Nivolumab (NIVO) + 5-fluorouracil/leucovorin/oxaliplatin (mFOLFOX6)/bevacizumab (BEV) versus mFOLFOX6/BEV for first-line (1L) treatment of metastatic colorectal cancer (mCRC): Phase 2 results from CheckMate 9X8.

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Background: Standard 1L therapies for mCRC include a fluoropyrimidine with oxaliplatin and/or irinotecan, and a biologic agent. NIVO may enhance antitumor activity in combination with 1L standard therapies within a subset of patients (pts) with mCRC. CheckMate 9X8 evaluated NIVO + mFOLFOX6/BEV vs mFOLFOX6/BEV in 1L mCRC (NCT03414983). **Methods:** Adults with previously untreated, unresectable, mCRC were randomized 2:1 to NIVO 240 mg + mFOLFOX6/BEV Q2W (NIVO + standard-of-care [SOC]) or mFOLFOX6/BEV Q2W (SOC). Primary endpoint was progression-free survival (PFS) assessed by blinded independent central review (BICR) per RECIST v1.1. Key secondary endpoints included objective response rate (ORR), disease control rate (DCR), time to response (TTR), duration of response (DOR), overall survival (OS), and safety. **Results:** 195 pts were randomized to NIVO + SOC (n = 127) or SOC (n = 68). Median (range) follow-up was 23.7 (0–33.2) months (mo; NIVO + SOC) vs 23.2 (0–32.3) mo (SOC). Median (range) duration of therapy was 9.9 (0.1–31.8+) mo (NIVO + SOC) and 7.7 (0.1–26.7+) mo (SOC). The HR (95% CI) for PFS was 0.81 (0.53–1.23; $P = 0.30$), which did not meet the prespecified threshold for statistical significance (median PFS, 11.9 mo in both arms; Table). PFS rates after 12 mo were higher with NIVO + SOC vs SOC (Table). ORR was 60% (NIVO + SOC) and 46% (SOC; odds ratio 1.72 [95% CI 0.96–3.10]) and median (95% CI) DOR was 12.9 (9.0–13.1) mo (NIVO + SOC) and 9.3 (7.5–11.3) mo (SOC; Table). Rates of grade 3−4 treatment-related adverse events (TRAEs) were higher with NIVO + SOC; however, no new safety signals were identified (Table). Biomarker analyses, including tumor mutational burden and baseline CD8 levels, will be presented. **Conclusions:** The primary endpoint of PFS was not met; however, NIVO + SOC showed higher PFS rates after 12 mo, a higher response rate, and more durable responses compared with SOC, along with acceptable safety, in 1L mCRC. Clinical trial information: NCT03414983. Research Sponsor: Bristol Myers Squibb.

Efficacy	NIVO + SOC n = 127	SOC n = 68
PFS[a]	11.9	11.9
Median, mo (95% CI)	(8.9–15.7)	(10.1–12.2)
HR vs SOC (95% CI; *P* value)	0.81	–
15-mo rate, % (95% CI)	(0.53–1.23;	21.5 (9.7–36.4)
18-mo rate, % (95% CI)	*P* = 0.30)	9 (2.4–21.8)
	45	
	(35.4–54.8)	
	28	
	(19.0–38.4)	
ORR,[a] n (%)	76 (60)	31 (46)
DCR,[a] n (%)	115 (91)	57 (84)
Median TTR,[a,b] mo (range)	2.8	2.8 (1.8–8.3)
	(1.5–12.2)	
DOR,[a,b]	12.9	9.3 (7.5–11.3)
Median, mo (95% CI)	(9.0–13.1)	31 (14–50)
≥ 12-mo rate, % (95% CI)	52 (39–64)	0 (NE)
≥ 18-mo rate, % (95% CI)	29 (17–42)	
Median OS,[c] mo (95% CI)	29.2	Not reached
	(24.0–NE)	(24.4–NE)
Safety	**n = 123**	**n = 62**
Any-grade/grade 3−4 TRAEs, n (%)	120 (98)/92	60 (97)[d]/30 (48)
	(75)	
Any-grade/grade 3–4 TRAEs leading to discontinuation, n (%)	70 (57)/31	22 (35)[d]/6 (10)
	(25)	

[a]BICR; [b]Responders only (NIVO + SOC, n = 76; SOC, n = 31); [c]Minimum follow-up for OS, 21.5 mo; [d]One grade 5 event. NE, not estimable.

Association of circulating tumor DNA dynamics with clinical outcomes in the adjuvant setting for patients with colorectal cancer from an observational GALAXY study in CIRCULATE-Japan.

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Background: Circulating tumor DNA (ctDNA)-based molecular residual disease (MRD) has the potential to select patients who may benefit more from standard-of-care (SOC) adjuvant chemotherapy (ACT) by accurately assessing recurrence-risk post-surgery and by evaluating ACT efficacy. Here we present an analysis from GALAXY study, an observational study monitoring MRD, to evaluating the association of ctDNA dynamics with a short-term clinical outcome and ACT efficacy. **Methods:** A personalized tumor-informed assay (Signatera bespoke multiplex-PCR NGS assay) was used for post-surgical MRD detection in colorectal cancer (CRC) patients. Six-month disease-free survival (6M-DFS) rates were analyzed excluding patients enrolled in associated phase III trials (VEGA and ALTAIR). **Results:** Total 1,365 CRC patients enrolled between June 2020 and April 2021 were included in this analysis; 116 pStage I, 478 pStage II, 503 pStage III, and 268 oligomet resectable pStage IV (16% [42/268] received neoadjuvant chemotherapy). 6M-DFS rate by ctDNA dynamics from 4w to 12w were 98% in 'negative to negative' group (N = 618), 59% in 'negative to positive' (N = 32), 100% in 'positive to negative' (N = 58), and 45% in 'positive to positive' (N = 78), with a significant difference between 'positive to negative' and 'positive to positive' groups with hazard ratio (HR) of 52.3 (95% CI: 7.2-380.5; $p < 0.001$), with a median follow-up time of 6.6 months. Further, out of 188 patients who were MRD+ at 4w with available MRD status at 12w, 95 received SOC ACT (80/95 received fluoropyrimidine [FP] + oxaliplatin and 15 received FP alone) by an investigator's decision. ctDNA clearance rate at 12w was significantly higher in ACT vs. non-ACT; 57% (54/95) vs. 8% (7/93) in pStage I-IV ($p < 0.001$), and 58% (42/72) vs. 11% (4/37) in pStage II-III ($p < 0.001$). In addition, ctDNA clearance rate at 24w was also significantly higher in ACT vs. non-ACT; 26% (7/27) vs. 0% (0/30) in pStage I-IV ($p = 0.003$), and 33% (7/21) vs. 0% (0/15) in pStage II-III ($p = 0.03$). Cumulative incidence of ctDNA clearance was significantly higher in ACT vs. non-ACT (67% vs. 7% by 24w; cumulative HR = 17.1; 95% CI: 6.7-43.4, $p < 0.001$). Among 4w-MRD+ patients, 6M-DFS rate was significantly higher in ACT vs. non-ACT; 84% vs. 34% (HR = 0.15; 95% CI: 0.078-0.25; $p < 0.001$), which was seen in all stages, including pStage II. **Conclusions:** This analysis from the GALAXY study, is the largest MRD study to date, demonstrating the association of ctDNA dynamics with improved clinical outcomes in MRD+ patients. Our study shows that stratifying post-surgical treatment decisions using the assay can identify patients likely to benefit from ACT across all stages, including pStage II. ctDNA-guided adjuvant strategy will further be established by ongoing randomized VEGA and ALTAIR studies and will be presented in the future conferences. Clinical trial information: jRCT1031200006. Research Sponsor: Japan Agency for Medical Research and Development.

A randomized phase III trial of mFOLFOX7 or CapeOX plus bevacizumab versus 5-FU/*l*-LV or capecitabine plus bevacizumab as initial therapy in elderly patients with metastatic colorectal cancer: JCOG1018 study (RESPECT).

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Background: It is uncertain if the addition of oxaliplatin (OX) to fluoropyrimidine plus bevacizumab (BEV) is suitable as initial therapy in elderly patients (pts) with metastatic colorectal cancer (MCRC). Therefore, we conducted a randomized controlled trial to confirm the superiority of the addition of OX in terms of progression-free survival (PFS). This JCOG trial was originally planned as a paralell study with NCCTG, but the NCCTG trial was terminated early. **Methods:** Key eligibility criteria included unresectable metastatic colorectal cancer, and histologically confirmed adenocarcinoma, aged 70-74 with PS 2 or 75 or older with ECOG PS 0-2. Eligible pts were randomized (1:1) to either no addition of OX or addition. Whether using 5-FU+levoleucovorin calcium (5-FU/*l*-LV) or capecitabine (CAPE) was declared before study entry; options included 5-FU/*l*-LV+BEV (C), CAPE+BEV (D), mFOLFOX7+BEV (E), or CapeOX+BEV (F). 5-FU/*l*-LV regimen omitted bolus 5-FU from the original sLV5FU regimen. The dose of CAPE was adjusted by estimated creatinine clearance. The primary endpoint was PFS. The planned sample size was 250 pts in total to detect a hazard ratio (HR) of 0.75, with a one-sided alpha of 5% and 70% power. The decision rule is that the primary endpoint is met, and the point estimate of HR of overall survival (OS) is less than 0.8. **Results:** Between Sep 2012 and Mar 2019, 251 pts were randomized. 125 pts were allocated to no addition of OX and 126 pts to addition. Median age was 79, aged 70-74/75-79/80-84/85+:5%/45%/37%/13%, PS 0/1/2:53%/39%/7%. Of 251 pts, 241 pts had PFS events and 223 pts had OS events. Median PFS (mPFS) was 9.4 months (M) (95%CI 8.3–10.3) in no addition of OX and 10.0M (9.0–11.2) in addition (HR 0.837, 90.5%CI [0.673–1.042], one-sided p = 0.086). Median OS was 21.3M (18.7-24.3) in no addition and 19.7M (15.5–25.5) in addition of OX (HR 1.054 [0.810–1.372]). Response rate was 29.5% (21.2-38.8) in no addition of OX and 47.7% (38.1-57.5) in addition. Proportion of pts whose EQ-5D scores improved from baseline to post-treatment in overall score did not differ (odds ratio 0.94 (0.51-1.75)). The deaths of 1 pt in no addition of OX and in 3 pts in addition were deemed treatment-related. **Conclusions:** The addition of OX has no survival benefit over no addition. OX was not recommended for elderly MCRC pts as initial therapy. Clinical trial information: UMIN000008866. Research Sponsor: Japan Agency for Medical Research and Development, Other Government Agency, National Cancer Center Research and Development Fund.

	N	Median PFS (95% CI)	Median OS (95% CI)
No addition of OX	125	9.4M (8.3-10.3)	21.3M (18.7-24.3)
The addition of OX	126	10.0M (9.0-11.2)	19.7M (15.5-25.5)
		HR:0.837 (0.648-1.033)	HR:1.054 (0.810-1.372)
		P = 0.086	
5FU/*l*-LV+BEV (C)	71	8.5M (6.3-9.9)	20.5M (16.7-23.3)
CAPE+BEV (D)	54	10.3M (9.1-11.8)	24.7M (18.4-29.6)
mFOLFOX7+BEV (E)	67	10.0M (9.0-11.6)	24.2M (16.6-27.8)
CapeOX+BEV (F)	59	10.0M (7.2-12.2)	16.4M (11.8—25.5)

Prognostic impact of early treatment discontinuation and early oxaliplatin discontinuation in patients treated with 6 months of oxaliplatin-based adjuvant chemotherapy for stage III colon cancer: an ACCENT/IDEA pooled analysis of 11 trials.

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Background: Six months of oxaliplatin-based adjuvant chemotherapy in patients with stage III colon cancer (CC) remains a standard in high-risk stage III patients. Early treatment discontinuation (ETD) could worsen the prognosis. In addition, there is current lack of data on the prognostic impact of early oxaliplatin only discontinuation (EOD). **Methods:** We studied the prognostic impact of ETD and EOD in patients with stage III CC who participated in 11 relevant clinical trials of the ACCENT and IDEA databases, where patients were planned to receive 6 months of adjuvant fluoropyrimidine plus oxaliplatin (FOLFOX or CAPOX). ETD was defined as discontinuation of treatment before 75% of cycles of chemotherapy. EOD was defined as discontinuation of oxaliplatin only, while continuing the fluoropyrimidine, before 75% of cycles of oxaliplatin. Association between ETD/EOD and overall survival (OS) and disease-free survival (DFS) was assessed by Cox model adjusted for prognostic factors. **Results:** ETD analysis included 10,444 patients (FOLFOX n = 7,033; CAPOX n = 3,411), with 20.9% of patients with ETD (17.8% with FOLFOX and 27.2% with CAPOX, $p < 0.001$). Out of 7,243 patients, 18.8% experienced EOD (17.4% FOLFOX versus 21.4% with CAPOX, $p < 0.001$). Compared to patients without ETD or EOD, patients with ETD or EOD were statistically more likely to be women, older, with higher ECOG-PS ≥ 1, and in addition for ETD, a Body Mass Index (BMI) < 18.5 kg/m^2. In multivariate analyses, ETD was associated with a decrease in DFS and OS in the overall population (HR: 1.40 95%CI 1.23-1.58, $p < 0.001$ and HR: 1.51 95%CI 1.31-1.74, $p < 0.001$, respectively). The same pattern was present with FOLFOX and CAPOX regimen, and also in low-risk and high-risk groups for each regimen with the exception of the CAPOX regimen in the low-risk group for DFS and OS. By contrast, EOD was not associated with reduced DFS or OS in the overall population (HR: 1.10 95%CI 0.77-1.58, p = 0.6 and HR: 0.97 95%CI 0.62-1.52, p = 0.9, respectively), in the low-risk group (HR: 0.97 95%CI 0.56-1.66, p = 0.9 and HR: 0.97 95%CI 0.51-1.82, p = 0.9, respectively) and high-risk group (HR: 1.22 95%CI 0.74-2.02, p = 0.4 and HR: 1.05 95%CI 0.53-2.08, p = 0.9, respectively) and for all subgroups of regimen. **Conclusions:** In patients treated with 6 months of oxaliplatin-based adjuvant chemotherapy for stage III CC, ETD was associated with a decrease in DFS and OS. By contrast, EOD was not significantly associated with poorer outcomes. In case of relevant neurotoxicity during a 6 months schedule, these data are not in favor of continuing oxaliplatin beyond 75% of planned cycles of adjuvant chemotherapy, and demonstrate that fluoropyrimidines remain the cornerstone of adjuvant chemotherapy in localized CC. Research Sponsor: None.

Phase I/II trial of encorafenib, cetuximab, and nivolumab in patients with microsatellite stable, *BRAF*^{V600E} metastatic colorectal cancer.

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Background: Encorafenib (E) and cetuximab (C) offers short-lived response and survival benefit for patients (pts) with MSS, *BRAF*^{V600E} metastatic colorectal cancer (CRC). BRAF + EGFR inhibition induced a transient MSI-H phenotype in preclinical models of MSS, *BRAF*^{V600E} CRC and may prime these tumors for response to immunotherapy with anti-PD-1 antibodies like nivolumab (N). **Methods:** In this single-arm, single-institution, phase I/II clinical trial, pts with treatment-refractory MSS, *BRAF*^{V600E} metastatic CRC were eligible. No prior BRAF inhibitors, anti-EGFR antibody, or immunotherapy was permitted. Pts received E (300 mg PO daily), C (500 mg/m^2 IV q14 days), and N (480 mg IV q28 days). The primary endpoints were best overall response (RECIST 1.1) and safety/tolerability (CTCAE v5). A Simon two-stage design (H_0: $p \leq .22$; H_a: $p \geq .45$, where p= percentage of pts with radiographic response) was employed using a one-sided α=.05 and β=.20. In the first stage, $\geq$ 4/15 responses were needed in order for the trial to enroll 11 additional pts. Median progression-free survival (PFS) and overall survival (OS) were estimated via Kaplan-Meier. **Results:** All 26 pts have been enrolled - 23 patients treated, and 21 evaluable for response so far. Median age is 59 years (range, 32-85), and 14 (54%) are female. No dose-limiting toxicities occurred. Grade 3-4 treatment-related adverse events (AE) occurred in 4/22 (18%) patients. Grade 3 AEs included colitis, maculopapular rash, leukocytosis, and elevated amylase/lipase (all N=1). Grade 4 AEs in a single patient were myositis/myocarditis. Overall response rate is 45% (95% CI, 23-68), and disease control rate is 95% (95% CI, 75-100). Median PFS is 7.3 months (95% CI, 5.5-NA). Median OS is 11.4 months (95% CI, 7.6-NA). For the 9 pts thus far with responses, median duration of response is 8.1 months (95% CI, 7.3-NA). Updated results will be presented. **Conclusions:** E + C + N is effective and well-tolerated for pts with MSS, *BRAF*^{V600E} metastatic CRC. The E+C+N regimen met its predefined efficacy endpoint and suggests a role for immunotherapy as a novel combination approach for this specific subpopulation of MSS metastatic CRC. A follow-up randomized phase II trial (SWOG 2107) to evaluate encorafenib/cetuximab with or without nivolumab in pts with MSS, *BRAF*^{V600E} metastatic CRC will activate in early 2022. Clinical trial information: NCT04017650. Research Sponsor: Pfizer, Bristol Myers Squibb.

One-year duration of nivolumab plus ipilimumab in patients (pts) with microsatellite instability-high/mismatch repair-deficient (MSI/dMMR) metastatic colorectal cancer (mCRC): Long-term follow-up of the GERCOR NIPICOL phase II study.

