pts with specific *RAS/BRAF* mutations, considering their widely disparate prognosis and putative downstream signaling mechanisms. Dynamic molecular simulation to understand conformational changes in proteins associated with specific mutations will be pivotal to optimizing precision therapeutic strategies. Research Sponsor: None.

4051 **Poster Session (Board #43), Fri, 8:00 AM-11:00 AM**

Randomized phase II trial of avelumab alone or with cetuximab for unresectable, locally advanced or metastatic squamous cell anal carcinoma progressed to at least one line of treatment: The CARACAS study.

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Background: Advanced squamous cell anal carcinoma (advSCAC) is a rare disease with poor prognosis. No standard therapies beyond first line are currently available, yet a promising activity was documented for the anti-EGFR cetuximab (CET) and for anti-PD-1 agents in previous retrospective case series and phase I-II studies, respectively. In experimental models combination of EGFR and PD-L1 blockade was synergistic as PD-L1 blockade led to NK cells activation enhancing cetuximab ADCC. In this trial we aimed to evaluate safety and activity of the anti-PD-L1 avelumab (AVE) alone or in combination with CET in pretreated advSCAC. **Methods:** This was an open-label, prospective, multicenter randomized phase 2 trial (NCT03944252). Patients (pts) with advSCAC progressed after at least 1 line of treatment were randomized 1:1 to receive either AVE 10 mg/kg (arm A) or AVE + CET 500 mg/sqm (arm B) as bi-weekly regimens. A Simon's two-stage Mini-Max design was used. The null hypothesis of a true response rate 5% was tested against the one-sided alternative of a true response rate 20% in each arm. Setting type I error at 0.05 and power at 80%, 30 pts per arm had to be randomized. No formal comparison between the two arms was planned. Primary endpoint was overall response rate (ORR); secondary endpoints were Progression-Free Survival (PFS), Overall Survival (OS) and safety. **Results:** Sixty pts were enrolled, 30 in each arm. All baseline characteristics were well balanced between the two arms. Median age was 63 years; M/F was 19/41; 12 out of 30 pts in each arm had distant metastases; 7 in arm A and 10 in arm B received >1 previous lines of treatment. At a median follow up of 8.7 months, 3 out of 30 pts in each arm obtained PR (ORR 10%); SD was observed in 12 pts in arm A (40%) and 14 in arm B (47%). Disease control rate was thus 50% in arm A and 57% in arm B. Duration of disease control was 6.1 (95%CI 3.7–11.0) and 6.1 (95%CI 4.1–9.6) months in arm A and B, respectively. Median PFS was 2.1 (95%CI 1.8–4.0) in arm A and 3.9 months (95%CI 2.1–5.6) in arm B. Grade 3-4 adverse events were 13.3% in arm A and 33.3% in arm B: anemia 10% vs 13.3%, fatigue 0 vs 6.7%, skin toxicity 0 vs 6.7%. Treatment interruption due to AE occurred in 3 pts, 1 in arm A and 2 in arm B. Translational analyses will be performed on tissue and blood samples for exploratory purpose. **Conclusions:** The CARACAS trial was the first clinical study to test dual EGFR and PD-L1 blockade in advSCAC. Both AVE monotherapy and AVE-CET showed promising activity with manageable safety profile. Clinical trial information: NCT03944252. Research Sponsor: Veneto Institute of Oncology IRCCS, Pharmaceutical/ Biotech Company.

4052 **Poster Session (Board #44), Fri, 8:00 AM-11:00 AM**

Characterization of sociodemographic and clinicopathological features and associated outcomes of patients (Pts) with anal squamous cell cancer (ASCC): Analysis of 44,084 pts in the National Cancer Database (NCDB).

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Background: ASCC incidence is rising. There are limited data on the relationships between sociodemographic & clinicopathological features and outcomes of ASCC pts. **Methods:** Pts diagnosed with ASCC between 2004 and 2016 were retrospectively reviewed. Data obtained from the NCDB were used to examine the impact of sociodemographic status on clinicopathological features and outcomes. Pts were categorized based on low (median $<$ \$38,000) or high ($\geq$\$68,000) income and low ($>$ 21% with no high school diploma) or high ($<$ 7% with no high school diploma) education areas based on zip code at time of diagnosis. Logistic regression and chi-square were used to examine differences between groups. **Results:** In total, 44,084 pts with ASCC were identified: median age, 59 yrs, 86% white; 11% black; 64% female. Most pts (84%) resided in metro areas; 29.7% vs 19.8% lived in high vs low income areas; 22.9% vs 17.8% lived in high vs low education areas. Seven percent were uninsured, 50% had government (Gov), and 43% had private insurance. Male gender (HR 1.62, CI 1.41-1.85, $p < 0.001$), low income area (HR 1.28, CI 1.19-1.37, $p = 0.014$), and insurance status (Gov, HR 1.55, CI 1.32-1.82, $p < 0.001$ and uninsured, HR 1.37, CI 1.37-1.85, $p = 0.039$) were associated with a higher risk of death. After adjusting for age, sex, race, stage, grade, insurance status, and comorbidity, pts from low income/education (n = 6695) vs high income/education (n = 4316) areas had a 33 % increased risk of death (HR: 1.33, $p < 0.001$). Pts with stage IV ASCC in the low income/education (n = 227) vs high income/education (n = 295) groups had worse overall survival (mOS, 1.4 vs 1.9 yrs, $p < 0.020$). Of the 44,084 pts, 5461 (12.4%) had confirmed HPV status. Of these, 2658 (48.7%) were HPV+ (high risk subtypes) and 2803 (51.3%) were HPV-. Compared to the HPV- pts, HPV+ pts were more likely to be women (71.8% vs 67.8%, $p = 0.001$), have stage 3 (38.1% vs 33.6%) or 4 (7.9% vs 5.9%, $p < 0.001$) cancer, and have poorly differentiated (29.5% vs 25.6%, $p < 0.001$) tumors. There were no significant differences in race, education, income, metro area, insurance status, or comorbidity between the HPV+ and HPV- pts. Moreover, HPV status did not impact OS (HR 0.92, CI 0.81-1.04, $p = 0.195$). **Conclusions:** HPV status was not correlated to income, education or insurance status, and did not impact OS in ASCC pts. Male gender and insurance status were associated with increased risk of death. Pts living in low income and low education areas were associated with worse survival. Research Sponsor: None.

4053 **Poster Session (Board #45), Fri, 8:00 AM-11:00 AM**

Prospective study of biomarkers in squamous cell carcinoma of the anal canal (SCCAC) and their influence on treatment outcomes: Five-year long-term results.

Camila Motta Venchiarutti Moniz, Rachel Pimenta Riechelmann, Maria Ignez Braghiroli, Suilane Coelho Ribeiro, Thomás Giollo Rivelli, Giovanni M. Bariani, Andre Tsin Chih Chen, Caio Nahas, Renata Colombo Bonadio, Cinthia Ortega, Rejane Franco, Sibele Meireles, Allan Andresson Lima Pereira, Jorge Sabbaga, Renata A. Coudry, Paulo Marcelo Hoff; Instituto do Câncer do Estado de São Paulo, Universidade de São Paulo, São Paulo, Brazil; Instituto do Câncer do Estado de São Paulo, São Paulo, Brazil; Universidade Federal do Piaui, Teresina, Brazil; ABC Foundation School of Medicine, Santo André, Brazil; Hospital Sirio Libanes, São Paulo, Brazil; ICESP, São Paulo, Brazil

Background: Chemoradiation (CRT) is a curative treatment for SCCAC. However, some patients (pts) present primary CRT resistance. As a rare tumor, there is a lack of prospective studies of prognostic factors in this setting. **Methods:** This prospective cohort study was aimed to evaluate predictive biomarkers (Ki-67, PD-L1, Human papillomavirus (HPV), HIV status, and tumor DNA mutations) in SCCAC. We published the 6 months (m) response rate (RR) of this cohort showing that HIV- were 5.7 times more likely to achieve response 6m post CRT (OR 5.72, CI 95% 2.5-13.0, $P < 0.001$). Now we report the long-term follow-up results of 5-year progression-free survival (PFS) and overall survival (OS). Eligible pts had T2-4/N0-3/M0 disease and were candidates to standard CRT. DNA mutations were analyzed by next-generation sequencing (NGS). HPV positivity was tested by PapilloCheck Test. KI-67 and PD-L1 were evaluated by immunohistochemistry. **Results:** 78 pts were recruited from Jan/2011 to Dec/2015. 75 were evaluable for PFS and OS. The median age was 57 years; 49 (65%) were stage III, and 9 (12%) were HIV+. HPV was evaluated in 67 and found in 47 (70.1%); HPV16 was the most common. PD-L1 was tested in 61; 10 (16.4%) had positive expression $> 1\%$. Ki-67 was performed in 65, with a median of 50% (range 1-90%). The median follow up is 66m. 5-year PFS and OS rates were 63.3% (95% CI 51.2-73.2%) and 76.4% (95% CI 64.8-84.6%), respectively. In a multivariate analysis, age (HR 1.06, $P = 0.022$, IC 95% 1.01-1.11) and absence of complete response at 6m (HR 3.36, $P = 0.007$, IC 95% 1.39-8.09) was associated with inferior OS. The OS rate was 62.5% in HIV+ group (95% CI 22.9-86%) in comparison with 78% (95% CI 65.7-86.3%) among HIV- pts, although this difference was not statistically significant ($P = 0.400$). A tendency to inferior OS was observed among pts with p53 codon 72 polymorphism (HR 2.83, $P = 0.181$, 95% CI 0.61-13.02). Other tumor mutations, HPV, Ki-67 expression, and PD-L1 expression, were not associated with PFS and OS. **Conclusions:** HIV- pts were 5.7 times more likely to achieve response 6m post CRT. The absence of complete response at 6m was the main factor associated with poor 5-year OS. New strategies of follow up and complementary treatment should be studied in late responders and HIV+ pts to ensure the success of curative treatment. Clinical trial information: 36211. Research Sponsor: FAPESP-Fundação de Amparo a Pesquisa do Estado de São Paulo (Sao Paulo State Research Support Foundation).

4054 **Poster Session (Board #46), Fri, 8:00 AM-11:00 AM**

PDL1 expression predicts therapeutic outcome in non metastatic anal squamous cell carcinoma (NMASCC).

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Background: NMASCC is a rising incidence disease with up to 30% of treatment failure to achieve complete response (CR) after standard chemoradiotherapy (CRT) leading to severe morbidity and death. Stage III-TNM, p53 mutations, HPV negativity, HIV infection are linked to treatment failure. We investigated the predictive/prognostic role of TNM, CR, HPV, PDL1 positivity and CD3/CD8 densities in NM-ASCC from a single institution. **Methods:** All 79 eligible consecutive NMASCC pts (available FFPE pre-treatment samples) seen from October-2009 to April-2019 having completed definitive CRT (50.4 Gy Pelvic Radiotherapy with Mitomycin-C 12mg/m2/IV/d1-5 / FU 1000mg/m2/d1-4 d29-32 (28%), Mitomycin-C/Capecitabine 825 mg/m2/bid (38%), Cisplatin 60 mg/m2/IV d1-29 and 5FU (34%) were analyzed. Mean age: 59 (range 26-87), 72% female, Stage III: 59%, HPV positive: 86% (HPV-16: 80%);14% HIV positive. IHC assessed by two pathologist for PD-L1 expression (ClonSP263) and CD3-CD8+ TILS densities (Clone 2GV6, Clone SP57). HPV-DNA assessed by PCR (BSGP5+/6+ multiplexed with beta-globin). Kaplan-Meier survival, CR, DFS, OS and Univariate analyses were performed using Cox proportional hazard model. **Results:** CR achieved within 6 months of treatment completion was 68%(53pts). Median follow-up after treatment completion: 35 months (range 6 –149). As of February 2020, 82% (65 pts) are alive, no evidence of disease:(57%) 46 pts, recurrence rate: 26%(22 pts), cancer death: 18% (14 pts). PDL1+ tumors ($>$ 1% positivity-CPS score): 56%, expression levels: 1-5% (57%,26p), $>$ 10%-100% (43%,19p). PDL1+ had a strong association with CR ($p = 0.021$); higher PDL1+ levels had 8-fold of CR-likelihood than PDL1 negative.(OR 8.50 vs. 1.12). Significative Spearman correlation between PDL1 tumors with CR and CD3-CD8 TILS density was observed ($R = 0.43, p = 0.0017$ and $R = 0.36, p = 0.00094$ respectively), albeit CD3-CD8 failed to reach significance as prognostic factors for either CR, DFS or OS. Only CR and PDL1 positive were strongly significantly associated to DFS (HR 0.10 [IC 95% 0.04-0.28] $p < 0.001$ and HR 0.28 [IC 95% 0.11-0.73] $p = 0.006$) and OS (HR 0.12 [IC 95% 0.03-0.45] $p < 0.001$ and HR 0.15 [IC 95% 0.03-0.68] $p < 0.004$). Low prevalence of HPV negative, early tumors, HIV positive cases in our series probably impacted in statistical power for prognosis correlation. **Conclusions:** PDL1 positivity was the strongest predictive/prognostic factor in NM-ASCC. Alternative therapeutics options to standard CRT should be explored on poor-risk patients as HPV-negative, P53-mutated and PDL1 negative patients. Research Sponsor: None.

4055 **Poster Session (Board #47), Fri, 8:00 AM-11:00 AM**

Patient-reported gastrointestinal outcomes in patients with anal cancer.

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Background: Among patients with anal cancer, chemoradiotherapy tends to offer an excellent prognosis but is often associated with undesirable toxicities that diminish quality of life. We sought to quantify the gastrointestinal-related patient-reported outcomes (PROs) of anal cancer patients receiving chemoradiotherapy in order to improve patient-physician communication and shared decision making. **Methods:** We prospectively followed patients with non-metastatic squamous cell carcinoma of the anal canal who received definitive chemoradiotherapy. Patients reported outcomes were collected using the bowel subdomain of the Expanded Prostate Cancer Index Composite (EPIC) questionnaire before treatment and at 4 subsequent timepoints. We used descriptive statistics to summarize the patients' characteristics and EPIC scores, then used the paired Wilcoxon test to compare EPIC scores at different timepoints. **Results:** The study included 21 patients (16 women and 5 men), whose median age was 57 years. Most patients (52%) had T2, and either N0 (38%) or N1 (43%) disease. Most patients (91%) received standard of care chemoradiotherapy. Compared with the patients' median overall summary score at baseline (66), their median score at 1 week (82) was significantly higher ($p = 0.009$), whereas their median score at 5 weeks (54) was significantly lower ($p = 0.025$). However, the patients' median overall summary score at baseline and at 3 months did not differ significantly ($p = 0.919$). Three months after radiotherapy, most patients (73%) reported rarely or never having bloody stools, and most (82%) reported rarely or never being bothered by bloody stools. Overall, EPIC scores show initial improvement of all domains, followed by some worsening of symptoms before returning to baseline levels. **Conclusions:** Anal cancer patients' gastrointestinal-related PROs tend to fluctuate during radiotherapy but return to baseline by 3 months, at which time most patients report few or no residual side effects. Our data provide a clear timeline of gastrointestinal acute toxicity using sequential PRO measurements that will improve patient-physician communication regarding expectations for cancer treatment and help in shared decision making. Research Sponsor: None.

4056 **Poster Session (Board #48), Fri, 8:00 AM-11:00 AM**

Socioeconomic status based on race in early-stage anal squamous cell carcinoma undergoing locoregional therapy.

Suleyman Yasin Goksu, Muhammet Ozer, Muhammad Shaalan Beg, Syed Mohammad Ali Kazmi, Aravind Sanjeevaiah, David Hsieh, Todd Anthony Aguilera, Mary Claire Maxwell, Nina Niu Sanford; The University of Texas Southwestern Medical Center, Dallas, TX; Capital Health Regional Medical Center, Trenton, NJ

Background: Anal Squamous Cell Cancer (ASCC) is a highly curable cancer. Underserved and vulnerable populations are particularly at risk of developing this disease. We aimed to study racial disparities and overall survival (OS) in patients with ASCC who received radiation therapy (RT) or chemo-RT (CRT) using the National Cancer Database. **Methods:** We identified adult patients with early-stage (stage I-II) ASCC diagnosed between 2004-2016 who underwent RT or CRT. We compared the clinical and treatment characteristics of white and black patients. The chi-square test was used for categorical variables. Kaplan-Meier and Cox regression method performed for survival analyses. We used 1:1 nearest neighbor propensity score matching to eliminate selection bias. **Results:** A total of 10,014 patients; 90.2% were white and 9.8% were black. White patients were more likely to be female, older age, have higher rate high-school education, private insurance, higher income, and travel a longer distance (all $p < .001$). Black patients were more likely to be higher comorbidity score and be treated at an academic/research facility. White patients had a higher rate of CRT and significantly better overall survival (OS) as compared to black patients (5-year survival 76% vs. 70%, $p < .001$) which persisted after propensity score matching (5-year survival 76% vs. 70%, $p = .002$). This difference continued after adjusting for clinically important factors, including HPV status (unmatched $p < .03$, matched $p = .008$). In the patients who received CRT, white patients were associated with improved OS versus black patients (unmatched 77% vs. 71%, $p < .001$; matched 77% vs. 71%, $p = .011$), and even after multivariate Cox analysis (unmatched $p < .001$; matched .014) (Table). **Conclusions:** White patients had significantly better OS as compared to black patients with early-stage ASCC as well as in the patients who received CRT. White patients were associated with high education level, higher income, and private insurance. The rate of HPV positive was similar among groups. Further investigations are needed to enlighten these disparities and target the increase education of the population at risk. Research Sponsor: None.

	Unmatched			Matched		
	White	Black	*p-value*	White	Black	*p-value*
5-year survival (%)	76	70	*< .001*	76	70	*.002*
HR (95% CI)	Ref	1.15 (1.01-1.32)	*.03*	Ref	1.27 (1.06-1.52)	*.008*
CRT received						
5-year survival (%)	77	71	*< .001*	77	71	*.011*
HR (95% CI)	Ref	1.77 (1.01-1.36)	*.02*	Ref	1.26 (1.04-1.53)	*.014*
HPV (%)	8	9	*NS*	9	9	*NS*

17-year incidence trends of anal squamous cell carcinoma.

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Background: Anal Cancer is a rare neoplasm with 9 out of 10 cases being Anal Squamous Cell Carcinoma (SCCA). We did a population-based analysis to assess the incidence trends in patients with SCCA and identify any significant change in the direction of trends using the Surveillance, Epidemiology, and End Results (SEER) database. **Methods:** Data was extracted from SEER database for the years 2000-2016 for the US population, across all gender, ages, and races. Joinpoint regression models of SCCA incidence were fitted to identify any discrete joints (year) that represent statistically significant changes in the direction of the trend. The average annual percentage change (APC) in the age-adjusted incidence rate in the pre- and post-joinpoint era were measured. Subgroup analysis for gender, ages, and races was also done. **Results:** 27,721 new adult cases of SCCA were identified from 2000 to 2016. The incidence was higher amongst females (62.44%) compared to males (37.56%) with the white population contributing 85.41% to incidence compared to black (11.84%) and other (2.75%) population. The age-based incidence rate for different groups has been mentioned in Table. A significant jointpoint for SCCA incidence was observed in 2009. The APC was 4.6% (3.5-5.6 95% CI) in 2000-2009 which reduced to 2.1% (0.7-3.4 95% CI) in 2009-2016 indicating a 54% relative reduction in the average annual APC in the US population after 2009. Subgroup analysis revealed significant joinpoints for incidence decrease in Ages 40-59, 80 and above and females of all ages. No significant changes in APC were seen when stratified by race (Refer to Table). **Conclusions:** Our study, in our knowledge, is the first study assessing incidence trends of SCCA over 17-years. The overall incidence of SCCA is increasing but a statistically significant trend towards decreasing rate of growth in incidence was observed in 2009 and later. Further studies are needed to analyze the causality of such changes in the trend of SCCA. Research Sponsor: None.

Gender	Age	Race	Incidence(N)	Joinpoint year	APC pre-joinpoint year (95% CI)	APC post-joinpoint year (95% CI)	APC reduction
Both	All	White	23,677(85.41%)	No trend change			
Both	All	Black	3,281(11.84%)	No trend change			
Both	All	Other	763(2.75%)	No trend change			
Both	20-39 years	All	1,056(3.81%)	No trend change			
Both	40-59 years	All	12,705(45.83%)	2009	5.7% (4.3- 7.0)	-0.3% (-1.8- 1.3)	105%
Both	60-79 years	All	11,100(40.04%)	No trend change			
Both	80+ years	All	2,860(10.32%)	2010	5.1% (3.9-6.3)	1.0% (-0.9-3.0)	80%
Male	All	All	10,411(37.56%)	No trend change			
Female	All	All	17,310(62.44%)	2009	5.2% (4.3- 6.1)	2.8%(1.8-3.7)	46%

4059 **Poster Session (Board #51), Fri, 8:00 AM-11:00 AM**

Utilization and trends in palliation-directed treatments for stage II-IV anal squamous cell carcinoma patients.

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Background: Anal squamous cell carcinoma (ASCC) is associated with significant symptom burden including pain, bleeding, and obstructive symptoms. However, the proportion of patients requiring palliation-directed treatments in ASCC is unknown. Palliation-directed treatments can control and improve symptoms and affect quality of life. We aimed to study trends, factors, and outcomes associated with utilization of palliation-directed treatment in ASCC. **Methods:** Using the National Cancer Database (NCDB), adult patients with stage II-IV ASCC diagnosed 2004-2015 were identified and stratified by receipt of palliation-directed treatments. Using chi-square test and logistic regression, we evaluated the associations of demographic, clinical, and pathological factors with palliation-directed treatment utilization. **Results:** Out of 17,988 ASCC patients in this study, palliation-directed treatments were used by 504 patients (2.8%) with stages II-IV ASCC as first line treatment. Two percent received palliation-directed surgery, chemotherapy, and radiotherapy, 0.3% received pain management, and 0.4% utilized combination therapy approach. On univariable analysis, palliation-directed treatments were associated with older age, lower income level ($p=0.004$), Medicare insurance, and higher comorbidity score (*all other* $p<0.001$). Palliation-directed treatments were also more frequent in academic/research facilities ($p=0.01$), in East North Central USA ($p=.001$), and in stage 4 versus stage 2/3 ASCC ($p<.001$). Palliation-directed treatments have increased in recent years (2004-06 vs. 2013-15; $p=.005$) and were more frequently used within 6 months of patient death ($p<.001$). On multivariable analysis stage 4 disease and life expectancy $<$ 6 months were the only variables that maintained significance. **Conclusions:** In our study, palliation-directed treatments were used by 2.8% of the patients as codified by NCDB. Its use was higher in stage 4 ASCC and within the last six months of life. Palliation-directed treatment utilization has incrementally increased in recent years. Additional research is warranted in determining the phase of care wherein palliation-directed treatments are utilized in ASCC. Research Sponsor: None.

4060 **Poster Session (Board #52), Fri, 8:00 AM-11:00 AM**

The role of fibroblast growth factor receptor 4 (FGFR4) signaling in anti-EGFR resistance in colon cancer.