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Background: Optimal treatment duration with immune checkpoint inhibitors (ICI) for MSI/dMMR mCRC pts remains to be determined. Different durations are used, usually a fixed duration of 2 years or treatment until progression or toxicity. The GERCOR NIPICOL phase II study evaluated 1 year of therapy with nivolumab plus ipilimumab for MSI/dMMR mCRC pts. Here, we present the efficacy data with 16 months of additional follow-up since the primary analysis. **Methods:** MSI/dMMR mCRC pts previously treated with fluoropyrimidine, oxaliplatin, and irinotecan ± targeted therapies received nivolumab 3 mg/kg plus ipilimumab 1 mg/kg Q3W for 4 cycles, then nivolumab 3 mg/kg Q2W until progression or a maximum of 20 cycles. Second course of nivolumab was permitted for pts who completed the predefined year of treatment and had later progressive disease (PD). Objectives were to evaluate response rates, progression-free survival (PFS) per iRECIST, and overall survival (OS). A landmark analysis was performed for PFS in pts who remained alive and progression-free at 1 year (theoretical end of treatment). **Results:** Of 57 pts included between Dec 2017 and Nov 2018, 36 (63%) completed the predefined 1-year duration of treatment. Reasons of premature treatment discontinuation were PD or death (n = 13), adverse event (n = 7), and the pt wish (n = 1). Overall median follow-up was 34.5 months. One, 2, and 3-year PFS rates were respectively 75.4% (95% CI 62.0-84.6), 70.0% (95% CI 56.2-80.1), and 70.0% (95% CI 56.2-80.1). One, 2, and 3-year OS rates were 84.1 (95% CI 71.7-91.4), 78.4% (95% CI 65.1-87.1), and 73.1% (95% CI 58.4-83.4), respectively. 42/57 pts were progression-free and alive at 1 year. Among them, median follow-up was 35.0 months and the 24-month PFS rate was 92.9% (95% CI 79.5-97.6%). PD was observed in three pts whose 12-month status was stable disease (SD). These three pts received a second course of nivolumab: two achieved PR and one had PD. **Conclusions:** Nivolumab plus ipilimumab with a fixed duration of 1 year continued to show durable activity in pts with chemoresistant MSI/dMMR mCRC after 3 years of follow-up. Reexposure to nivolumab seems to provide additional antitumor activity for pts experiencing late resistance after discontinuation of immunotherapy. Clinical trial information: NCT033501260. Research Sponsor: Bristol-Myers Squibb, GERCOR.

Robotic versus laparoscopic surgery for middle and low rectal cancer (REAL): Short-term outcomes of a multicenter randomized controlled trial.

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Background: Robotic surgery for rectal cancer is gaining popularity, but persuasive evidence on long-term oncological outcomes is lacking. This multicenter randomized controlled trial compared robotic and conventional laparoscopic surgery regarding surgical quality and long-term oncological outcomes among patients with middle and low rectal cancer. **Methods:** This superiority trial was undertaken at 11 hospitals in 8 Chinese provinces. Patients with middle ($>$ 7–12 cm from anal verge) or low (0–7 cm from anal verge) rectal adenocarcinoma, cT1–T3 N0–1 or ycT1–T3 Nx after preoperative radio-/chemoradiotherapy, and no evidence of distant metastasis were enrolled and randomly assigned in a 1:1 ratio to receive robotic or conventional laparoscopic surgery. Secondary (short-term) end points (surgical quality, pathological radicality, and postoperative recovery) were compared using modified intention-to-treat (mITT) analysis. Three-year locoregional recurrence rate as the primary endpoint is expected by the end of 2023. This trial was registered with ClinicalTrials.gov (NCT02817126). **Results:** Between July 2016 and December 2020, 1240 patients were enrolled; 1180 were included in the mITT analysis (591 in robotic and 589 in laparoscopic group). There were significantly more sphincter-preserving surgeries (low anterior resections) performed in the robotic group (83.1% vs. 76.9%, p = 0.008). With more macroscopic complete resections (95.4% vs. 91.9%, p = 0.012), robotic surgery had better integrity of the mesorectal fascia, and had lower circumferential resection margin positivity rate (4.0% vs. 7.1%, difference = -3.1%, 95% confidence interval = -6.0% to -0.5%, p = 0.023) and more lymph nodes harvested (median, 15.0 vs. 14.0, p = 0.004). Robotic surgery also reduced the open conversion rate (1.7% vs. 3.9%, p = 0.021), estimated blood loss (median, 40.0 ml vs. 50.0 ml, $p < 0.001$), intraoperative complication rate (5.4% vs. 8.7%, p = 0.029), and 30-day postoperative complication rate (Clavien-Dindo grade II or higher, 16.1% vs. 22.9%, p = 0.003), leading to better postoperative recovery and shorter postoperative hospital stay (median, 7.0 days vs. 8.0 days, $p < 0.001$). The 30-day postoperative mortality was similar between the two groups (0.2% vs. 0.2%, $p > 0.999$). **Conclusions:** Robotic surgery for middle and low rectal cancer significantly reduced surgical injury, improved oncological radicality, and promoted postoperative recovery compared with conventional laparoscopic surgery. Clinical trial information: NCT02817126. Research Sponsor: The Shenkang Hospital Development Center, Shanghai Municipal Health Commission (Shanghai, China), and Zhongshan Hospital, Fudan University (Shanghai, China).

Phase I/II study of regorafenib (rego) and pembrolizumab (pembro) in refractory microsatellite stable colorectal cancer (MSSCRC).

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Background: Immune check point inhibitors (ICI) are ineffective in MSSCRC. Combination of ICI with targeted agents has the potential to alter the tumor microenvironment and render these tumors vulnerable to ICI. We report the results of the multicenter study of rego and pembro in a diverse patient population with advanced MSSCRC. **Methods:** This was an investigator-initiated study and enrolled patients (pts) who had failed/were intolerant of chemotherapy at 3 sites. A 3+3 design was used for phase I to evaluate escalating doses of rego (80,120,160, days 1-14/21) in combination with pembro (200m/q3weeks). The primary endpoint was dose limiting toxicities during the first cycle. For phase II, pts received rego at the recommended phase II dose (RP2D) with pembro. The primary endpoint was progression free survival (PFS). Secondary endpoints were overall survival (OS) and objective response rate (ORR). The study was powered to show an improvement in PFS from 1.9 months (CORRECT data) to 2.85 months. Estimated sample size for phase II was 63 pts. **Results:** Study started in 7/2019 and accrual completed in 7/2021. Of 73 pts, 10 enrolled in phase I and 63 in phase II. RP2D of rego was 80 mg, days 1-14/21, and 70 pts treated at that dose. As of Sep 14, 11 pts remain on treatment. At baseline, median age was 54 years (23-81), 51% female, 53% white, 19% Asian, 12% black, and 11% Hispanic, median prior lines of therapy 2 (1-5), primary tumor location rectosigmoid/rectal 13%, KRAS mutated 68%, BRAF mutated 5%. Liver metastases was present in 78% of the pts. There was no grade 4 toxicity. The most common grade 3 toxicities were rash (20%), followed by hand-foot syndrome and HTN (7%). Dose modification was required in 14%. The most common reason for discontinuation was disease progression (85%), followed by withdrawal of consent (12%). With a median follow up of 5.3 (range:0.6-24.4) months, median PFS was 2.0 (1.8 -3.5) months, and median OS was 10.9 (5.3-NR) months. In 16 pts (23%), with non-liver metastatic disease PFS was 4.3 (1.9-8.4) months. No objective response was observed. Stable disease was observed in 49% of pts, median duration of stable disease was 2 (0.2-18.8) months. **Conclusions:** This is the largest trial of combination of ICI + rego in MSSCRC reported to date. The trial didn't meet its primary endpoint, though the median OS is provocative. Analysis of biomarkers for identification of pts with longer duration of benefit is ongoing. Clinical trial information: NCT03657641. Research Sponsor: Bayer and Merck.

PD-1 blockade alone for mismatch repair deficient (dMMR) locally advanced rectal cancer.

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Background: Total neoadjuvant therapy with induction chemotherapy and chemoradiation (chemoRT) is the standard treatment for locally advanced rectal adenocarcinomas. Mismatch repair deficient (dMMR) rectal tumors respond poorly to neoadjuvant chemotherapy. PD-1 blockade is effective in patients with metastatic dMMR colorectal cancers, but its efficacy has not been established in the neoadjuvant setting. The purpose of this study is to evaluate the clinical benefit of neoadjuvant PD-1 blockade in dMMR locally advanced rectal cancer. **Methods:** We designed a prospective, single-arm, phase II study in which patients with stage II and III dMMR rectal cancer receive neoadjuvant dostarlimab (anti-PD-1) for a total of 6 months. The co-primary objectives are to determine the overall response rate (ORR) and pathologic complete response (pCR) or clinical complete response rate (cCR) with or without chemoRT. Tumor assessment with endoscopic evaluation is performed at baseline, 6 weeks, 3 months and 6 months; imaging is performed at pretreatment baseline, 3 months and 6 months. Patients with cCR by previously established criteria are eligible for non-operative management without chemoRT. Those with residual disease after neoadjuvant dostarlimab receive standard chemoRT. Following chemoRT, any patient failing to achieve a cCR is then managed surgically. **Results:** A total of 13 patients have been enrolled, with median age 52 years (range 26-78), 77% female, and 92% with node-positive disease by rectal MRI. The ORR is 100% in the 12 patients who have undergone at least a 3-month evaluation. Seven patients have completed induction therapy and all 7 (100%) have achieved a cCR and are undergoing observation without chemoRT or surgery. The rate of progressive disease thus far is 0%. No patients have required chemoRT or surgery. There have been no serious adverse events. **Conclusions:** Single agent neoadjuvant PD-1 blockade with dostarlimab is effective and well-tolerated in locally advanced dMMR rectal adenocarcinoma and allows patients to avoid chemoradiation and surgery. This suggests a potential new paradigm for treatment of dMMR locally advanced rectal cancer. Follow up and further patient accrual is ongoing. Clinical trial information: NCT04165772. Research Sponsor: GlaxoSmithKline, Other Government Agency.

17 **Poster Session**

Association between tumor mutation profile and clinical outcomes among Hispanic-Latino patients with metastatic colorectal cancer.

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Background: According to the World Health Organization GLOBOCAN database, in 2019, approximately 1.8 million new colorectal cancer cases were diagnosed, and almost 861,000 deaths were reported. In the United States, CRC is the third most frequent type of cancer and the second leading cause of cancer-related death. Although the overall incidence of CRC among the Hispanic population has been declining over the last decades, recently, a dramatic increase in CRC incidents among Hispanics younger than 50 years of age (early-onset CRC) has been reported. The increase in the incidence of early-onset CRC is markedly more significant in Hispanic-Latino (HL) patients population (45%) than in non-Hispanic Whites (NHW) (27%) and African-Americans (AA) (15%). Additionally, in contrast to NHW, Hispanics have a worse survival rate. The exact reason for these racial disparities and the biology of CRC in the HL population are not well understood. Therefore, we performed this study to better understand the biology of the disease in HL patients, which might help to identify new directions for targeted therapy. **Methods:** For the study, 52 formalin-fixed paraffin-embedded (FFPE) tumor tissue samples were collected and analyzed. We compared the results with individual patient clinical histories and outcomes. Of 52 patients with mCRC, 52 (100%) were identified as HL. We identified several commonly altered genes in HL patients (*APC, TP53, KRAS, GNAS, PICK3CA,* and *NOTCH).* Compared to those in other studies. **Results:** Mutation frequencies in the *APC* gene were significantly higher among HL patients with mCRC. Moreover, the prevalence of the *APC* mutation was significantly higher among male HL patients compared to female patients. The combination of mutations in the *APC, NOTCH,* and *KRAS* genes in the same tumors was associated with a higher risk of progression after the first-line of chemotherapy and worse overall survival. In addition, mutations in the combination of *GNAS* and *AURKA* genes were associated with a significantly higher risk of progression after the first-line of chemotherapy. **Conclusions:** The data support the notion that the molecular drivers of colon cancer might be different in HL patients compared to other racial/ethnic groups. Research Sponsor: None.

Racial disparities in colon cancer management in the National Cancer Database.

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Background: Racial and ethnic minorities in the US are at increased risk of developing and dying from colorectal cancer. Reasons for these disparities are multifactorial, among which are delayed presentation and initial disease management. We aimed to identify groups at highest risk to help address these disparities. **Methods:** Using the 2010-2017 National Cancer Database (NCDB), we analyzed clinical tumor stage at presentation and pathologic stage for adult patients (age≥18) diagnosed with primary colon cancer. We also examined trends in upstaging, downstaging, and delays >42 days between presentation and surgical intervention. We compared these outcomes by race/ethnicity using multivariable logistic or median regression, with select demographics, facility factors, and treatment details as covariates. **Results:** Fifty-one percent of patients with known clinical tumor stage (122,452/239,939) were diagnosed with stage III/IV at presentation, and 41% of those with known pathologic stage (123,009/298,716) had stage III/IV disease. In multivariable analysis, Black (OR 1.18, p<0.01) and Southeast Asian (OR 1.12, p=0.02) patients were significantly more likely than White patients to present with clinical stage III/IV. Black (OR 1.08, p<0.01), Hispanic (OR 1.07, p<0.01), East Asian (OR 1.28, p<0.01), and Southeast Asian (OR 1.40, p<0.01) patients were significantly more likely than White patients to have pathologic stage III/IV. Both clinical and pathological stage were available for 96,959 patients. Among those with clinical stage 0/I/II, Hispanic (OR 1.08, p=0.04), East Asian (OR 1.38, p<0.01) and Southeast Asian (OR 1.27, p=0.01) patients had significantly higher odds than White patients of being upstaged to pathologic stage III/IV. Among those with clinical stage III/IV, Black patients (OR 0.85, p=0.02) had significantly lower odds than White patients of being downstaged to pathologic stage 0/I/II. Black (OR 1.42, p<0.01), Hispanic (OR 1.33, p<0.01) and Southeast Asian (OR 1.23, p=0.05) patients had higher odds than White patients of waiting >42 days between presentation and surgery. **Conclusions:** Upstaging of colon cancer between diagnosis and surgery is disproportionately experienced by non-white patients. Surgical delays may partly explain this finding. Targeted interventions to avoid surgical delays as well as further research on the reasons (e.g., differences in tumor characteristics) for upstaging are needed to address this disparity. Research Sponsor: None.

Disease staging & surgical delays, by race/ethnicity.

Race/Ethnicity	OR (Clinical Stage III/IV)	p-value	OR (Pathologic Stage III/IV)	p-value	OR (Being Upstaged)	p-value	OR (>42 day delay)	p-value
Black	**1.18**	**<0.01**	**1.08**	**<0.01**	1.03	0.22	**1.42**	**<0.01**
Hispanic	1.03	0.15	**1.07**	**<0.01**	**1.08**	**0.04**	**1.33**	**<0.01**
East Asian	0.92	0.06	**1.28**	**<0.01**	**1.38**	**<0.01**	0.86	0.11
Southeast Asian	**1.12**	**0.02**	**1.40**	**<0.01**	**1.27**	**0.01**	**1.23**	**0.05**

OR = Odds Ratio

19 **Poster Session**

Chemotherapy delivery in early-onset colorectal cancer is impacted by urban versus rural settings in Colorado.

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Background: While colorectal cancer (CRC) incidence has been decreasing overall, incidence in adults under age 50 has been rising both nationally and across Colorado. National guidelines have adapted to recognize this trend, but knowledge gaps regarding early-onset CRC remain. This group has previously established rising early-onset CRC incidence in Colorado, as well as later stage at diagnosis and worse prognosis. This study examines demographics, treatment, survival, and concomitant disease among patients < 50 and diagnosed with CRC across a multicenter healthcare system in Colorado in order to better understand early-onset CRC. **Methods:** We analyzed 1,192 CRC cases in patients < 50 from the Colorado Health Data Compass database and cross-referenced these cases with the Colorado Central Cancer Registry to examine for association of gender, race/ethnicity, BMI, zip code, insurance type, stage, and concomitant medical conditions with overall survival and oncologic treatment modality. Logistic regressions were used to evaluate the relationships between chemotherapy and the important variables while adjusting for covariates, with 95% confidence intervals reported. Cox proportional hazard regressions were used to evaluate the relationships between overall survival and the important variables while adjusting for covariates, with 95% confidence intervals reported. **Results:** Overall, early-onset CRC in our population was 2.8% stage I, 6.3% stage II, 12.7% stage III, 18.5% stage IV, and 59.8% were unstageable or no stage recorded. Surgical treatment was associated with a 52% improvement in overall survival. Chemotherapy treatment was not associated with any survival changes in stage II disease. Radiation treatment, insurance type, number of concomitant conditions, geographic location, and race/ethnicity were not associated with overall survival. Upon exploring chemotherapy relationships, patients from urban areas were significantly more likely to receive chemotherapy than patients from rural areas, while adjusting for ethnicity, inpatient encounters, and stage (OR 5.55, $p = 0.001$). **Conclusions:** While less is known about CRC in patients < 50, trends are emerging that are not as well described in a traditional CRC population. The difference between urban and rural patients and their rates of chemotherapy points to a potential disparity in access to care, particularly when considering advanced stage CRC. This persisted through insurance type, indicating that distance from an infusion center, rather than ability to pay, is more likely to be driving this relationship. Further research is needed to determine if these findings are generalizable to the larger early-onset CRC population, and how access may be affecting care for this population. Research Sponsor: U.S. National Institutes of Health.

20 **Poster Session**

Incomplete preoperative staging results in suboptimal treatment in rectal cancer patients: A population-based study.

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Background: Individuals with rectal cancer require a number of pre-treatment investigations to determine the local-regional and overall stage of disease. Stage of rectal cancer determines treatment plan; therefore incomplete or inadequate staging may result in sub-optimal care and outcomes. **Methods:** This is a population based study of all individuals undergoing surgical resection for rectal cancer in Ontario, Canada (population 14.6 million) between 2010 and 2019. Individuals were identified using the Ontario Cancer Registry which includes approximately 95% of all incident cases of rectal cancer in the province. "Complete Staging" in Rectal Cancer has previously been defined and includes assessments of distant metastasis, local-regional stage and an attempt at colonic assessment for synchronous lesions. Patient and care provider characteristics, staging investigations, stage of disease, treatments and long-term outcomes were determined using linked administrative databases. **Results:** The study cohort included 10,957 individuals with rectal cancer; 24% Stage I, 21% Stage II, 40% Stage III, 7% Stage IV, 8% Missing Stage. The average age was 65 (STD 12.6) and males accounted for 63% of the study population. Incomplete staging occurred in 26%, with incomplete local regional staging being the most common deficiency (21%). Increasing patient age (< 0.001), low volume surgeons ($P < 0.001$) and low volume hospitals ($P < 0.001$) were associated with incomplete staging. There was significant regional variation in the completeness of staging (low 68% - High 84%). In those with locally advanced rectal cancer (Stage II and Stage III), incomplete staging was associated with lower rates of preoperative radiation oncology assessments (27% vs. 80%, $P < 0.001$) and medical oncology assessments (12% vs. 39%, $P < 0.001$). In addition, incomplete staging was associated with lower rates of any radiation (pre or postoperative) (45% vs. 82%, $P < 0.001$), lower rates of preoperative neoadjuvant therapy (22% vs. 74%, $P < 0.001$) and higher rates of post operative radiation (23% vs. 8.3%, $P < 0.001$). Those with incomplete staging had a lower 5 year overall survival (73% vs. 81%, $P < 0.001$). **Conclusions:** In this study, we identified several modifiable risk factors for incomplete staging prior to treatment for rectal cancer. Incomplete staging likely results in suboptimal care in this population, as demonstrated by less oncology referrals and less use of appropriate neoadjuvant therapy. Research Sponsor: CIHR, Queen's University Internal Grant.

21 **Poster Session**

Colorectal cancer incidence in Texas border versus non-border counties.

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Background: There are 32 counties and 2.8 million people in the Texas border region. The population is 88.4% Hispanic with estimates that 47% lack health insurance - not including non-US citizens, who are more likely to lack health insurance than US citizens. In 2014, 7 of the 20 US counties with the lowest CRC screening rates were in Texas, 6 of which were Texas border counties. It is unknown how the incidence of CRC in Texas border counties has changed over time compared to non-border counties. In this study, we investigate changes in the incidence of CRC in Texas border counties between 2000 and 2017. **Methods:** Data were obtained from the Texas Department of State Health Service's Texas Cancer Registry. Cases of patients aged 18 or older between 2000 and 2017 were included in our analysis. Cases were excluded if they contained incomplete information regarding age, sex, year of diagnosis, site of diagnosis or poverty level. Simple descriptive statistics were calculated for all covariates. Chi-square tests of independence were created to examine the association between each categorical variable and border county status. Age-adjusted incidence rates (AAIR) were created for the state overall and by border status. SAS v9.4 was used for all data analysis. **Results:** In border counties from 2000 to 2017, the overall AAIR decreased from 65.9 (per 100,000) to 56.7. In those 50-64 years old and 65 years and older residing in border counties, the AAIR increased from 63.3 to 78.1 and decreased from 244 to 176.1, respectively. In non-border counties from 2000 to 2017, the overall AAIR decreased from 85.2 (per 100,000) to 57.3. In those 50-64 years old and 65 years and older residing in non-border counties, the AAIR decreased from 94.9 to 78.0 and from 303 to 168.5, respectively. **Conclusions:** The overall AAIR of CRC was lower in Texas border counties compared to non-border counties, which is likely a consequence of lower screening rates in border counties. The overall AAIR decreased at a slower rate in Texas border counties compared to non-border counties, which may represent lower rates of utilization of CRC screening over time in border counties. The increase in the AAIR among those 50-64 years old in Texas border counties warrants further investigation. Research Sponsor: None.

22 **Poster Session**

Outcomes of IBD-associated colorectal cancer and implications in early-onset colorectal cancer.

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Background: Inflammatory bowel disease (IBD) increases the risk of developing colorectal cancer (CRC), and colitis-associated CRC (CA-CRC) mortality is on the rise. It has been postulated that CA-CRC may be contributing to the increasing prevalence of early-onset CRC (EOCRC) but supportive studies are currently lacking. Molecular and clinical differences between CA-CRC and sporadic-CRC (S-CRC) have been reported, however outcomes for CA-CRC remains unclear. Signet ring cell carcinoma (SRC) is a rare subtype of CRC which is seen at higher frequencies, along with mucinous histology, in both CA-CRC and EOCRC. In this study, we validate the association of SRC and mucinous (SRC/M) histology with CA-CRC and EOCRC, and utilize it to estimate the amount of EOCRC attributable to undiagnosed or subclinical IBD. **Methods:** A retrospective study was conducted using three independent mCRC patient datasets from MDACC. The mATTACC discovery cohort consisted of 32 IBD- and 425 S-mCRC patients enrolled in a prospective biomarker trial. Validation of tumor histology was completed with a tumor registry (n=1696), excluding the MSI-High samples, and a real-world evidence (RWE) cohort from MDACC containing 269 CA-mCRC and 29,596 S-mCRC patients, was used as our validation cohort. **Results:** In the mATTACC cohort SRC/M histology was found in 37.5% of CA-mCRC and 11.7% of S-mCRC, showing a strong association between SRC/M and CA-mCRC (OR = 4.54, 95% CI: 2.19-9.43). The RWE cohort confirmed the correlation of SRC/M with CA-mCRC (28.6%) relative to S-mCRC (11.4%) patients (OR = 3.13, 95%CI: 2.39-4.09). An association was found between SRC/M and EOCRC (OR = 1.35; 95% CI: 1.24-1.47). By comparing the prevalence of SRC/M in EOCRC and late-onset CRC and correcting by the proportion of CA-CRC cases with SRC/M histology, we estimate that between 8.28% to 10.15% of EOCRC may attributable to undiagnosed/subclinical IBD. Using the RWE cohort, median overall survival was determined to be lower for CA-mCRC (31m) relative to S-mCRC (39m; p=0.007), yielding a HR of 1.26 (95% CI: 1.06-1.48). CA-mCRC patients with EOCRC (25m) were also found to have significantly worse outcomes than S-mCRC patients (40m) with EOCRC (p=0.0005; HR = 1.61, 95%CI: 1.23-2.11). Within CA-mCRC, patients with SRC or SRC/M histology (21m) had decreased OS compared to mucinous histology (51m), indicating the poor prognosis of SRC in CA-mCRC (p=0.028; HR=0.53, 95% CI: 0.3-0.94). **Conclusions:** Tumor biology consistent with CA-CRC, including SRC/M histology, may be present in 8.3% – 10.2% of patients with EOCRC without a clinical diagnosis of IBD, and harbors worse outcomes. Although other confounding biology may be underlying this association, recognition of undiagnosed IBD in CRC patients, especially those with metastatic disease, is important as it may impact prognosis and treatment strategies for this high-risk patient population. Research Sponsor: None.

23 **Poster Session**

CRC-PREVENT: Clinical validation trial to show expedited and diverse recruitment for the non-invasive RNA-FIT test that can detect advanced colorectal neoplasia with high sensitivity.

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Background: Prevailing methods for patient recruitment in large prospective studies can be time consuming, expensive, and introduce selection bias against patients with low health literacy or reduced access to healthcare. Previous clinical trials have reported low recruitment of women, minorities, and individuals who face socioeconomic barriers; a concern which has been exacerbated by the COVID-19 pandemic. Here we describe a novel recruitment strategy that helps to address healthcare disparities. This study will support a pre-market approval application to the FDA for a multi-factor RNA-FIT assay for detection of colorectal neoplasia in average-risk individuals between the ages of 45-75. **Methods:** A decentralized clinical trial (CRC-PREVENT) was launched through a digital campaign (https://www.colonscreeningstudy.com/; NCT04739722) after the RNA-FIT test system entered design-lock. Online advertisements were published on multiple social media sites and engagement with materials directed patients to an online screener. Participants who completed the screener were considered eligible for enrollment if they met CRC-PREVENT inclusion/ exclusion criteria and were willing to complete all components of the clinical trial, including providing a stool sample prior to an optical colonoscopy. **Results:** After 3 months of active enrollment, 51,588 individuals have engaged with digital advertisements and completed pre-screener surveys to determine eligibility. In total, 35,280 individuals were deemed eligible based on survey response, and 13,294 eligible individuals also expressed interest in the CRC-PREVENT clinical trial. Of these individuals, 48% were female and 34% were over the age of 60 years old. Regarding race, interested individuals directly represented the intended use population: 17% were Black or African American, 2.7% were Asian, and 1.3% were Native Hawaiian, Pacific Islander, American Indian, or Alaskan Native. With respect to ethnicity, 8.4% identified as Hispanic or Latinx. The decentralized approach also permitted access to individuals with socioeconomic healthcare inequities: 27% had income under $29,999 and 14% were on Medicaid. Individuals were derived from all 48 continental United States, and of those who reported their residential location, approximately 3% were from rural areas. **Conclusions:** Use of a decentralized recruitment strategy permitted highly successful enrollment in the face of challenges associated with COVID-19. With respect to race, ethnicity, socioeconomic status, and geography, all metrics represented significantly more diverse populations than observed in traditional clinical studies. Decentralized enrollment mitigated selection bias, and will result in data more reflective of the intended use population. Clinical trial information: NCT04739722. Research Sponsor: Geneoscopy.

Medicaid expansion to reduce racial disparity in the incidence of early onset colorectal cancer.

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Background: Early onset colorectal cancer (EO-CRC, age $<$ 50 years) is an emerging public health crisis, especially in minorities. We evaluated and compared the effects of Medicaid expansion on the incidence of EO-CRC among Hispanics, Blacks, and Whites across the United States. **Methods:** The National Cancer Data Base was used to collect data on newly diagnosed cases of EO-CRC (40-49 years) among the three races, across all stages, from 2010-2017. Data for 21 expansion states (ES) that expanded Medicaid in 2014, and 16 non-expansion (NES) states was analyzed, excluding the states which expanded after 2014.The yearly state-wise population of all three races was collected from the U.S Census Bureau for 2010-17. A segmented Poisson regression model with generalized estimating equations was used for statistical analysis. **Results:** Annual incidence (AI) of EO-CRC pre and post expansion, in ES was 6/100,000 and 9/100,000 in Hispanics; 17/100,000 and 21/100,000 in Blacks and 14/100,000 and 18/100,000 for Whites. In NES the AI, pre and post 2014 was 8/100,000 and 10/100,000 among Hispanics, 19/100,00 and 24/100,000 among Blacks and 16/100,000 and 20/100,000 among Whites. Rate of change in AI of EO-CRC among Hispanics was 4.3% per year (2010-14), and 9.8% (2014-17) for ES states; and 6.4% (2010-14), and 1% (2014-17) in NES; among blacks was 3.8 % per year (2010-14), and 1.3% (2014-17) for ES states; and 1.6% (2010-14), and 3.2% (2014-17) in NES. Among Whites, increase in AI was 4.3% per year (2010-14), and 6.3% (2014-17) for ES states; and 4.0% (2010-14), and 5.7% (2014-17) in NES. ES showed greater change in incidence after expansion compared to pre-expansion in the incidence of EO-CRC as compared to NES (p=0.03) in Hispanics, however no significant difference was noted among Blacks (p=0.33) and Whites(p=0.94). Racial groups did significantly differ with respect to the degree of change in pre and post expansion (2014) rates of incidence of EO- CRC in the ES, however, in the NES, there were significant difference between the Hispanics and Whites (p=0.01), but not between Blacks versus Whites. **Conclusions:** Medicaid expansion reduces racial disparities in detection of EOCRC. Research Sponsor: None.

Comparison of yearly incidence rate of change by racial groups (Expansion year-2014).

	Hispanics		Blacks		Whites	
	Before expansion	After expansion	Before expansion	After expansion	Before expansion	After expansion
Non-expansion states	6.4% (2.2%, 10.7%)	1.0% (-3.8%, 6.0%)	1.6% (-0.7%, 3.9%)	3.2% (-0.1%, 6.6%)	4.0% (2.7%, 5.3%)	5.7% (3.6%, 7.7%)
Expansion states	4.3% (0.7%, 8.0%)	9.8% (5.2%, 14.7%)	3.8% (-0.1%, 7.9%)	1.3% (-2.5%, 5.3%)	4.3% (2.1%, 6.6%)	6.3% (4.5%, 8.0%)
p-value	0.03	0.33	0.94			

25 **Poster Session**

Colorectal cancer biomarker, AABH (Aspartyl [Asparaginyl] β- hydroxylase), a companion imaging and treatment strategy.

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Background: Colorectal cancer (CRC) is the third most common type of cancer diagnosed in the US and Canada. WHO, Canadian Cancer Society (CCS), the National Comprehensive Cancer Network (NCCN) and American Cancer Society (ACS) recommend that men and women begin CRC screening at age 50 or younger if at high risk. Recommended screening procedures: Annual occult fecal blood test (OFBT), a colonoscopy every 5 years, OFBT and colonoscopy every 5 years, or a colonoscopy every 10 years. According to The Surveillance, Epidemiology, and End Results (SEER) Program, only 39% of CRC are diagnosed in stage I, 36% are diagnosed in stage II, 19% are diagnosed with metastasis. The corresponding 5-year survival rates are 89.8%, 67.7%, and 10.3%. Neither the CCS nor the ACS recommends a blood test to be done as part of screening. This is due to the fact that, until now, there has not been a blood test with adequate sensitivity or specificity for screening. **Methods:** In this study we discovered that aspartyl (asparaginyl) β-Hydroxylase (AABH) measurement in serum can be used as a screening test for CRC. AABH has been detected by immunohistochemical staining (IHC) on the cell surface of different cancers including CRC. It has been detected by IHC in $>$ 97% of tumor specimens tested (n $>$ 210) but has not been found in tissue samples from normal individuals. **Results:** This observation and the observation that AABH is found in the serum of patients with cancer, but not in non cancer patients, led us to develop a Sandwich ELISA Assay to measure AABH in serum. In the current study we have quantified AABH levels in CRC patients and compared it with normal individual. Increased levels of AABH were found in the serum of 99% of patients with CRC in all different stages of Cancer (n = 277). In normal individuals, AABH was essentially undetectable in serum (n = 195). AABH was identified in serum from patients with CRC irrespective of cancer stage. All serum AABH levels for stages I, II, III and IV were more than 3.0 ng/mL. **Conclusions:** Thus, our data indicate that by measuring AABH in the serum, we should be able to detect CC at an earlier stage than it is currently detected, resulting to a much better 5-year survival for colon cancer. Research Sponsor: Next Pharma Inc.

26 **Poster Session**

Detection of minimal residual disease (MRD) in colorectal cancer (CRC) patients UICC stage II/III by ultra-deep sequencing of cfDNA from post-surgery plasma.

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Background: Detection of primary tumor mutations in cell-free DNA (cfDNA) of post-surgery plasma of patients with R0-resected not-metastasized solid tumors is a strong indicator of recurrence of disease. We explored whether ultra-deep sequencing of cfDNA could improve sensitivity and specificity with respect to time-to-progression. **Methods:** 84 CRC patients UICC stage II/III were recruited into the prospective, observational study "Molecular Signatures in Colorectal Cancer". Matched tumor tissue samples, plasma depleted blood cells (PDBC), and cfDNA (drawn 1 to 34 days after R0-resection, median 7 days) were processed with the Roche AVENIO Tumor Tissue and ctDNA Surveillance Kits*. Samples of 79 patients passed all quality controls, in particular cfDNA was sequenced ultra-deep with a median of 180 Mio. instead of 50 Mio. reads/sample. Somatic variants were identified with AVENIO Oncology Analysis software 2.0*. PDBC informed germline variants were removed. If a tissue baseline variant was detected in cfDNA with a significant adjusted p-value, the patient was defined ctDNA+, and ctDNA- otherwise. **Results:** 8 ctDNA+ patients (28 variants, median AF = 0.15%) were identified of which 4 had a progression of disease at two years. Sensitivity was 44% (95% CI [0.137, 0.788]), specificity was 94% (95% CI [0.86, 0.984]), positive predictive value was 50% (95% CI [0.157, 0.843]), and negative predictive value was 93% (95% CI [0.843, 0.977]). Comparison of time-to-progression of ctDNA+ and ctDNA- patients using the log-rank test resulted in a p-value of 0.0058. Comparison of survival times of ctDNA+ and ctDNA- patients resulted in a p-value of 0.0333. Multivariate analyses of times-to-progression resulted in ctDNA-status (p = 0.0022, hazard ratio (HR) = 7.098) and neoadjuvant therapy (p = 0.0010, HR = 6.618) as significant parameters. **Conclusions:** Even in this small cohort of CRC UICC stage II/III patients, MRD detection in post-surgery plasma is the strongest predictor of shorter time to progression. Ultra-deep sequencing of cfDNA samples did not influence MRD detection on a patient-level. *for Research Use Only; not for use in diagnostic procedures. Research Sponsor: F. Hoffmann-La Roche Ltd.

The association between preoperative CEA, the systemic inflammatory response and survival in colon cancer.

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Background: Prior to curative surgery for colon cancer, carcinoembryonic antigen (CEA) has been reported to be a poor prognostic factor recommended for routine measurement, however the majority of studies evaluating this have not adjusted for the preoperative systemic inflammatory response (SIR) –widely shown to be associated with worse outcomes. The present study aims to analyse the association between preoperative CEA and long-term outcomes when adjusted for other factors including Systemic Inflammatory Grade (SIG). **Methods:** The effect on overall/cancer specific survival (OS/CSS) of preoperative CEA (<5/5+) was examined in a regional cohort of patients undergoing surgery for colon cancer after adjustment for other clinicopathological factors including the SIR as measured by Systemic Inflammatory Grade (SIG). **Results:** 624 patients were identified undergoing curative surgery for colon cancer with a preoperative CEA available. For 3-year OS stratified by TNM Stage, CEA offered further prognostic value in patients with TNM Stage I (98% vs 75%, p=0.002), but not Stage II (p=0.444) or Stage III (p=0.351) disease. For 3-year OS stratified by SIG, CEA did not add further significant prognostic value for any SIG (all p>0.05). On multivariate analysis, age (HR 1.65, p=0.020), sex (HR 0.53, p=0.001), mode of presentation (HR 1.93, p=0.008), TNM Stage (HR 1.83, p<0.001) and SIG (HR 1.30, p<0.001) remained significant for OS, but not CEA (p=0.620). **Conclusions:** The present results show that there is limited prognostic value of preoperative CEA. The SIR as measured by SIG should be routinely measured prior to curative colonic surgery. A mandatory reporting dataset is required in colorectal cancer and should include SIG. Research Sponsor: None.

Overall and cancer specific survival stratified by clinicopathological variables including preoperative CEA (uni and multivariate analysis).

	Cancer Specific Survival (CSS)				Overall Survival (OS)			
	UVA		MVA		UVA		MVA	
Variable	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age	1.43 (1.13-1.82)	0.003	1.38 (1.05-1.80)	0.020	1.65 (1.35-2.01)	<0.001	1.65 (1.30-2.09)	<0.001
Sex	0.77 (0.53-1.12)	0.170	-	-	0.68 (0.50-0.92)	0.012	0.53 (0.37-0.76)	0.001
SIMD	0.85 (0.74-0.97)	0.014	-	0.096	0.86 (0.77-0.95)	0.004	-	0.069
Mode of presentation	2.27 (1.36-3.81)	0.002	-	0.226	2.30 (1.52-3.50)	<0.001	1.93 (1.18-3.14)	0.008
Smoking	1.04 (0.78-1.37)	0.799	-	-	1.22 (0.98-1.52)	0.076	-	0.093
TNM	3.19 (2.29-4.43)	<0.001	2.65 (1.74-4.05)	<0.001	2.07 (1.64-2.61)	<0.001	1.83 (1.39-2.42)	<0.001
EMVI	3.78 (2.51-5.67)	<0.001	2.24 (1.38-3.65)	0.001	2.38 (1.76-3.23)	<0.001	-	0.272
Differentiation	1.50 (0.98-2.30)	0.062	-	0.957	1.52 (1.08-2.15)	0.017	-	0.219
SIG	1.51 (1.29-1.75)	<0.001	1.39 (1.19-1.63)	<0.001	1.45 (1.29-1.64)	<0.001	1.30 (1.13-1.49)	<0.001
Preop anaemia	1.20 (0.94-1.53)	0.135	-	-	1.42 (1.18-1.71)	<0.001	-	0.987
CEA	1.61 (1.18-2.18)	0.002	-	0.812	1.86 (1.28-2.70)	0.001	-	0.620

Combining the quantitative fecal immunochemical test and full blood count to rule out colorectal cancer in a symptomatic patient referral pathway.