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Background: Anti-EGFR therapy has been used as a standard treatment for metastatic colon cancer, but the innate resistance is still issues of increasing significance. Fibroblast growth factor receptor 4 (FGFR4) plays an important role in cell proliferation, invasion and anti-apoptosis, through the pathway of MAPK-ERK and PI3K-AKT. We investigated potential crosstalk between FGFR4 and EGFR signaling to identify new resistant mechanism of anti-EGFR therapy and how to overcome it in colon cancer. **Methods:** RNA-Seq was used to identify the associated signal pathway and down targets induced by FGFR4. Molecular studies including RTK array, RT-qPCR, western blotting were performed to validate the interaction between FGFR4 and EGFR signaling *in vitro* and *in vivo*. Next, the effect of FGFR4 in cetuximab resistance was investigated *in vitro* and in colon cancer patients. **Results:** FGFR4 overexpression in colon cancer cells activates downstream signaling, such as, PI3K/Akt and RAS/RAF/Erk pathway. Gene Ontology (GO) analysis from RNA-seq revealed that differentially expressed genes (DEGs) altered by expression of FGFR4 were related to biological functions, including cell proliferation, epidermal growth factor receptor signaling, NIK/NF-kB signaling, interferon-gamma signaling, wound healing. RT–qRCR showed that FGFR4 promotes the EGFR and ErbB3 by inducing the expression of EGFR ligands such as AREG, BTC, EREG, HBEGF. In vivo tumorigenesis, we found that FGFR4 promotes tumor growth and high expression of AREG in xenograft tumors. FGFR4 expression reduced the sensitivity to cetuximab in colon cancer cells and synergistic effect was shown when treated with FGFR4 inhibitor with cetuximab. A positive correlation between FGFR4 and AREG expression was observed in cancer, but not in normal tissues and high FGFR4 or AREG expression showed significantly inferior overall survival than low expression in patients treated with cetuximab for metastatic colon cancer. **Conclusions:** We demonstrated a pivotal mechanism of FGFR4 in colon cancer progression and cetuximab resistance through inducing AREG. Our data point to FGFR4 as a new biomarker to predict cetuximab response and dual targeting of FGFR4 and EGFR may be a promising treatment modality for colon cancer. Research Sponsor: National Research Foundation of Korea (NRF) grants (NRF-2017R1A2B4005003, NRF-2018R1A5A2024181), grant (HCRI17904-21) Chonnam National University Hwasun Hospital Institute for Biomedical Science.

4061 **Poster Session (Board #53), Fri, 8:00 AM-11:00 AM**

Consensus molecular subtypes in colorectal cancer differ by geographic region.

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Background: The consensus molecular subtypes (CMS) have emerged as a novel classification in colorectal cancer (CRC). However, these subtypes, were mostly derived from a US/European population, and have scant data in other ethnic groups. This study aimed to demonstrate molecular subtypes of CRC across geographic regions. **Methods:** Formalin fixed paraffin embedded (FFPE) tissue from untreated patients with stage II-III colon cancer from Brazil, Canada, Mexico, Thailand, and the US were evaluated. Gene expression profiling was performed at the University of Texas MD Anderson Cancer Center using NanoString's nCounter technology and an optimized classifier for FFPE. **Results:** A total of 366 samples were included in this study, evenly distributed between the 5 international sites. While the US population matched previously reported distributions, the distribution of CMS subtypes varied substantially by region ($P < 0.0001$). While CMS1 was still associated with right-sided tumors ($P < 0.001$) and deficient mismatch repair (dMMR) ($P < 0.001$), the prevalence varied between 8% in Brazil to 30% in Mexico. CMS2 was found vary from 14% in Mexico to 47% in Brazil. The metabolic CMS3 subtype was present in only 3% in Thailand, but as high as 19% in Brazil. CMS4 was confirmed to be associated with higher stage ($P = 0.047$), and the prevalence was lowest in Brazil (14%) compared to 44% and 49% in US and Mexico, respectively. Expansion of study cohort is ongoing. **Conclusions:** CMS subtype prevalence differs substantially by geographic region in CRC. These variations suggest that transcriptomic-defined disease biology in international populations may be more heterogeneous than previously appreciated. Further studies in global populations are required to validate and extend these findings, which may have important impact for novel therapeutic development. Research Sponsor: Moon Shot funding.

4062 **Poster Session (Board #54), Fri, 8:00 AM-11:00 AM**

Initial correlative studies from a trial of cetuximab and pembrolizumab in metastatic colorectal cancer (mCRC).

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Background: Cetuximab is an EGFR-targeting IgG1 mAb. Pre-clinical data suggests cetuximab induces $CD8^+$ cytotoxic T-cell (CTL) infiltration of tumors. We hypothesized that augmentation of CTLs in the tumor microenvironment (TME) may provide the proper milieu for effective PD-1 inhibition in metastatic colorectal cancer (mCRC). We conducted a phase Ib/II study of cetuximab with the PD-1 antibody, pembrolizumab, in mCRC. Correlative blood and tissue samples were collected to assess the impact of this treatment on CTLs, as well as potential compensatory alterations in regulatory T-cells (Tregs) and suppressive MDSCs (NCT02713373). **Methods:** 3 week treatment cycles included pembrolizumab at 200 mg on day 1 and cetuximab 250 mg/m2 following the 400 mg/m2 loading dose. Tumor biopsies were obtained at baseline and at c4d1 (Day 64). Peripheral blood (PB) was drawn at baseline, c2d1 (day 22) and c4d1 (Day 64). Flow cytometry was performed within 24 hours with additional samples stored for future analysis. In the present analysis, we assessed changes in levels of the cellular populations of interest between cycle 4 and cycle 1. **Results:** Forty-two RAS-wt patients were enrolled through October 2019. Paired tumor tissues were successfully analyzed for 16 patients and PB for 38. Intratumoral CTLs ($CD3^+CD8^+$) increased significantly (+47%, $p < .05$). In PB, there was a slight overall decrease in PB CTLs (-5%, p = NS) and a significant decrease in $CD8^+CD45RO^+PD1^+$ cells (-42%, $p < .05$). We saw simultaneous decreases in $PD\text{-}1^+$ CTLs in the tumor and PB. There was a trend for increase in Tregs (CD4+ Cd25+ FoxP3+) in PB (+11%, p = NS), but an overall increase in the Teff:Treg ratio (+30%, p = NS). $CD4^+CTLA4^+$ cells significantly increased (+37%, $p < .05$). Granulocytic MDSCs ($CD11b^+CD14^-CD33^+HLADR^-$) in PB decreased significantly on-treatment (-30%, $p < 0.5$). The sample size and tissue limitations prohibited meaningful evaluation of tissue Tregs and MDSCs via the present methods. **Conclusions:** Cetuximab and pembrolizumab induced dynamic changes in the TME and PB. The treatment associated increase in intratumoral CTLs was particularly pronounced, consistent with their local expansion and/or influx. This was accompanied by a decrease in PB CTLs. Decreases in multiple $PD\text{-}1^+$ lymphoid populations were observed in both tumor and PB, notably $PD\text{-}1^+$ CTLs. Of note, we saw a synchronous increase in immunosuppressive $CD4^+CTLA4^+$ T-cells in PB. Patient outcomes are pending maturation. Further analyses are planned, coupled with integration of clinical data. Clinical trial information: NCT02713373. Research Sponsor: Merck.

4063 **Poster Session (Board #55), Fri, 8:00 AM-11:00 AM**

Development of drug resistance in colon cancer patients following chemotherapy, a contributing factor in the failure of oxaliplatin-based HIPEC to improve survival in the Prodige 7 trial.

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Background: Numerous studies suggest benefit for heated intra-peritoneal chemotherapy (HIPEC) in colon cancer but the Prodige 7 trial in 265 colon cancer patients randomized to HIPEC or observation after neo-adjuvant chemotherapy (NACT) didn't confirm benefit with median OS of 41.7 vs. 41.2 mos. (p = 0.99) (Proc. ASCO, 2018). One concern is that prior drug exposure selects for drug resistance blunting HIPEC effect. To test the hypothesis we examined the impact of prior chemotherapy on drug resistance in human tumor organoids isolated from colon cancer patients. **Methods:** Data query identified 111 colorectal cancers (87 colon & 24 rectal) tested for Oxaliplatin sensitivity by ex vivo analysis of programmed cell death (EVA/PCD), a primary culture platform that examines drug induced cell death (apoptotic & non-apoptotic) by morphology, metabolism & histology. Five-point dose response curves interpolated to provide lethal concentration 50% (LC50) were compared by Z score to distribute Oxaliplatin LC50 values around the mean using standard deviation units as the metric of sensitivity or resistance. Of 87 colon 54(62%) were untreated and 33 (38%) treated with 21/33 (64%) having received FOLFOX. To approximate Prodige 7, treated patients were separated by having received FOLFOX $< 2 >$ months before EVA/PCD analysis and also compared Mitomycin (14 vs 41), Irinotecan (18 vs 47) & 5-FU (19 vs. 52) activity to assess cross-resistance. **Results:** Compared to chemo-naïve, FOLFOX-treated patients were significantly more resistant to Oxaliplatin ($P < 0.01$) with the degree of resistance increasing significantly for patients who received treatment < 2 months prior to EVA/PCD compared to those with chemotherapy > 2 months prior to EVA/PCD ($P < 0.01$). Activity for Mitomycin & Irinotecan was not significantly different for chemo-naïve vs. treated patients, but 5 FU was more resistant ($P = 0.048$) in previously treated. **Conclusions:** The failure of Prodige 7 to improve survival with HIPEC following NACT may reflect diminished Oxaliplatin activity in patients whose residual disease has been selected for Oxaliplatin & 5FU resistance. Resistance was not observed for Mitomycin or Irinotecan. This suggests that those using HIPEC may i) examine other classes of drugs or drug combinations for IP administration ii) improve the selection of candidates for HIPEC administration or iii) consider HIPEC administration earlier in the course of therapy when chemotherapy-induced drug resistance may be less evident. Research Sponsor: None.

4064 **Poster Session (Board #56), Fri, 8:00 AM-11:00 AM**

The landscape of DNA damage response (DDR) pathway in colorectal cancer (CRC).

Hiroyuki Arai, Andrew Elliott, Jingyuan Wang, Francesca Battaglin, Shivani Soni, Wu Zhang, Davendra Sohal, Richard M. Goldberg, Michael J. Hall, Aaron James Scott, Mohd Khushman, Jimmy J. Hwang, Emil Lou, Benjamin A. Weinberg, John Marshall, Albert Craig Lockhart, Phillip Stafford, Jian Zhang, W. Michael Korn, Heinz-Josef Lenz; Chiba Cancer Center, Chibashi, Japan; CARIS Life Sciences, Irving, TX; USC Norris Comprehensive Cancer Center, Los Angeles, CA; Division of Medical Oncology, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA; USC Keck School of Medicine, Los Angeles, CA; Cleveland Clinic, Cleveland, OH; West Virginia University Cancer Institute, Morgantown, WV; Fox Chase Cancer Center, Philadelphia, PA; Banner-University of Arizona Cancer Center, Division of Hematology and Oncology, Tucson, AZ; Mitchell Cancer Institute, Mobile, AR; Levine Cancer Institute, Charlotte, NC; University of Minnesota School of Medicine, Minneapolis, MN; Georgetown University Medical Center, Washington, DC; Georgetown University, Washington, DC; University of Miami Sylvester Cancer Center, Miami, FL; Caris Life Sciences, Phoenix, AZ

Background: Abnormal DDR is a hallmark of cancer, relating to genome instability, anti-tumor immunity, and sensitivity to chemotherapeutic agents and radiation. We conducted a large-scale investigation to clarify the alteration of DDR pathway in CRC. **Methods:** Tumor samples from 9321 CRC patients were retrospectively reviewed. Next-Generation Sequencing (NGS) on a custom-designed panel enriching 592 gene targets was performed. Samples with mutations detected in any of 29 DDR-related genes were deemed DDR-mutant (DDR-MT); the rest DDR-wild type (DDR-WT). Microsatellite instability (MSI) status was tested with a combination of immunohistochemistry (IHC), fragment analysis and NGS. Tumor mutational burden (TMB) was calculated based on somatic nonsynonymous missense mutations. PD-L1 was tested by IHC (SP142). Consensus molecular subtype (CMS) was developed using RNA sequencing data. **Results:** Of 9321 cases, 1290 (13.8%) were DDR-MT. DDR-MT frequency was higher in right vs. left sided (20.9% vs 10.8%, $p < 0.001$) and MSI-H vs. MSS (76.4% vs 9.5%, $p < 0.001$) cases. In the MSS cases, right-sided had marginally higher frequency of DDR-MT than left-sided (10.6% vs 9.1%, $p = 0.055$), with much higher frequency of Fanconi anemia pathway alteration in right-sided (1.5% vs 0.7%, $p < 0.01$). CMS1 subtype had the highest frequency of DDR-MT (34.8%); CMS2 had the lowest (7.1%). DDR-MT cases (vs. DDR-WT) had higher mutation rate of *ARID1A* (55.0% vs 19.1%, $p < 0.0001$), *PIK3CA* (22.6% vs 15.8%, $p < 0.0001$) and *BRAF* (20.4% vs 7.3%, $p < 0.0001$), and lower mutation rate of *TP53* (48.2% vs 76.1%, $p < 0.0001$), *APC* (60.5% vs 74.5%, $p < 0.0001$) and *KRAS* (44.0% vs 49.8%, $p < 0.001$). Mean TMB was much greater in DDR-MT than DDR-WT (All: 20.9/Mb vs 7.7/Mb, $p < 0.0001$; MSS: 13.7/Mb vs 7.6/Mb, $p < 0.05$). *PD-L1* positivity was also higher in DDR-MT compared to DDR-WT (All: 10.1% vs 2.7%, $p < 0.0001$; MSS: 4.8% vs 2.4%, $p < 0.0001$). **Conclusions:** Alteration of the DDR pathway was strongly associated with MSI status in CRC. The primary tumor sidedness might also be related, as DDR-MT was more prevalent in right-sided tumors. Elevated TMB and PD-L1 expression in DDR-MT CRC indicate more activated anti-tumor immune profiles compared to DDR-WT, regardless of MSI status, suggesting possible therapeutic benefit from immune checkpoint inhibitors in DDR-MT CRC. Research Sponsor: None.

4065 **Poster Session (Board #57), Fri, 8:00 AM-11:00 AM**

Tumor-infiltrating lymphocytes and tumor budding refine prognostication in patients with low- and high-risk stage III colon cancers (NCCTG NO147)[Alliance].

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Background: Tumor infiltrating lymphocytes (TILs) and tumor budding (linked to epithelial mesenchymal transition) may influence metastatic potential and patient prognosis. We analyzed these features and their relative contribution to survival among low (T_{1-3} N_1) and high (T_4 and/or N_2) risk groups, defined by the IDEA study, used to inform the duration of adjuvant chemotherapy in stage III colon cancer. **Methods:** Among 1,532 patients (low risk n=804; high risk n=728) treated in a phase III adjuvant trial of FOLFOX + cetuximab (x 6 months), intraepithelial TIL densities and tumor budding were quantified at microscopy in routine histologic sections. Optimal cutpoints were determined in association with 5-yr disease-free survival (DFS). Relative contribution of variables to DFS was calculated using $\chi 2$ from Harrell's rms R package based on multivariable Cox regression models. **Results:** In the overall cohort, the tumor budding/TILs combined variable was more robust for predition of DFS than either alone. Budding/TILs was significantly associated with DFS in both low (HR_{adj}, 1.59; 95% CI, 1.02-2.48; p=.0273) and high (HR_{adj}, 2.82; 95% CI, 1.72-4.63; p<.0001) risk patients. We then determined its relative contribution (%) to DFS (Table). Among low risk, budding/TILs ranked second (24.4%) behind *KRAS* status (45.5%) and ahead of treatment arm (7.2%) and mismatch repair (MMR) status (6.1%). Among high risk, budding/TILs contributed the most to DFS (45.4%) followed by primary tumor sidedness (13.0%), performance status (12.0%), and MMR (10.4%). **Conclusions:** Tumor budding/TILs provides robust prognostic stratification by risk group to improve anatomic tumor staging. The relative contribution of budding/TILs to DFS was second only to *KRAS* status in low risk patients, and was the most important predictor of DFS in high risk patients. Evaluation in patients treated with 3 vs 6 mos of adjuvant chemotherapy is warranted. Research Sponsor: U.S. National Institutes of Health.

Relative contribution to patient DFS.

Low Risk (T1-3N1)	Percent (%)	High Risk (T4 and/or N2)	Percent (%)
KRAS	45.5	Budding/TILs	45.4
Budding/TILs	24.4	Sidedness	13.0
Treatment	7.2	Performance Status	12.0
MMR	6.1	MMR	10.4
Performance Status	5.0	*KRAS*	9.1
BRAF	5.0	Treatment	5.1
Age	3.8	Histologic Grade	2.8
Sidedness	2.3	Other	2.2
Histologic Grade	0.8		

4066 **Poster Session (Board #58), Fri, 8:00 AM-11:00 AM**

Somatic alterations of *NF1* in colorectal cancer.

Hiroyuki Arai, Andrew Elliott, Joanne Xiu, Jingyuan Wang, Francesca Battaglin, Shivani Soni, Wu Zhang, Davendra Sohal, Richard M. Goldberg, Michael J. Hall, Aaron James Scott, Mohd Khushman, Jimmy J. Hwang, Emil Lou, Benjamin A. Weinberg, John Marshall, Albert Craig Lockhart, Anthony Frank Shields, W. Michael Korn, Heinz-Josef Lenz; Chiba Cancer Center, Chibashi, Japan; CARIS Life Sciences, Irving, TX; Caris Life Sciences, Phoenix, AZ; USC Norris Comprehensive Cancer Center, Los Angeles, CA; Division of Medical Oncology, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA; USC Keck School of Medicine, Los Angeles, CA; Cleveland Clinic, Cleveland, OH; West Virginia University Cancer Institute, Morgantown, WV; Fox Chase Cancer Center, Philadelphia, PA; Banner-University of Arizona Cancer Center, Division of Hematology and Oncology, Tucson, AZ; Mitchell Cancer Institute, Mobile, AR; Levine Cancer Institute, Charlotte, NC; University of Minnesota School of Medicine, Minneapolis, MN; Georgetown University Medical Center, Washington, DC; Georgetown University, Washington, DC; University of Miami Sylvester Cancer Center, Miami, FL; Karmanos Cancer Institute, Wayne State University, Detroit, MI

Background: *NF1* encodes neurofibromin, which is a key GTPase-activating protein that downregulates RAS activation. Inactivating mutations in *NF1* result in sustained activation of RAS signaling, a key driver for development of colorectal cancer (CRC), and have been suggested to be a potential mechanism of resistance to EGFR inhibition in *RAS*-wild type (WT) CRC. Little is known about molecular characteristics of *NF1*-mutated (MT) CRC. **Methods:** Tumor profiles from 8150 CRC patients (pts) with available *NF1* mutation status were retrospectively reviewed. NextGen sequencing by a customized 592-gene panel was performed. Microsatellite instability (MSI) / mismatch repair (MMR) status, tumor mutational burden (TMB) and PD-L1 expression were tested. Molecular profiles between *NF1*-MT and *NF1*-WT pts were compared. **Results:** Out of 8150 pts, 176 (2.2%) had somatic *NF1* mutations with pathogenic or presumed pathogenic function. A higher *NF1*-MT frequency was observed in MSI-H/dMMR vs MSS/pMMR (13.5% vs 1.4%, $p < 0.0001$), in right-sided vs left sided (2.9% vs 1.8%, $p < 0.01$), and in *RAS*-WT vs *RAS*-MT (3.0% vs 1.4%, $p < 0.0001$). In MSS/pMMR tumors, no association with sidedness was observed (right: 1.3% vs left: 1.2%, NS). The most prevalent co-mutations with *NF-1* were *APC* (63.2%), *ARID1A* (57.5%), *TP53* (51.5%), *KMT2D* (32.9%) and *KRAS* (32.4%) in all cases, and *APC* (76.2%), *TP53* (69.5%), *KRAS* (38.8%), *ARID1A* (34.4%) and *FBXW7* (21.5%) in MSS/pMMR cases. *POLE* mutation was observed in 18.4% of *NF1*-MT/MSS/pMMR pts. Compared to *NF1*-WT pts, *NF1*-MT pts had more frequent mutations in *ARID1A* (All: 57.5% vs 23.3%, $p < 0.0001$; MSS/pMMR: 34.4% vs 15.2%, $p < 0.05$), and less frequent mutations in *KRAS* (All: 32.4% vs 49.0%, $p < 0.0001$; MSS/pMMR: 38.8% vs 50.3%, $p < 0.05$). Also, *NF1*-MT pts had more frequent alterations in homologous recombination pathway compared to *NF1*-WT pts (All: 39.8% vs 7.5%, $p < 0.0001$; MSS/pMMR: 17.5% vs 4.4%, $p < 0.0001$). Mean TMB was significantly greater in *NF1*-MT than *NF1*-WT (All: 48.9/Mb vs 10.0/Mb, $p < 0.0001$; MSS/pMMR: 48.3/Mb vs 8.2/Mb, $p < 0.0001$). Also, PD-L1 positivity was higher in *NF1*-MT compared to *NF1*-WT (All: 12.9% vs 3.6%, $p < 0.0001$; MSS/pMMR: 7.1% vs 2.6%, $p < 0.05$). **Conclusions:** While more frequent than in *RAS*-MT pts, *NF1*-MT CRC was a small subset in *RAS*-WT pts. *NF1*-MT was associated with alterations in chromatin remodeling and DNA damage response pathways, as well as elevated TMB and PD-L1 expression, which may provide alternative therapeutic strategies beyond EGFR inhibition. Research Sponsor: None.

4067 **Poster Session (Board #59), Fri, 8:00 AM-11:00 AM**

Prognostic differences of RAS mutations: Results from South Australian (SA) metastatic colorectal (mCRC) registry.

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Background: Effective targeting of RAS mutations has proven elusive until recently. AMG 510, a novel agent which targets KRAS G12C mutations (G12C MT), has shown promise in early phase clinical trials that included patients with mCRC. Prior reports have suggested that G12C MT may be predictive of poor outcome. **Methods:** We aimed to assess the prognostic implications of individual RAS in a population-based registry. The SAmCRCR collects data from all patients diagnosed with mCRC in South Australia prospectively. Individual RAS mutation data from patients entered into the SAmCRCR between February 2006 and December 2018 was reviewed. Survival was analysed for the more frequent mutations using Kaplan Meier method. **Results:** 1605 (33%) of the 4905 patients entered onto the registry had RAS mutation results available. Of these, 658 (41%) had RAS MT. The nature of the RAS MT was available in 563 (85.7% of those with RAT MT). Patient characteristics, frequency of individual RAS MT and median overall survival (OS) per RAS MT are noted in table. Low frequency MT made up an additional 16.3%. There were numerical differences in survival however there was no statistical difference in survival when comparing the various RAS MT, including the comparison of G12C to G12S ($p = 0.38$). **Conclusions:** Whilst the G12S mutation was associated with the longest survival numerically, the observed survival for patients with the most common RAS mutations (G12C, G12V, G12A, G12D and G13D) did not significantly differ. Research Sponsor: None.

RAS MT (percentage)	G12C (9.6%)	G12A (10.7%)	G12D (22%)	G12S (4.4%)	G12V (23.6%)	G13D (13.3%)
Median age (yrs)	64.6	65.7	65.5	65.2	66.7	64.6
Female	28%	39%	37%	27%	34%	43%
Stage 2/3/4 at diagnosis(%)	11/9/76	13/13/74	12/20/67	19/30/50	14/17/67	12/28/59
Right primary	17%	23%	38%	19%	40%	41%
Site liver or lung only (%)	35/9	55/9	37/6	42/15	32/11	28/16
Poorly diff path	11%	17%	27%	11%	20%	21%
Chemotherapy	80%	71%	82%	73%	80%	81%
Liver resection	18.5%	15.6%	12%	11.5%	12.7%	9.3%
Median OS (mths)	21.6	20.6	20.8	29.7	21.4	22.3

4068 **Poster Session (Board #60), Fri, 8:00 AM-11:00 AM**

Impact of tumor side on clinical outcomes in stage II and III colon cancer with known microsatellite instability status.