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Background: The faecal immunochemical test (FIT) has proven utility for colorectal cancer (CRC) detection in symptomatic patients. Most studies have examined FIT in symptomatic patients subsequently referred from primary care. We investigated associations between CRC and FIT in both referred and non-referred symptomatic patients. **Methods:** A retrospective, observational study of all patients with a FIT submitted Aug'18-Jan'19 in NHS GG&C was performed. Referral to colorectal/gastroenterology and decision to perform colonoscopy were recorded. FIT results were grouped as f-Hb<10/10-149/150-399/≥400ug/g. The MCN cancer registry identified new cases of CRC. Covariables were compared using the χ^2 test. Multivariate binary logistic regression identified independent predictors of CRC. **Results:** 4968 patients were included. Raised FIT correlated with decision to refer ($p<0.001$) and scope ($p<0.001$). With 23-month median follow-up, 61 patients were diagnosed with CRC. These patients were older (median 69 vs. 59 years, cancer and no cancer respectively, p=0.001), more likely to be male (55.7% vs. 42.1%, p=0.033) and to report rectal bleeding (51.7% vs. 36.1%, p=0.013). FIT (<10 μg/g 8.2% vs. 76.7% and ≥400 μg/g 55.7% vs. 3.8%, $p<0.001$) and anaemia (45.9% vs. 19.7%, $p<0.001$) were associated with CRC. On multivariate analysis, age (p=0.023), male sex (p=0.04), FIT (≥400 OR 54.256 (95% CI: 20.683-142.325; $p<0.001$)) and anaemia (OR 1.956 (1.071-3.574;p=0.029)) independently predicted CRC. 1 patient (0.04%) with a negative FIT and normal haemoglobin had CRC. **Conclusions:** Referral from primary care and secondary care investigation patterns were influenced by FIT. The combination of normal Hb and f-Hb excluded CRC in 99.96% of cases, providing excellent reassurance to those prioritising access to endoscopy services. Research Sponsor: None.

29 **Poster Session**

Correlation of circulating tumor DNA (ctDNA) with clinical outcomes in appendiceal cancers (AC).

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Background: Appendiceal Cancers are a heterogenous group of rare tumors with distinct histopathologic and genomic alterations. These often have peritoneal spread that might not be easily detected on current imaging modalities, and conventional tumor markers may not lend diagnostic support. Hence, novel diagnostic techniques are needed. Measurement of ctDNA for recurrence risk prediction, response to therapy and and early diagnosis is a promising technique. However, limited published data exist in AC to validate the role and utility of ctDNA in clinical practice. Here we present a single institution experience of ctDNA analysis in patients with AC. **Methods:** ctDNA measurements of 37 pts with stage II-IV AC treated between 1/1/2019 and 9/15/2021 were reviewed retrospectively. ctDNA analysis was done using Signatera bespoke mPCR NGS assay. ctDNA results were compared to crossectional imaging, CEA levels, and clinical evaluation. **Results:** 19/37 patients (51%) had at least one positive ctDNA test result. Of those, 8 had testing done during the surveillance setting (two with grade 3, one with grade 2, two with grade 1, and three with unknown grade). Of those, 5 pts (62.5%) had positive ctDNA detected, while 33.33% had elevated CEA level, 25% had radiographic and 42.9% had clinical evidence of recurrence (Table). 7/14 (50%) pts had high-grade pathology and positive ct-DNA, 3/6 (50%) patients had low-grade (grade 1) pathology and positive ct-DNA findings. 4 patients had longitudinal ct-DNA measurements available which correlated well with their disease course. Median duration to recurrence (radiographic or laparoscopic) was 376 days. Median duration to the first positive ctDNA test was 370 days. Median duration to positive CEA after initial treatment was 475 days. **Conclusions:** Measurement of ctDNA can be a useful tool to follow disease course and to guide management decision-making in patients with AC. Prospective studies with serial measurements of ctDNA are planned. Research Sponsor: None.

ct-DNA findings compared to CEA, radiographic and clinical evidence of recurrence in patients with AC.

Ct-DNA detection	5/8 (62.5%)
CEA elevation	2/6 (33.3%)
Radiographic recurrence	2/8 (25%)
Clinical evidence of recurrence	3/7 (42.9%)

30 **Poster Session**

COVID-19 vaccination in gastrointestinal cancer patients receiving chemotherapy: A single institute experience.

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Background: Early approval of COVID-19 vaccine has significant benefits for cancer patients treated under the COVID-19 pandemic worldwide. However, there has been limited reports that investigated the safety and efficacy of vaccination in cancer patients and the optimal timing of vaccination during chemotherapy. We therefore investigated the effects of vaccination on treatment in cancer patients receiving chemotherapy. **Methods:** Our retrospective observational study included 52 patients with gastrointestinal (GI) cancer receiving chemotherapy at the medical hospital of Tokyo Medical and Dental University in Tokyo who had two doses of mRNA COVID-19 vaccine (Pfizer-BioNTech or Moderna) between May 2021 and September 2021. All patients had no history of COVID-19 infection. Treatment- and vaccination-related adverse events were recorded by outpatient interviews and self-reports. All adverse events were evaluated using CTCAE v5.0. **Results:** Characteristics of patients were as follows (N = 52): median age, 70y (range, 49–89); male/female, 30/22; ECOG PS 0, 75%; local/metastatic, 12/40; mean BMI, 23.4±4.1; comorbidities in 36 (cardiovascular in 24, diabetes in 8, kidney disease in 8, liver disease in 6, lung disease in 1); treatment (cytotoxic in 45, biologics in 23, immune checkpoint inhibitor in 4). Of the 52 patients, 45 received chemotherapy prior to vaccination; days from last dose to first vaccination, median 11 (range, 1–70); days from first to second vaccinations, median 21 (range, 21–41); days from first vaccination to chemotherapy, median 10 (range, 2–34). 11 patients (24.4%) changed treatment schedule: 3 for safety reasons, 4 for myelosuppression and 4 for convenience. 4 patients stopped treatment due to disease progression. Following the first vaccination, 37 patients (82.2%) had adverse events (AEs): injection site pain (n = 35), fatigue (n = 6), fever (n = 3), headache (n = 2), gastrointestinal symptoms (n = 2), redness (n = 1), insomnia (n = 1). There was no treatment- and vaccine-related deaths. **Conclusions:** Our findings suggest that vaccine-related AEs in GI cancer patients receiving chemotherapy are tolerable, and treatment schedule changes could be minimized. Although careful monitoring is required, COVID-19 vaccination is also recommended for cancer patients toward the convergence of the COVID-19 pandemic. Research Sponsor: None.

Impact of the COVID-19 pandemic on primary care access for patients with gastrointestinal malignancies.

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Background: Primary care physicians (PCPs) provide essential support for cancer patients. Both primary and cancer care have been affected by the COVID-19 pandemic. In the US, cancer related encounters and screening decreased over 40% and 80% respectively in January to April 2020 compared to 2019 (London et al JCO Clin Cancer Inform 2020). However, the impact of the pandemic on primary care access for cancer patients remains unclear. **Methods:** This was a population-based, retrospective cohort study using administrative healthcare databases held at ICES in Ontario, Canada. Patients with a new gastrointestinal (GI) malignancy diagnosed within the year prior to the pandemic, between July 1 and Sept 30, 2019 (COVID-19 cohort), were compared to patients diagnosed in years unaffected by the pandemic, between July 1 – Sept 30, 2018 and July 1 – Sept 30, 2017 (pre-pandemic cohort). Both groups were followed for 12 months after initial cancer diagnosis. In the COVID-19 cohort, this allowed for at least 4 months of follow-up data occurring during the pandemic. The primary outcome was number of in-person and telemedicine visits with a PCP. Secondary outcomes were number of in-person and telemedicine visits with a medical oncologist, number of emergency department (ED) visits, and number of unplanned hospitalizations. Outcomes, reported as number of visits per person-year, were compared between the COVID-19 and pre-pandemic cohorts. **Results:** 2833 individuals diagnosed with a new GI malignancy in the COVID-19 cohort were compared to 5698 individuals in the pre-pandemic cohort. The number of in-person visits to PCPs per person-year significantly decreased from 7.13 [95% CI 7.05 – 7.20] in the pre-pandemic cohort to 4.75 [4.66 – 4.83] in the COVID-19 cohort. Telemedicine visits to PCPs increased from 0.06 [0.05 – 0.07] to 2.07 [2.01 – 2.12]. Combined in-person and telemedicine visits to PCPs decreased from 7.19 [7.11 – 7.26] to 6.82 [6.71 – 6.92]. In-person visits to medical oncologists decreased from 3.73 [3.68 – 3.79] to 2.87 [2.80 – 2.94], and telemedicine visits increased from 0.10 [0.10 – 0.11] to 0.95 [0.91 – 0.99]. Combined in-person and telemedicine visits to medical oncologists remained stable (3.84 [3.78 – 3.89] vs. 3.82 [3.74 – 3.90]). The number of ED visits per person-year decreased from 1.04 [1.01 – 1.07] in the pre-pandemic cohort to 0.93 [0.89 – 0.97] in the COVID-19 cohort. Unplanned hospitalizations did not show a significant change (0.56 [0.54 – 0.58] vs. 0.53 [0.50 – 0.56]). **Conclusions:** PCP visits for patients with newly diagnosed GI malignancies overall decreased during the pandemic, with a dramatic shift from in-person to telemedicine visits. Visits to medical oncologists also shifted from in-person to telemedicine, but the overall combined visits remained the same. While the number of ED visits decreased, the shift in ambulatory practices did not seem to impact the number of unplanned hospitalizations. Research Sponsor: Canadian Institutes of Health Research, Other Government Agency.

33 **Poster Session**

COVID-19 impact on diagnosis and staging of colorectal cancer: A single tertiary Canadian oncology center experience.

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Background: COVID-19 pandemic urged public health to imposed drastic reduction on endoscopic activities and surgery, leading to delays that still not have been caught up today. The Ministry of Health and Social Services (MSSS) of Quebec conducted a study of the impact of those measures and reported a 66% reduction of colonoscopy and a 30% reduction of colorectal cancer (CRC) surgery activities during the first wave (March to May 2020). Whether those reduction had an impact on diagnosis and staging of CRC remains unknown. **Methods:** Demographic information of CRC diagnosed at Centre Hospitalier de l'Université de Montréal (CHUM) between January 1 2018 and March 12 2020 (pre-pandemic period), and March 13 2020 and June 30 2021 (pandemic period) were obtained from the SARDO registry and data regarding colonoscopy, surgery and staging at diagnosis (clinical or pathological as appropriate) were collected. Priority of elective colonoscopy was defined using the MSSS grading system ranging from P1 to P5. We compared delays to colonoscopy, delays to surgery and CRC staging of the pandemic period to the pre-pandemic period using one-way ANOVA, t tests and Chi-square tests as appropriate. Only delays in elective surgeries intended as first and curative treatment were analyzed. **Results:** 280 CRC diagnosis were made at the pre-pandemic period compared to 127 CRC diagnosis during the pandemic period. Mean diagnosis rates of the pandemic period tend to be lower (8.3 vs. 10.5 diagnosis/month, p=0.03) compared to the pre-pandemic period. 37.6% of patient in the pandemic period had a diagnosis of CRC during a hospitalization compared to 25.9% at the pre-pandemic period (p=0.048). 51.7% of elective colonoscopy leading to a diagnostic of CRC during the pandemic period did not meet required delays according to priority compared to 38.3% (p=0.049) during the pre-pandemic period. P3 colonoscopies (mostly indicated for a positive FIT and iron deficiency anemia) were the most affected (58.9 vs. 106.5 days, p<0.001). P2 colonoscopy (indicated for suspected colorectal cancer) did not experienced an augmentation in delays (20.9 vs. 25.2 days, p=0.39). A mean of 3.5 elective curative surgeries per month were performed during the pandemic period compared to 3.4 at the pre-pandemic period (p=0.96), and mean delays for surgery were not affected (60.4 vs. 57 days, p=0.59). Stages at diagnosis did not differ (p=0.2). Most of the delayed colonoscopies led to a stage 0 or I CRC and did not lead to a higher stage at diagnosis (p=0.2). **Conclusions:** In our center, the COVID-19 pandemic led to overall less CRC diagnosis and increased diagnostic endoscopic delays without a higher rate of advanced stage disease. Delays for elective surgeries were quite similar once the CRC diagnostic established. Research Sponsor: None.

34 **Poster Session**

Patient care satisfaction and emergency room utilization among young adult colorectal cancer survivors during the SARS-CoV-2 pandemic.

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Background: Survivors of colorectal cancer (CRC) are at risk for late effects of therapy and recurrence of cancer. With recurrence rates ranging between 30-40% (Siegal et al., 2020), consistent, survivor-focused follow-up care is needed for early detection of late effects and recurrence (Jeffery et al., 2019). CRC-related care delivery has been significantly disrupted by the SARS-CoV-2 pandemic, with decreases of 40% in CRC services in the United States between April 2020 and 2019 (Jammu, 2020). Consequentially, survivors may be left with fewer options for care, potentially causing increases in emergency room (ER) utilization. **Methods:** This cross-sectional study examined the patterns of ER utilization during the SARS-CoV-2 pandemic among young adult CRC survivors and assessed the relationship between self-reported care satisfaction and ER use. Eligible participants were diagnosed with colon or rectal cancer between 18-39 years, between 6-36 months from diagnosis/relapse, English speaking, and based in the United States. Questions on care satisfaction were Consumer Assessment of Healthcare Providers and Systems (CAHPS) questions. A multivariable logistic regression was conducted to assess the association between patient satisfaction and ER utilization, adjusting for factors related to the pandemic. Covariates for this analysis were chosen based on a significance of $p < 0.1$ at the univariate level, as well as general clinical significance. **Results:** The overall sample was N = 196, mean age (SD) was 32.1 years (4.5), and 116 survivors (59%) were male. Tumor location was colon or rectal in 42% and 57%, respectively, and the majority (56%) were diagnosed with stage 2 disease; 42.6% reported relapsed disease, and 20% had an ostomy. The majority of survivors (72.5%) had between 1-4 visits to an emergency room in the last 12 months and were categorized as *normal* users. Approximately 24.7% of the sample had greater than 4 visits to the ER in the last 12 months and were categorized as *super*-utilizers (Johnson et al., 2015). Colorectal cancer survivors that reported a delay in their follow-up cancer care as a result of the pandemic were two times (OR: 2.05, 95% CI 0.99, 4.24) more likely to be super-utilizers of the ER. Higher self-reported satisfaction with overall care was associated with a 13.7% (OR: 0.86, 95%CI: -0.68, 1.09) lower likelihood of being a super-utilizer. **Conclusions:** This study found strong associations between delays in care, self-reported care satisfaction, and being a super-utilizer of the ER during the pandemic among young adult CRC survivors off treatment. Increasing patient satisfaction and minimizing care interruptions amongst this vulnerable population may aid in mitigating over-utilization in the ER during an ongoing pandemic. Research Sponsor: The Aflac Archie Bleyer Young Investigator Award in Adolescent and Young Adult Oncology from the Children's Oncology Group.

35 **Poster Session**

Colorectal cancer conversations on Twitter: A content analysis of global perceptions and outreach efforts.

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Background: Screening is highly effective at reducing colorectal cancer (CRC) mortality. Social media is extensively used to communicate about cancer care, yet little is known about the role of these online platforms in promoting CRC screening and early diagnosis. This study tracked Twitter discussions about CRC and characterized participating users to better understand public communication and perceptions of CRC on social media. **Methods:** Tweets containing references to CRC were collected from January 2020 to April 2021 using Twitter's Application Programming Interface. Account metadata was used to predict user demographic information and classify users as either organizations, individuals, or influencers. Influencers represent high-impact users, defined by sizeable follower counts or verified Twitter status. Latent Dirichlet Allocation, a natural language processing model, was used to identify observed topics of discussion in the collected tweets. **Results:** There were 72,229 unique CRC-related tweets by 31,170 users. Tweets reached a daily maximum after Chadwick Boseman, a well-known American actor, died from CRC. Individuals accounted for the majority of users (62.8%); organizations (35.2%); influencers (2%). Influencers made the most median impressions (35,853 impressions). Tweets contained the following topics: bereavement (27.9%), appeals for early detection (19.4%), research (14.0%), National Colorectal Cancer Awareness Month (NCCAM) (13.7%), screening access (12.5%), and risk factors (12.4%). Tweets referencing bereavement had the most user engagement. Links to clinical trial enrollment information were the least shared type of embedded content (0.3%). **Conclusions:** Discussions about CRC largely focused on bereavement and early detection. Online coverage of NCCAM, personal experiences, and celebrity deaths related to CRC effectively stimulated goal-oriented tweets about early detection. Our findings suggest that Twitter may be a suitable platform for promoting and communicating future public health recommendations about CRC. Research Sponsor: None.

36 **Poster Session**

Comparative analysis of overall survival in patients with HER2-amplified treatment-refractory metastatic colorectal cancer treated with pertuzumab plus trastuzumab in Mypathway and patients treated in the real-world.

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Background: ML28897 (MyPathway) is a multi-basket trial evaluating the efficacy and safety of targeted therapies in non-indicated tumor types harboring relevant genetic alterations. In MyPathway, patients with treatment-refractory HER2-amplified metastatic colorectal cancer (mCRC) were enrolled and received pertuzumab plus trastuzumab. In order to facilitate contextualization of the outcome of pertuzumab plus trastuzumab in MyPathway, we conducted a retrospective study to compare with the outcome in real-world HER2-amplified mCRC patients. **Methods:** Overall survival (OS) was used as the endpoint to compare outcomes from MyPathway (PER/HER arm) and the external control of HER2-amplified mCRC patients treated with any therapy except anti-HER2 therapy in the refractory setting (EC arm) from the US-based de-identified Flatiron Health-Foundation Medicine Clinico-Genomic Database (CGDB). The de-identified data originated from approximately 280 US cancer clinics (~800 sites of care). OS was defined as time from first treatment to death in the PER/HER arm and from index date (initiation of treatment in the refractory setting) to death in the EC arm. For patients in the CGDB who had met study eligibility criteria at multiple index dates, all eligible index dates were used for the analysis. Standardized mortality ratio weighting based on propensity score was used for deriving the pseudo-population (post-weighting population). In the post-weighting population, multivariate Cox regression models and Kaplan-Meier analyses were used to compare between the arms. A series of sensitivity analyses were conducted to investigate the robustness and consistency of the primary analysis results. **Results:** The PER/HER arm consisted of 57 patients who had treatment-refractory mCRC with HER2 amplification and enrolled in the MyPathway by August 1, 2017 data cutoff. For the EC arm, 64 HER2-amplified mCRC patients were selected from CGDB collected between January 1, 2011 and December 31, 2019. After applying the predefined inclusion/exclusion criteria set to be similar to those in the MyPathway, 27 eligible index dates were selected from 18 eligible patients and used for primary analysis. In the post-weighting population, the hazard ratio (HR) for OS estimated by multivariate Cox regression model was 0.729 (95% CI: 0.184-3.900) and median survival in the PER/HER arm and the EC arm were 11.47 months (95% CI: 7.72-22.11) and 9.72 months (95% CI: 7.43-22.21), respectively. The results of the all sensitivity analyses were consistent with those in the primary analysis in terms of the point estimate of HR. **Conclusions:** Despite a small sample size, the totality of findings suggests that the combination of pertuzumab and trastuzumab could have a potential benefit in OS for this population. Research Sponsor: None.