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Background: Microsatellite instability high (MSI-H) status indicates better prognosis in early stage colon cancer (CC) compared to microsatellite stable (MSS). However, the impact of tumor side, left side (L) versus right side (R), is not described on clinical outcomes based on MSI status. **Methods:** Patients with pathological stage II and III primary adenocarcinoma of the colon between 2010 and 2015 were identified in the National Cancer Database (NCDB) using ICD-O-3 morphology and topography codes: 8140-47, 8210-11, 8220-21, 8260-63, 8480-81, 8490 and C18.0, 18.2,18.3, 18.5,18.6, 18.7. Univariate (UVA) and multivariable (MVA) survival analyses were conducted, and Kaplan-Meier Curves were used to compare overall survival (OS) based on tumor location and treatment received with Log-rank test. **Results:** A total of 35,071 patients with stage II (n = 17,629) and III (n = 17,442) CC were identified. 51.3% female; 81.5% Caucasian; median age 66 (range, 18-90). Majority of stage II and III tumors were R, 61.2% (n = 10,794) and 56.0% (n = 9,763). MSI-H was more common in stage II compared to III, 23.3% (n = 4,115) vs 18.2% (n = 3,171) ($p < 0.0001$). Survival was better in stage II MSI-H compared to MSS, 5 year-OS 75.1% vs 71.8% ($p = 0.0057$). However, stage III CC survival was better in MSS compared to MSI-H, 5-year OS 60.5% vs 58.0% ($p < 0.001$). In stage II MSI-H CC R was more common than left, 78.3 % (n = 3223) vs 21.7% (n = 892). There was no significant difference in survival between stage II MSI-H L vs R (5-year OS 76.2% vs 74.7%, $p = 0.1578$). Stage II MSS CC R was more common than L, 56.0% (n = 7571) vs 44.0% (n = 5943), and survival was better in L vs R (5-year OS 73.2% vs 70.8%, $p = 0.0029$). Stage III MSI-H CC was more common in R than L, 75.6% (n = 2397) vs 24.4% (n = 774) and survival was better in L (5-year OS 62.5% vs 56.5%, $p = 0.0026$). Stage III MSS CC was more common in R than L, 51.6% (n = 7366) vs 48.4% (n = 6905), and survival was better in L vs R (5-year OS 67.0% vs 54.4%, $p < 0.001$). **Conclusions:** Survival was better in left sided tumors compared to right in stage II MSS, stage III MSS and stage III MSI-H CC. Research Sponsor: None.

4069 **Poster Session (Board #61), Fri, 8:00 AM-11:00 AM**

Association of postoperative serum carcinoembryonic antigen (CEA) with disease-free survival in patients with stage III colon cancer: ACHIEVE phase III randomized clinical trial.

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Background: ACHIEVE, as part of the IDEA collaboration, was a multicenter trial randomizing patients with stage 3 resected colon cancer to either 3 versus 6 months of adjuvant FOLFOX/CAPOX. We previously reported that the hazard ratios (HRs) in disease-free survival (DFS) of 3 versus 6 months duration according to risk stage (low-risk [T1-3 and N1] or high-risk [T4 or N2]) and regimen (FOLFOX or CAPOX) as well as in overall population were consistent with those observed in the whole IDEA. This study aimed to clarify the significance of post-operative serum carcinoembryonic antigen (CEA) on DFS in stage 3 colon cancer. **Methods:** Eligibility included post-operative serum CEA value of ≤10 ng/ml at registration in the ACHIEVE trial, which enrolled 1313 patients between 2012 and 2014, out of whom 1291 pts were the modified ITT (mITT) population and used in this study. The cutoff values of CEA analyzed for prognostic analyses were the median value (1.8 ng/ml) in the mITT, the upper limit of normal (ULN) level (5.0 ng/ml), and the half of ULN (2.5 ng/ml). The association of post-operative CEA with DFS were measured by Cox regression analyses. **Results:** Of the 3 cutoff values, the ULN (5.0 ng/ml) was associated with DFS more strongly than the median (1.8 ng/ml) or half of ULN (2.5 ng/ml), with a HR of 1.75 (95%CI, 1.24-2.46) (Table). The 99 patients (7.7%) were identified as the CEA > ULN and 1192 (92.3%) as < ULN. In univariate analysis, regimen (CAPOX or FOLFOX), ECOG PS (0 or 1), T factor (T1-3 or T4), N factor (N1 or N2-3) and CEA (< ULN or > ULN) were significantly associated with DFS. Multivariate Cox regression identified CEA > ULN as an independent poor risk factor (HR = 1.45; 95%CI, 1.03-2.05). Shorter DFS in patients with CEA > ULN than in those with CEA < ULN was consistently observed in each subgroup of baseline factors, including treatment duration, regimen, age, gender, PS, T-stage, N-stage, no of lymph nodes examined, and tumor location; no interaction was observed between CEA and these factors. **Conclusions:** Post-operative serum CEA is also a strong prognostic factor for DFS in stage 3 colon cancer. Clinical trial information: 000008543.
Research Sponsor: Japanese Foundation for Multidisciplinary Treatment of Cancer.

cut-off value		EVENT/N	3-year DFS (95% CI)	5-year DFS (95% CI)	HR (95% CI)	p value
1.8ng/ml	≤	185/668	77% (74-80% j	72% (68-75%)	1.29 (1.04-1.61)	0.0226*
		138/623	81% (77-84%)	78% (74-81%)		
2.5ng/ml	≤	129/426	75% (70-79%)	69% (65-74%)	1.41 (1.13-1.76)	0.0026*
		194/865	81% (78-83%)	77% (74-80%)		
5.0ng/ml	≤	37/99	64% (54-73%)	62% (52-71%)	1.75 (1.24-2.46)	0.0014*
		286/1192	80% (78-82%)	76% (73-78%)		

4070 **Poster Session (Board #62), Fri, 8:00 AM-11:00 AM**

Prognostic importance of primary tumor resection and synchronous metastasis on overall survival in metastatic colorectal cancer: Data from the FIRE-3 (AIO KRK-0306) study.

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Background: The FIRE-3 study (AIO KRK-0306) was designed as a randomized multicenter trial to compare the efficacy of FOLFIRI plus cetuximab (cet) to FOLFIRI plus bevacizumab (bev) as first-line treatment in KRAS WT mCRC patients. FOLFIRI plus cet as first-line treatment of KRAS WT mCRC patients resulted in comparable overall response rates (ORR) and progression free survival (PFS) when compared to FOLFIRI plus bev. Overall survival (OS) was significantly longer in the FOLFIRI plus cet arm. **Methods:** In the present analysis of the FIRE-3 trial we explored the impact of primary tumor resection on outcome in relation to anti-EGFR vs. anti-VEGF treatment. Furthermore, we investigated the prognostic value of synchronous versus metachronous metastases. **Results:** In patients with synchronous disease no significant difference in OS was detected when comparing resected (n=339) vs. non-resected (n=97) patients (p-value: 0.29, HR: 1.17, 95%-CI: 0.88 – 1.55). In the cetuximab arm, resection (n=167) showed no significant benefit in OS when compared to non-resection (n=52) (p-value: 0.51, HR: 1.15, 95%-CI: 0.77 – 1.71). Treated with bevacizumab, similar results were present, when comparing resection (n=172) vs. non-resection (n=45); (p-value: 0.29, HR: 1.25, 95%-CI: 0.83 – 1.9). A strong trend was seen when comparing OS in treatment arms cet. (n=219) vs. bev. (n=217)) for patients with synchronous disease; (p-value: 0.05, HR: 1,26, 95%-CI: 1.0 - 1.59). 436/592 pts suffered from synchronous, 153/592 from metachronous disease (in 3/592 pts the information was not given). Median OS in pts with synchronous disease was 24.5 months and 29.5 in pts with metachronous disease (p-value: 0.02, HR: 0.76, 95%-CI: 0.6 - 0.96). In pts treated in the cetuximab arm metachronous disease (n=77) was associated with a trend towards longer OS when compared to synchronous disease (n= 219) (p-value: 0.13, HR: 0.76, 95%-CI: 0.54 – 1.1). The same effect was present in the bevacizumab arm (p-value: 0.05, HR: 0.73, 95%-CI 0.53 – 1.0) when comparing pts with synchronous disease (n=217) vs. pts. with metachronous disease (n=76). **Conclusions:** In the FIRE-3 study, metachronous disease was associated with superior OS compared to synchronous disease. This finding was accentuated in the bevacizumab arm. The role of resection of the primary tumor had no impact on survival. Clinical trial information: NCT00433927. Research Sponsor: Merck KGaA, Darmstadt, Germany.

4071 **Poster Session (Board #63), Fri, 8:00 AM-11:00 AM**

Utility of circulating tumor DNA (ctDNA) versus tumor tissue genotyping for enrollment of patients with metastatic colorectal cancer (mCRC) to matched clinical trials: SCRUM-Japan GI-SCREEN and GOZILA combined analysis.

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Background: We recently reported that ctDNA genotyping had advantages compared with tumor tissue testing in terms of enrollment to matched clinical trials across a wide range of GI cancers (Nakamura Y, et al. ASCO-GI 2020). Here, we investigated the utility of ctDNA genotyping in mCRC in a SCRUM-Japan GI-SCREEN and GOZILA combined analysis. **Methods:** In GI-SCREEN, tumor tissue genotyping was performed using a next generation sequencing (NGS)-based assay, Oncomine Comprehensive Assay since Feb 2015. In GOZILA, NGS-based ctDNA genotyping was performed using Guardant360 since Feb 2018. All tests were conducted centrally in a CLIA-certified and CAP-accredited laboratory. Patients with actionable alterations were enrolled into matched company-sponsored or investigator-initiated interventional clinical trials. **Results:** As of Apr 2019, 2,791 mCRC patients (2,754 eligible for analysis) in GI-SCREEN and 470 (464 eligible for analysis) in GOZILA were enrolled. There were no significant differences in baseline patient characteristics between GI-SCREEN and GOZILA. Most of trials affiliated with GI-SCREEN (81%) or GOZILA (78%) targeted the RTK/RAS/RAF pathway. Compared with tumor testing, ctDNA genotyping significantly improved turnaround time (median, 12 vs. 34 days, $P < 0.0001$), sequencing success rate (96.1 vs. 92.3%, $P = 0.002$), and detection rate of actionable alterations (73.3 vs. 62.2%, $P = 0.02$). Among patients with actionable alterations, enrollment to matched clinical trials was achieved in 5.0% in GI-SCREEN and 12.1% in GOZILA ($P < 0.0001$). Median time from enrollment in the respective screening study to enrollment in a matched clinical trial was 6.5 months in GI-SCREEN and 0.9 months in GOZILA, respectively ($P < 0.0001$). Objective response rate and progression-free survival were similar in both groups (tissue vs. ctDNA; ORR: 18.8 vs. 17.1%, $P = 1.00$; median PFS: 2.2 vs. 2.2 months, HR=1.05 [95% CI, 0.71–1.55], $P = 0.79$). **Conclusions:** For patients with mCRC, ctDNA genotyping had advantages over tissue genotyping with shorter turnaround time and higher sequencing success and actionable alteration detection rate, which were associated with improved clinical trial enrollment without compromising the efficacy. Funding: SCRUM-Japan Funds. Clinical trial information: UMIN000029315. Research Sponsor: SCRUM-Japan Funds.

4072 **Poster Session (Board #64), Fri, 8:00 AM-11:00 AM**

Colorectal cancer under the age of 50 years in U.S. Department of Veterans Affairs: Is there a role of early screening?

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Background: While the overall incidence of colorectal cancer (CRC) is decreasing, the rate has increased in population under 50, with higher stages at diagnosis and a greater proportion of African Americans (AA). Hence, there is an ongoing debate about the age of CRC screening. These trends have not been studied in the VA population. **Methods:** ICD-10 codes C18-C20 were used to identify the cases of colon and rectal cancer in National VA Cancer Cube Registry. 43,544 cases of colon cancer, 1,278 below and 42,254 above age 50, and 19,815 cases of rectal cancer, 862 below and 18,948 above age 50 were identified between 2003-17. Younger age group was defined as patients less than 50 years old. IRB approval was obtained. **Results:** Our data comprised $>$ 97% of male patients. In younger group, in the 5 year periods, 2003-07, 2008-12 and 2013-17, colon cancer rate increased from 2.59% to 2.79% to 3.59%, while for rectal cancer it increased from 3.5% to 4.3% to 5.3% ($p < .0001$). Blacks comprise 31.6% cases of colon cancer and 27.15% cases of rectal cancer in under 50 group, compared to 18.5% and 15.9% of cases in above 50 group respectively ($p < .0001$). For under 50 group, 48.6% cases of colon and 42.2% cases of rectal cancer were diagnosed in stage III or IV compared to 35.7% and 34.05% cases in above 50 group respectively ($p < .0001$). For colon cancer, 51.87% of patients in the younger group have a $<$ 5 year survival, worse compared to 45.05% in 50-60 group ($p < .0001$) and similar to 49.3% in 60-70 group ($p = .08$). For rectal cancer, 5 year survival showed no difference between these groups. Stage specific survival shows no difference for either colon or rectal cancer across $<$ 50, 50-60 and 60-70 age groups. **Conclusions:** Rate of CRC is rising in $<$ 50 age group with more advanced stage at diagnosis and higher proportion of African Americans. For colon cancer, $<$ 50 group has a worse 5 year survival as compared to 50-60 age group likely due to increased proportion of patients in stage III or IV, as there is no difference in stage specific survival. For rectal cancer, the 5 year survival or stage specific survival shows no difference in $<$ 50, 50-60 and 60-70 groups. These results add to our understanding of the trends of CRC and should be accounted for in the screening guidelines.
Research Sponsor: None.

4073 **Poster Session (Board #65), Fri, 8:00 AM-11:00 AM**

Translational research of voltage-A1: Efficacy predictors of preoperative chemoradiotherapy and subsequent nivolumab monotherapy in patients with microsatellite-stable locally advanced rectal cancer.

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Background: In VOLTAGE-A1, after 5 cycles of nivolumab (240 mg q2 weeks) plus radical surgery following chemoradiotherapy (CRT; 50.4 Gy with capecitabine 1,650 mg/m^2), a major pathologic response is observed in 38% (AJCC tumor regression grade 0-1) of 37 patients with microsatellite-stable locally advanced primary rectal cancer. Here, biomarkers for predicting the efficacy of this treatment were investigated. **Methods:** Serial tumor biopsies and blood collections were performed at 4 time points; before CRT, after CRT, after 3 cycles of nivolumab, and before surgery. Tumor-infiltrating lymphocytes (TILs) and DNA/RNA were extracted from tumor samples, and peripheral blood mononuclear cells (PBMCs) were extracted from blood samples. We analyzed the immune status of the patients by flow cytometry using the collected TILs and PBMCs. Whole exome and RNA sequencing analyses were conducted using the extracted DNA and RNA, respectively. The PD-L1 status of tumor samples was also evaluated by *in vitro* diagnostic immunohistochemistry staining. **Results:** Among the 24 patients whose samples were serially collected, 11 (46%) were AJCC grade 0-1 and 13 were 2-3. Before CRT, effector regulatory T (eTreg) cells in TILs were higher in patients with AJCC grade 2-3, and both the CD8$^+$ T cell/eTreg cell ratio in TILs and PD-L1-positive tumor cells ($\geq$1%) were higher in patients with AJCC grade 0-1 ($p = 0.047$, $p = 0.083$, respectively). Ki67 expression by CD8$^+$ T cells in TILs was higher before CRT in patients with AJCC grade 0-1 ($p = 0.037$) and increased after CRT in all patients. Patients with consensus molecular subtype (CMS) 1 and CMS3 achieved AJCC grade 0-1 at rates of 100% (2/2) and 60% (4/6), respectively. In contrast, patients with CMS2 and CMS4 achieved AJCC grade 0-1 at rates of 43% (3/7) and 29% (2/7), respectively. The tumor mutation burden of pre-CRT samples was significantly higher in patients with AJCC grade 0-1 (median 1.45/MB) than in patients with AJCC grade 2-3 (0.84/MB) ($p = 0.016$). **Conclusions:** A higher CD8$^+$ T cell/eTreg cell ratio, PD-L1-positive, Ki67 expression by CD8$^+$ T cells in TILs, CMS1 or 3, and higher tumor mutation burden are good predictors of the efficacy of the sequential combination of CRT and nivolumab. Further results will be reported in the meeting. Clinical trial information: NCT02948348. Research Sponsor: Ono phrmaceutical Co.,Ltd.

4074 **Poster Session (Board #66), Fri, 8:00 AM-11:00 AM**

Neoadjuvant chemoradiation (CRT) for locally advanced rectal cancer (LARC) with or without oxaliplatin (OX): Individual patient data (IPD) meta-analysis of three randomized controlled trials (RCTs) with subgroup analyses of age cohorts.

Elisa Fontana, Clizia Zichi, Elizabeth Catherine Smyth, Murielle E. Mauer, Claus Roedel, Emmanouil Fokas, Ralf Dieter Hofheinz, Dirk Arnold, Hans-Joachim Schmoll, Eric Van Cutsem, Karin Haustermans, Alexander Stein, Jean-Pierre Gerard, Thierry Conroy, Claire Jouffroy-Zeller, Markus H. Moehler, Florian Lordick, Irit Ben-Aharon, Massimo Di Maio, Adolescent and Young Adult Gastrointestinal Task Force, EORTC; Sarah Cannon Research Institute, London, United Kingdom; Department of Oncology, University of Turin, Ordine Mauriziano Hospital, Turin, Italy; Addenbrookes Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom; EORTC, Brussels, Belgium; Department of Radiation Oncology, University Hospital Frankfurt, Goethe-Universität Frankfurt, Frankfurt, Germany; German Cancer Consortium (DKTK) Core Center Heidelberg and DKTK Partner Site Frankfurt, Oxford, United Kingdom; University Medical Center Mannheim, Tagestherapiezentrum am ITM, Mannheim, Germany; Asklepios Tumorzentrum Hamburg AK Altona, Hamburg, Germany; Martin Luther University, Halle, Germany; University Hospitals Gasthuisberg Leuven, KU Leuven, Leuven, Belgium; University Hospital Gasthuisberg, Leuven, Belgium; University Medical Center Hamburg-Eppendorf, Department of Oncology, Haematology, Stem Cell Transplantation and Pneumology, Hamburg, Germany; Centre Antoine Lacassagne, Nice, France; Institut de Cancérologie de Lorraine, Vandoeuvre-Les-Nancy, France; Unicancer, Paris, France; University Medical Center Mainz, I. Dept. of Internal Medicine, Mainz, Germany; University Cancer Center Leipzig, Leipzig, Germany; Division of Oncology, Rambam Health Care Center, Haifa, Israel; Department of Oncology, A.O. Ordine Mauriziano Hospital, University of Turin, Turin, Italy

Background: Neoadjuvant CRT with fluoropyrimidine (FP) is standard treatment for LARC, which is increasing in younger patients (pts). RCTs examining the addition of OX are still controversial. A *post hoc* analysis of the CAO/ARO/AIO-04 trial showed significant benefit in pts < 60y. We hypothesised that younger pts with LARC might have improved outcomes with OX-CRT. **Methods:** Systematic review and IPD meta-analysis were performed. Data from 3 RCTs (CAO/ARO/AIO-04, ACCORD-12, PETACC-6) testing the addition of OX to standard FP-based CRT in LARC were available (of 9 RCTs identified). Primary endpoint: disease-free survival (DFS), secondary endpoints: pathologic complete response (pCR), overall survival (OS). Analyses were by intention to treat (ITT), stratified by trial. Age cut-offs were 60y and 50y. Given the focus on young age a multivariate analysis evaluating all possible confounders was not intended in the current work. **Results:** IPD from 2914 pts were included (48.5% of available literature). Median age was 63; 70% were male; 79% had a performance status = 0; 72% were stage ≥III. In ITT (Hazard Ratio [HR] 0.88, 95%CI 0.77-1.01, p = 0.06), DFS was not significantly improved by the addition of OX (Table). In < 60y (n = 1166, 40% total), DFS was significantly improved by OX (HR 0.77, 95%CI 0.62-0.96, p = 0.02). In < 50y (n = 350, 12% total) there was a numerically better DFS, although not significant (HR 0.73, 95%CI 0.49-1.08, p = 0.12). Interaction test between age and DFS was non-significant (60y p = 0.11; 50y p = 0.44). In ITT, OX increased pCR from 13% to 16% (Odds Ratio [OR] 1.28, 95%CI 1.04-1.57, p = 0.024 [stratified by trial]), without significant interaction with age (60y p = 0.11, 50y p = 0.74). No OS benefit was demonstrated (HR 0.97, 95%CI 0.82-1.15, p = 0.75). **Conclusions:** This first IPD meta-analysis of three RCTs evaluating the addition of OX to CRT did not show significant interaction of OX with age. However, we confirm a signal for DFS benefit in pts < 60y and a non-significant increment in DFS in < 50 y although this analysis may be underpowered. Stage-stratified analyses and feasibility/toxicity data in age cohorts will be presented. Research Sponsor: None.

ITT - DFS	HR	0.88	95%CI	0.77-1.01	p-value	0.06
< 60 - DFS		0.77		0.62-0.96		0.02
< 50 - DFS		0.73		0.49-1.08		0.12
> 60 - DFS		0.95		0.80-1.12		0.54
> 50 - DFS		0.90		0.78-1.04		0.14
ITT pCR	OR	1.28		1.04-1.57		0.02
< 60 - pCR		1.04		0.75-1.44		0.89
< 50 - pCR		1.17		0.65-2.11		0.72
> 60 - pCR		1.47		1.12-1.93		0.01
> 50 - pCR		1.30		1.04-1.62		0.02

4075 **Poster Session (Board #67), Fri, 8:00 AM-11:00 AM**

Duration of FOLFOX adjuvant chemotherapy in high-risk stage II and stage III colon cancer with deficient DNA mismatch repair.

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Background: In the IDEA collaboration, noninferiority was not confirmed for 3 months versus 6 months of FOLFOX adjuvant chemotherapy among patients with high-risk stage II and stage III colon cancer (CC). Patients with deficient DNA mismatch repair (dMMR) have a good prognosis, but for whom, whether limiting the duration of adjuvant therapy will compromise oncologic outcomes remains undefined. We evaluated the impact of 3 months of FOLFOX adjuvant chemotherapy or surgery alone in comparison with 6 months of FOLFOX on disease-free survival (DFS) in dMMR CC patients. **Methods:** This retrospective study included all consecutive patients who underwent curative surgical resection for high-risk stage II or III dMMR CC between May, 2011 and July, 2019. Prognostic factors were analyzed using Cox models, and hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. **Results:** A total of 242 dMMR CC patients were included (43.4% high-risk stage II, 56.6% stage III). The patients received 6 months of FOLFOX adjuvant chemotherapy (n = 66; median cycles [rang] = 12 [10-12]), 3 months of FOLFOX (n = 87; median cycles [rang] = 6 [4-8]), or surgery alone (n = 89). Three groups were generally well balanced, although more patients with stage III were in the 6-month therapy group (74.2%), compared with the 3-month therapy group (57.5%) and the surgery alone group (42.7%). As compared with 6 months of FOLFOX adjuvant chemotherapy in the overall population, 3 months therapy reduced DFS in multivariable analysis (HR, 2.78; 95CI, 1.18 to 6.47; P = 0.02), similar to surgery alone (HR, 2.30; 95CI, 0.99 to 5.38; P = 0.05). In the subgroup analysis, a therapy duration of 6 months was statistically superior to a duration of 3 months only in the patients with stage III, with a 3-year rate of DFS of 86.2% versus 70.8% (HR, 3.06; 95% CI, 1.14 to 8.19; P = 0.026). **Conclusions:** This study supports the 6-month duration of FOLFOX adjuvant chemotherapy in stage III dMMR CC. Research Sponsor: None.

4076 **Poster Session (Board #68), Fri, 8:00 AM-11:00 AM**

The mutation of homologous recombination repair genetics is a potential biomarker for immunotherapy in microsatellite stable colon cancer.

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Background: Patients with microsatellite instability-high (MSI-H) colonic adenocarcinoma (COAD) are always immunotherapy-sensitive for the use immune checkpoint inhibitors, however, the vast majority of COAD patients (85%) are microsatellite stable (MSS). Homologous recombination deficiency (HRD) is demonstrated to be a response predictor to immunotherapies in gynecologic cancers, while limited studies were reported in colon cancer. We focus herein on the mutational pattern of HRR related genes in a large Chinese COAD cohort and further analyze the relationship between HRR-gene mutations and clinical response to immunotherapy in MSS COAD. **Methods:** The genomic profiling of Genecast cohort which is consisted of 406 Chinese patients with COAD were analyzed in a panel of 543 cancer related genes via next generation sequencing (NGS). The correlation between HRR-gene mutations and tumor immunity or clinical outcome using two COAD genomics datasets (TCGA and MSK-COAD) by the bioinformatic approach. **Results:** In Genecast Cohort, seventy of 406 (17.2%) patients were identified genomic alterations in HRR-gene, the most frequently mutated genes were *ATM* (9%), *BRCA2* (4%), *ATR* (3%), *RAD50* (3%) and *BRIP1* (3%). In MSK-COAD cohort (treated with immune checkpoint inhibitors), HRR-mut group (n = 34) had a significantly better OS than HRR-wt group (n = 50) (log-rank test, $P = 0.0087$). From the analysis of TCGA cohort, we found that mutations of HRR-gene could increase immune activity in MSS COAD, including increased cytotoxic cells infiltration ($P = 0.035$), increased exhausted CD8 T cells infiltration ($P = 0.0098$) and higher IFN-g score ($P = 0.03$). In contrary, similar results were not found in MSI-H COAD (all $P > 0.05$). **Conclusions:** Mutations of HRR-gene could significantly increase immune activity in patients with MSS COAD, implying the feasibility of using HRR-mut as a response predictor of immunotherapy in MSS-COAD. Research Sponsor: None.

4077 **Poster Session (Board #69), Fri, 8:00 AM-11:00 AM**

Tumor mutational load, microsatellite instability and actionable mutations in metastatic colorectal cancer: Results from the TRIBE2 study.

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Background: In the TRIBE2 study molecularly unselected and untreated mCRC patients were randomized to receive FOLFOXIRI/bevacizumab (bev) followed by the same agents after disease progression (PD) or FOLFOX/bev followed by FOLFIRI/bev after PD. We performed a comprehensive NGS analysis of samples from randomized patients in order to investigate the prognostic impact of tumor mutational load (TML), its additional value with respect to the assessment of microsatellite instability (MSI), and the overall prevalence of potentially actionable alterations. **Methods:** Tumor DNA was obtained from formalin-fixed, paraffin-embedded blocks from primary tumors of 296 (44%) out of 679 randomized patients and underwent NGS analysis using the Caris MI TumorSeek panel, assessing 592 genes. TML was defined low, intermediate or high if < 7, 7-16 or > 16 mutations/Mb were found. MSI status was determined both by NGS and by IHC. **Results:** TML and MSI were successfully determined by NGS in 224 (76%) cases. NGS and IHC results were concordant in 221 (99%) cases. TML was low, intermediate or high in 56 (25%), 157 (70%) and 11 (5%) cases, respectively. When compared with TML low and intermediate tumors, TML high were more frequently right-sided ($p = 0.013$), mucinous ($p < 0.001$) and MSI-high ($p < 0.001$). TML high tumors were MSI-high or MSS in 8 (73%) and 3 (27%) cases, respectively. Two out of 3 TML high and MSS tumours showed a pathogenic *POLE* mutation (p.S459F and p.P286R). The other TML high, MSS and *POLE* wt tumor was dMMR at IHC (loss of MSH6 expression) and showed a pathogenic *MSH6* mutation (p.F1040fs). As compared with low and intermediate TML, high TML was associated with longer PFS (median PFS: 17.3 vs 10.6; HR: 0.54 [95%CI: 0.35-1.09], $p = 0.098$) and OS (median OS: not reached vs 23.7: HR: 0.45 [95%CI:0-28-1.13], $p = 0.106$). No interaction effect between TML and treatment arm was observed, and no difference between TML low and intermediate tumors was reported in terms of baseline characteristics and prognosis. Actionable alterations (*HER2* mutations [N = 2] and amplifications [N = 4], KRAS G12C [N = 10] and BRAF V600E mutation [N = 39]) were found in 55 (19%) out of 296 cases. No *NTRK/ROS/ALK* or *MET* amplification was found. **Conclusions:** TML high tumors are not limited to MSI-high ones but showed *POLE* or *MSH6* somatic mutation and shower longer PFS and OS. No differences are reported between TML low and intermediate tumors. Molecular alterations predictive of benefit from targeted strategies currently available are detectable only in a small percentage of mCRCs. Research Sponsor: GONO foundation.

4079 **Poster Session (Board #71), Fri, 8:00 AM-11:00 AM**

Circulating tumor DNA as a promising biomarker of relapse risk for stage II-III colorectal cancer.

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Background: About 30-50% colorectal cancer patients undergoing a curative resection will experience disease recurrence ultimately. Early detection of recurrence is of great significance for improving the prognosis of colorectal cancer patients. Circulating tumor DNA (ctDNA) has been suggested to be a promising biomarker for postoperative surveillance and prognosis prediction in various cancers including colorectal cancer. However, its performance in predicting early recurrence of colorectal cancer as well as appropriate testing procedures still needs large-scale prospective studies to evaluate. **Methods:** A total of 246 patients with stage II-III colorectal cancer and underwent curative resection from three clinical centers of China were enrolled in this multicenter prospective cohort study. Tissue samples as well as serial plasma samples before surgery, 7 days and 6 months after surgery and 3 months interval afterwards until recurrence were collected, and subjected to deep targeted-panel sequencing containing 425 cancer-related genes. ctDNA baseline genomic alterations and dynamic changes were analyzed. Its performance in predicting early recurrence was evaluated and compared with other clinical routine investigations, including serum biomarkers CEA and CA199, and CT examination. **Results:** The ctDNA positive rates at baseline (before surgery) and 7 days after surgery were 72.9% and 18.1% respectively. Among 199 patients with complete survival data, 18 patients were recurrent during follow up period with a median disease-free survival of 280.5 days (114-461 days). At baseline, high clinical stage ($p = 0.035$), and *PTEN* mutation ($p = 0.009$) were significantly associated with increased recurrent risk; while *APC* mutation ($p = 0.04$) predicted a decreased recurrent risk. Detection of ctDNA 7 days after surgery [HR: 5.9 (1.94-17.97); $p = 0.0004$] or any time point before clinical recurrence [HR: 6.14 (2.3-16.38); $p < 0.0001$] was associated with a significantly higher recurrent risk, and the HR increased accordingly with ctDNA mutation level. In multivariate analyses, ctDNA status was independently associated with relapse after adjusting for known clinicopathological risk factors. CEA status was not significantly ($p > 0.4$) associated with disease-free survival. A risk scoring model comprising of clinical variables and ctDNA detection after surgery was constructed and can predict 18-month recurrence with an AUC of 0.77. **Conclusions:** ctDNA is a promising marker of risk stratification, and early relapse detection in resected stage II/III CRC patients. Clinical trial information: NCT03312374. Research Sponsor: None.

4080 **Poster Session (Board #72), Fri, 8:00 AM-11:00 AM**

Mutation of DNA damage repair genes confers an immune-privileged tumor microenvironment in colorectal cancer with a prognostic value.

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Background: Microsatellite instability high (MSI-H)/mismatch-repair-deficient (dMMR) has been proved as a validated biomarker in solid tumors receiving immune checkpoint inhibitors (ICIs). Recently, mutational status of the DNA damage repair (DDR) genes has been linked to anti-tumor immune response in bladder cancer. Therefore, it would be of great interest to unravel the implications of DDR in shaping the immune responsiveness in CRC. **Methods:** The genomic correlates were examined in a publicly available cohort from Memorial Sloan Kettering Cancer Center (MSK ICI cohort). To explore the associations between DDR mutation and immune features, the genomic data of The Cancer Genome Atlas (TCGA) colorectal adenocarcinoma (COADREAD) dataset was analyzed. Further, we determined DDR mutation and MSI status in a Chinese CRC cohort via a 543-gene panel sequencing. **Results:** First, we observed that DDR pathway was commonly mutated (21.79%) in the multi-cancer MSK ICI cohort, with the highest frequency of 36.36% in CRCs. Second, survival analysis revealed that the median overall survival (mOS) in patients with DDR mutations was significantly longer than that in the DDR wild-type subgroup, in both pan-cancer (P = 0.0008; mOS 31 vs 16 months) and CRC patients (P = 0.016; mOS 34 vs 13 months) in the MSK ICI cohort. However, in the TCGA COADREAD dataset, there was no significant difference in OS or progression free survival (PFS) between DDR mutant and DDR wild-type subgroups. These observation indicated a specific prognostic value for DDR mutation in patients with ICI treatment while not conventional treatment. Third, in the TCGA COADREAD dataset, DDR mutations were associated with increased TMB, enrichment of immune cell infiltration and immune checkpoint molecule expression, suggesting an improvement of various steps of the cancer immunity cycles in DDR mutant CRCs. Lastly, we investigated the DDR mutational pattern, and its associations with MSI-H and other genomic features in a Chinese CRC cohort. Notably, MSI-H and DDR mutation account for 5.7% and 13.4% respectively, suggesting that DDR may identify a higher proportion of potential responders than MSI-H. **Conclusions:** Our data suggest that DDR mutation is a potential prognostic biomarker for ICI-treated CRCs. Functional analysis in TCGA dataset revealed that DDR mutation might be an indication of enhanced cancer immunity. The higher incidence of DDR mutation in Chinese CRCs emphasized the future utility of panel-based DDR evaluation in guiding ICI treatment. Research Sponsor: None.

4081 **Poster Session (Board #73), Fri, 8:00 AM-11:00 AM**

The role of primary tumor (PT) site as prognostic factor after resection of colorectal (CRC) liver metastases (LM): A mono-institutional cohort study.

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Background: Radical resection of LM is the only chance of cure for liver-only mCRC pts. Besides the evaluation of technical resectability, several factors must be taken into account for the evaluation of recurrence risk. Among them we should consider the Fong Risk Score and its modified version, including RAS/BRAF status (Brudvik's score). Tumor sidedness is an important prognostic factor in CRC. The impact of PT site on the outcome of LM resection is still debated. Hence, we retrospectively analysed mCRC pts, underwent to radical LM resection at our Institution, investigating the impact of PT site on DFS and OS. **Methods:** Liver-only mCRC pts underwent to radical LM resection were included. The association of PT site with DFS and OS was evaluated. The following variables were collected: gender; age ($\geq$ vs $<$ 75 years); ECOG PS; CEA baseline level; PT site; RAS and BRAF status; mucinous histology; grading (G1-2 vs G3); RECIST response during preoperative treatment; resected PT; synchronous vs metachronous; number of LM; bilobar vs unilobar LM; LM diameter $\geq$ 5 cm; R0 vs R1 resection. Univariate and multivariate analyses for DFS and OS were performed. **Results:** A total of 463 liver-only mCRC pts underwent to radical LM resection were included. Seventy (15%) pts had a right-sided (r-s) tumor and 393 (85%) pts a left-sided (l-s) tumor. R-s CRC pts more often had RAS/BRAF mutations in comparison to l-s tumors (76% vs 37%; $p < 0.0001$). Median DFS and OS was 13.1 and 41.6 months, respectively, in r-s CRC vs 16.0 ($p = 0.65$) and 62.2 months ($p = 0.033$), respectively, in l-s tumors. At the multivariate analysis no significant association with survival parameters was shown for tumor sidedness. At the multivariate analysis, R0 resection was independently associated both with better DFS and OS; RAS/BRAF wt CRC and resected PT were significantly associated with improved OS. Considering all wt CRC pts (N = 237), 14 (6%) pts had r-s tumor and 223 (94%) l-s tumor. No significant association of tumor sidedness with survival was shown (DFS r = 10.0 vs l = 16.0 months, p = 0.62; OS r = 40.3 vs l = 66.2 months, p = 0.12). **Conclusions:** Our results showed that a significant smaller proportion of r-s CRC underwent to radical LM resection, indirectly confirming its worse prognosis. Among radically resected pts, r-s CRC was associated to a shorter OS (significant) and DFS (not significant) compared to l-s CRC, but it was not confirmed at the multivariate analysis. We can conclude that right PT site should not be considered as a contraindication for radical LM surgery, when feasible. Research Sponsor: None.

4082 **Poster Session (Board #74), Fri, 8:00 AM-11:00 AM**

Efficacy of third-line anti-EGFR-based treatment (tx) versus (vs) Regorafenib/TAS-102 (R/T) according to primary tumor site in RAS/BRAF wild-type (wt) metastatic colorectal cancer (mCRC) patients (pts).

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Background: Right- (R) and left-sided (L) mCRCs exhibit different clinical and molecular features. Several retrospective analyses showed that the survival benefit of anti-EGFR-based tx is limited to *RAS/BRAF* wt L-sided mCRC pts, which a larger effect in the first-line setting. Few data are available concerning the anti-EGFR efficacy according to primary tumor site in third line. **Methods:** Pts affected by *RAS/BRAF* wt mCRC treated with third-line anti-EGFR-based tx or R/T were retrospectively collected. The objective of the analysis was to compare tx activity and efficacy according to tumor site. Primary endpoint was PFS; secondary endpoints were OS and RR. PFS and OS analyses were performed using Kaplan-Meier method, and survival curves were compared using the log-rank test. RR was evaluated according to RECIST criteria and it was compared in the two groups using Fisher's exact test. Statistical significance was set at $p = 0.05$ for a bilateral test. Univariate and multivariate analyses for PFS and OS were performed. **Results:** A total of 76 *RAS/BRAF* wt mCRC pts, treated with third-line anti-EGFR-based tx or R/T, were enrolled. Of those, 19 (25%) pts had R-sided tumor (9 pts received anti-EGFR tx and 10 pts received R/T) and 57 (75%) pts had L-sided tumor (30 pts received anti-EGFR tx and 27 pts received R/T). As shown in the table, a significant PFS and OS benefit in favor of anti-EGFR tx vs R/T was observed in L-sided pts, while no difference both in PFS and OS was observed in R-sided pts. RR was significantly higher in L-sided pts treated with anti-EGFR vs R/T, no difference was shown in R-sided pts. At the multivariate analysis, tx regimen was indipendently associated with PFS in L-sided pts, but not in R-sided pts. **Conclusions:** Our study confirmed the results deriving from the retrospective analysis of the phase III study 20020408. Our results demonstrated a different benefit from third-line anti-EGFR tx according to primary tumor site, confirming the role of L-sided tumor in predicting benefit from third-line anti-EGFR vs R/T, while no difference was observed in R-sided tumors. Research Sponsor: None.

	R-sided	R-sided	L-sided	L-sided
	Anti-EGFR (N = 9)	R/T (N = 10)	Anti-EGFR (N = 30)	R/T (N = 27)
Median PFS (months)	3.5	3.8	7.3	3.6
	HR = 1.4 (95%CI 0.53-3.75), p = 0.49		HR = 0.47 (95%CI 0.26-0.85), p = 0.0028	
Median OS (months)	9.3	9.2	15.2	11.0
	HR = 0.83 (95%CI 0.30-2.26), p = 0.696		HR = 0.58 (95%CI 0.31-1.08), p = 0.0428	
RR	11% p = 0.99	10%	43% p < 0.0001	0%

4083 **Poster Session (Board #75), Fri, 8:00 AM-11:00 AM**

Intra-tumoral microbes and overall survival in colorectal cancer patients.

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Background: The presence of certain bacteria among or adjacent to tumor cells may contribute to colorectal cancer (CRC) development. However, the effect of the tumor microbiome on survival in CRC patients undergoing treatment is poorly understood. We hypothesize that intra-tumoral microbes correlate with overall survival (OS) in CRC patients. **Methods:** We obtained RNA-seq data from CRC tumor biopsies from patients treated at The Ohio State University Comprehensive Cancer Center as part of the Oncology Research Information Exchange Network (ORIEN). Reads were aligned to human and exogenous genomes using TopHat2 and Kraken2/Bracken, respectively. **Results:** The analyzed cohort included 99 CRC patients with an age range from 31-83 years, 62% female, and 44% with metastatic CRC. Therapies received prior to sample collection were grouped into chemotherapy with or without radiation (37%), antiVEGF/EGFR therapies (33%), no systemic therapy (23%), immunotherapy (3%); 3% were unknown. Overall, eleven bacteria were significantly associated with shorter OS, including a species in the genus Clostridium and Vibrio. Conversely, five other bacteria including several commensal gut microbes, were associated with longer OS. In patients who received chemotherapy with or without radiation (n = 38), several microbes were significantly associated with shorter OS, including a member of the genus *Streptomyces*. Only three bacteria were significantly associated with longer OS. In the patients who received antiVEGF/EGFR therapies (bevacizumab, cetuximab, panitumumab) (n = 33), several bacterial taxa were associated with shorter OS. In addition, bacteria including a member of the genera Bacillus and Staphylococcus were significantly associated with metastatic CRCs. ($p < 0.05$ for all, Fisher's Exact tests). **Conclusions:** This study suggests that demonstrating the presence or absence of certain microbes in tumor biopsies could have important therapeutic implications for CRC patients. Only bacteria (no fungi, viruses, archaea, etc.) were found to significantly associate with OS across the entire cohort and within treatment subsets. The presence of bacteria was mostly, but not always, associated with worse OS. Antibiotics targeted towards bacterial species associated with negative outcomes could have the potential to improve OS in CRC patients. Research Sponsor: Award Number UL1TR002733.

4084 **Poster Session (Board #76), Fri, 8:00 AM-11:00 AM**

Consensus molecular subtype (CMS) as a novel integral biomarker in colorectal cancer: A phase II trial of bintrafusp alfa in CMS4 metastatic CRC.

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Background: Consensus Molecular Subtype 4 (CMS4) colorectal cancer (CRC) features increased TGFβ signaling, which may account for de novo resistance to immunotherapy for patients (pts) with microsatellite stable mCRC. To date, no prior trial has incorporated CMS status as an integral biomarker. Bintrafusp alfa (M7824) is a dual PD-L1 antibody/TGFβ trap with acceptable safety. **Methods:** Primary tumors from pts with metastatic CRC underwent CMS testing in a CLIA setting. In this Simon two-stage phase II trial (Ho: $p < .05$; Ha: $p \geq .25$) for CMS4 mCRC, pts received bintrafusp alfa 1200mg IV every 14 days. RT (8Gy/day x 3 days) to a single metastatic lesion with abscopal intent was administered between doses 2 and 3. The primary objective was to estimate response rate (RR) per iRECIST. Correlative studies including RNA sequencing were performed on pre- and on-treatment biopsies. **Results:** 53 of 137 tested pts (39%) between June 2018-December 2019 had CMS4 mCRC. 13 of 15 treated pts received the agent with RT. All pts were evaluable for toxicity, and 13 for response. Median number of doses was 3 (IQR, 2-4). There was one grade 3 immune-related adverse event (colitis) requiring study discontinuation. There were 2 pts with stable disease and 11 with progressive disease as best response (RR 0%, 95% CI 0-22%). Enrollment was stopped after first stage for futility. Median PFS and OS were 1.6 months and 5.0 months, respectively. In paired samples, treatment with bintrafusp alfa resulted in an increase in the expression of IFNγ signature in nonirradiated metastatic lesions ($p < .001$, $q < .001$). Updated results will be presented. **Conclusions:** This is the first reported clinical trial to utilize CMS status as an integral biomarker for pts with metastatic CRC and capitalizes on treating CRC subpopulations with targeted agents based upon validated RNA-based signatures. Although the efficacy for bintrafusp alfa and RT is low, changes in IFNγ signature provides a potential signal for refining therapeutic strategies based upon TGFβ enrichment in pts with mCRC. Clinical trial information: NCT03436563. Research Sponsor: EMD-Serono.

4085 **Poster Session (Board #77), Fri, 8:00 AM-11:00 AM**

The effect of aspirin on colorectal cancer incidence in African Americans.

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Background: From 2011 to 2016, the incidence and mortality rate of colorectal cancer(CRC) were highest among African Americans(AA), compared to other US racial/ethnic groups. Long-term aspirin use is recommended as a strategy to reduce the risk of CRC. Yet, there is scant information on the chemopreventive effect of aspirin among AA. It is imperative to assess whether the reported chemopreventive effect also occurs in AA. Our central hypothesis is that aspirin use in AA is associated with a lower incidence of CRC, irrespective of race/ethnicity. **Methods:** We conducted a secondary analysis, using data from AA participants in the Atherosclerosis Risk in Communities(ARIC) longitudinal study, who did not have CRC at enrollment, from 1987 to 1998. We extracted demographic, clinical and mortality data to compare the incidence of CRC among participants taking aspirin compared to those who were not taking aspirin, stratified by age, tobacco use, and body mass index. All-cause mortality and CRC mortality will also be assessed, and we will use Cox proportional hazard regression to determine the relationship between aspirin use and CRC incidence, and mortality. **Results:** At baseline in 1987, 15,026 participants enrolled in the ARIC study, 25% of whom were AA, median age 54(range 44-66), including 46.7% who reported using aspirin. We analyzed follow-up data from 10,960 participants in 1996-1998, 20% of whom were AA, and 56.9% of whom were taking aspirin. Non-AA participants were more likely to report using aspirin at baseline and follow-up, compared to AA, 53% vs 30% and 59% vs 50% respectively. After 10years, the total incidence of CRC in AA participants was 1% compared with 1.1% in non-AA($p = 0.7$). There was no difference in CRC incidence by aspirin use among all participants, and when stratified by race(among all participants $p = 0.81$, amongAA $p = 0.68$, among non-AA $p = 0.94$). **Conclusions:** We found no difference in the incidence of CRC among AA compared to Caucasians, by aspirin use. Investigation of consistency and/or dose of aspirin use by race may provide further insights on the relationship between aspirin use and CRC incidence, comparing AA to Caucasians. Research Sponsor: None.

4086 **Poster Session (Board #78), Fri, 8:00 AM-11:00 AM**

Predictive and prognostic value of *HER2* gene expression and *HER2* amplification in patients with metastatic colorectal cancer (mCRC) enrolled in CALGB/SWOG 80405 (Alliance).