WJOG13219G: Triplet versus doublet in patients with previously untreated *BRAF*^{V600E}-mutant metastatic colorectal cancer: A multi-institutional real-world data analysis (BRACELET study).

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Background: The survival benefit of FOLFOXIRI plus bevacizumab (Triplet) over Doublet in patients (pts) with *BRAF*^{V600E}-mutant metastatic colorectal cancer (mCRC) remains controversial. We compared Triplet therapy with Doublet and explored the pts subgroups that could benefit from intensive chemotherapy (chemo) using real-world data. **Methods:** WJOG13219G was a multicenter, retrospective registry-based study of pts with *BRAF*^{V600E}-mutant mCRC who received first-line doublet or triplet chemo with/out molecular targeted agents in January 2014–December 2019. Primary analysis focused on pts who received VEGF inhibitor-containing chemo. To adjust pts background, the inverse probability of treatment weighting (IPTW) method based on propensity scores calculated by age, ECOG PS, and disease status (recurrent/metastatic) was used. **Results:** A total of 232 pts from 33 hospitals were registered. After excluding 18 pts treated with anti-EGFR antibody-containing regimen and 44 without any targeted agents, 79 pts with Triplet and 91 with Doublet were analyzed. Baseline pts disposition was as follows: median age, 61 y; male proportion, 51%; PS 0/1/≥2, 63%/32%/5%; recurrent/metastatic, 26%/74%; and right/left primary, 68%/32%. Significant differences were noted in age and PS between the two groups. At median follow-up of 24.0 months, no statistical difference was noted in progression-free survival (PFS) (median 9.7 months of Triplet vs. 7.8 months of Doublet, HR = 0.89, P = 0.49) and overall survival (OS) (median 18.7 vs. 18.3 months, HR = 0.87, P = 0.52). The objective response rate was 53% in the Triplet group and 41% in Doublet (P = 0.10). Curative surgery after chemo was more frequent in the Triplet group than in Doublet (13% vs. 3%, P = 0.02). Two pts (3%) in the Triplet group and 6 (7%) in Doublet received immunotherapy as subsequent chemo; 13 (16%) and 6 (7%) also received BRAF inhibitor-containing therapy. IPTW analysis showed no difference between the two groups in PFS (HR = 0.82, P = 0.07) and OS (HR = 0.92, P = 0.57). In the subgroup analysis, pts with right-sided primary tumor in the Triplet group showed favorable trends of PFS (HR, 0.87; 95% CI, 0.65–1.16) and OS (HR, 0.71; 95%CI, 0.50–1.01), whereas pts with left-sided tumor in the Triplet group showed the reverse trends of PFS (HR, 1.17; 95% CI, 0.77–1.78) and OS (HR, 1.68; 95% CI, 0.97–2.91). **Conclusions:** Some baseline characteristics were significantly different between real-world pts in the Triplet and Doublet groups. Although the Triplet group did not show any survival benefit compared with Doublet in the original and IPTW cohorts, pts with right-sided *BRAF*^{V600E}-mutant mCRC could benefit from Triplet therapy. Research Sponsor: None.

A twice-daily or a three-times-daily tegafur-uracil and leucovorin calcium regimen as adjuvant therapy in patients with resected colorectal cancer: A phase III study.

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Background: Tegafur-uracil (UFT)/leucovorin calcium (LV) is an adjuvant chemotherapy treatment for colorectal cancer. We conducted a multicenter randomized trial to assess the noninferiority of a twice-daily compared with a three-times-daily UFT/LV regimen for stage II/III colorectal cancer in an adjuvant setting. **Methods:** Patients were randomly assigned to group A (three doses of UFT [300 mg/m2 per day]/LV [75 mg per day]) or B (two doses of UFT [300 mg/m2 per day]/LV [50 mg per day]). The schedule of 28-day oral administration followed by a 7-day rest period was repeated. Five 35-day cycles were repeated. The primary endpoint was 3-year disease-free survival. The secondary endpoints included 5-year overall survival and toxicity. **Results:** In total, 386 patients were enrolled between July 28, 2011, and September 27, 2013. The 3-year disease-free survival rates of group A (n = 194) and B (n = 192) were 79.4% and 81.4% (95% confidence interval, 72.6-84.4-74.5-85.9), respectively. The 5-year overall survival rates of group A and B were 89.7% and 91.0% (95% confidence interval, 83.3-92.8-84.8-93.8), respectively. The most common grade 3/4 adverse events in group A and B were diarrhea (3.9% vs. 7.3%), neutropenia (2.9% vs. 1.6%), increase in aspartate aminotransferase (4.0% vs. 3.9%), increase in alanine aminotransferase (6.2% vs. 6.8%), nausea (1.7% vs. 3.4%), and fatigue (1.1% vs. 2.3%). **Conclusions:** Group B outcomes were not inferior to group A outcomes, and adverse events did not increase. Clinical trial information: UMIN000005594. Research Sponsor: Clinical Study Group of the Osaka University Colorectal Group (CSGOCG).

39 **Poster Session**

A real-world comparison of trifluridine/tipiracil and regorafenib in refractory metastatic colorectal cancer in the United States.

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Background: For patients with refractory metastatic colorectal cancer (mCRC), both trifluridine/tipiracil (TAS-102) and regorafenib have received approval for use in the United States. The approvals of these agents were based on modest improvements in overall survival (OS) when compared to best supportive care plus a placebo in the RECOURSE and CORRECT trials, respectively. However, TAS-102 and regorafenib have never been directly compared in a prospective clinical trial. This study utilized a large real-world database to compare clinical outcomes with use of these agents. **Methods:** The nationwide de-identified Flatiron Health EHR-derived database was reviewed for patients diagnosed with mCRC between 2015 and 2020. Patients who received at least two lines of guideline recommended therapy for advanced disease followed by treatment with TAS-102 and/or regorafenib in the third line or greater 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 propensity score weighted models were used to compare survival outcomes between groups. **Results:** The records of 22,078 patients with mCRC were reviewed. Of the 4,407 patients that received at least two lines of standard therapy, 2,072 subsequently received regorafenib and/or TAS-102. Of these, 813 (39.2%) received TAS-102 alone, 275 (13.3%) TAS-102 followed by regorafenib, 736 (35.5%) regorafenib alone, and 248 (12.0%) regorafenib followed by TAS-102. Median OS for patients treated with TAS-102 alone or prior to receiving regorafenib was 6.66 months (95% CI 6.16-7.18) compared to 6.30 months (95% CI 5.80-6.79) for those treated with regorafenib alone or prior to receiving TAS-102 ($p = 0.36$). A propensity score weighted analysis controlling for age, race, stage at initial diagnosis, performance status at start of therapy, MSI/MMR status, RAS/RAF status, and line in which TAS-102 or regorafenib was received did not demonstrate a significant difference in survival between groups (HR 0.99, 95% CI: 0.90 -1.09, $p = 0.82$). A subgroup analysis did not identify any significant differences in outcomes stratified by age, performance status, MSI status, or RAS/RAF status. **Conclusions:** This analysis of real-world data did not identify a significant difference in survival outcomes in mCRC patients who were treated with TAS-102 or regorafenib. Median OS with both agents in a real-world setting was similar to that shown in the clinical trials that led to their approvals. This data should be considered when discussing the risks and benefits of TAS-102 and regorafenib with mCRC patients who are eligible for third line or greater treatment. Research Sponsor: None.

The potential long-term comparative effectiveness of larotrectinib versus entrectinib for treatment of metastatic TRK fusion colorectal cancer.

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Background: Commonly used systemic therapies in metastatic colorectal cancer (CRC) for patients who have progressed through available first- and second-line regimens are regorafenib or trifluridine/tipiracil. For the subset of metastatic CRC patients with neurotrophic receptor tyrosine kinase (*NTRK*) gene fusions, there are two additional approved options, larotrectinib or entrectinib. Our objective was to estimate and compare expected life-years (LYs) and quality-adjusted life-years (QALYs) for metastatic TRK fusion CRC patients receiving larotrectinib versus entrectinib. **Methods:** We developed a partitioned survival model to project long-term comparative effectiveness of larotrectinib vs. entrectinib. Extrapolation was necessary as follow-up for both drugs was less than three years at the time of data reporting. Survival data for larotrectininb, assessed by independent review committee, were derived from a July 2020 analysis of 8 adult (≥18 years of age) TRK fusion CRC patients from the larotrectinib clinical trials program (NCT02122913, NCT02637687, and NCT02576431). Survival inputs for entrectinib were derived from 7 TRK fusion CRC patients from an October 2018 integrated analysis of three single arm trials (EudraCT 2012-000148-88, NCT02097810, and NCT02568267). Progression-free survival (PFS) and overall survival (OS) for both treatments were estimated using parametric survival distributions (Exponential, Weibull, Log-logistic, and Log-normal) fit to the available data. Exponential curves were used based on goodness-of-fit and clinical plausibility. QALYs were estimated by adjusting the time spent in the pre-progression and post-progression health states by health state utilities derived from publicly available literature. A constant discount rate of 3% was applied to LYs and QALYs. Model uncertainty was evaluated using one-way sensitivity analysis and probabilistic sensitivity analysis with 10,000 simulations. **Results:** Larotrectinib resulted in 2.11 LYs and 1.60 QALYs compared to 0.53 LYs and 0.41 QALYs for entrectinib. These estimates yielded additional gains for larotrectinib of 1.58 LYs and 1.19 QALYs against entrectinib. **Conclusions:** In metastatic TRK fusion CRC, larotrectinib may produce substantial life expectancy and quality-adjusted life-year gains compared to entrectinib. Additional data with longer follow-up times will further inform this comparison. Research Sponsor: Bayer US LLC.

41 **Poster Session**

The potential long-term comparative effectiveness of larotrectinib versus regorafenib or trifluridine/tipiracil for treatment of metastatic TRK fusion colorectal cancer.

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Background: Colorectal cancer (CRC) is the third leading cause of cancer-related mortality in the US, driven primarily by those with metastatic disease. For patients with metastatic disease who have progressed through available first- and second-line options, the standard of care systemic therapies are regorafenib or trifluridine/tipiracil. Larotrectinib is approved for patients with TRK fusion advanced solid tumors including metastatic CRC. Our objective was to compare expected life-years (LYs) and quality-adjusted life-years (QALYs) for metastatic CRC patients eligible to receive larotrectinib, regorafenib or trifluridine/tipiracil. **Methods:** We developed a partitioned survival model to project long-term comparative effectiveness of larotrectinib vs. regorafenib or trifluridine/tipiracil. Larotrectinib survival data, assessed by independent review committee, were derived from a July 2020 analysis of 8 adult (≥18 years of age) metastatic TRK fusion CRC patients from the larotrectinib clinical trials program (NCT02122913, NCT02637687, and NCT02576431). Survival inputs for regorafenib and trifluridine/tipiracil were derived from the CORRECT trial (NCT01103323) and the RECOURSE trial (NCT01607957), respectively. Progression-free (PFS) and overall survival (OS) for larotrectinib, regorafenib, and trifluridine/tipiracil were estimated using survival distributions (Exponential, Weibull, Log-logistic, and Log-normal) fit to the available data. Exponential fits were used based on goodness-of-fit and clinical plausibility. QALYs were estimated by adjusting the time spent in the pre-progression and post-progression health states by health state utilities derived from publicly available literature. In accordance with standard practice in health economics and outcomes research on future health benefits, a constant discount rate of 3% was applied to the LYs and QALYs. Model uncertainty was evaluated using one-way sensitivity analysis and probabilistic sensitivity analysis with 10,000 simulations. **Results:** Larotrectinib resulted in 2.11 LYs and 1.60 QALYs compared to 0.83 LYs and 0.59 QALYs for regorafenib and 0.85 LYs and 0.60 QALYs for trifluridine/tipiracil. These estimates yielded additional gains for larotrectinib of 1.28 LYs (1.01 QALYs) and 1.26 LYs (0.99 QALYs) against regorafenib and trifluridine/tipiracil, respectively. **Conclusions:** In metastatic CRC, larotrectinib may produce substantial life expectancy and quality-adjusted life-year gains compared to regorafenib or trifluridine/tipiracil. Additional data with longer follow-up times will further inform this comparison. Research Sponsor: Bayer US LLC.

Quality of life among colorectal cancer (CRC) survivors participating in a pilot trial of a web-based dietary intervention with text messages.

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Background: Diet may be associated with survival and health-related quality of life (HRQOL) among CRC survivors. Behavioral interventions using web and mobile technology are feasible and acceptable approaches to modify dietary behavior. Little is known about the effect of web-based dietary interventions on HRQOL among CRC survivors. **Methods:** The Survivor Choices for Eating and Drinking study (SUCCEED) was a pilot randomized wait-list controlled trial designed to determine the feasibility and acceptability of a 12-week (wk) web-based dietary intervention with daily text messages. In this secondary analysis, we estimated the effect of the intervention on HRQOL. Between 2017-2018, 50 CRC survivors were randomized (1:1) to intervention or control. Participants in the intervention arm received the intervention in wk 1-12 and were followed from wks 12-24. Participants assigned to the control arm for 1-12 wks had the option to receive the intervention in wks 13-24. In both arms, HRQOL and sleep quality were assessed using the EORTC QLQ–C30 and CR29 and the Pittsburgh Sleep Quality Index at 0, 12, and 24 wks. Within- and between-group mean changes in HRQOL from enrollment to 12 and 24 wks were evaluated using independent t-test and paired t-test. **Results:** Follow-up was 88% complete at 12 and 24 wks in the intervention arm and 92% and 80% complete at 12 and 24 wks in controls. Participants mean age was 56 ± 9 y; 34% were men, 70% identified as non-Latinx White, 12% identified as Latinx, and 70% had stage III cancer. Between 0 and 12 wks, an increase in emotional functioning was observed in the intervention arm [mean change: 9.1; 95% confidence interval (CI): 2.2,16.0], while a decrease in emotional functioning was observed in controls (mean change: -5.1; 95%CI: -14.5,4.1; between-group mean difference: 14.3; 95%CI: 3.0,25.6). Between 0 and 24 wks, an increase in social functioning (mean change in intervention: 12.1; 95%CI: 2.1,22.1; between-group mean difference: 13.8; 95%CI: 2.1,25.5) and a decrease in fatigue (mean change in intervention: -9.1; 95%CI: -17.1,-1.1; between-group mean difference: -4.1; 95% CI: -15.8,7.6) was observed in the intervention arm. No other measures of HRQOL or sleep quality differed within or between arms. **Conclusions:** A web-based dietary intervention with daily text messages may improve emotional and social functioning among CRC survivors. Further study to evaluate the effect of web-based interventions on HRQOL among CRC survivors in larger studies may be merited. Clinical trial information: NCT02965521. Research Sponsor: U.S. National Institutes of Health.

43 **Poster Session**

Real-world data analysis of antiangiogenic targeted treatments in second-line following anti-EGFR antibodies and FOLFOX in first-line for patients with metastatic colorectal cancer.

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Background: Three antiangiogenic (AA) drugs, bevacizumab (BEV), ramucirumab (RAM) and aflibercept (AFL) are recommended as the second-line (2L) treatment for metastatic colorectal cancer (mCRC) in the CRC treatment guidelines of multiple countries and regions including the US, EU and Japan. However, little evidence of 2L RAM and AFL after anti-EGFR antibodies (EGFRab) in first- line (1L) has been reported. This study assessed treatment sequence for mCRC patients who received 2L irinotecan-based chemotherapy with AA drug after FOLFOX + EGFRab in 1L, treatment duration from the start of 2L to the end of last treatment line (treatment duration from 2L) and factors associated with the treatment duration from 2L. **Methods:** This is a real-world observational study using a hospital-based claims database of 393 hospitals in Japan. The mCRC patients who started 1L treatment with FOLFOX + EGFRab between May 2016 and Sep 2019 (identification period) and further treated with irinotecan-based chemotherapy + AA drug were enrolled. The key outcomes were the treatment sequence, treatment duration from 2L by AA drug, and factors associated with the treatment duration from 2L. Survival curves were estimated using the Kaplan–Meier method. Associated factors were investigated using Cox regression analysis. **Results:** Among 2,453 patients with 1L FOLFOX + EGFRab during the identification period, 506 patients who received the intended 2L therapies were enrolled in this study (mean age 63.5 years, male 66.6%). Number (%) of patients who used BEV, RAM and AFL in 2L was 345 (68.2), 120 (23.7) and 41 (8.1), respectively. Patient characteristics involving tumor location, metastatic site and prior anti-tumor therapy before starting 2L were similar among BEV, RAM and AFL. The treatment duration from 2L (median month and its 95%CI) was 11.1 (10.2-12.5) in the overall population and was similar among the patients who received BEV (10.8 [9.9-13.1]), RAM (11.2 [10.0-14.2]) and AFL (12.8 [6.9-NA]) in 2L. The treatment duration from 2L (median month and its 95%CI) for the patients who took or didn't take proteinuria tests during 2L was 12.5 (11.1-15.2) and 8.5 (6.5-11.2), respectively. Factors positively associated with treatment duration from 2L were left-sided CRC (HR [95%CI] = 0.71 [0.53-0.96]) and ≥6 months of 1L duration (0.72 [0.56-0.93]); having renal disease (1.92 [1.28-2.88]) or received NSAIDs (1.63 [1.25-2.13]) within 60 days before starting 2L were associated negatively. **Conclusions:** The real-world data revealed that treatment duration were similar among BEV, RAM and AFL in 2L after EGFRab. Tumor location and 1L duration were associated with the treatment duration from 2L positively, while negative association was observed with renal disease and received NSAIDs. Treatment management was important for treatment continuation. Research Sponsor: Eli Lilly Japan K.K.

Survival outcome and treatment response of patients with young-onset locally advanced rectal cancer (YO-LARC) receiving total neoadjuvant therapy (TNT).