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Background: The randomized phase III CALGB/SWOG 80405 trial found no difference in overall survival (OS) in first-line mCRC pts treated with either bevacizumab (Bev) or cetuximab (Cet) combined with the same chemotherapy. We investigated the potential prognostic and predictive value of *HER2* amplification and *HER2* gene expression using NGS and Nanostring data. **Methods:** Primary tumor DNA from 559 patients (pts) was profiled for *HER2* amplification by NGS (Foundation One). Tumor tissue from 925 pts was tested for Nanostring gene expression using an 800 gene panel. OS and progression free survival (PFS) were the endpoints as time-to-event variables. Cox proportional hazard models with gene expression fitted with linear spline (one internal knot at median) were used, adjusting for pts baseline characteristics, treatment assignment, and molecular features (microsatellite instability, *BRAF*, all *RAS*). **Results:** Of 505 tumors with both NGS and Nanostring data, 16 harbored *HER2* amplification (copy number variation > 6), limited to microsatellite stable tumors and significantly associated with *HER2* expression ($P < 0.001$) and wild-type *RAS* ($P = 0.036$). *HER2* amplification was neither prognostic nor predictive for OS or PFS. Conversely, *HER2* expression higher than median was associated with longer PFS ($P = 0.018$) but not OS ($P = 0.13$). Among pts with *HER2* not amplified, higher *HER2* expression was associated with better OS (hazard ratio [HR], 0.83; 95%CI, 0.72-0.97; $P = 0.016$) and PFS (HR, 0.85; 95%CI, 0.74-0.98; $P = 0.027$) when the expression was less than median. Additionally, in pts with no *HER2* amplification and *HER2* expression lower than median, treatment with Cet was associated with worse PFS compared to Bev (HR, 1.46; 95%CI, 1.12-1.90; $P = 0.005$). This effect was not observed with expression higher than median regardless of *HER2* amplification status. **Conclusions:** To our knowledge, this is the largest analysis of *HER2* amplification and gene expression in mCRC pts treated with standard therapy. Our results provide novel insight on the predictive and prognostic value of *HER2* gene expression in pts treated with Cet- and Bev-based regimens. Upon validation, these findings could inform pts selection and the design of more effective treatment options for pts with low *HER2* expression. Clinical trial information: NCT00265850. Research Sponsor: U10CA180821, U10CA180882; U10CA180888, UG1CA180830 (SWOG); BMS, Genentech, Pfizer, Sanofi; https://acknowledgments.alliancefound.org.

Novel methylated DNA markers in plasma detect distant recurrence of colorectal cancer.

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Background: Methylated DNA markers (MDMs) are broadly informative for early detection of colorectal cancer (CRC) but have not been extensively studied for post-treatment surveillance and disease monitoring. We aimed to assess the feasibility of novel CRC-associated MDMs for detection of distant recurrent CRC (rCRC) in plasma. **Methods:** A panel of 13 MDMs previously identified to be discriminant for primary CRC was selected. In a cross-sectional analysis of plasma samples, MDMs were assayed blindly (by target enrichment long-probe quantitative amplified signal assay) from 160 age/sex-balanced patients (60 healthy controls, 60 with resected CRC and no evidence of disease (NED), and 40 rCRC after primary tumor resection). Plasma-derived carcinoembryonic antigen (CEA) was measured on all patients. Random forest modeling was used to derive a prediction algorithm of MDMs (with and without CEA) for the endpoint of rCRC relative to healthy controls. The accuracy of the algorithm was summarized as sensitivity, specificity, and area under the receiver operating characteristic curve (AUC) with 95% confidence intervals (CI) in the test set. **Results:** Median patient age was 55 (interquartile range: 49-64) years. As shown in the Table below, a single MDM with the highest AUC was significantly better than CEA (p= 0.02). On cross validation, CEA provided no additional improvement to the performance of the panel of 13 MDMs (p= 0.2). The cross-validated panel of MDMs detected rCRC liver metastases with 96% (79-100%) sensitivity, lung metastases with 78% (40-97%) sensitivity, and peritoneal/nodal metastases with 57% (18-90%) sensitivity. Lesions with Response Evaluation Criteria in Solid Tumors sum $>$ 4 cm were detected with 94% (73-100%) sensitivity and $\leq$4 cm with 78% (52-94%) sensitivity. **Conclusions:** Novel MDMs in plasma detect rCRC with promising accuracy. The clinical utility of MDMs for non-invasive post-treatment surveillance and treatment monitoring in CRC warrants further evaluation in longitudinal studies with sufficient follow-up to exclude sub-clinical recurrence in those with NED. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology, Exact Sciences provides the LBgard (Biomatrica) blood tubes and provided the TELQAS assays at no cost.

Modeling	Marker	AUC (95% CI)	rCRC Sensitivity (95% CI)	NED Sensitivity (95% CI)	Healthy controls Specificity (95% CI)	*P*
No cross-validation	A single MDM	0.93 (0.87-1)	88% (73-96%)	13% (6-25%)	95% (86-99%)	0.02
	CEA (cutoff: 3 ng/ml)	0.79 (0.69-0.9)	65% (48-79%)	12% (5-23%)	87% (75-94%)	
2:1 cross-validation	13 MDM algorithm	0.96 (0.91-1)	85% (70-94%)	22% (12-34%)	95% (86-99%)	0.20
	13 MDM+CEA algorithm	0.96 (0.91-1)	85% (70-94%)	22% (12-34%)	95% (86-99%)	

4089 **Poster Session (Board #81), Fri, 8:00 AM-11:00 AM**

Consensus molecular subtypes (CMS) as a marker for treatment and disease biology in metastatic colorectal cancer (CRC).

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Background: Consensus molecular subtypes (CMS) categorize colorectal cancer (CRC) into groups based on gene transcription and are prognostic in early-stage and first-line metastatic settings. Their impact on treatment history is unknown. We hypothesized that the best prognosis CMS2 would have higher utilization of liver-directed therapies and maintenance chemotherapy over the worst prognosis CMS4. **Methods:** Primary surgical resection specimens were annotated for CMS on a translational protocol in a 5FU-refractory metastatic CRC population. Specimens that had neoadjuvant chemotherapy or radiation were excluded. CMS1, CMS3 and indeterminate CMS were also excluded. Liver-directed therapies were defined as any surgery, direct injection of cytotoxics or microspheres, radiation or radiofrequency ablation. Multiple occurrences of liver-directed therapies or maintenance chemotherapy in the same patient were recorded once for statistical tests of association. **Results:** CMS1 (7.4%), CMS3 (8.2%) and indeterminate calls (4.1%) accounted for 20% of all samples tested. There were 43 (44%) CMS2 and 55 (56%) CMS4 patients eligible. Age, stage at diagnosis, mismatch repair and RAS mutational status were similar in both groups. Left-sided tumors were more common in CMS2 (79%) than CMS4 (42%), $p = .001$. The median overall survival (OS) from stage IV diagnosis was 40 [34 - 51] versus (vs) 28 [21 – 33] months ($p < .0001$) for CMS2 vs CMS4 respectively. Liver-directed therapy was greater in CMS2 (53%) vs CMS4 (31%), $p = .024$. The number further increased when multiple treatments in a single patient were taken into account. Microsphere injection, radiation and liver surgery combined with RFA were the most skewed towards CMS2 over CMS4. No difference in median OS was seen from first liver-directed therapy in CMS2 vs CMS4 (29 vs 27 months, $p = .31$). There was a trend towards greater maintenance chemotherapy in CMS2 (47%) vs CMS4 (29%), $p = .076$. **Conclusions:** Better prognosis with CMS2 is consistent with other studies. Significantly increased liver-directed therapy was observed in CMS2. Selection criteria for liver-directed therapy such as slowly progressing, oligometastatic and hepatic-confined disease may be enriching for CMS2 and gives insight into the natural history of this subtype. Research Sponsor: U.S. National Institutes of Health.

4090 **Poster Session (Board #82), Fri, 8:00 AM-11:00 AM**

Treatment effects (TEs) of EGFR monoclonal antibodies (mAbs) in metastatic colorectal cancer (mCRC) patients (pts) with KRAS, NRAS, and BRAF mutation (MT) status: Individual patient data (IPD) meta-analysis of randomized trials from the ARCAD database.

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Background: EGFR mAbs have become incorporated into clinical practice for the management of mCRC over the last decade. KRAS and NRAS mutations are used as predictive biomarkers and BRAF V600E mutations are associated with an adverse prognosis. The observed TE within biomarker subpopulations has varied between studies. **Methods:** IPD from randomized trials with head-to-head comparison between EGFR mAb versus no EGFR mAb (chemotherapy alone or BSC) in mCRC, across all lines of therapy (first, second and later), were pooled. Biomarker subpopulations are defined in the table. Overall survival (OS) and progression-free survival (PFS) were compared between groups by Cox model, stratified by studies and adjusted by age, gender, and performance status. TEs were estimated by adjusted hazard ratio (HR_{adj}) and 95% confidence interval (CI). Within each biomarker subgroup, EGFR mAb efficacy was explored according to multiple exploratory factors, including line of therapy, type of backbone chemo, gender, sidedness and site of metastasis. Interaction tests were performed. P-values < 0.01 were considered statistically significant to account for multiple comparisons. **Results:** 5729 pts from 8 studies with data available for ≥ 1 biomarker were analysed. PFS benefits (median 9.2 mos in EGFR mAbs, 8.0 mos in no EGFR mAbs) were confirmed in triple-WT pts, but not for OS (refer to table). No OS/PFS benefits were observed for pts with any of the MT tumors. Exploratory analyses showed a potential detrimental TE of EGFR mAbs in KRAS MT mCRC with liver metastasis (OS: HR_{adj} 1.22, p = .003, $p_{interaction}$ .0056; PFS: HR_{adj} 1.24, p = .0009, $p_{interaction}$ .0008). These results were confirmed within the subgroup of pts with all 3 biomarkers available. **Conclusions:** This is the largest IPD analysis to explore the predictive value of RAS/BRAF biomarkers in mCRC. Our findings demonstrate that there is no evidence of efficacy of EGFR mAbs in KRAS, BRAF and/or NRAS MT mCRC. EGFR mAbs might have a detrimental effect in KRAS MT mCRC with liver metastases. Research Sponsor: National Health and Medical Research Council of Australia Project Grant.

		OS		PFS	
	N of trials (N of pts)	HR_{adj} (95% CI)	p	HR_{adj} (95% CI)	p
KRAS MT	8 (2397)	1.07 (.98, 1.16)	.13	1.05 (.96, 1.14)	.30
NRAS MT	3 (88)	1.35 (.81, 2.24)	.24	1.61 (.97, 2.65)	.062
BRAF MT	6 (232)	.94 (.70, 1.25)	.65	.90 (.67, 1.21)	.49
Triple WT	3 (1039)	.93 (.81, 1.07)	.30	.75 (.66, .85)	< .0001

4092 **Poster Session (Board #84), Fri, 8:00 AM-11:00 AM**

The development and validation of a novel targeted methylation sequencing technology detecting 0.003 percent tumor signal in early-stage cancer plasma.

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Background: Methylation analysis in cell-free DNA holds great potential for early cancer detection. In the plasma of early stage cancer patient, the tumor content is estimated to be less than 0.1%, therefore demands a highly sensitive assay. Targeted Methylation Sequencing (TMS) is the most promising approach; however, the current sensitivity and specificity are compromised by low efficiency and low recovery of target enrichment, and further hampered by background noise associated with large panels. The ideal solution would be an in-depth analysis using a focused small cancer-specific methylation biomarker panel, but is not supported by existing technologies. **Methods:** Here we present a new technology designed for TMS analysis in cfDNA: Point-n-Seq, featuring an enrichment of target molecules directly from cfDNA before bisulfite conversion and amplification. Particularly, this technology enables small focused panel that interrogates the methylation status of 1 to ~1000 markers. We designed a CRC panel covering 100 methylation markers in 3 steps: identify ~1000 CRC-specific markers from public databases; eliminate makers with high background signal in baseline cfDNA of healthy population; finalize the list with the most differentiating markers between patient and healthy cfDNA. **Results:** The capture of Point-n-Seq CRC panel is highly efficient resulting in high uniformity (94% $>$ 0.5X) and on-target rate ($>$ 80%). For 20 ng cfDNA input, more than 1000 deduped informative reads were obtained for each marker on average, despite the high GC content ($>$ 80%). The output of informative reads was linear to the cfDNA input ranging from 1 ng to 40 ng. In titration studies, 0.6 pg (0.2X genome equivalent) methylated DNA in 20 ng cfDNA (0.003%) was reliably detected over cfDNA background. Using plasma samples from patients with CRC - early stage (I, n = 7; II, n = 7), late stage (III, n = 11; IV, n = 3), and control individuals (n = 105), the average fractions of methylated signal are 0.0034%, 0.013%, 0.09%, 0.17%, 0.29% for control, stage I, II, III, IV accordingly. With a simple cut-off using methylation fraction, Point-n Seq CRC panel achieved a sensitivity of 86% for stage I, 100% for stage (II-IV) at a specificity of 91%, with AUC = 0.96. **Conclusions:** Point-n-Seq TMS is the first hybridization based NGS technology enables the small focused methylation panel (e.g. 100 markers) sequencing using cfDNA, and it will greatly facilitate the development of practical and cost-effective methylation assays for clinical use. Research Sponsor: Avida Biomed seed fund.

4093 **Poster Session (Board #85), Fri, 8:00 AM-11:00 AM**

Can FIT rule out colorectal cancer in symptomatic patients? Diagnostic test accuracy results from 9,822 patients in the NICE FIT study.

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Background: The faecal immunochemical test (FIT) is a non-invasive quantitative test that measures occult blood in faeces (faecal haemoglobin, FHb). FIT is already used worldwide in colorectal cancer (CRC) screening programmes. Bowel symptoms have low specificity for CRC; to diagnose one patient with CRC, a large number of symptomatic patients require investigation. A negative FIT test, when blood is not detected, could be used to rule out CRC in symptomatic patients without invasive investigations such as colonoscopy. We report on the largest diagnostic accuracy study to date of FIT in symptomatic patients. **Methods:** Patients were eligible for recruitment if they experienced bowel symptoms meeting national high-risk criteria and were triaged to investigation with colonoscopy. Patients were excluded from analysis if they did not provide a valid FIT or did not undergo complete colonoscopy. Colonoscopy results were compared to FIT measurements of FHb, and the conduct of the tests was double-blinded. Quality assurance of endoscopy and clinical data was performed by senior clinicians. External statisticians analysed anonymised data. **Results:** 9822 patients from 50 sites across England participated in the study between October 2017 to March 2019. The most common colonoscopy finding was absence of any colorectal disease (31%). The prevalence of CRC at colonoscopy was 3.3%. The sensitivity of FIT at FHb thresholds of 2, 10 and 150 μg/g significantly decreased from 97.0% to 90.9% and 70.8% respectively ($p < 0.01$). FIT positivity rate at these thresholds increased from 7.6%, to 19% and 37.2% respectively ($p < 0.01$). The positive predictive value of FIT for CRC at FHb thresholds of 2, 10 and 150 μg/g was 8.7%, 16.1% and 31.1% respectively and the negative predictive value of FIT at these thresholds was 99.8%, 99.6% and 98.9% respectively. **Conclusions:** The results of this study support the use of FIT at the threshold of detectable blood (2μg/g) as an initial CRC rule-out test to triage patients with high risk CRC symptoms, reducing the number of unnecessary investigations. This is the first study to report that at the lowest threshold of detectable blood, FIT sensitivity is equivalent to the current gold standard investigation of colonoscopy. Clinical trial information: ISRCTN49676259. Research Sponsor: RM Partners, the West London Cancer Alliance hosted by The Royal Marsden NHS Foundation Trust and sponsored by Croydon University Hospital NHS Trust. The study was also supported by the National Institute for Health Research.

4094 **Poster Session (Board #86), Fri, 8:00 AM-11:00 AM**

APC and TP53 as potential biomarkers for EGFR sensitivity in colorectal cancer.

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Background: The Consensus Molecular Subtypes (CMS) of colorectal cancer (CRC) have prognostic and predictive value in identifying patients that derive benefit from EGFR targeted therapies. The CMS2 cohort was specifically noted to predict response to cetuximab. Besides CMS classification, we recently reported a two-gene mutation signature of APC and TP53 (AP) that predicts potential response to cetuximab. In this study, we hypothesize AP mutations, in addition to CMS cohorts, predict cetuximab sensitivity. **Methods:** A prespecified and validated 203 gene expression signature score measuring cetuximab sensitivity (CTX S-score) was used as a surrogate for response to cetuximab sensitivity. A cohort of 458 patients with colorectal cancer was accrued between October 2006 and September 2011. The population classified into CMS cohorts, and CTX-S scores were determined across each of the cohorts based on AP mutation status. **Results:** Among 458 tumor samples sequenced, AP mutations were identified as significantly associated with higher CTX-S scores. Among the CMS 1-4 cohorts identified, AP mutations were noted in 13 of 77 (17%) patients in CMS1 cohort, 87 of 116 (75%) patients in CMS2 cohort, 15 of 64 (23%) patients in CMS3 cohort, 46 of 112 (41%) patients in CMS4 cohort, indicating that AP mutations are dominant in CMS2 cohort. Further CTX-S score comparisons across CMS cohorts based on AP status show that AP mutated tumors have higher CTX-S scores than non-AP mutated tumors—irrespective of the CMS cohorts ($p<0.05$ unpaired, two-tailed t tests). **Conclusions:** In our study, we noted CMS2 cohort has high predicted sensitivity to cetuximab. Across other CMS cohorts, AP mutations were associated with higher CTX-S scores compared to those with AP wild-type tumors, suggesting both CMS2 and AP mutations contribute to CTX sensitivity. Research Sponsor: U.S. National Institutes of Health.

4095 **Poster Session (Board #87), Fri, 8:00 AM-11:00 AM**

A population-based study of young-onset colorectal cancer patients: Effect of knowledge gaps among patients and providers on stage at diagnosis and quality of life.

Ronit Yarden, Kim Lynn Newcomer, Danielle Peterson, N2Young Advisory Board; Colorectal Cancer Alliance, Washington, DC

Background: Colorectal cancer (CRC) is one of the leading cause of cancer-related death in the US. Despite a decrease in overall incidence and mortality, there has been an alarming increase in CRC diagnosis among young adults (20-49 years old) and causes remain unknown. To explore the unique challenges and unmet needs of the young-adult patients many still establishing their life-long goals, the Colorectal Cancer Alliance launched a comprehensive survey for young-onset CRC patients and survivors via social media to track the self-reported pre-diagnosis awareness, path to diagnosis, and post-diagnosis quality of life experiences of this often overlooked group. **Methods:** A cross-sectional study, conducted in the form of an online survey, was launched via multiple channels of social media. The questionnaire was based on established instruments including PROMIS, EORTC-QOL-30, and EORTC-CR-29 and EORTC-SHC-22. **Results:** The survey was completed by 885 patients and survivors. The median age at diagnosis was 42 +/-7, significantly lower than the recommended screening age. Only 6% of respondents were diagnosed with Lynch syndrome although 29% reported some family history. Most respondents (63%) indicated they were not aware that CRC can affect people younger than 50, which may explain why the majority of patients waited more than 3 months and 23% waited over 12 months after noticing their symptoms to visit their doctor. The majority, 75%, of all patients visited 2+ doctors and 11% of those patients visited 10+ doctors before their doctor suspected colorectal cancer. A significant number of patients felt their doctors were dismissive of their symptoms. 77% of patients were diagnosed with advanced disease and were subjected to aggressive therapies that substantially affected their quality of life including neuropathy, anxiety, clinical depression, sexual morbidity, unemployment, and financial toxicity. Many young patients indicated that their doctors did not inform them about fertility preservation. **Conclusions:** Our survey indicates that medical professionals and young adults need to be aware of the increasing incidence of young-onset CRC, and the importance of timely screening when signs and symptoms are present, regardless of age. Research Sponsor: Colorectal Cancer Alliance.

4096 **Poster Session (Board #88), Fri, 8:00 AM-11:00 AM**

Adjunctive local therapy in metastatic colorectal cancer in an unselected cohort: Improved patient-survival in comparison to systemic therapies.

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Background: Patients with distant metastases in colorectal cancer have a poor prognosis and a low overall survival (OS). In addition to systemic treatments and irradiation, the tumor burden can be reduced by loco-regional therapeutics, including microwave ablation (MWA), radiofrequency therapy (RFA) and trans-arterial chemoembolization (TACE) available. To evaluate the benefit of such local therapies, we compared OS of a single-centre study population to a reference population of patients who underwent no loco-regional treatment within the German Tumor Registry Colorectal Cancer (TKK). **Methods:** The study population consists of a cohort of 51 patients (n = 51) treated loco-regionally in addition to systemic therapy. The patients were recruited in a single cancer centre in Mülheim, Germany during the years 2006 to 2015. A reference population of 788 patients was chosen from a prospective, longitudinal registry of the TKK. Time to event data analysis included the estimation of Kaplan-Meier cumulative survival probabilities and hazard ratios (HR) with corresponding 95% confidence intervals (95% CI) from Cox proportional hazards regression. **Results:** The median OS was 31.3 months (95% CI 26.8 - 41.6) in the study population, as compared to the reference population, where it was 21.9 months (95% CI 20.1 – 24.6). Patients with liver and lung metastases in the study population had an OS of 41.6 months (95% CI 30.5 – 78.2), the corresponding patients from the reference population 21.7 months (95% CI 16.7 – 24.6). Furthermore, patients in the reference group had a 1.79-fold death-rate, as compared to patients treated with additional loco-regional therapy (HR = 2.02; 95% CI: 1.29-3.16). **Conclusions:** Additional treatment with loco-regional therapies of distant metastases in patients with metastatic colorectal cancer appears to be associated with improved OS by nearly 10 months compared to systemic treatments only. Research Sponsor: None.

Overall survival	Liver metastases only	Liver and lung metastases only	Total
Study population	N = 20	N = 23	N = 51
Events, n (%)	12 (60.0%)	14 (60.9%)	32 (62.7%)
Censored, n (%)	8 (40.0%)	9 (39.1%)	19 (37.3%)
Median OS (months)	26.9	41.6	31.3
95% Confidence interval	19.2 - 33.4	30.5 - 78.2	26.8 – 41.6
Reference population	N = 583	N = 168	N = 788
Events, n (%)	298 (51.1%)	96 (57.1%)	416 (52.8%)
Censored, n (%)	285 (48.9%)	72 (42.9%)	372 (47.2%)
Median OS (months)	23.0	21.7	21.9
95% Confidence interval	20.4 - 26.2	16.7 - 24.6	20.1 – 24.6

4097 **Poster Session (Board #89), Fri, 8:00 AM-11:00 AM**

Phase II trial of adjuvant mFOLFOX6 after metastasectomy for pulmonary metastasis of colorectal cancer: WJOG5810G.

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Background: Resection of pulmonary metastasis (PM) is widely accepted to improve the prognosis in selected patients (pts) with metastatic colorectal cancer (CRC). However, the clinical implication of adjuvant chemotherapy after metastasectomy of PM is unknown. We conducted a multi-center phase 2 trial of adjuvant chemotherapy with mFOLFOX6 after metastasectomy of PM-CRC. **Methods:** Main eligibility criteria were first curative metastasectomy of 4 or less PMs and no prior chemotherapy except for adjuvant chemotherapy with fluoropyrimidine monotherapy after curative resection of primary or extrathoracic CRC metastasis. The study treatment was 12 courses of mFOLFOX6 (oxaliplatin 85 mg/m^2, l-leucovorin 200 mg/m^2, 5-fluorouracil 400 mg/m^2 bolus followed by 2400 mg/m^2 continuous infusion, every 2 w). The primary endpoint was overall survival (OS). The secondary endpoints included disease-free survival (DFS), adverse events (AEs), and recurrence sites. The sample size was determined to be 93 expecting 5-year OS rate of 50% with threshold 35% (90% power, alpha error 5%). **Results:** Fifty-two pts from 34 institutions were enrolled between July 2011 and July 2014. Patient enrollment was closed prematurely because of slow accrual. Four patients were ineligible after enrollment and the safety and efficacy cohort comprised 52 and 48 patients, respectively. Patient backgrounds were as follows: gender (male/female) 31/21, median age (range) 63 (42-75) years, ECOG PS (0/1) 48/4, primary site (colon/rectum) 18/34, number of PM (1/2/3/4) 36/9/5/2, synchronous/metachronous PM 11/41, and unilateral/bilateral PM 40/12. With the median follow-up time of 6.0 (1.8-7.7) years, 5-year OS rate was 86% (95% CI: 72-93) and 5-year DFS rate was 59% (95% CI: 43-71). Tumors recurred in 19 patients (13 lung, 3 liver and 7 others). Total 41 pts (79%) completed 12 courses of mFOLFOX6 (reasons for discontinuation: AEs in 3, refusal due to AEs in 8). AEs ($>$ Grade 3) were neutropenia 50%, fatigue 8%, peripheral sensory neuropathy 8%, appetite loss 4%, diarrhea 4%, febrile neutropenia 2% and allergic reaction 2%. There was no treatment related death. **Conclusions:** Adjuvant mFOLFOX6 is feasible and may be effective after metastasectomy for PM-CRC, considering much better OS than we had expected. Clinical trial information: UMIN000005693. Research Sponsor: None.

4098 **Poster Session (Board #90), Fri, 8:00 AM-11:00 AM**

Is there a benefit of oxaliplatin in neoadjuvant treatment of locally advanced rectal cancer? An updated meta-analysis.

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Background: Neoadjuvant fluoropyrimidine (5FU or capecitabine)-based chemoradiotherapy (CRT) has been considered the standard of care for locally advanced rectal cancer (LARC). Whether addition of oxaliplatin (OXP) will further improve clinical outcomes is still unclear. **Methods:** To identify clinical trials combining oxaliplatin in preoperative CRT or perioperative chemotherapy for LARC published until December 2019, we searched PubMed, the Cochrane Library. We also search for relevant ASCO conferences. Primary endpoint was Disease-Free-Survival (DFS). Data were extracted from every study to perform a meta-analysis using Review Manager (version 5.3). **Results:** A total of 7 Randomized Clinical Trials (ACCORD-12, CARO-AIO-04, FOWARC, JIAO, NSABP, PETACC-6 and STAR-01) with 5782 stage II or III rectal cancer patients were analysed, including 2727 patients with OXP + 5FU regimen and 3055 patients with 5FU alone regimen. Compared with 5FU-based regimen group, OXP-based regimen group improved DFS (HR = 0.90, 95% CI: 0.81−0.99, P = 0.03) and increased pathologic Complete Response (OR = 1.21, 95% CI: 1.07−1.37, P = 0.002). Patients treated with OXP-regimen had significantly less metastatic disease (OR = 0.79; 95% CI, 0.67 to 0.94; p = 0.007). Considering Adverse Events (AEs), there was more grade 3-4 diarrhoea with OXP (OR = 2.41, 95% CI: 1.74−3.32, P < 0.00001). However, there were no significant differences grade 3-4 haematologic AEs (OR = 1.16, 95% CI: 0.87−1.57, P = 0.31). **Conclusions:** Combining oxaliplatin with capecitabine or 5FU in preoperative chemoradiotherapy or perioperative chemotherapy seems beneficial significantly and improved DFS. It remains necessary to identify which patients benefit most from the addition of oxaliplatin. Research Sponsor: None.

4099 **Poster Session (Board #91), Fri, 8:00 AM-11:00 AM**

Clinicopathological and molecular biological characteristics of early-onset stage II/III colorectal adenocarcinoma: An analysis of 25 studies with 47,184 patients (pts) in the adjuvant colon cancer end points (ACCENT) database.

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Background: Colorectal cancer (CRC) incidence and mortality has decreased since the 1970s but the incidence is increasing in young adults (age 20-49). The incidence of early onset CRC (eoCRC) will keep increasing significantly based on the trends of the SEER CRC registry data. There is limited data suggesting eoCRC may have different behaviors compared to traditional CRC (tCRC, age $\geq$ 50). **Methods:** Individual pt data of 47184 stage II/III CRC pts from 25 randomized studies in the ACCENT database were pooled. The distributions of demographics, clinicopathological features, biomarker status, and treatment-related data were summarized by age group. Overall survival (OS), disease-free survival (DFS), recurrence-free rate (RFR), and survival after recurrence (SAR) were assessed by Kaplan-Meier curves and Cox models stratified by treatment arms within studies, adjusting for stage, performance status (PS), BMI and grade. **Results:** Using 5% difference between age groups as clinically meaningful cutoff, eoCRC had similar gender, race, ethnicity, PS, risk group, disease sidedness and T stage as tCRC. eoCRC were less likely overweight (30 vs 36%) and more pts had $\geq$ 12 lymph nodes resected (63 vs 51%). eoCRC had more frequent dMMR status (18 vs 12%), less BRAF mutations (5 vs 13%), and more dMMR/BRAF wild type (WT) status (17 vs 7%). Overall, eoCRC had better OS, DFS, and SAR, with the most significant differences between the $<$ 30 and $>$ = 70 age groups. Similar results were observed within pMMR pts. eoCRC experienced less hematological side effects, diarrhea, and stomatitis, but had more nausea and/or vomiting. **Conclusions:** eoCRC have unique characteristics; although statistically significant, the clinical differences in outcomes between eoCRC and tCRC are potentially due to the difference seen in extremely young and old pts. eoCRC have a different adverse events panel compared to tCRC. Research Sponsor: U.S. National Institutes of Health.

	eoCRC	tCRC	Adjusted Hazard Ratio	95% Confidence Interval
Overall				
n	8242	38942		
5-y OS,%	78.9	74.4	0.75	0.69-0.82**
5-y DFS, %	68.9	65.2	0.87	0.81-0.93**
5-y RFR, %	70.2	68.8	0.94	0.88-1.01
median SAR, mos	25.2	21.6	0.81	0.74-0.89**
pMMR				
n	2121	9710		
5-y OS,%	81.3	78.8	0.76	0.66-0.88**
5-y DFS, %	70.8	67.9	0.86	0.76-0.97*
5-y RFR, %	72.2	70.8	0.95	0.83-1.07
median SAR, mos	30.0	25.2	0.87	0.75-1.02
dMMR				
n	471	1364		
5-y OS,%	86.7	80.7	0.62	0.41-0.93*
5-y DFS, %	80.0	75.9	0.74	0.53-1.04
5-y RFR, %	81.2	80.6	0.86	0.60-1.23
median SAR, mos	27.6	15.6	0.78	0.48-1.28

4100 **Poster Session (Board #92), Fri, 8:00 AM-11:00 AM**

Short-term results of VOLTAGE-A: Nivolumab monotherapy and subsequent radical surgery following preoperative chemoradiotherapy in patients with microsatellite stable and microsatellite instability-high locally advanced rectal cancer.

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Background: Chemoradiotherapy (CRT) followed by radical surgery (S) is standard therapy for patients (pts) with locally advanced rectal cancer (LARC). Sequential use of an anti-PD-1 antibody after radiation demonstrates synergistic effects in *in vivo* models, and an anti-PD-1 antibody is effective in pts with microsatellite instability-high (MSI-H) metastatic colorectal cancer (mCRC). We studied nivolumab (nivo) and radical S following CRT (50.4 Gy with capecitabine 1,650 mg/m^2) in T_{3-4} $N_{any}M_0$ LARC. **Methods:** After the quality-assured CRT, 240 mg q2 weeks x 5 cycles of nivo and radical S were investigated. In cohort A-1, for pts with microsatellite stable (MSS) LARC, the primary endpoint was a centrally confirmed pathological complete response (pCR) rate using AJCC tumor regression grading. The estimated required sample size assuming null and alternative hypotheses pCR = 10% and 30% was 37 pts, with a 1-sided alpha of 5% and power of 90%. In Cohort A-2, 5 pts with MSI-H LARC were included in an exploratory manner. **Results:** From Jan/2017 to Oct/2019, a targeted number of pts was included and assessed. In cohort A-1, 30% (11/37; 90% CI 18-44%) of pCR (AJCC grade (gr) 0) rate and 38% (14/37) of major pathological response (MPR) (AJCC gr 0+1) rate were observed. Clinical CR was observed in one additional pt (3%) refusing S after nivo. In cohort A-2, 60% (3/5) of pCR rate and 60% (3/5) of MPR rate were observed. As of Jan/2020, only 2 pts (1 local and 1 metastatic) in cohort A-1 and none in cohort A-2 recurred. Immune-related severe adverse events were observed in 3 pts (gr 3 myasthenia, gr 3 interstitial nephritis, and gr 2 peripheral motor neuropathy); all fully recovered and received radical S. During the follow-up period, one additional pt with gr 2 colitis was observed. No treatment-related deaths were observed. **Conclusions:** Promising pCR rates of 30% and 60%, with mild toxicities, were shown in MSS and MSI-H LARC pts treated with nivo plus radical S after CRT, suggesting the candidate therapy for the future non-surgical approach. Clinical trial information: NCT02948348. Research Sponsor: ONO Pharmaceutical.

4101 Poster Session (Board #93), Fri, 8:00 AM-11:00 AM

ARISTOTLE: A phase III trial comparing concurrent capecitabine with capecitabine and irinotecan (Ir) chemoradiation as preoperative treatment for MRI-defined locally advanced rectal cancer (LARC).

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Background: Phase II studies reported high pathological complete response (pCR) rates and acceptable toxicity using irinotecan and fluoropyrimidine chemoradiation in LARC (ISRCTN:09351447). **Methods:** This phase III, multicentre, open-label trial funded by Cancer Research UK, randomly assigned (1:1) patients with MRI defined LARC threatening or involving resection margins without metastases, to pre-operative radiotherapy (RT) 45Gy/25 fractions combined with either capecitabine 900mg/m^2(CRT) or 650 mg/m2 bd weekdays with Irinotecan iv once-weekly 60mg/m2 weeks 1-4 (IrCRT). The primary endpoint is disease-free survival (DFS). Secondary endpoints include treatment compliance, safety and pCR. **Results:** 75 UK sites randomised 564 eligible patients from Oct/11 to July/18; 284 to CRT and 280 to IrCRT. 370 (66%) male; median age 61 years (range:29-83). Staging in both arms was similar: mrT3 (432/564(77%), mrT4 (89/564(16%); mrCRM involved (275/564(49%); threatened $\leq$1mm (215/564(38%). Compared with CRT, IrCRT patients were less likely to receive 45Gy RT (207/276(75%) vs 251/283(89%), $p < 0.001$) or receive $\geq$90% capecitabine dose in 188/276(68%) vs 253/283(89.4%)$p < 0.001$). A total of 204/276(74%) received $\geq$90% irinotecan dose. The grade 3-4 gastrointestinal adverse event rate was 21%(58/276) with IrCRT and 12%(34/283) with CRT ($p = 0.004$). Patients receiving IrCRT had significantly more diarrhoea 38/276(13.8%) vs 10/283(3.5%)$p < 0.001$) and neutropenia 27/276(9.8%) vs 3/283 (1.1%) $p < 0.001$). Two CRT and three IrCRT patients experienced a treatment related death. 237/276(86%) IrCRT and 241/283(85%) CRT patients had surgery. The median time from end of RT to surgery(10.6 weeks), the surgical procedure APE 262/478(55%), AR 189/478(40%), Hartmann's 10/478(2%); and the surgical complications(any event) 38%(181/478) were similar in both arms. The pCR rate is available in $>$ 95% patients and is 20.2%(46/228) for IrCRTvs.17.4%(40/230) for CRT ($p = 0.45$), A $>$ 84% CRM-ve resection rate is similar in both arms. **Conclusions:** For patients with MRI defined high risk LARC low rates of CRM involvement were observed in both arms reflecting high quality multidisciplinary care. The addition of irinotecan did not significantly improve the pCR rate, was associated with a decrease in the RT and capecitabine compliance and a higher rate of adverse events. Surgical procedure or complications were unaffected. Longer follow-up is required to assess DFS and translational data. Clinical trial information: 09351447. Research Sponsor: Cancer Research UK.

4102 **Poster Session (Board #94), Fri, 8:00 AM-11:00 AM**

Randomized phase II trial of modified (m) FOLFOX6 induction chemotherapy with or without aflibercept before standard chemoradiotherapy (CRT) and total mesorectal excision (TME) in patients with high-risk rectal adenocarcinoma (HRRC): Final results of the GEMCAD 1402, and by molecular subtypes.

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Background: Neoadjuvant chemotherapy (CT) followed by CRT and TME is a treatment option for clinically staged HRRC. The goal of the GEMCAD 1402 trial was to evaluate the benefit of adding an antiangiogenic drug to the neoadjuvant CT. The analysis of primary endpoint showed a better response rate in the experimental arm (Fernandez-Martos et al. Jama Oncol 2019). Here we present 3-year disease-free survival (DFS) and a retrospective analysis of consensus molecular subtypes by Immunohistochemistry (CMSs-IHQ). **Methods:** Patients (p) with middle or distal third, mrT3/T4/N2 rectal adenocarcinoma were randomly assigned (2:1), to mFOLFOX6 with (arm 1, n=115) or without Aflibercept (arm 2, n=65) prior to CRT (capecitabine with 50.4 Gy in 28 fractions) and TME. Tissue microarrays from 90 (58 arm1, 32 arm 2) p were stained for nine markers (CDX2, FRMD6, HTR2B, ZEB1, KER, MSH2, MSH6, PMS2 and MLH1) by IHQ using both semiquantitative and quantitative approaches. Cases were classified as CMS1-IHQ1, CMS-IHQ2/3 or CMS-IHQ 4 (immune, epithelial or mesenchymal subtypes). **Results:** In the intention-to-treat population after a median follow-up time of 38 months, 29 p (25%) in arm 1 had a DFS-related event, as compared with 14 p (21%) in arm 2 (HR 1.2063, 95% confidence interval 0.6374 to 2.2829, P=0.5644. The rate of DFS at three years was 75.2% (95% confidence interval, 66.1% to 82.2%) in arm 1 and 81.5% (95% confidence interval, 69.8% to 89.1%) in arm 2 (P=0.5638 by the exact stratified log-rank test). Overall 0/80/10 p were classified as CMS-IHQ1, CMS-IHQ2/3 or CMS-IHQ4 respectively. The pathological complete response (pCR) rate (ypT0N0) was achieved in 27.5% and 0% in epithelial and mesenchymal subtypes respectively. A trend towards worse survival for the mesenchymal subtype was observed. **Conclusions:** Adding aflibercept to induction mFOLFOX6 is not associated with an improvement in DFS. Our findings suggest that CMSs-IHQ subtypes could be predictive for pCR with this treatment strategy. Clinical trial information: NCT02340949. Research Sponsor: SANOFI.

4103 **Poster Session (Board #95), Fri, 8:00 AM-11:00 AM**

Utilization of adjuvant chemotherapy in "ideal candidates" with stage III colon cancer.

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Background: Prior studies have observed under-utilization of adjuvant chemotherapy (ACT) in stage III colon cancer. Our aims were to observe the rate of utilization of ACT in very healthy or "ideal candidates", identify reasons for omission and socioeconomic factors associated with ACT use, and observe patient outcomes. **Methods:** We queried patients from the National Cancer Database (NCDB) with stage III colon cancer, age<65, and Charlson-Deyo score of 0 who underwent resection in the United States between 2004-2015. Patients who received ACT were compared to patients who had surgery only (SO). We used chi-square test for categorical variables, Kaplan-Meier and Cox regression method for survival analyses. **Results:** Out of 243,388 stage III colon cancer patients during the study time, a total of 49,046 patients met the specific criteria of "ideal candidate". Out of these, 88.5% received ACT and 11.5% underwent SO. The primary reason for chemotherapy omission was: no reason given (54.2%), patient/guardian refusal (26.7%), physician recommended against (9.3%), patient died (3%), unknown (6.7%). Patients who received ACT were more likely to be female, non-Hispanic white, have a higher level of education, travel shorter distance for cancer treatment, have private insurance or higher income as compared to counterpart (*all p<.001).* Patients who received ACT had significantly better overall survival (5-year survival rate 74% vs. 54%, *p<.001*). This persisted after multivariable Cox regression analysis [HR:0.48 (CI:0.45-0.50), *p<.001]*. **Conclusions:** We observed a high rate of utilization (88.5%) of ACT in patients with stage III colon cancer who were under age 65 and without comorbidities. However, the omission of chemotherapy in this population remains a problem, partially due to patient refusal. Socioeconomic factors associated with lower utilization were primarily related to insurance status (private vs non-private). Patients who received ACT had significantly improved survival as compared to SO group. Research Sponsor: None.

Rate of utilization of adjuvant chemotherapy in "ideal candidates" from 2004-2015.

Characteristics	Adjuvant Chemotherapy	Surgery Only	p value
Total Population	43,382 (88.5%)	5,664 (11.5%)	
Private Insurance	32,426 (90%)	3,280 (9.2%)	*<0.001*
Medicaid/Uninsured	6,868 (83%)	1,371(17%)	*<0.001*
Distance > 50 miles	3,094 (84%)	605 (16%)	<0.001
Income<$40,227	8,230 (86%)	1,336 (14%)	*<0.001*
5-year survival rate %	74	54	*<0.001*

4104 **Poster Session (Board #96), Fri, 8:00 AM-11:00 AM**

Pharmacokinetically-guided preoperative FOLFOX chemotherapy for locally advanced colon cancer patients.

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Background: Preliminary results from ongoing randomised trials suggest that neoadjuvant chemotherapy (NAC) may be an alternative approach to conventional adjuvant therapy. We assessed the feasibility and activity of incorporating a pharmacokinetically (PK) guided dose adjustment of 5-FU within preoperative Folfox. **Methods:** Radiologically staged LACC pts, T4 or T3 with extramural depth >5mm beyond the muscularis propia, were planned to receive 4-6 biweekly cycles of Oxalipatin (85mg/m^2), Leucovorin (400 mg/m^2), bolus 5-FU (400 mg/m2) and infusional 5-FU (initial dose of 2400mg/m^2 in 46h and subsequent cycles tailored according to PK monitoring in order to reach a target 5-FU area under the curve (AUC) between 20-30 mg•h•L-1). Dihidrouracil deshidrogenase was determined before the first cycle in order to detect pts with 5-Fu intolerance. Three serum samples were obtained during the 5-Fu infusion in the first two cycles. Pathological tumor regression was graded according to the MSKCC classification and toxicity to the NCI-CTCAE 4.0. **Results:** From June 2012 to August 2017, 45 pts (M/F: 35/10; median age 63) with LACC (T3: 66.7%; T4: 31.1%; T2: 2.2%; N+:66.6%) were evaluated. Median dose of 5-FU was 4500 mg. 48.9% of the pts required a 5-FU dose increase to reach the target AUC. Side effects profile included G3 neutropenia (3 pts), G2 diarrhea (2 pts) and G2 asthenia (9 pts). NAC was discontinued in 3 pts due to small bowell obstruction requiring surgery (no progressive disease during NAC). R0 resection rate was 100% (93.3% laparoscopy-assited). MSKCC score included grades 4, 3+ and 3 in 11.1%, 26.7% and 28.9% of pts, respectively. A complete pathological response was found in 5 pts (11.1%). Median number of harvested nodes was 16 (7-51), 80% ypN0. Those pts with AUC 25-30 had a 3-fold higher likelihood of achieving a MSKCC 3, 3+ and 4 responses. Median time to hospital discharge was 7 days (range 4-22). After a median follow-up of 60 months (44-66), 5-year actuarial PFS is 88.8%. **Conclusions:** Preoperative PK-adjusted FOLFOX in LACC pts is safe and well tolerated, achieving remarkable rates of major pathological responses and R0 resections. Research Sponsor: None.

4105 **Poster Session (Board #97), Fri, 8:00 AM-11:00 AM**

Immunoscore as a parameter predicting time to recurrence and disease-free survival in T4N0 stage II colon cancer patients.

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Background: Risk assessment is particularly important to decide when to propose an adjuvant treatment for Stage II Colon Cancer (CC) patients. However, the current tumor risk features are imperfect and additional risk factors are needed to guide treatment decisions. The consensus Immunoscore is an alternative and powerful approach that could be used in the T4N0 Stage II colon cancer population. Immunoscore is an *in vitro diagnostic* test that predicts the risk of relapse in patients with CC by measuring the host immune response at the tumor site. **Methods:** From the international Immunoscore consortium study (n = 2681) (Pagès et al. *The Lancet* 2018), a subgroup analysis was performed on T4N0 Stage II colon cancer patients (n = 208). **Results:** In stage II T4N0, Int+Hi Immunoscore represented 65.4% of the population and low-Immunoscore only 34.6%. T4N0 patients with Int+Hi Immunoscore presented a significantly prolonged survival for TTR compared to low Immunoscore patients (5 years recurrence rate Int+Hi: 84.6% (78.3-91.5), Lo: 46.3% (35.1-61); unadjusted HR [Int+Hi *vs* Lo] = 0.21; (95% CI 0.11-0.4); $P< 0.0001$), representing a restricted mean survival time (RMST) difference of 80.9 months (95% CI 51.1-110.6) ($P< 0.0001$). The DFS was significantly different between Int+Hi and Low Immunoscore (5 years recurrence rate Int+Hi: 70.5% (95% CI 62.7-79.1), Lo: 38.5% (95% CI 28.2-52.5); unadjusted HR [Int+Hi *vs* Lo] = 0.31; (95% CI 0.19-0.49); $P< 0.0001$). Using restricted mean survival time (RMST) a significant ($P< 0.0001$) difference of 60.4 months (95% CI 32.6-88.1) was observed between the 2 groups Importantly, Cox multivariate analysis in Stage II T4N0 colon cancer patients, revealed that Immunoscore was the only remaining significant parameter (HR [Int+Hi *vs* Lo] = 0.15; (95% CI 0.05-0.46); $P= 0.0009$). In contrast, all other parameters, gender, sidedness, mucinous, grade, T-stage, VELIPI, MSI were not significant in multivariate analysis. Finally, Immunoscore showed the highest relative contribution to predict relapse (76.2% chi2 relative contribution), stronger than all the other parameters, MSI (16.1%), Grade (5%), sidedness (2%), gender (2%), VELIPI (1%). **Conclusions:** Immunoscore is the most powerful parameter to predict the risk in T4N0 population, and could be a good tool for adjuvant treatment decision in Stage II patients. Research Sponsor: French National Institute of Health and Medical Research, the LabEx Immuno-oncology, the Transcan ERAnet Immunoscore European project, Association pour la Recherche contre le Cancer, CARPEM, AP-HP, Institut National du Cancer, Italian Association for Canc.

4106 **Poster Session (Board #98), Fri, 8:00 AM-11:00 AM**

Impact of antibiotics (ATB) on the recurrence of resected colorectal cancer (CRC): Results of EVADER-1 a nation-wide pharmacoepidemiologic study.

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Background: Recent studies suggest that ATB increase the overall risk of CRC incidence through disruption of gut microbiota. Impact of ATB on the risk of CRC recurrence after curative resection remains unknown. **Methods:** Using the French nation-wide *Institut National du Cancer* (INCa – Système National des Données de Santé) database of cancer patients, all newly diagnozed localized CRC patients resected between 01/2012 and 12/2014 were involved. The perioperative ATB intake (6 month before until 1 year after surgery) was classified according to the spectrum, doses and period of use. The primary endpoint was 3-year Disease-Free Survival (3-DFS), stratified on chemotherapy (chemo) administration (yes/no), and assessed using multivariate Cox models. **Results:** Out of 219,884 CRC patients, the present study included 36,640 patients: male 53%, age≥75 years 39%, left colon/rectal 59%, exposure to chemo 44%, at least one ATB intake 74%. At 3-years, 29% of patients had recurred and 18% had died. In multivariate analysis, in patients not receiving chemo, ATB intake as an out-patient was significantly associated with better 3-DFS [HR (one ATB only) = 0.88 (0.82-0.94)]. This effect remained in the same range whatever the number of ATB or cumulative exposure to ATB. In patients receiving chemo, ATB intake as an out-patient had a significant detrimental effect on 3-DFS [HR (one ATB only) = 1.15 (1.08-1.23)], increasing with the number of ATB [HR (≥5 ATB) = 1.54 (1.39-1.71)] and longer exposure [HR (> 30 days) = 1.39 (1.31-1.48)]. Penicillin A, quinolones and ATB combinations were associated with worse 3-DFS. The timing of ATB intake related to chemo revealed that the strongest deleterious effect was observed when ATB were taken during chemo [HR = 1.64 (1.53-1.75)]. No difference in the mean number of chemo cycle was observed comparing patients receiving ATB or not. **Conclusions:** This nation-wide study is the first to suggest that ATB modulate 3-DFS in resected CRC with a differential impact according to chemo exposure. Importantly, ATB intake with chemo is detrimental in a dose- and time-dependent manner suggesting that dysbiosis of gut microbiota during adjuvant chemo might increase risk of recurrence. Research Sponsor: None.