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Background: Despite an alarming rise in incidence, data on survival outcome and treatment response of young-onset (age $<$ 50 years) locally advanced rectal cancer (YO-LARC) patients receiving total neoadjuvant therapy (TNT) are sparse. We retrospectively compared the outcome between YO-LARC and later-onset (aged 50 years or older) LARC (LO-LARC) patients treated with TNT. **Methods:** After the institutional review board approval, electronic medical records of the LARC (T3/T4 or node-positive) patients treated with TNT at a tertiary care cancer center between January 1, 2015, and June 30, 2020, were reviewed for data collection. TNT consisted of systemic chemotherapy with oxaliplatin-based regimens for 16 weeks followed by long-course radiation with concurrent capecitabine or 5-fluorouracil (CRT). Patients receiving only preoperative CRT were excluded. Most patients underwent surgical resection following the TNT. Non-operative management was offered to patients if TNT resulted in clinical complete response (cCR). The following comparisons between the YO-LARC and the LO-LARC patients were performed: patient characteristics, pathological complete response (pCR) rate, combined pCR + cCR rate, disease-free survival (DFS), and overall survival (OS). **Results:** Of 72 patients included in the analysis, 44(61%) were male, 49 (68%) were Caucasian, and 62 (86%) had clinical stage III disease. The study included 26 (36%) patients with YO-LARC (median age, 43 years) and 46 (64%) patients with LO-LARC (median age, 64 years). The comparison of patient characteristics that included gender, clinical stage, baseline carcinoembryonic antigen level, the distance of the tumor from the anal verge, presence of high-risk features, and histologic grade did not differ significantly between the groups. There were no statistically significant differences in pCR and combined pCR+cCR rates ($p = 0.16$) between the groups: YO-LARC, 12 % (3/26) and 15 % (4/26), respectively; LO-LARC, 22% (10/46) and 30% (14/46), respectively. Either group did not reach median DFS and OS after a median follow-up of 38 months for survivors. The estimated 5-year OS rates in patients with YO-LARC and LO-LARC were 86 % (95% confidence interval [CI], 69% to 100%) and 84% (95% CI, 68% to 100%), respectively ($p = 0.92$). The estimated 3-year DFS rates in patients with YO-LARC and LO-LARC were 67 % (95% CI, 50% to 89%) and 83% (95% CI, 72% to 95%), respectively ($p = 0.19$). **Conclusions:** The current retrospective analysis did not demonstrate significant differences in the pCR rates, combined pCR +cCR rates, DFS, or OS between the YO-LARC and LO-LARC patients treated with TNT. Research Sponsor: None.

45 **Poster Session**

General and mental health status following colorectal cancer treatment and its association with mortality among a racially diverse population-based cohort.

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Background: Patient-reported outcomes (PROs) are recognized as strong predictors of cancer prognosis, outcomes, and care. However, racial/ethnic minorities with colorectal cancer (CRC) tend to report poorer general health status (GHS) and mental health status (MHS) compared to non-Hispanic whites. The objectives of this study were to determine: (1) if there are racial/ethnic differences in GHS and MHS within 36 months of CRC diagnosis and (2) if poorer GHS and MHS in recently diagnosed CRC patients are associated with mortality. **Methods:** We used the population-based Surveillance, Epidemiology, and End Results (SEER)-Consumer Assessment of Healthcare Providers and Systems (CAHPS) dataset to analyze Medicare beneficiaries aged ≥65 years who were diagnosed with CRC between 1998 and 2011, received surgical resection for their tumor, and completed a CAHPS survey within 6-36 months post-diagnosis. CAHPS surveys captured patient-reported GHS and MHS on a five-point Likert scale ranging from "poor" to "excellent." We used stepwise multivariable logistic regression to examine associations between patient race/ethnicity and fair or poor health status, adjusting for clinical and sociodemographic factors. Additionally, a multivariable Cox proportional hazards regression was used to determine the risks of mortality associated with fair or poor GHS and MHS. **Results:** Of 1,867 patients with CRC, 79.5% were non-Hispanic white (NHW), 6.4% were non-Hispanic black (NHB), 7.5% were Hispanic, and 6.6% were non-Hispanic Asian (NHA). In Model 1 of our stepwise logistic regression, NHB patients had higher unadjusted odds for fair or poor GHS (OR 1.56, 95% CI 1.06-2.28) compared to NHW patients while Hispanic patients had higher unadjusted odds for both fair or poor GHS (1.48, 1.04-2.11) and MHS (1.92, 1.23-3.01). In Model 2, this relationship persisted after adjusting for clinical factors, with NHB patients being more likely to report fair or poor GHS (1.62, 1.10-2.40) and Hispanic patients being more likely to report fair or poor GHS (1.49, 1.04-2.13) and MHS (1.92, 1.22-3.00). In Model 3, after adjusting for both clinical and sociodemographic factors, the association between race/ethnicity and fair or poor GHS ($p = 0.53$) and MHS ($p = 0.23$) no longer remained. Reporting fair or poor GHS and MHS was associated with a greater risk of mortality among all CRC patients (HR 1.52, 95% CI 1.31-1.76 and 1.62, 1.34-1.99, respectively). **Conclusions:** Our study illustrates that racial/ethnic differences in PROs are largely driven by sociodemographic factors as opposed to clinical factors. As fair or poor GHS and MHS shortly after diagnosis reflect a higher risk of mortality in CRC patients, efforts to understand unmet biopsychosocial concerns may help further elucidate racial differences in CRC survival that may be otherwise overlooked in standard clinical practice.
Research Sponsor: None.

46 **Poster Session**

Age-related trends in the incidence of metastatic colorectal cancer over the last 10 years: A retrospective analysis in commercially-insured population in the United States.

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Background: Previous studies have suggested age-related shifts in the incidence of metastatic colorectal cancer (mCRC). However, more contemporary data is needed to further understand the continuous changes in the distribution of mCRC and patient characteristics across different age groups. **Methods:** A retrospective observational study was conducted using the Optum Clinformatics database to estimate the incidence rates (IRs) and temporal trends of newly diagnosed mCRC during 2010-2019, stratified by age categories (18-49; 50-64; and 65+). IRs were calculated as the actual patient number of newly diagnosed mCRC divided by the overall enrollment number. The IRs were standardized to the 2010 US population and trends over time were characterized using annual percentage changes (APCs). **Results:** Total of 23,970 newly diagnosed patients with mCRC were identified during 2010-2019. Median age was 71 years, 65% of patients were white, and 68% of patients had commercial Medicare insurance. Most patients (69%) were 65 years of age or older at the time of mCRC diagnosis. Patients characteristics were similar across age groups, except for race and geographic region. The proportion of Hispanic (12.6%) and Asian (4.7%) mCRC patients was higher in the younger 18-49 group than in the 50-64 (respectively 9.4% and 3%) and 65+ groups (respectively 9.5% and 2.9%). Higher proportions in the 18-49 (44.4%) and 50-64 (47.5%) groups than in the 65+ group (37.6%) were from the South, while higher proportions in the 65+ group were from the West and Northeast (24.4% and 14%). Standardized IRs of mCRC decreased by 22% from 64.4 in 2010 to 50.5 per 100,000 in 2019 among patients 65+, with an APC of -2,11. Standardized IRs increased over the same period by 15% in the 50-64 group, APC = 2.33 and by 22% in the 18-49 age group, APC = 2.8. **Conclusions:** Temporal changes in mCRC incidence in a large commercially insured population during 2010-2019, showed an increasing trend in younger patients and a decreasing trend in patients 65+. The highest increase in IRs from 2010 to 2019 occurred in the 18-49 age group. Hispanic and Asian patients were more present among the 18-49 than among the older patient groups, and there were geographic differences among the age groups. The changes in age- distribution and evolving patient characteristics need to be considered in the delivery of treatments and care for mCRC. Research Sponsor: Bayer Corporation.

Options beyond BRAF targeted therapy in second-line treatment of patients with BRAFV600E mutant (BRAFmt) metastatic colorectal cancer (mCRC).

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Background: BRAFmt is a negative prognostic factor in mCRC but also identifies a patient population that may benefit from BRAF targeted therapy. Results from recent trials (BEACON and SWOG1406) demonstrate improved survival outcomes in second- and third-line settings when combining a BRAF inhibitor, an EGFR inhibitor (EGFRi) +/- a MEK inhibitor. In both trials, irinotecan and cetuximab was the control arm with a dismal response rate of 2-4% and progression free survival (PFS) of only 2 months. This suggests chemotherapy plus an EGFRi may not be the optimal approach where BRAF-targeted therapies are not available or have failed. **Methods:** Data from July 2009 to September 2021 was analysed from TRACC, a multi-site Australian mCRC comprehensive prospective registry enrolling consecutive patients. Patient characteristics, treatment and survival outcomes were examined for patients treated with chemotherapy (CT) alone, with bevacizumab (BEV) or with an EGFRi. **Results:** Of 2046 registry patients, 256 (13%) harboured a BRAFmt. 72 BRAFmt patients had received second-line (28%) treatment, including CT alone (n = 28), CT plus BEV (n = 26), and CT plus EGFRi (n = 18). Baseline characteristics are shown in the table. Median second-line PFS was 3.3, 4.7 and 1.8 months, for CT alone, CT plus BEV and CT plus EGFRi respectively. Median overall survival (OS) was 8.7, 7.9 and 2.5 months respectively. In multivariate analysis, PFS when treated with CT plus EGFRi trended inferior to CT alone ($p = 0.054$) and CT plus BEV ($p = 0.061$), whereas for OS, treatment with CT plus EGFRi was inferior to CT alone ($p = 0.038$) and CT plus BEV ($p = 0.015$). Poor PFS was associated with age ≥ 65 years (HR 3.03, $p < 0.001$) and ECOG ≥ 2 (HR 2.62, $p = 0.004$), but not associated with a right side primary ($p = 0.17$), mismatch repair (MMR) status ($p = 0.86$), or ≥ 3 organs with metastases ($p = 0.32$). Poor OS was associated with age ≥ 65 years (HR 3.11, $p < 0.001$), ECOG ≥ 2 (HR 7.32, $p < 0.001$), right side primary (HR 3.03, $p = 0.002$) and proficient MMR status (HR 3.57, $p = 0.018$), but not associated with ≥ 3 organs with metastases ($p = 0.17$). **Conclusions:** Less than one-third of BRAFmt mCRC patients received second-line therapy in a real-world setting, indicating an urgency to explore activity of BRAF targeted therapy in the first line setting. Treated patients received limited benefit, with CT plus EGFRi PFS outcomes comparable to BEACON control arm (1.8 vs 2.0 months) and trending inferior to other options. The best OS outcomes were achieved with CT alone or CT plus BEV. Research Sponsor: Pierre-Fabre.

	All treated patients (n = 72)	CT alone(n = 28)	CT plus BEV(n = 26)	CT plus EGFRi(n = 17)
Age ≥ 65 years	25 (35%)	12 (43%)	9 (35%)	4 (24%)
Female (%)	42 (58%)	21 (75%)	18 (69%)	3 (18%)
ECOG ≥ 2 (%)	7 (10%)	1 (4%)	2 (8%)	4 (24%)
≥ 3 organs with metastases (%)	19 (26%)	8 (29%)	2 (8%)	9 (53%)
Right side primary (%)	49 (68%)	16 (57%)	19 (73%)	12 (71%)
dMMR status (%)	8 (11%)	2 (7%)	5 (19%)	1 (6%)

Impact of previous adjuvant oxaliplatin combination therapy on survival in elderly colorectal cancer patients with recurrence.

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Background: The benefit of adjuvant chemotherapy with oxaliplatin for elderly patients with colorectal cancer (CRC) remains controversial. Our study could not demonstrate the benefit of adding oxaliplatin for elderly CRC patients aged over 70 years as with the previous clinical trials. Here, we evaluated the prognosis after recurrence in the elderly patients who received adjuvant chemotherapy. **Methods:** This retrospective study included patients aged over 70 years who were diagnosed with high-risk stage II and stage III CRC and received adjuvant chemotherapy in our two hospitals (The Jikei University Hospital and Katsushika Medical Center) between January 2010 and December 2019. The patients were divided into two groups; patients who received fluoropyrimidine monotherapy were included in Fp group and those who received fluoropyrimidine plus oxaliplatin were included in Fp+OX group. Moreover, we evaluated patient characteristics, treatment, and survival in the patients with recurrence and compared them between two groups. **Results:** A total of 127 patients received adjuvant chemotherapy; 75 patients in Fp group and 52 patients in Fp+OX group. With a median follow-up time of 64.5 months, the 5-years disease-free survival and 5-years overall survival in Fp group/Fp+OX group were 70.6/67.1% (hazard ratio [HR] 1.10, 95% confidence interval [CI] 0.61–1.98) and 89.0/71.8% (HR 1.48, 95% CI 0.76–2.88), respectively. The benefit of adding oxaliplatin was not observed. Among them, 15 patients in Fp group and 14 patients in Fp+OX group were relapsed; median age was 78 (range: 72-83) and 78 (range: 72-86) years, male was 67% and 64%, PS of 0/1 was 67/33% and 86/14%, primary tumor site of right/left was 47/53% and 57/43%, and RAS mutation was 20% and 29%, respectively. Median relapse-free survival was 17.7 and 14.3 months ($p = 0.453$). There were no significant differences in treatment after recurrence; aggressive treatment (surgery/chemotherapy) was 73% (33/40%) and 86% (21/65%), best supportive care was 7% each, and unknown was 20% and 7%, respectively. However, the median overall survival from the date of relapse was significantly worse in Fp+OX group than Fp group (45.0 and 14.4 months, $p = 0.011$). **Conclusions:** Recurrence after receiving adjuvant oxaliplatin combination therapy was considered as one of the poor prognostic factors. It might attenuate the benefit of adding oxaliplatin in adjuvant setting in elderly patients. Research Sponsor: None.

Real-world persistence and adherence with oral trifluridine/tipiracil or regorafenib in patients with colorectal cancer.

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Background: Trifluridine/tipiracil (FTD/TPI) and regorafenib are among the limited treatment options in later lines of therapy for patients with advanced colorectal cancer (CRC). While these treatments have demonstrated similar efficacy, differences have been observed in tolerability and data on the impact of such differences on real-world outcomes are limited. To better understand the real world use of FTD/TPI and regorafenib in the US, we report data for adherence/persistence among patients with CRC initiating these therapies. **Methods:** This was a retrospective cohort study among adults with CRC identified from the IBM MarketScan Commercial Claims and Medicare Supplemental Databases, who initiated FTD/TPI or regorafenib (index) from October 2015-September 2019 and had 6 months of continuous enrollment before the index date. Follow-up was until disenrollment or end of study period. Treatment cohorts were propensity score 1:1 matched, adjusting for differences in socio-demographics, comorbidities, and other baseline characteristics. Adherence and persistence outcomes included time to discontinuation (medication gap of >45 days), medication possession ratio (MPR; number of treated days/ duration of treatment), proportion of days covered (PDC; number of treated days/ days in specified time period), and number of prescriptions received. **Results:** A total of 1477 patients were included: 892 initiating FTD/TPI (60%) and 585 regorafenib (40%). Demographics were similar prior to matching: mean age was 58 and 59 years, and 57% and 59% were male, in the FTD/TPI and regorafenib groups, respectively. Mean Charlson Comorbidity Index score (excluding cancer) was 0.69 for FTD/TPI initiators and 0.62 for regorafenib initiators. For the matched cohorts (n=585 in each), measures of adherence and persistence (Table) showed longer time to discontinuation (2.5 vs. 2.0 months; $p<0.01$), and a higher MPR (0.90 vs. 0.87; $p<0.01$), PDC (at 3 months, 0.74 vs. 0.63; $p<0.01$), and proportion of patients receiving ≥2 prescriptions (76% vs. 63%; $p<0.01$) with FTD/TPI vs. regorafenib. **Conclusions:** Results of this real-world study suggest that patients with CRC initiating FTD/TPI have improved adherence and persistence with therapy compared with those initiating regorafenib. Reasons for this difference and potential impacts on health outcomes require further study. Research Sponsor: Taiho Oncology, Inc.

Adherence and persistence with FTD/TPI and regorafenib (matched cohorts).

	FTD/TPI (n=585)	Regorafenib (n=585)	P value
Months to discontinuation, mean	2.5	2.0	< 0.01
MPR, mean	0.90	0.87	< 0.01
PDC 3 months, mean	0.74	0.63	< 0.01
PDC 6 months, mean	0.55	0.47	< 0.01
PDC 12 months, mean	0.38	0.32	0.06
PDC 18 months, mean	0.35	0.23	0.01
≥2 prescriptions, %	76	63	< 0.01
≥4 prescriptions, %	32	25	0.02
≥6 prescriptions, %	15	10	0.03

Long-term survival outcomes following resection of lung metastases (LM) from a colorectal primary.

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Background: Liver metastatectomy in oligometastatic colorectal cancer (CRC) can result in long-term disease control[1]. The benefit of resecting LM is unclear, with good survival outcomes from medical therapy (MT) alone and a recent randomised controlled trial failed to demonstrate an overall survival (OS) benefit[2]. **Methods:** We examined TRACC (Treatment of Recurrent and Advanced Colorectal Cancer), a multisite registry for metastatic colorectal cancer (mCRC) patients (pts) from September 2002 – July 2021, focusing on the longer-term outcomes for pts with lung only metastatic disease (LOM). Key clinicopathological, treatment and outcome variables were analysed. Survival outcomes were determined by Kaplan-Meier method. **Results:** Of 3928 pts, 341 (8.7%) had LOM. The median OS was significantly improved for LOM vs. all mCRC pts (44.5 months vs. 24.8 months, p = <0.0001). Of 341 LOM pts, 142 (42%) had lung resection (LRes),128 (38%) had MT, 71 (20%) best supportive care. Key clinicopathological characteristics are summarised in Table. OS was significantly longer for LRes vs. MT (3yrs-80.1% vs. 41.9%, p = <0.0001, 5 yrs-65.2% vs. 21.1%, p = 0.0001). 10 yr survival for LRes was 50%, with no survivors from MT. The median palliative chemotherapy free interval was 13 months (95% CI 3.1 – 18.7) with recurrence after LRes/death. 20/142 (14%) of the LRes pts had recurrent LRes (median time to repeat resection of 11.4 months, median survival of 66.9 months from repeat LRes). **Conclusions:** LM from mCRC have an indolent course, with good survival outcomes with MT alone. LRes provides a clinically meaningful palliative chemotherapy free interval and long term survival in selected pts. Significant differences in prognostic factors may have contributed to the observed survival differences between LRes and MT. Reference Dexiang Z, Li R, Ye W, Haifu W, Yunshi Z, Qinghai y, Shenyong Z, Bo X, Li L, Xiangou P, Haohao L, Lehi Y, Tianshu L, Jia f, Xinyu Q, Jianmin X. Outcome of patients with colorectal liver metastasis: analysis of 1,613 consecutive cases. Ann Surg Oncol. 2012 Sep;19(9):2860-8. doi:10.1245/s10434-012-2356-9.Epub 2012 Apr 12. PMID: 22526903. Treasure, T., Farewell, V., Macbeth, F. *et al.* Pulmonary Metastatectomy versus Continued Active Monitoring in Colorectal Cancer (PulMiCC): a multicentre randomised clinical trial. *Trials* **20**,718 (2019). https://doi.org/10.1186/s13063-019-3837-y Research Sponsor: Roche and other multiple pharmaceutical sponsors for this mCRC registry.