4107 **Poster Session (Board #99), Fri, 8:00 AM-11:00 AM**

Total mesorectal excision compared to local excision in locally advanced rectal cancer achieving complete pathological response with neoadjuvant therapy: A National Cancer Database Analysis.

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Background: Total mesorectal excision (TME) is the standard surgical intervention for patients with locally advanced rectal cancer (LARC) regardless of response to neoadjuvant therapy. In this study, we perform a comprehensive review of the National Cancer Database (NCDP) to compare the clinical and surgical outcomes of TME to local excision (LE) in patients with LARC. **Methods:** NCDP was systematically researched to abstract all patients with stage II and III rectal adenocarcinoma between the years 2004 and 2015. We subsequently excluded all the patients who did not achieve complete pathological response (pT_0) after neoadjuvant therapy. The patients were then divided into two groups; those who underwent TME and those who underwent LE. Data were analyzed using SPSS v. 26.0, SAS v. 9.4. **Results:** A total of 4,705 were included in the study; 4,589 in the TME group and 116 in the LE group. Baseline characteristics were similar between the groups except for age. A total of 81(1.8%) of patients in the TME group and 8(6.9%) of patients in the LE group did not receive radiation (p=0.006) and 19(0.4%) of patients the TME group and 4(3.4%) of patients in the LE group did not receive chemotherapy. There was no difference in median overall survival between TME and LE groups. The median length of hospital stay was remarkably shorter in the LE group compared to the TME group (1 day vs 6 days, $p<0.0001$). The rate of 30-day and 90-day postoperative mortality were similar between the two groups (p-value=0.334 and 0.06, respectively). In the LE group, 4 (3.4%) of patients were readmitted within 30 days of the resection compared to 374 (8.5%) in the TME group but was not a statistically significant difference (p=0.059). **Conclusions:** In this study, TME and LE had similar overall survival and time to 25% mortality in patients with LARC who achieved complete pathological response after neoadjuvant therapy. Also, LE had a shorter hospital stay compared to the TME group. This study is limited by its retrospective nature, however these interesting observations warrant further investigation in randomized clinical trials. Research Sponsor: None.

	Local excision (N=116)	TME	P
Age (years)	64.6	59.7	0.00
Sex			0.92
Male	70 (60.3%)	2788(60.8%)	
Female	46 (39.7%)	1801 (39.2%)	
Race			
White	103 (88.8%)	3944 (85.9%)	0.397
Black	9 (7.8%)	342 (7.5%)	
Other	4 (3.4%)	303 (6.6%)	
Readmission within 30 days of surgical discharge	4/115 (3.5%)	376(8.4%)	0.059
90 day mortality after surgery	1 (0.9%)	44 (1.%)	0.06
Median duration of surgical admission	1 days	6.0 days	<0.001

4108 **Poster Session (Board #100), Fri, 8:00 AM-11:00 AM**

Tumor-informed assessment of molecular residual disease and its incorporation into practice for patients with early and advanced-stage colorectal cancer (CRC-MRD Consortia).

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Background: Circulating tumor DNA (ctDNA) testing can be used for the assessment of molecular residual disease (MRD) in patients with early-stage or advanced colorectal cancer (CRC). Prospective evaluation of this methodology in clinical practice has been limited to-date. **Methods:** A personalized and tumor-informed multiplex PCR assay (Signatera 16-plex bespoke mPCR NGS assay) was used for the detection and quantification of ctDNA for MRD assessment. We analyze and present results from an ongoing early adopter program of ctDNA testing across the spectrum of CRC management. **Results:** Here we present a total of 250 patients with colon (n=200), rectal (n=40), and other lower gastrointestinal cancers (n =10; anal, appendiceal, small bowel). MRD positivity rates and ctDNA quantification (mean tumor molecules/mL) are shown in Table. ctDNA detection was significantly associated with stage of disease ($p<0.0001$ Chi-square: 70.33). Additionally, in patients with radiologically measurable active metastatic disease, ctDNA detection rate was 100%. On the contrary, patients with advanced/metastatic disease who had partial response to treatment or no evidence of disease (NED) showed 28.5% and 19.2% of ctDNA-positivity, respectively. **Conclusions:** This is the first large, real-world study reporting on the results from a clinically validated MRD assay. For the first time we delineate MRD rates and quantify ctDNA concentration in patients with early-stage and advanced CRC. Furthermore, we provide an initial readout that effective ongoing treatment in patients with CRC may be correlated with ctDNA clearance. Ongoing analysis expanded to a cohort of 1200 clinical cases including correlation with genomic and serial testing will be presented. Research Sponsor: Natera, Inc.

MRD rates and quantity of ctDNA detected in patients with early-stage and advanced CRC.

Stages	MRD rates	Quantity of ctDNA (MTM/ml)
Stage I (T1-2N0)	0/6 (0%)	Mean: 41.91.8 Median: 0.63 Range: 0.11-673.01
Stage II (T3N0)	2/28 (7.1%)	
Stage II (T4N0)	2/6 (33%)	
Stage III, low-risk (T1-3N1)	2/18 (11%)	
Stage III, high-risk (T4, N1-2, T Any, N2)	7/19 (37%)	
Stage IV (Oligo-metastatic S/P resection/ ablation MRD setting)	14/31 (45.2%)	
Stage IV (Metastatic)*	22/49 (44.9%)	Mean 1858 Median: 2.95 Range: 0.17 – 27,077

* Breakdown of ctDNA-positivity by clinical scenario is described in results

4109 **Poster Session (Board #101), Fri, 8:00 AM-11:00 AM**

Inpatient mortality, healthcare resource utilization, and complications of elective laparoscopic versus open colectomy in colon cancer patients: A nationwide inpatient sample analysis.

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Background: Laparoscopic colectomy (LC) has become an accepted safe and alternative technique to open surgical colectomy (OC) as a treatment option for colon cancer. We compared inpatient mortality, hospital resource utilization and complications in patients who underwent LC vs OC. **Methods:** All patients with known diagnosis of colon cancer who underwent elective colonic resection were identified using Nationwide Inpatient Sample (NIS) 2017. Univariate and multivariate linear and logistic regression was performed to compare the outcomes of patients who underwent LC vs OC. **Results:** In our cohort, 171, 480 adult patients with colon cancer were identified. The number of males and females were equal. The mean age was 67.2 years. They were predominantly Caucasians (67.6%). OC was performed on 3,869 patients. Of 1,345 patients who underwent LC, 385 were converted to OC. As compared to OC, LC was associated with lower postoperative complications including anastomotic leak, stricture, intestinal obstruction(1% vs 10.8%, $p<0.01$), blood transfusion(2.2 % vs 11.2% p=0.01), malnutrition(0.2% vs 4.4% p=0.02), shock(0.7% vs 1.8%,p=0.04), ICU care(1.9% vs 5.3%), mean length of stay (5.9 days vs 8.7 days, p=0.01), lower hospital charge (88,642$ vs 106,315 $,$p<0.01$) and lower mortality(0.3% vs 1.9%(p=0.02). There was a trend towards decreased venous thromboembolism (0.3% vs 1.7 %, p=0.9) and post-operative ileus (0.1% vs 0.7% p=0.60) in LC as compared to OC. On multivariate analysis, independent predictors of undergoing LC were younger age, teaching and large bed-sized hospital and lower Charlson comorbidity index. Race, insurance status and income had no significant association with selection of operative approach (Table). **Conclusions:** In our cohort, laparoscopic colectomy was found to have better peri and post-operative clinical outcomes including decreased inpatient mortality and hospital resource utilization. It should be promoted as the curative surgical option for colon cancer whenever clinically indicated. Research Sponsor: None.

Multivariate analysis for patients undergoing laparoscopic colectomy.

Variables	Adjusted OR (95% CI)	P value
Age (>70 years)	1.21(1.04-1.73)	**<0.01**
Teaching hospital	1.71 (0.95-2.53)	**<0.01**
Charlson Comorbidity score (<=1)	1.87 (1.77-2.99)	**0.029**
Large bed-size hospital	1.17 (1.11-2.46)	**<0.01**
Medicaid insurance	1.03 (0.04-1.29)	>0.05
Private insurance	1.36 (1.00-1.54)	>0.05
African American	0.78 (0.70-1.94)	>0.05
Hispanic	0.66(0.22-1.84)	>0.05

4110 **Poster Session (Board #102), Fri, 8:00 AM-11:00 AM**

Does neoadjuvant FOLFOX chemotherapy improve the oncological prognosis of high-risk stage II and III colon cancers ? Three years' follow-up results of the Prodige 22 phase II randomized multicenter trial.

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Background: Neoadjuvant chemotherapy in a perioperative setting has proven valuable in locally advanced resectable colon cancer (CC) in terms of toxicity, postoperative morbidity and downstaging, but its effect on oncological outcomes remains uncertain. **Methods:** Prodige 22 was a randomized multicenter phase II trial in patients with resectable high-risk T3, T4 and/or N2 CC on baseline CT-scan. Patients were randomized to receive either 6 months of adjuvant FOLFOX after colectomy (control) or perioperative FOLFOX for 4 cycles before surgery and 8 cycles after (FOLFOX peri-op). In RAS wild-type (wt) patients a third arm testing perioperative FOLFOX-cetuximab was added. Primary endpoint was the Tumor Regression Grade. Secondary endpoints were 3-years overall (OS), disease-free survival (DFS) and time to recurrence (TTR). **Results:** 120 patients were enrolled. At interim analysis, the FOLFOX-cetuximab arm was stopped for futility. The remaining 104 patients (control, n = 52; FOLFOX peri-op n = 52) represented our intention-to-treat population. In the FOLFOX peri-op group, 96% received the schedule 4 cycles prior to surgery and all but one underwent adjuvant FOLFOX for a total of 12 cycles. In the control arm, 38 patients received adjuvant FOLFOX (1 postoperative death and 13 low-risk stage II patients). Median follow-up was 54.3 months [48.5-57.2]. Nineteen deaths and 26 disease recurrences were observed leading to a 3 years-OS of 90.3% in both arms (p = 0.7) and to a 3-years DFS of 76.8% and 69.2% in the peri-op and control arm respectively (p = 0.6). A trend to a better TTR in the peri-op arm was observed with a 3-years TTR of 82% as compared to 72% in the control arm (p = 0.3). No benefit from adding Cetuximab was observed in the 16 RAS-wt treated patients. **Conclusions:** In this pilot randomized study, perioperative FOLFOX chemotherapy has no detrimental effect on long term oncological outcomes and may be an option for some patients with locally advanced CC. A pooled analysis of randomized trials testing peri-operative strategies in this setting is warranted. Clinical trial information: NCT01675999. Research Sponsor: PHRC 2010, Pharmaceutical/Biotech Company.

4111 **Poster Session (Board #103), Fri, 8:00 AM-11:00 AM**

Early ileostomy closure is safe and feasible during adjuvant chemotherapy after total mesorectal excision surgery for rectal cancer.

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Background: The aim of this study was to evaluate the comparative clinical and oncological outcomes of temporary ileostomy closure during or after adjuvant chemotherapy in patients with total mesorectal excision (TME) for rectal cancer. **Methods:** This randomized controlled trial investigated 87 patients (51 males, 36 females) with rectal cancer undergoing TME surgery with temporary ileostomy from January 2016 to December 2018. Patients were randomized divided into 2 groups: early group (43 patients, mean age: 60.35) who underwent stoma closure during adjuvant chemotherapy (3 months after primary surgery) and late group (44 patients, mean age 61.80) who underwent stoma closure after adjuvant chemotherapy (6 months after primary surgery). Both clinical and oncological outcomes were analyzed. **Results:** No significant differences were observed in operative time, blood loss, postoperative hospital stay, postoperative complications or hospital costs in ileostomy closure between the 2 groups. Stoma-quality of life (QOL) of patients in early group was significantly better than late group (52.02 ± 5.68 vs 46.91 ± 5.68, $P < 0.05$). No significant difference in overall survival ($P = 0.702$) or progression-free survival ($P = 0.638$) was observed between the 2 groups. **Conclusions:** Ileostomy closure during adjuvant chemotherapy was clinically safe, and interruption of chemotherapy due to ileostomy closure did not change oncologic outcomes. Early ileostomy closure can improve QOL in those patients. Clinical trial information: NCT02665026. Research Sponsor: None.

4112 **Poster Session (Board #104), Fri, 8:00 AM-11:00 AM**

Patient and tumor characteristics as determinants of overall survival (OS) in *BRAF* V600 mutant (mt) metastatic colorectal cancer (mCRC) treated with doublet or triplet targeted therapy.

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Background: *BRAF* V600 mt mCRC is an aggressive disease with poor OS under standard chemotherapy. Treatment with doublet and triplet targeted combinations, such as *BRAF* inhibitor+ antiEGFR+/- *MEK* inhibitor, has been shown to improve outcomes. Prognostic factors in this targeted treated population remain to be studied. **Methods:** Prospective international cohort of patients who received doublet or triplet anti-BRAF combinations in clinical trials or as compassionate use. Univariate Cox models for OS were constructed and the strongest predictors in stepwise variable selection were used to develop a prognostic score. The final multivariate model with selected predictors was stratified by prior lines. **Results:** In total, 42 patients were enrolled. Median age 60.7 y (33-83), 61% female, 61% right-sided tumors, 26% received 2 or more prior chemotherapy lines. One patient (2.6%) achieved complete response and 36% had partial response with median follow-up of 14.3 months. Median progression-free survival was 5.5 months (CI95% 4.4-10.4) and median OS (mOS) was 10.7 months (CI95% 8.4-22.1). In univariate models, ECOG performance status (1 vs 0), CEA levels (high - $>$ 3.5 ng/mL- vs low - $<$ 3.5 ng/mL), CA 19.9 (high vs. low), LDH (high vs. low), number of metastatic sites and presence of liver metastasis were significant prognostic factors. On the other hand, MSI status and peritoneal or nodal metastasis did not associate with outcome. In multivariable model, strongest determinants of OS were ECOG and baseline CEA levels. If high-risk for both factors (ECOG 1 and CEA high, 46% of the patients), mOS was 5.6 months (CI95% 4.2-NA); if intermediate-risk (either ECOG 1 or CEA high, 33%), mOS was 13.5 months (CI95% 10.6-NA); if low-risk (ECOG 0 and CEA low, 21%), mOS not reached (CI95% 16.5-NA). Differences between intermediate- and high-risk prognostic groups compared to low-risk were significant (HR = 5.9, p = 0.03; and HR = 25.9, p $<$ 0.001, respectively). **Conclusions:** Patients characteristics such as ECOG and surrogates of tumor burden like CEA levels remain important OS determinants in *BRAF* V600 mt mCRC treated with doublet or triplet targeted therapy. In fact, there are not prognostic scores regarding BRAF mt mCRC treated with targeted therapies. Our study suggests that these prognostic factors may be considered as stratification factors in future clinical trials. Research Sponsor: None.

4113 **Poster Session (Board #105), Fri, 8:00 AM-11:00 AM**

The landscape of *MAP3K1/MAP2K4* alterations in gastrointestinal (GI) malignancies.

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Background: Inactivating alterations in *MAP3K1/MAP2K4* occur in various solid tumors, sensitize cancer models to MEK inhibitors, and have co-mutation partners which may enable therapeutic targeting. **Methods:** We retrospectively reviewed 20290 GI malignancy patients (pts), comprised of 9986 colorectal carcinoma (CRC) and 10304 non-CRC, whose tumors were profiled with Caris Life Sciences from 2015-2019. Profiling included immunohistochemistry (IHC) with programmed death ligand-1 (PD-L1), next-generation sequencing (NGS), tumor mutational burden (TMB) and deficient mismatch repair or microsatellite instability-high status (dMMR/MSI-H). **Results:** *MAP3K1/MAP2K4*-alteration (*MAP3K1/MAP2K4*-MT) was more frequent in CRC than non-CRC pts (2.0% v. 1.2%, $p<0.0001$), with truncating mutations representing the majority of lesions along both genes. While *MAP3K1/MAP2K4*-MT CRC pts were similar in age and gender to wild-type (WT), mutated non-CRC pts were older (median age 69 v. 65 years) and more likely female (51% v. 42%) compared to WT (both $p<0.05$). *MAP3K1/MAP2K4*-MT CRC (25% v. 7%) and non-CRC (30% v. 3%) were more frequently dMMR/MSI-H than WT pts (both $p<0.0001$). *MAP3K1/MAP2K4*-MT CRC cases were affiliated with higher TMB and similar rate of PD-L1 expression compared to WT. A higher rate of *MAP3K1/MAP2K4*-MT CRC pts were right-sided (36% v. 22%, $p<0.0001$) and transverse (8% v. 4%, $p<0.05$) compared to WT, whereas a higher frequency of WT cases were left-sided (20% v. 28%, $p<0.05$) and rectal (15% v 23%, $p<0.05$). Of microsatellite stable (MSS) CRC pts, those with *MAP3K1/MAP2K4*-MT were more likely *PIK3CA* (26% v. 17%) and *APC* (85% v. 78%) and less-likely *TP53* (64% v. 77%) co-mutated versus WT MSS pts (all $p<0.05$); no difference was seen in *BRAF* V600E, *ERBB2*/*ERBB3* or *KRAS* co-mutation rate in MSS pts. In both all-comers and MSS CRC, *MAP3K1/MAP2K4*-MT pts were more frequently co-mutated than WT with *ARID1A*, *POLE*, *ATM, BRCA2* and *PIK3R1* (all $\geq$7% of *MAP3K1/MAP2K4*-MT pts, $p<0.0001$). A higher frequency of all-comer non-CRC GI malignancy pts with *MAP3K1/MAP2K4*-MT were co-mutated with *PIK3CA* (13% v. 6%), *ERBB2/ERBB3* (8% v. 3%) or *APC* (13% v. 5%) compared to WT (all $p<0.01$). For MSS non-CRC GI cases, *ARID1A* (50% v. 30%) and *SMAD4* (21% v. 12%) were more frequently co-mutated in *MAP3K1/MAP2K4*-MT versus WT pts (all $p<0.05$). **Conclusions:** Truncating *MAP3K1/MAP2K4* alterations occur in nearly 2% of GI malignancy pts and are more commonly associated with dMMR/MSI-H than WT. Potentially targetable co-mutation partners implicated in MAPK and PI3K pathways as well as *POLE*, *BRCA2* and *ATM* warrant further evaluation. Research Sponsor: None.

TPS4114 **Poster Session (Board #106), Fri, 8:00 AM-11:00 AM**

A phase I/II study of PI3Kinase inhibition with copanlisib combined with the anti-PD-1 antibody nivolumab in relapsed/refractory solid tumors with expansions in MSS colorectal cancer.

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Background: Certain somatic mutations are thought to promote immune evasion and resistance to immunotherapy. PIK3CA was identified in an *in vivo* genomic screen for mechanisms of resistance to anti-PD1 therapy. MC38 cells (murine colon adenocarcinoma) were engineered to express a library of human cancer-associated mutations from TCGA. Resultant tumors *in vivo* were exposed to immune pressure with anti-PD1 therapy. Cells that proliferated were then analyzed for mutations that impart immune resistance. Multiple activating mutations in *PIK3CA* conferred resistance to anti-PD1 therapy. Coadministered PI3K inhibition reversed this resistance. Multiple studies have shown the impact of the phosphatidylinositol 3-kinase (PI3K) pathway on the tumor microenvironment, and 20% of colorectal cancer (CRC) tumors have an activating mutation of PI3K. **Methods:** A multi-center, open-label, phase I/II study with the combination copanlisib and nivolumab, a PD1 inhibitor, in relapsed/refractory solid tumors with expansions in relapsed/refractory microsatellite-stable (MSS) CRC was developed. Copanlisib is an inhibitor of PI3K and exhibits its most potent inhibitory effect on the isoforms PI3Kα and PI3Kδ. The first phase seeks to determine the maximum tolerated dose (MTD) of copanlisib with fixed dose nivolumab of 480 mg given every 4 weeks. Following determination of the MTD the second phase seeks to determine the 6-month objective response rate of the combination in MSS CRC patients and contains two cohorts 1) PIK3CA wildtype, 2) PIK3CA mutated. The study is planned with 21 evaluable subjects per cohort and allows early termination for lack of efficacy. Tumor assessments will be made using RECIST 1.1. Patients will have a pre-treatment biopsy followed by nivolumab on Day 1 of each 4 week cycle and copanlisib on Day 1, 8 and 15. A second biopsy will occur after six weeks. Eligibility criteria includes completed NGS for PI3K status, and patients must have received at least 2 prior lines of standard therapy. Patients can not have received a prior checkpoint inhibitor or PI3K inhibitor. Secondary and exploratory objectives, in addition to survival and safety outcomes, include exploring immune cell subsets in the local tumor microenvironment and in the peripheral circulation, as well as investigating immune activation and suppressive pathways through RNA expression and additional NGS techniques. The clinical study was activated in January 2019 (NCT03711058). Clinical trial information: NCT03711058. Research Sponsor: American Association for Cancer Research (AACR), Stand Up To Cancer (SU2C), Pharmaceutical/Biotech Company.

TPS4115 **Poster Session (Board #107), Fri, 8:00 AM-11:00 AM**

A phase III study of comparing FOLFOX+/-bevacizumab with FOLFOX+/-bevacizumab+ high-dose intravenous vitamin C as first-line therapy in patients with advanced colorectal cancer.

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Background: Previous studies showed that high dose vitamin C especially when administered intravenously might have anti-cancer effect. A recent preclinical study found that human colorectal cancer cells harboring KRAS or BRAF mutations are selectively killed by high dose vitamin C. Our phase I dose-escalation and expansion study has shown that high dose (up to 1.5g/kg) intravenous vitamin C with FOLFOX or FOLFIRI is well tolerated in patients with colorectal or gastric cancer. This trial is a randomized, multicenter, phase III study of high dose vitamin C infusion combined with FOLFOX +/- bevacizumab versus FOLFOX +/- bevacizumab as first-line therapy in patients with advanced colorectal cancer. **Methods:** This study has enrolled patients with histologically confirmed metastatic adenocarcinoma of colorectum, normal G6PD status and no prior treatment for metastatic disease. 432 patients are randomized 1:1 into one of two groups. Patients in the control group are treated with mFOLFOX6 (oxaliplatin 85 mg/m^2 d1 concurrent with leucovorin 400 mg/m^2, followed by bolus 5FU 400 mg/m^2 d1, followed by infusional 5FU 2400 mg/m^2 over 46 hours) with or without bevacizumab (5mg/kg, d1) every 2 weeks. Patients in the experimental group are treated with vitamin C intravenously (1.5g/kg/day, d1-3) in combination with mFOLFOX6 with or without bevacizumab every 2 weeks. Randomization is stratified by the location of primary site (left-sided or right-sided) and treatment with bevacizumab (with or without). The primary endpoint is progression free survival (assessed by investigator per RECIST v1.1). Secondary endpoints are overall survival, response rate, assessment of treatment-related adverse events, progression free survival and overall survival in RAS or BRAF mutant patients. Genome, microbiome and metabolome are also assessed. Clinical trial information: NCT02969681. Research Sponsor: Sun Yat-Sen University Clinical Research 5010 Program.

TPS4116 **Poster Session (Board #108), Fri, 8:00 AM-11:00 AM**

A phase Ib/II study of the polo-like kinase 1 (PLK1) inhibitor, onvansertib, in combination with FOLFIRI and bevacizumab for second-line treatment of patients with KRAS-mutated metastatic colorectal cancer (mCRC).