Clinicopathological characteristics of LOM pts, treated with LRes vs. MT.

	LRes (n = 142)	MT (n = 128)	p-value
Mean age (yrs)	64.6	66.8	0.13
ECOG 0-1	135/138 (97.8%)	114/126 (90.4%)	**0.010**
(Charlson <3)	59/138 (43%)	50/126 (40%)	0.61
Primary sidedness (left vs. right)	112 (83%) vs. 23 (17%) n=135	103 (82.4%) vs. 22 (17.6%) n= 125	0.90
Primary resected	139/142 (97.8%)	104/128 (81.2%)	**<.0001**
Mutation			
KRAS/NRAS	61/98 (62.2%)	63/105 (60%)	0.74
BRAF	2/75 (2.7%)	4/79 (5.1%)	0.44
MSI (MSS vs MSI-H)	75 (96%) vs 3 (3.8%) n=78	74 (98.6%) vs 1 (1.3%) n=75	0.33

51 **Poster Session**

Integrated approach to collecting patient reported toxicities in a colorectal cancer trial.

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Background: Understanding the toxicities experienced by patients treated with advanced CRC is critical when considering appropriate dose modifications, standard drug dosing, and quality of life. A workflow that makes available Patient Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE) to clinicians to inform overall toxicity assessment should be easy to use and focus on clinically relevant issues. The value of a system that not only collects PRO-CTCAE but integrates it with clinician grading to inform overall symptomatic adverse event assessment during clinical trials is unclear. **Methods:** Patients were simultaneously enrolled in a phase II multi-center clinical trial that evaluated a genotype-guided dosing strategy for irinotecan by prospectively analyzing efficacy in 100 mCRC patients receiving FOLFIRI (5-fluorouracil, leucovorin, irinotecan) and bevacizumab. On day 1 and day 15 of each cycle patients provided PRO-CTCAE responses on 13 symptoms (26 questions) which were made available to clinicians at the time of their toxicity assessment. Descriptive statistics were used to summarize patient demographic and clinical characteristics. Concordance was defined as both patient and clinician giving the same response (both positive or both negative). **Results:** 100 patients participated in the study, of which 48% were female and 83% White. Overall, 96% of both patients and providers completed at least 80% of PRO-CTCAE forms available to them, demonstrating the feasibility of an integrated workflow for patient-clinician toxicity grading. Across all symptoms, concordance was high (73%) for the patient and provider reporting severe symptoms. 39% of patient-provider pairs reported at least 1 severe symptom and 34% of pairs never reported a severe symptom. In 23% of pairs the patient reported a severe symptom and the provider never did, and in 3% of pairs, the provider reported a severe symptom, but the patient never did. On the symptom level, the concordance was highest ($>$90%) for dysphagia and vomiting, and lowest (74-82%) for abdominal pain, fatigue, and pain. 52 patients required dose decreases, with the first decrease most often due to hematologic toxicity (80%). In 46% of cases the patient reported at least one severe toxicity prior to or on the same day as the dose decrease, compared to 19% of cases where the provider reported at least severe toxicity prior to or on the same day as the dose decrease. **Conclusions:** A workflow that brings patient-reported toxicity to clinicians at the time of clinical toxicity rating is feasible. Nevertheless, discordance continues to exist between patient-reported and clinician-reported toxicity ratings, consistent with prior research. Further research could formally compare concordance when using an integrated vs a non-integrated toxicity rating workflow and could ascertain the reasons for continued discordance within an integrated workflow. Research Sponsor: University Cancer Research Fund.

An open-label, multicenter, randomized controlled study of mXELIRI versus FOLFIRI in combination with bevacizumab as the first-line treatment in metastatic colorectal cancer: A single-center report.

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Background: The first-line treatments in metastatic colorectal cancer were FOLFOX, CAPOX, FOLFIRI and even FOLFOXIRI as basic chemotherapy regimen combined with targeted therapy. XELIRI regimen was not recommended because of the concerns about the toxicity, efficacy and controversy in optimal dosage. An increasing number of studies indicated promising efficacy with manageable safety profile of dosage and administration-adjusted XELIRI regimen. Therefore, the present study investigated the efficacy, safety and appropriate dosage of mXELIRI regimen in the first-line treatment of advanced colorectal cancer. **Methods:** The EXIST study was a multicenter, randomized controlled, non-inferiority study and we performed stratification based on the tumor location (left or right side). In the mXELIRI+Bev group, patients received intravenous infusion of irinotecan (a reduced dosage,150mg/m^2) with bevacizumab (5mg/kg) on day 1 and oral administration of capecitabine (2000mg/m^2/day) tablet on day 1-10/Q14 days. Patients in FOLFIRI+Bev group received intravenous infusion of irinotecan (180mg/m^2), calcium folinate (400mg/m^2) and 5-Fu (400mg/m^2) bolus with bevacizumab (5mg/kg) on day 1 followed by a 46-hour continuous infusion of 5-Fu (2400mg/m^2)/Q14 days. The primary endpoint was progression-free survival rate at 12 month($PFSR_{12m}$) and the secondary endpoints included ORR,OS and safety. **Results:** 142 patients were enrolled and randomly assigned to receive mXELIRI+Bev (n=76) or FOLIRI+Bev (n=66) in our center between May 2018 and April 2021. Baseline characteristics were well balanced between two groups. In the mXELIRI+Bev group, 70 patients were evaluable with an ORR of 60.0% (1 complete response, CR; 41 partial response, PR; 24 stable disease, SD; 4 progression disease PD). While 57 patients were evaluable in the FOLFIRI+Bev group, with an ORR of 63.2% (36 PR; 15 SD; 6 PD). The $PFSR_{12m}$ for two groups were 32.3% and 21.3%, the median PFS were 9.72 months and 8.77 months, respectively. For safety profiles, no statistical differences were observed in adverse events, such as nausea, vomiting, diarrhea, bone marrow suppression and abnormal liver function. While 10 serious adverse events were recorded in the mXELIRI+Bev group, including intestinal obstruction occurred in 8 patients, intestinal perforation occurred in 1 patients and venous thrombosis occurred in 1 patient. In the FOLIRI+Bev group, intestinal obstruction, venous thrombosis and pulmonary thrombosis was reported in one patient respectively. **Conclusions:** The modified biweekly XELIRI plus bevacizumab regimen demonstrated promising effect and could be well tolerated based on the data from a single center. Clinical trial information: NCT04247984. Research Sponsor: None.

53 **Poster Session**

Metastasectomy in colorectal cancer patients with concurrent lung and liver metastasis: Trends in utilization and impact on survival.

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Background: Colorectal cancer (CRC) frequently presents with concurrent metastasis to the lung and liver. Metastasectomy may offer extended disease control in a select group of patients but its utilization is unknown. We aimed to investigate the trends in utilization of metastasectomy in CRC patients with concurrent lung and liver metastasis and explore its impact on survival. **Methods:** We queried the National Cancer Database and identified stage 4 CRC patients with concurrent lung and liver metastasis between 2010 – 2016 and categorized them into those that underwent metastasectomy vs. those that did not. Categorical variables were compared using the chi-square test, and statistically significant factors were included in multivariable logistic regression analysis. In addition, 1:2 propensity score matching was performed, and a multivariable Cox regression model was used to define survival predictors among matched cohorts. The Kaplan-Meier method was used to estimate the median survival. **Results:** Out of total 77,719 stage 4 CRC patients, 10,106 (13.0%) patients had concurrent lung and liver metastasis. Six percent (n = 630) of these patients underwent metastasectomy of both sites. Patients that underwent metastasectomy were more likely to be younger (< 50 years; $p = 0.009$), female ($p < 0.001$), and White ($p = 0.01$). These patients were also more likely to have right-sided CRC ($p = 0.001$) and had resection of the primary site ($p < 0.001$). Additionally, they were more likely to have private health insurance ($p < 0.001$) and receive treatment at an academic center ($p = 0.03$). On adjusted multivariable analysis, female gender, care at an academic center, primary tumor resection and receiving chemotherapy were associated with the metastasectomy group. We did not find a statistically significant difference between comorbidity score, KRAS status and microsatellite status between the 2 groups. In the matched analysis, overall survival (OS) was significantly improved for patients who underwent metastasectomy (23.2 months) vs. those who did not (11.6 months, $p < 0.001$). On multivariable analysis, this difference remained, and metastasectomy was an independent predictor of better OS (HR 0.74 [0.65-0.85], p < 0.001). **Conclusions:** The utilization of metastasectomy in concurrent lung and liver metastasis is low. It is more frequently used in younger, female and White patients, as well as in patients treated at an academic center. Metastasectomy is independently associated with improved overall survival in patients eligible for such an approach. Research Sponsor: None.

Real-world experience of pembrolizumab in microsatellite instability-high CRC: A Scottish multicenter analysis.

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Background: KEYNOTE-177 established pembrolizumab as a new standard of care in untreated microsatellite instability-high (MSI-H) metastatic colorectal cancer (mCRC). Patients within clinical trials are not always representative of the general population. This underpins the importance of real-world data to offer insights into the outcomes achieved with anti-cancer therapies in routine practice. We report the initial efficacy and safety outcomes of patients treated with pembrolizumab for MSI-H CRC in Scotland. **Methods:** A retrospective analysis of all patients with advanced MSI-H CRC treated with pembrolizumab in the Scottish National Health Service was undertaken. Patient demographic and clinicopathological data were collated via a standardised collection tool. Statistical analysis was performed using SPSS version 28. **Results:** 39 patients were identified (37 metastatic, 2 with locally advanced unresectable disease). All but 2 patients were treated in the first line setting. The median age was 68 years (range 48-82). 23 (59%) were age ≥65 years. 12 (30.7%) of patients were of Eastern Cooperative Oncology Group performance status (PS) 0, 23 (58.9%) of PS 1 and 4 (10.2%) of PS 2. 21 (53.8%) had BRAF V600E mutations. The median duration of pembrolizumab therapy was 24 weeks (range 2-104). After a median follow-up of 36 weeks (range 3-193), 5 deaths had occurred. The median progression free survival had not been reached. The overall response rate was 51% (20/39 patients), with 1 complete response observed. Radiological disease progression occurred in 7 patients (18%), 6 (86%) of which were BRAF V600E mutant. Treatment failure (radiologically confirmed disease progression or clinical suspicion of progression without radiological confirmation) occurred in 15 patients (38%). 3 out of 4 patients with PS 2 achieved a partial response. There were no grade ≥3 immune related adverse events. There was 1 treatment suspension due to grade 2 immune toxicity but no permanent discontinuations. **Conclusions:** Our real-world Scottish population was of poorer performance status than those recruited to KEYNOTE-177 (31% PS 0 vs. 49% in KEYNOTE-177). They were also older (59% age ≥65 years vs. 48% in the trial). Patients of PS 2 were excluded from the study, however 3 of our 4 PS 2 patients demonstrated a partial response to treatment, suggesting that PS 2 should not be an absolute contraindication to treatment. Our observed overall response rate was greater than that observed in KEYNOTE-177 (43.8%). Pembrolizumab was safe and well tolerated in this setting. These preliminary findings support the results of KEYNOTE-177. Long term survival data in our population is awaited. Further follow-up and patient numbers will allow for determination of possible clinico-pathological predictors (BRAF and KRAS status, Glasgow Prognostic Score, metastatic burden) of response to immunotherapy in this population. Research Sponsor: None.

55 **Poster Session**

Baseline treatment patterns of the first 277 patients in PROMETCO: A real-world, prospective, longitudinal cohort study on the continuum of care in metastatic colorectal cancer (mCRC).

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Background: Tumor shrinkage and disease control with preservation or improvement in quality of life are the primary treatment goals for patients with unresectable mCRC. When not possible, emphasis lies in slowing disease progression and prolonging survival. Advances in mCRC treatment have now improved survival to an average of 30 months in clinical trials. Here, we present initial baseline treatment patterns from the PROMETCO study (NCT03935763), the first international, prospective real-world study to investigate the continuum of care in the mCRC population, collecting data on all patients regardless of treatment. **Methods:** Enrolment in PROMETCO began in March 2019. On October 1, 2020, systemic treatment characteristics from 277 mCRC patients were analyzed. Adult patients with two disease progressions since the first diagnosis of metastatic disease who were willing to receive subsequent treatment were included. Treatments started prior to study inclusion were analyzed by line and by patients' molecular status (RAS/BRAF and MSI). **Results:** In the overall population, first-line treatment data were available for 257 patients. Doublet/triplet chemotherapy (dt/t CT) + anti-VEGF/EGFR therapy was received by 70% (180) of patients, and 20% (51) received dt/t CT alone, in contrast to current guidelines. At second line (n = 209), 68% (142) of patients received dt/t CT + anti-VEGF/EGFR therapy. The proportion of dt/t CT given alone was consistent between first and second line. Median duration of treatment decreased with progressing line of treatment (mirrored in the molecular status subgroups). In the RAS/BRAF patient population, 14% (40) had unknown status at inclusion, 0.7% (2) were RAS/BRAF mutant (mut), and the BRAF mut subgroup had too few numbers from which to draw conclusions. The proportion of patients receiving dt/t CT alone was higher in the RAS mut (23%; 31/135) vs RAS/BRAF WT (12%; 9/76) groups. Dt/t CT + anti-VEGF was received by 64% (87/135) and 21% (16/76) of the RAS mut and RAS/BRAF WT patients, respectively. There were no unexpected results in treatments received between molecular groups at second line, nor in terms of the length of treatment. Fifty percent of the population had unknown MSI status, and MSI low/high groups had too few numbers from which to draw conclusions. The treatment distribution in MSS patients at first line (n = 124) and second line (n = 102) followed a similar trend to the overall population. **Conclusions:** Preliminary data from PROMETCO provide key insights as to the treatments received by real-world mCRC patients. Further analysis of patients in a larger cohort will be important to better understand discrepancies in treatment choice (ie adherence to guidelines), and country-based differences in testing/reimbursement, which may help elucidate the missing data seen in the molecular-status subgroups. Clinical trial information: NCT03935763. Research Sponsor: Servier Affaires Médicales.

Clinical utility of microsatellite instability (MSI-H) identified on liquid biopsy in advanced gastrointestinal cancers (aGI).

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Background: Identification of MSI-H is clinically meaningful in patients with aGI given the associated approval of multiple immune checkpoint inhibitors. MSI-H has long been assessed via tissue analysis; and insights from plasma-based approaches are limited to small validation studies. We sought to assess prevalence of initial and acquired MSI-H status across aGI and report real-world outcomes of colorectal (CRC) patients who received ICI after MSI-H identification by a commercially available liquid biopsy (LBx) assay. **Methods:** Genomic results from a well-validated LBx assay (Guardant360) completed as part of usual clinical care between 10/1/2018-9/7/2021 in patients with aGI were queried to assess MSI-H prevalence and identify cases of potential acquired MSI-H. Real-world evidence (RWE) was sourced from the GuardantINFORM database comprised of aggregated payer claims and de-identified records from 11/1/2018-3/31/2021. Patients with plasma-identified MSI-H who started new therapy $<$ 60 days after assay report date were sorted into treatment groups: chemotherapy +/- biologic therapy ("chemo") or immunotherapy via pembrolizumab or nivolumab ("ICI"). Real-world time to discontinuation (rwTTD) and real-world time to next treatment (rwTTNT) were assessed as proxies for progression free survival. Log-rank tests were used to assess differences in rwTTD, rwTTNT and overall survival. **Results:** Prevalence of MSI-H was ~2% across aGI (Table). Five cases were observed to have potential acquired MSI not attributable to tumor shed identified on serial LBx tests. Of 222 MSI-H CRC patients eligible for RWE analysis, 89(40%) started new therapy within 60 days of results: 42(48%) received ICI, 39(44%) received chemo, 8(9%) received other/mixed regimens. Patients who received ICI had significantly longer rwTTD and rwTTNT compared to patients who received chemo [median months to discontinuation = 7.5 (95% CI 3.4-12.3) vs. 2 (95% 1.4-3.3) $p<0.001$; median months to next treatment = 23.8 (95% 10.6-NA) vs. 4.5 (95% CI 2.9-NA) p=0.006]; no overall survival difference was observed (p=0.559). **Conclusions:** This LBx assay detected MSI-H at similar frequencies to published tissue cohorts and may identify acquired MSI-H following early lines of therapy. Patients who received ICI following LBx identification of MSI-H achieved responses in line with published data in previously treated aGI. Well-validated LBx is a viable tool to identify initial and acquired MSI-H in aGI and may expand the number of patients who could benefit from ICI therapy, particularly in cases where access to tissue specimens is not feasible. Research Sponsor: None.

MSI-H prevalence as identified by Guardant360.

	Number of Patients	MSI-H detected	%
Colorectal	15466	426	3%
Gastric/Esophageal	2906	105	4%
Pancreatic	9760	58	1%
Hepatocellular Carcinoma	1399	10	2%
Cholangiocarcinoma	120	2	1%

Investigating the prognostic value of *TP53* and *PIK3CA* mutations in metastatic colorectal cancer (mCRC): Applying Structured Query Language (SQL) algorithms to real-world data from a high-volume U.K. tertiary cancer center.

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Background: Real world data is a valuable research resource but manual data collection is time consuming and labour intensive. As there is no consensus on the prognostic role of *TP53* and *PIK3CA* mutations in mCRC, we assessed the feasibility of using SQL, a programming language, to derive data from routine electronic clinical notes to investigate the prognostic impact of *TP53* and *PIK3CA* mutations in mCRC. **Methods:** A cohort of patients (pts) diagnosed with metastatic or recurrent colorectal cancer as per ICD-10 classification from January 2015 to December 2017 and managed at the Royal Marsden Hospital were identified using SQL algorithms developed in-house. Baseline demographics, histopathological and molecular characteristics and death dates were derived from the Electronic Patient Record and extracted in a structured format for statistical analysis. Mutational analysis of *TP53* and *PIK3CA* were performed with standard of care *KRAS*, *NRAS* and *BRAF* testing using next generation sequencing. Overall survival (OS) according to *TP53* or *PIK3CA* mutational status was estimated using the Kaplan-Meier method. Uni- and multivariate Cox regression included *KRAS*, *NRAS*, *BRAF*, sidedness and mismatch repair (MMR) status. Association between *TP53* or *PIK3CA* and MMR status was tested by the Chi squared test. **Results:** A total of 367 mCRC pts were identified; 10 were excluded due to ineligibility or inadequate data availability. Based on a final dataset of 357 pts, 342 and 354 pts had *TP53* and *PIK3CA* results available. The incidence of *TP53* mutations was 75% (n = 257/342) and *PIK3CA* 16% (n = 55/354). Co-mutations with *KRAS*, *NRAS* and *BRAF* were seen (Table). The overall median follow-up was 42.3 and 42.7 months for *TP53* and *PIK3CA* respectively. There was no difference in OS between *TP53* mutant (MT) and wild type (WT) pts (22.0 vs. 22.8 months, p = 0.96) and between *PIK3CA* MT and WT pts (21.7 vs. 22.4 months, p = 0.49). Right sided and *BRAF* MT tumours were associated with poorer survival than left sided and *BRAF* WT tumours when all other factors were constant for *TP53* ($p<0.001$ & p=0.033 respectively) and *PIK3CA* (both $p<0.001$) OS on multivariate analysis. MMR deficient tumours were significantly more frequent in *TP53* WT compared to *TP53* MT tumours (15% vs. 4%, p=0.001) while they were significantly more frequent in *PIK3CA* MT compared to *PIK3CA* WT tumours (20% vs. 5%, $p < 0.001$). **Conclusions:** Bespoke SQL algorithms enables large-scale data extraction to facilitate research. Based on this dataset, we have shown that *TP53* and *PIK3CA* mutations have no prognostic impact in mCRC. Research Sponsor: None.