Daniel H. Ahn, Afsaneh Barzi, Maya Ridinger, Errin Samuelsz, Mark G. Erlander, Tanios S. Bekaii-Saab, Heinz-Josef Lenz; Ohio State University Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, OH; USC Keck School of Medicine Norris Comprehensive Cancer Center, Los Angeles, CA; Trovagene, San Diego, CA; Trovagene, Carlsbad, CA; Mayo Clinic, Scottsdale, AZ; USC Norris Comprehensive Cancer Center, Los Angeles, CA

Background: Chemotherapy in combination with targeted agents are standard-of-care options for patients for mCRC with response rates >50% in first line. In the second line setting, efficacy of chemotherapy and targeted agents are much lower with response rates of 5% for FOLFIRI (5-fluorouracil, leucovorin, irinotecan) + bevacizumab (anti-VEGF). New treatment options are urgently needed in particular for the 50 % of patients harboring a KRAS mutation. PLK1 is a serine/threonine kinase, master regulator of the mitotic checkpoint and cell division. PLK1 is overexpressed in CRC and its overexpression is associated with poor prognostic. A genome wide RNAi screen identified PLK1 as a synthetic lethal target in KRAS mutant CRC cells, inducing cell cycle arrest and apoptosis upon inhibition. Onvansertib is an oral, highly selective PLK1 inhibitor that demonstrates single agent and synergistic activity with irinotecan in preclinical CRC models. Additionally, KRAS mutated vs wild-type cells showed higher sensitivity to onvansertib. PLK1 inhibition is a potential target in KRAS-mutated mCRC, and the combination of onvansertib + FOLFIRI + bevacizumab may provide a new second-line treatment option. **Methods:** The primary objective of this single-arm Phase 1b/2 study is to assess the safety and preliminary efficacy of onvansertib in combination with FOLFIRI and bevacizumab in the second line setting for KRAS-mutated mCRC patients. For the Phase 1b segment, a standard 3 + 3 dose-escalation design is used to determine the maximum tolerated dose or recommended phase 2 dose (RP2D) of onvansertib. As of January 24, 2020, enrollment in the second dose level is ongoing. Efficacy will be determined by objective response rate (ORR) according to RECIST v1.1 (primary endpoint), progression-free survival and reduction in KRAS allelic burden in liquid biopsies (secondary endpoints). In the phase 2, based on a one-sided one sample log-rank test with 10% Type I error, there will be at least 90% power to detect an improvement in ORR from 5% to 20% with 26 patients. Exploratory endpoints include genomic studies of circulating tumor cells and ctDNA to evaluate altered pathways that correlate with patient clinical response. Clinical trial information: NCT03829410. Research Sponsor: Trovagene.

TPS4117 **Poster Session (Board #109), Fri, 8:00 AM-11:00 AM**

A multicenter phase Ib/II study of DNA-PK inhibitor peposertib (M3814) in combination with capecitabine and radiotherapy in patients with locally advanced rectal cancer.

Paul Bernard Romesser, Emma B. Holliday, Tony Philip, Barbara Sarholz, Mirjam Kuipers, Almudena Rodriguez, Ivan Diaz-Padilla, Eric David Miller; Memorial Sloan Kettering Cancer Center, New York, NY; The University of Texas MD Anderson Cancer Center, Houston, TX; Northwell Health Cancer Institute, Lake Success, NY; Merck KGaA, Darmstadt, Germany; Merck S.L., Madrid, Spain; Ares Trading S.A.–Merck Group, Eysins, Switzerland; The Ohio State University Comprehensive Cancer Center-James Cancer Hospital and Solove Research Institute, Columbus, OH

Background: Preoperative chemo-radiotherapy with or without sequential chemotherapy, followed by surgical intervention, is standard of care for patients with locally advanced rectal cancer (LARC). However, 1/3 of these patients still develop distant metastases, indicating the need for more effective therapies. DNA-dependent protein kinase (DNA-PK) regulates a key DNA damage repair pathway for double-strand break repair. Peposertib (M3814), a potent, selective, orally administered DNA-PK inhibitor, has been shown to potentiate the effect of ionizing radiation in a human colon cancer xenograft model and several colon cancer cell lines. Peposertib is being investigated in several different trials across multiple indications. This Phase Ib/II study (NCT03770689) aims to evaluate the safety, tolerability, pharmacokinetics (PK), and efficacy of the neoadjuvant treatment combination of peposertib, capecitabine, and radiotherapy (RT) in patients with LARC. **Methods:** Patients aged ≥18 years with histologically confirmed and resectable Stage II/III rectal adenocarcinoma are eligible. Induction chemotherapy is permitted, but residual disease must first be documented by MRI, digital rectal examination and endoscopy. Patients who received other anticancer therapies or those with prior pelvic RT are excluded. During open-label Phase Ib (open), 18–30 patients (n = 3 per cohort) are due to receive peposertib + capecitabine (orally, 825 mg/m^2 twice daily [BID]) + RT (45–50 Gy), 5 days/week. Peposertib 50 mg once daily (QD) is the starting dose. Additional dose levels will be between 100–800 mg QD. Dose escalation is determined by the safety monitoring committee and guided by a Bayesian 2-parameter logistic regression model. At Phase II (planned), 150 patients will be randomized (1:1) to receive oral capecitabine (825 mg/m^2 BID) + RT (45–50 Gy), with either oral peposertib (recommended phase II dose [RP2D]) or placebo, QD for 5 days/week. Primary objectives are to define a maximum tolerated dose and RP2D (Phase Ib), and to evaluate the efficacy of peposertib + capecitabine + RT in terms of pathological/clinical complete response (Phase II). Secondary objectives include assessment of antitumor activity (Phase Ib), quality of life outcomes (Phase II), and PK of peposertib, and the safety and tolerability of the combination therapy (both phases). One patient has received peposertib 50 mg QD and six patients have received peposertib 100 mg QD. Patients are currently receiving peposertib 150 mg QD. Clinical trial information: NCT03770689. Research Sponsor: Merck KGaA.

TPS4118 **Poster Session (Board #110), Fri, 8:00 AM-11:00 AM**

NIVACOR: Phase II study of nivolumab in combination with FOLFOXIRI/bevacizumab in first-line chemotherapy for advanced colorectal cancer RASm/BRAFm patients.

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Background: FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, and irinotecan) plus bevacizumab has been shown to be one of the therapeutic regimens in first line with the highest activity profile in patients (pts) with metastatic colorectal cancer (mCRC) unselected for biomolecular alterations. Tumors co-opt the PD-1/PD-L1 signaling pathway as one key mechanism to evade immune destruction. Anti-PD-1 monoclonal antibodies are FDA approved only for DNA mismatch repair deficient/microsatellite instability-high (MMRd/MSI-H), which are only about 5% among all mCRC. Nowadays, there are no data demonstrating anti-PD1 activity in stable and proficient (MMRp/MSS) disease. Another critical therapeutic target is the Vascular Endothelial Growth Factor A (VEGF-A), which acts on endothelial cells to stimulate angiogenesis; his inhibition with bevacizumab increase immune cell infiltration, giving a strong rationale for combining VEGF targeted agents with immune checkpoint inhibitors. Based on evidence, we explore the combination of triplet chemotherapy (FOLFOXIRI) with bevacizumab and nivolumab in pts with mCRC all-*RAS/BRAF* mutant regardless of microsatellite status. **Methods:** This is a prospective, open-label, multicentric phase II trial where pts with mCRC RAS/BRAF mutant in first line will receive nivolumab in combination with FOLFOXIRI/Bevacizumab every 2 weeks for 8 cycles followed by maintenance with bevacizumab plus nivolumab every 2 weeks. Bevacizumab will be administered intravenously at dose of 5 mg/kg every 2 weeks and nivolumab intravenously as a flat dose of 240 mg every 2 weeks. The primary endpoint is the overall response rate (ORR) and our hypothesis is that the treatment is able to improve the ORR from 66% to 80%. Secondary endpoints include overall survival, safety, time to progression, duration of response. Collateral translational studies evaluate the tumor mutational burden, and genetic alterations by circulating free DNA (cfDNA) obtained from plasma samples. The trial is open to enrollment, 4 of planned 70 pts have been enrolled. Clinical trial information: EudraCT Number: 2018-002893-38. Clinical trial information: NCT04072198. Research Sponsor: Bristol-Myers Squibb.

TPS4119 **Poster Session (Board #111), Fri, 8:00 AM-11:00 AM**

Multimodal fluorescence-guided surgery of colorectal peritoneal metastases, a phase I/II clinical trial.

Jan-Marie de Gooyer, Fortuné Elekonawo, Andre J.A. Bremers, Otto Boerman, Mark Rijpkema, Johannes H.W. de Wilt; Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands; Radboudumc, Nijmegen, Netherlands; Radboud University Medical Center, Nijmegen, Netherlands

Background: Successful treatment of patients with colorectal peritoneal carcinomatosis highly depends on complete surgical tumor resection of all tumor. Oncological outcomes can potentially be improved by intraoperative imaging using a tumor-targeting antibody conjugated to a fluorophore and a radiotracer. This enables preoperative radionuclide imaging, real-time intraoperative fluorescence imaging and gamma detection. In this study we investigate the feasibility, accuracy and safety of CEA-targeted preoperative SPECT/CT and intraoperative fluorescence imaging in patients with colorectal PC. **Methods:** In this phase I/II single arm protein dose escalation study patients with peritoneal metastases of colorectal origin who are scheduled for cytoreductive surgery and HIPEC will receive an intravenous injection of the CEA-targeting tracer ^{111}In-DOTA-labetuzumab-IRDye800CW. The first 15 patients will receive a single dose of 2,10 or 50 mg 6 to 7 days prior to surgery. Four to five days after injection SPECT/CT imaging of the thorax and abdomen is performed to determine intra-abdominal tumor load and detect extra-abdominal metatases. At day 6/7 after injection, standard cytoreductive surgical resection extended with real-time near-infrared fluorescence imaging and radio guidance is performed. After surgery, the peritoneal cavity will be re-examined for residual disease with fluorescence imaging. Resected specimens are analyzed microscopically, immunohistochemically (CEA and H&E) and by gamma counting. Blood samples are drawn for farmacokinetics and safety analysis at 180 minutes, 4 days, 6 days and 3 weeks after tracer injection. In the phase II dose expansion cohort, 14 more patients will receive the optimal dose as determined in the phase I trial. The primary objectives of the trial are to assess the safety, feasibility and accuracy of preoperative SPECT/CT and intraoperative fluorescence imaging after administration of 111In- labetuzumab-IRDye800CW in patients with peritoneal carcinomatosis of colorectal origin who will undergo cytoreductive surgery and HIPEC. The secondary objectives are to assess whether additional malignant lesions can be visualized by fluorescence imaging after cytoreductive surgery, to assess the intensity of fluorescence in malignant and non-malignant tissue, to assess the correlation between localization of the dual-labeled antibody and CEA expression in tumor and healthy tissue and to determine blood concentrations of the dual labelled antibody at several time points in patients. Clinical trial information: NCT03699332. Research Sponsor: Dutch Cancer Foundation.

TPS4120 **Poster Session (Board #112), Fri, 8:00 AM-11:00 AM**

TRACC: Tracking mutations in cell-free DNA to predict relapse in early colorectal cancer—A randomized study of circulating tumour DNA (ctDNA) guided adjuvant chemotherapy versus standard of care chemotherapy after curative surgery in patients with high risk stage II or stage III colorectal cancer (CRC).

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Background: Adjuvant chemotherapy (ACT) is routinely offered to patients with high risk (HR) stage II or stage III CRC following potentially curative surgery. Over 50% of stage III and $>$ 80% of stage II patients are cured by surgery alone but are being exposed to unnecessary chemotherapy with short- and long-term side effects. Post-operative ctDNA identifies minimal residual disease (MRD) after surgery in CRC. Our national study, TRACC, compares ctDNA guided versus standard of care (SoC) decision making in patients undergoing ACT. **Methods:** This is a UK-wide, multi-centre, prospective, two-arm, randomised trial. Patients with HR risk stage II or stage III CRC who have undergone R0 resection and have detectable ctDNA in their pre-surgical sample are eligible. Patients who undergo neoadjuvant chemoradiotherapy (CRT) for locally advanced rectal cancer with detectable ctDNA pre-CRT are also eligible. Patients are randomised in a 1:1 ratio to receive either SoC ACT or ctDNA guided ACT. In the ctDNA guided arm, patients who are ctDNA negative post-operatively have chemotherapy de-escalated i.e., 3 months(m) of Capecitabine and Oxaliplatin (CAPOX) doublet ACT is reduced to 3 m single agent Capecitabine; 6 m single agent Capecitabine reduced to no chemotherapy. In this group, ctDNA is re-tested at 3 months and if detectable, patients receive 3 months of CAPOX. Primary end-point is 3-year disease free survival (DFS). Secondary end-points include overall survival, neurotoxicity, quality of life and health economics. Based on a standard 3-year DFS of 75% in SoC ACT arm, to demonstrate a non-inferiority margin of 1.25, 810 patients are required per arm (85% power, $\alpha = 0.1$). Stratification is by tumour staging and site of primary tumour. Target accrual is over 4 years. The study opened to recruitment in January 2020 and is supported by the MRC-NIHR Efficacy and Mechanism Evaluation Grant (NIHR128529). Clinical trial information: NCT04050345. Research Sponsor: National Institute of Health Research- Biomedical Research Centre funding.

TPS4121 **Poster Session (Board #113), Fri, 8:00 AM-11:00 AM**

Phase II/III study of circulating tumor DNA as a predictive biomarker in adjuvant chemotherapy in patients with stage II colon cancer: NRG-GI005 (COBRA).

Van K. Morris, Greg Yothers, Scott Kopetz, Samuel A. Jacobs, Peter C. Lucas, Atif Iqbal, Patrick M Boland, Dustin A. Deming, Aaron James Scott, Howard John Lim, Norman Wolmark, Thomas J. George; NRG Oncology, and UT-MD Anderson Cancer Center, Houston, TX; NRG Oncology, and The University of Pittsburgh, Pittsburgh, PA; NRG Oncology and University of Texas MD Anderson Cancer Ctr, Houston, TX; NRG Oncology, and The University of Pittsburgh Cancer Institute, Pittsburgh, PA; NRG Oncology, and University of Pittsburgh School of Medicine, Pittsburgh, PA; NRG Oncology, and Baylor College of Medicine, Houston, TX; Rutgers Cancer Institute of New Jersey, and the Alliance, New Brunswich, NJ; University of Wisconsin Carbone Cancer Center, and ECOG-ACRIN, Madison, WI; University of Arizona Cancer Center, and SWOG, Tucson, AZ; British Columbia Cancer Vancouver, and CCTG Co-chair, Vancouver, BC, Canada; NRG Oncology, and The University of Florida Health Cancer Center, Gainesville, FL

Background: There are currently no validated predictive biomarkers for stage II resected colon cancer (CC) after adjuvant chemotherapy. However, circulating tumor DNA (ctDNA) that is shed into the bloodstream represents a highly specific and sensitive approach for identifying microscopic or residual tumor cells. For patients (pts) with CC, the detection of ctDNA is associated with persistent disease after resection and may outperform traditional clinical and pathological features as a prognostic factor to assess risk for recurrence. We hypothesize that for pts whose stage II colon cancer has been resected and who have no traditional high-risk features, a positive ctDNA status may identify those who will benefit from adjuvant chemotherapy. **Methods:** In this prospective phase II/III clinical trial, pts (N=1,408) with resected stage II CC without traditional high-risk features and whom the evaluating oncologist deems suitable for no adjuvant chemotherapy will be randomized 1:1 into 2 arms: standard-of-care/observation (Arm A), or prospective testing for ctDNA (Arm B). Postoperative blood will be analyzed for ctDNA with the GuardantHealth LUNAR panel, covering CC-relevant mutations and CC-specific methylation profiling. Pts in Arm B with ctDNA detected will be treated with 6 months of adjuvant (FOLFOX) chemotherapy. For all pts in Arm A, ctDNA status will be analyzed retrospectively at the time of endpoint analysis. The primary endpoints are clearance of ctDNA with adjuvant chemotherapy (phase II) and recurrence-free survival (RFS) for "ctDNA-detected" pts treated with or without adjuvant chemotherapy (phase III). Secondary endpoints will include time-to-event outcomes (OS, RFS, TTR) by ctDNA marker status and treatment, prevalence of detectable ctDNA in stage II CC, and rates of compliance with assigned intervention. Archived normal and matched tumor and blood samples will be collected for exploratory correlative research. The trial is actively accruing towards the phase II endpoint across all US and Canadian cooperative groups. Support: U10-CA-180868, -180822; UG1CA-189867; GuardantHealth. Clinical trial information: NCT04068103. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

TPS4122 **Poster Session (Board #114), Fri, 8:00 AM-11:00 AM**

Phase II study of durvalumab plus total neoadjuvant therapy (TNT) in locally advanced rectal cancer: The GEMCAD-1703 DUREC trial.

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Background: In clinical stages II and III (cT3-4 and/or N+), preoperative chemoradiotherapy (CRT) or short-course radiation followed by total mesorectal escision (TME) have been the standard of care for the last 15 years. Induction chemotherapy (CT) before CRT (strategy known as TNT) results in fewer toxic effects and improved compliance. TNT may release tumor-neoantigens with platinum-based induction CT, and radiotherapy has the potential ability to induce an immunogenic cell death and counteract an immune-suppressive tumor microenvironment that provides the rationale for combining with immunotherapies. In addition, the presence of tumor infiltrating lymphocytes has been demonstrated in patients with rectal cancer treated with neoadjuvant CRT, reinforcing the rational for immune check-point inhibitors in this setting. We hypothesize that combining TNT with durvalumab (an optimized monoclonal antibody directed against programmed cell death-1 ligand 1) would improve outcome. **Methods:** DUREC is a multicenter, single-arm, open-label, phase Ib/II study for patients with magnetic resonance (mr) image middle or distal third, mrT3c-d/T4/N2 rectal adenocarcinoma. Treatment: Patients will receive 6 cycles of modified FOLFOX6 prior to CRT (capecitabine with 50.4 Gy in 28 fractions) and TME, combined with durvalumab 1500 mg every 4 weeks during induction CT, CRT and waiting period until surgery. To assess the tolerability and toxicity profile we plan to perform a run-in treatment phase including the first 6 patients in the study, holding recruitment until all of them will be operated and 30-days post-surgery period completed. If $\leq$ 2 durvalumab-related dose-limiting toxicities (DLTs) are observed, recruitment will continue. The primary objective is pathological complete response (pCR) rate. Secondary endpoints include toxicity, tumor regression grade, R0 resections, clear circumferential margins, surgical complications, NAR score, disease-free survival and a biomarker program on tumor tissue, blood samples and stool microbiota. Statistical design: 58 evaluable patients (assuming a P0 of 16% and a P1 of 30%, with 0.1 alpha and 0.1 beta); Study started recruitment on December 2019. Clinical trial information: 2018-004835-56. Research Sponsor: AstraZeneca, GEMCAD (Spanish multidisciplinary Group of Digestive Cancers).

TPS4123 **Poster Session (Board #115), Fri, 8:00 AM-11:00 AM**

A phase II study of induction PD-1 blockade in subjects with locally advanced mismatch repair-deficient rectal adenocarcinoma.

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Background: The treatment of patients with locally advanced rectal cancer includes total neoadjuvant therapy with chemotherapy, chemoradiation followed by surgery. While most rectal cancers respond to combination induction chemotherapy, patients with mismatch repair deficient (dMMR) or MSI-H tumors have a significantly higher chance of progression with this treatment regimen. dMMR or MSI-H tumors have shown remarkable responses to PD-1 blockade, but the effect of neoadjuvant checkpoint inhibition has not been well studied. In this trial we will determine the pathologic complete response rate (pCR) of neoadjuvant anti-PD-1 blockade followed by standard chemoradiation in dMMR or MSI-H locally advanced rectal cancer. We hypothesize that treatment naïve dMMR or MSI-H rectal cancers will achieve a robust clinical response to PD-1 blockade and that the total neodjuvant therapy with PD-1 blockade followed by chemoradiation will improve pCR rates. **Methods:** Eligible patients $\geq$18 years of age with Stage II (T3-4, N-) or Stage III (any T, N+) histologically confirmed dMMR or MSI-H (by NGS) rectal adenocarcinoma will be enrolled. Patients will receive TSR-042 (500mg IV) every 3 weeks for a maximum of 8 cycles (6 months of treatment). Imaging, internal endoscopic exam and ctDNA blood draw will be performed at 6 weeks and every 3 months during induction anti-PD-1 treatment. Adverse events and surgical complications will be graded according to the NCI CTCAE v5 and the Clavien-Dindo classification, respectively. Following neoadjuvant checkpoint blockade, patients will undergo conventional chemoradiotherapy followed by surgical resection. The primary endpoint is pathologic complete response compared with historical control in pMMR patients. Patients will be followed up every 6 months for assessment of disease-free survival for up to five years. Clinical trial information: NCT04165772. Research Sponsor: Tesaro.

TPS4124 **Poster Session (Board #116), Fri, 8:00 AM-11:00 AM**

The PEGASUS trial: Post-surgical liquid biopsy-guided treatment of stage III and high-risk stage II colon cancer patients.

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Background: Moving stage III Colon Cancer (CC) into the precision medicine space is a priority in view of the lack of molecular markers driving adjuvant treatment. Retrospective studies have demonstrated the tremendous prognostic impact of circulating tumor DNA (ctDNA) analysis after curative intent surgery, and suggested that lack of conversion of ctDNA from detectable to undetectable after adjuvant chemotherapy reflects treatment failure. With these premises, we have designed the PEGASUS trial (NCT04259944). **Methods:** PEGASUS is a prospective multicentric study designed to prove the feasibility of using liquid biopsy (LB) to guide the post-surgical and post-adjuvant clinical management in 140 microsatellite stable Stage-III and T4N0 Stage-II CC patients. The LUNAR1 test (Guardant Health, Redwood City, CA, USA) will be used for ctDNA determination. For the efficacy analysis, the PEGASUS cohort will be compared with a 3:1 matched cohort of 420 patients from the TOSCA trial (NCT00646607). A LB executed 2-4 weeks post-surgery will guide a "Molecular Adjuvant" treatment: i) ctDNA+ patients will receive CAPOX for 3 months and ii) ctDNA- patients will receive capecitabine (CAPE) for 6 months but will be retested after 1 cycle, and if found ctDNA+ will be switched to CAPOX treatment. At the end of the "Molecular Adjuvant" treatment a further LB will be performed and instruct subsequent treatment. Positive patients (ctDNA+/+ and ctDNA-/+) will receive an up-scaled "Molecular Metastatic" systemic treatment for 6 months or until radiological progression or toxicity: i) ctDNA+/+ patients will be treated with FOLFIRI; ii) ctDNA-/+ patients with CAPOX. These patients will be subjected to a LB after 3 months and at the end of treatment: in case of positivity will be switched to FOLFIRI. ctDNA+/- patientswill receive a de-escalated treatment with CAPE for 3 months. 3 LB will be performed within 3 months and in case of positivity the patient will be switched to FOLFIRI. Patients with ctDNA-/- will be subjected to an interventional follow-up comprising 2 further LB and in case of positivity they will be switched to CAPOX treatment. PEGASUS is piggybacked to AlfaOmega (NCT04120935), a Master Observational Protocol that will follow patients from diagnosis to 5 years or recurrence/death (whichever comes first), collecting clinical data, radio-images and biological samples. AlfaOmega provides a clinical and logistic ecosystem for the seamless integration of PEGASUS clinical results with the biological underpinning of colon cancer. Clinical trial information: NCT04259944. Research Sponsor: Italian Association for Cancer Research.