Frequency of co-mutations between *TP53*, *PIK3CA*, *KRAS*, *NRAS* and *BRAF*.

Co-mutations	*n*	%
TP53*/*KRAS	102/342	30
TP53*/*NRAS	16/341	5
TP53*/*BRAF	36/336	11
TP53*/*PIK3CA	29/340	9
PIK3CA*/*KRAS	28/353	8
PIK3CA*/*NRAS	1/352	0.3
PIK3CA*/*BRAF	10/349	3

58 **Poster Session**

Treatment patterns and outcomes of patients with metastatic colorectal cancer in third-line and beyond systemic therapy: Real-world data from a setting with limited resources.

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Background: Regorafenib and trifluridine/tipiracil (TAS-102) are the only therapeutic options for patients with chemorefractory metastatic colorectal cancer (mCRC) with demonstrated benefit in overall survival (OS). However, they are not accessible worldwide. In Brazil, they have been recently approved, but they have not yet been provided by public health system or private health insurances. We aimed to describe the treatment patterns and clinical outcomes of that population in a setting with limited access to those drugs. **Methods:** Retrospective study evaluating 510 patients with mCRC who were treated at five Oncoclinicas centers in Brazil from January 2011 to December 2019. Demographic and clinical data were retrieved from electronic medical records. The median OS was calculated by Kaplan-Meier method and prognostic factors were evaluated via multivariable Cox Regression, calculating the Hazard Ratio (HR) and the confidence interval (CI95%). **Results:** A total of 163 patients (33% of the overall population) received third-line and 73 (15%) fourth-line systemic therapy. Median age was 62 years, 59% were male. Tumors were right-sided in 19%, *RAS* mutated 44%, *BRAF* mutated 3%, and high-frequency microsatellite instability 3%. Metastasectomy prior to third-line was performed in 62% of the patients. From the start of third-line therapy, median follow-up was 9.0 months, with 67% of deaths, and median OS was 13.7 months (CI95% 11.8m–20.0m). Most adopted regimens in third- and fourth-line were (1) rechallenge with oxaliplatin-based therapy (39% and 26%, respectively); (2) rechallenge with irinotecan-based therapy (32% and 34%); (3) rechallenge with anti-EGFR monoclonal antibodies (20% and 29%); (4) regorafenib (13% and 25%); and (5) TAS-102 (2% and 4%). In multivariable model including clinical and molecular variables, prior metastasectomy was the only significant prognostic factor for OS (HR 0.51, CI95% 0.31–0.83, p=0.007). **Conclusions:** In real-world, a meaningful proportion of patients with mCRC are eligible for third and later lines of therapy. Rechallenge with chemotherapy and anti-EGFR agents is overused in a setting of limited access to therapies with demonstrated OS benefit, such as regorafenib and TAS-102. Barriers to drug access impair the adoption of the best evidence-based continuum of care and strategies to overcome them are urgently needed. Refractory patients in later lines of therapy derive survival benefit from prior metastasectomy. Research Sponsor: Bayer.

59 **Poster Session**

Analysis of survival trends, clinical, and molecular characteristics of patients with early-onset colorectal cancer (EOCRC).

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Background: Over the last decades the incidence of EOCRC (age 50 or less) has dramatically increased, and so has the scientific interest in this field, given that clinical and molecular characteristics in these patients are not well understood, and may be critical to identify prognostic factors. **Methods:** We conducted a retrospective analysis of 554 patients with metastatic colorectal cancer (mCRC), analyzing the PFS and OS of 68 (12.25%) patients with EOCRC, as well as their clinical and molecular characteristics. We used a log-rank test to compare PFS and OS, and the estimate of hazard ratio (HR) between the studied groups was calculated by means of Cox proportional hazard model. We also used the exact test of Fisher to identify significant association between categoric variants, while Mann-Whitney test was applied to identify significant differences between numeric values. **Results:** We performed a survival analysis: those patients with EOCRC had significantly higher median PFS in first line of treatment (16.2 vs. 11.3 months, p = 0.042) and significantly higher median OS (121.5 vs. 58.1 months, p = 0.011). Several characteristics were significantly more frequent in patients with EOCRC (n=68): BMI $<$ 18.5 (n = 16, OR = 1.9, p = 0.046), primary tumor site at transverse colon (n = 9, OR = 2.61, p = 0.03) and ECOG 0 (n = 32, OR = 2.21, p = 0.003). Having peritoneal metastases almost reached statistical signification (n = 17, OR = 1.82, p = 0.055). Some other characteristics were less frequent: BMI 25-30 (n = 13, OR = 0.51, p = 0.046), primary tumor site at sigmoid colon (n = 14, OR = 0.49, p = 0.038) and former-smoker status (n = 7, OR = 0.44, p = 0.048). Moreover, mean values of LDH at diagnosis were significantly higher in EOCRC patients (359 U/L vs. 280 U/L, p = 0.015). EOCRC patients received a significantly higher number of lines of chemotherapy (2.94 vs. 2.38, p = 0.027) and underwent more surgeries (2,42 vs. 1.24, p $<$ 0,001) than patients with $>$ 50 years. Significant differences in tumor mutational status (BRAF, KRAS, NRAS, MSI, PI3K and HER2), sex, primary tumor resection or number of metastatic sites between groups were not found. **Conclusions:** This retrospective analysis showed that EOCRC patients had significant higher rates of PFS in first-line treatment and OS. Moreover, EOCRC patients had more frequently BMI $<$ 18.5, primary tumor located at transverse colon and ECOG 0. Research Sponsor: None.

Preferences for colorectal cancer screening of physicians and individuals at average risk in the United States: A discrete choice experiment.

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Background: Several colorectal cancer (CRC) screening options are considered in guidelines for individuals at average-risk (IAR). These options differ in aspects such as invasiveness, recommended frequency, and precision that need to be compared and weighed. This study elicited and compared the relative importance that physicians and IAR place on these screening aspects. **Methods:** Primary care physicians [PCPs] and gastroenterologists [GIs] who recommended/performed ≥1 screening one month prior to study and adult IAR completed a discrete choice experiment (DCE). Participants repeatedly chose between screening tests described by type of test, frequency, true-positive (TP), true-negative (TN), and adenoma TP (physicians only). The instrument was tested in qualitative (physicians: n=6; IAR: n=6) and quantitative pilots (physicians: n=100; IAR: n=202). A mixed logit model was used to estimate relative attribute importance (RAI) and predicted choice probabilities for colonoscopy, multitarget stool DNA (mt-sDNA), fecal immunochemical test (FIT), and methylated septin 9 (mSEPT9) blood test. Generalizability to the population was confirmed. **Results:** 1,249 IAR and 400 physicians participated. IAR were 46% male and the mean age was 58.9. Physicians were 79% male and their mean age was 53.4. Preferences were most affected by TP rates (IAR RAI=58%; physicians RAI=42%). Physicians also placed high importance (RAI=41%) on adenoma TP rates. TN rates (IAR RAI=33%; physician RAI=9%), frequency (IAR RAI=6%; physician RAI=2%) and type (IAR RAI=4%; physician RAI=6%) were less important. Despite both IAR and physicians placing most importance on precision, preferences for screening modalities differed. On average, physicians preferred colonoscopy, while IAR preferred mt-sDNA over colonoscopy ($p<0.001$). Both preferred mt-sDNA and colonoscopy over FIT ($p<0.001$), with a mSEPT9 blood test being least preferred ($p<0.001$). Preferences of IAR were heterogeneous with individuals who underwent colonoscopy or sigmoidoscopy screening preferring colonoscopy and the rest preferring mt-sDNA ($p<0.001$). **Conclusions:** While both GI and PCPs overwhelmingly preferred colonoscopy, preferences of IAR were heterogenous, with mt-sDNA being preferred on average other modalities. Offering choices in addition to colonoscopy could improve screening uptake. Research Sponsor: Exact Sciences Corporation.

Participant characteristics.	
Individuals at Average Risk (IAR): n=1249	
Age (years); mean ± SD	58.9 ± 9.1
Female (vs male); N (%)	670 (54%)
Caucasian (vs non-Caucasian); N (%)	1,021 (82%)
Screening naïve (vs screening experienced); N (%)	526 (42%)
Living rural or outskirts of small city (vs more urban); N (%)	520 (42%)
Physicians: n=400	
Duration practicing medicine; mean, years (SD)	22 ± 9.3
Primacy care specialist (vs Gastroenterologist); N (%)	200 (50%)
Patients recommended screening in past 3 months, mean ± SD	180 ± 192

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Colorectal cancer screening results in the regions of Kazakhstan with different levels of cancer prevalence.

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Background: In Kazakhstan colorectal cancer (CRC) occupies the third position in the structure of total oncological incidence and mortality. Kazakhstan is a country with a large territory, with different geographical, industrial characteristics and dietary habits of the population. So CRC prevalence levels vary from region to region: in 2013 the highest regional incidence rate is 6 times higher than the lowest. CRC population screening among men and women aged 50-70 years was started in 2011 in Kazakhstan. **Methods:** Within 10 years of the screening, 9 532 927 men and women were examined, 3419 CRC cases were detected. Coverage of target population ranged from 78.4% in 2012 to 53.1% in 2020. The analysis of screening indicators was carried out: cancer detection rate, the proportion of 0-1 stages, the ratio to the underlying incidence, the relationship with the dynamics of CRC incidence and mortality. According to the incidence rate in 2011-2020 regions of the country are conditionally divided into three groups: group A – high level (31.04-23.5 per 100 thousand population), group B – medium level (20.5-15.0‰), C - low level (11.6- 8.1‰). **Results:** The average annual CRC detection rate for 10 years of screening was 0.4% (4 cancer cases per 1000 examined), in groups A - 0.5%, B - 0.4% and C - 0.3%. The detection ratio of stage 0-I was 0.08%: in groups A - 0.10%, B - 0.09% and C - 0.05%. The average annual incidence rates were in groups A - 27.2 per 100 thousand population, B - 18.7‰ and C - 9.8‰. During time of g-FOBT applying (2011-2013), the average annual incidence rates in the groups were in groups: A - 25.8‰, B - 16.4‰, C - 8.2‰. During time of using FIT (i-FOBT, 2014-2020), the average annual incidence rates increased to 27.0‰, 20.0‰ and 9.9‰ respectively. The greatest increase in the incidence was noted in groups B and C (22.7% and 22.2%), the smallest in group A (4.7%). Screening increased the CRC incidence from 15.5‰ in 2011 to 16.5‰ in 2020 and reduced mortality from 9.3‰ (2011) to 8.0‰ (2020). **Conclusions:** Screening increased the incidence (6.5%) and decreased the mortality from CRC (14%) for 10 years in Kazakhstan. There is a particularly significant effect of screening on the growth of some indicators (incidence and mortality rates, cancer detection rate and early cancer detection) in regions with a low CRC prevalence. Research Sponsor: Government funding.

Can second-generation multitarget stool DNA panels reliably detect colorectal cancer and advanced precancerous lesions?

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Background: Population-based colorectal cancer (CRC) screening can reduce mortality by detecting and removing advanced precancerous lesions (APL) and early-stage invasive disease. One guideline-included strategy is the multi-target stool DNA test (mt-sDNA), which combines detection of methylation DNA markers (MDMs), *KRAS* mutations, and fecal hemoglobin. Since the mt-sDNA pivotal study was conducted, novel biomarkers have been discovered. A panel of highly discriminant MDMs (*LASS4, LRRC4, PPP2R5C*, and reference marker *ZDHHC1*) was identified through a blinded, case-control study of archival specimens. Here, we evaluated the performance of this novel mt-sDNA panel, combined with fecal hemoglobin, in archival stool samples weighted to early-stage CRC and prospectively collected APL, simulating a screening population. **Methods:** The verification study featured 777 samples—210 cases (112 CRC [49 stage I, 38 stage II, 17 stage III, and 8 stage IV] and 98 APL) and 567 controls (176 non-APL and 391 colonoscopy-negative)—from three trials (NCT01397747, NCT01260168, and NCT02503631). Median APL size was 12 mm (interquartile range: 10 mm to 15 mm), with 86.7% adenomas (n = 85) and 13.3% sessile serrated polyps (SSPs; n = 13). The average age was 65.5 years for cases (57% men) and 63.2 for controls (47% men). Samples were processed through homogenization, targeted MDM capture, bisulfite conversion, and MDM quantitation using Long-probe Quantitative Amplified Signal (LQAS). Fecal hemoglobin was quantified using enzyme-linked immunosorbent assay (ELISA). Samples were split into stratified 75%/25% training-testing sets and model outcomes were cross-validated 1,000 times. **Results:** Mean performance from the cross-validation analysis is summarized in the table below. Overall sensitivity was 95.2% for CRC and 57.2% for APL, with specificities of 89.8% (no CRC/APL) and 92.4% (no neoplasia). Subgroup analyses showed high sensitivity for early-stage CRC, with 93.4% at stage I and 94.2% at stage II. By APL subtype, sensitivity was 82.9% for high-grade dysplasia, 73.4% for villous lesions, 49.8% for tubular lesions, and 30.2% for SSPs. **Conclusions:** These data support high sensitivity and specificity for a second-generation mt-sDNA panel. A multicenter pivotal trial evaluating the panel is underway (NCT04144738). Research Sponsor: Exact Sciences Corporation.

Mean performance from cross-validation of novel mt-sDNA panel.

CRC	
Sensitivity	95.2%
AUC[1] (95% CI)	0.987 (0.946 – 0.988)
APL	
Sensitivity	57.2%
AUC[1] (95% CI)	0.802 (0.749 – 0.855)
Specificity (non-APL/CRC)	89.8%
Specificity (no neoplasia)	92.4%

[1]Calculated from all samples (n = 777).

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Adherence with the multitarget stool DNA test for colorectal cancer screening in rural southeastern Kentucky.

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Background: Colorectal cancer (CRC) screening has shown to improve early detection and reduce mortality. Despite, the availability of multiple screening tests for CRC, the current screening rates remains below the national goal. The multi-target stool (MTS) DNA test (commercially known as Cologuard) has contributed to an increase in population adherence to CRC screening and is currently recommended by multiple guidelines. Southeastern Kentucky (SE KY) has a high incidence of colorectal cancer and a low rate of CRC screening. The aim of this study is to assess the adherence to the MTSDNA test in rural SE KY. **Methods:** A retrospective review of all patients 45 and older with a MTSDNA test ordered between August 2020 and February 2021 at a large primary care group in SE KY. All patients had Tests ordered and kits delivered. Cross-sectional adherence was defined as completion and return of the kit within 180 days from test order and was assessed as overall adherence and by patient characteristics including age, sex and healthcare coverage. **Results:** 450 tests were ordered. 160 (35%) were male and 290 (65%) females. Mean age was 62 with age range (46-87). 207 tests were returned with a cross-sectional adherence of 46%. Adherence was significantly lower for age 45 - 55 at 35.2% (26.2-45.2) compared to age 55 - 65 at 48.9% (40.9-56.3), 65 and older at 50.0% (42.3-57.7) ($P = 0.04$). Highest adherence with Medicaid coverage 65.4% [44.3-82.8] and lowest in Managed Care Organization (MCO) coverage 34.0% [4.7-44.2] ($P < 0.01$). Gender was not associated with adherence ($P = 0.75$). **Conclusions:** This retrospective study showed that only 46% of patients were adherent to the MTS DNA test for colorectal screening which is significantly lower than previously reported in larger studies and further studies are needed to identify the barriers to non-adherence to this test, especially in the younger population with alarming increase in incidence of CRC. There is impending need to implement different strategies to improve screening adherence. Research Sponsor: None.

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Patterns of colorectal cancer (CRC) screening rates among the average risk U.S. population.

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Background: There is consensus that the proportion of the average-risk US population up-to-date with CRC screening (58-65%) is insufficient. However, estimates of average risk CRC screening rates are inconsistent and impacted by inclusion of higher-risk individuals, and differing study designs. Accurate measurement of population screening rates is key to addressing gaps in care and assessing the impact of newer CRC screening tests. **Methods:** The study included individuals aged 50-75 years in a large de-identified claims database, with continuous enrollment during year of analysis, and a variable length baseline enrollment of 1-10 years. Average-risk designation excluded higher risk diagnoses (CRC familial syndromes, colorectal polyp or history of colorectal polyp, history of/current CRC, family history of gastrointestinal cancer, and inflammatory bowel disease). Up-to-date status was assessed within guideline-based time periods: colonoscopy (10 years); FIT or FOBT (annually); mt-sDNA (3 years); flexible sigmoidoscopy/CT colonography (5 years). Analyses assessed the proportion estimated as up-to-date and examined the sensitivity to: a) patient population (average-risk only vs. including higher-risk); b) study design (yearly cross-sectional vs. cohort of 50-year-old patients; c) methods (percent in patients with 10 years of enrollment vs. Kaplan Meier (KM) of censored variable pre-screening period). **Results:** The cross-sectional analysis average-risk population included 5.3 million individuals. Estimates of the proportion of those up-to-date with screening guidelines for average-risk patients varied by study design, population, and estimation method. KM estimates among the average-risk population (50-75) showed 49-50% were up-to-date in each calendar year. Including higher-risk patients in the KM analysis resulted in 70% up-to-date among the mixed average+higher-risk population. Using a cohort study design (average-risk patients aged 60 with 10 years of baseline data), 65% were up-to-date by age 60. **Conclusions:** In the base case analysis only half of average risk individuals were up-to-date with CRC screening, a rate lower than typically cited. Sensitivity analyses resulted in substantially different estimates and demonstrate the importance of clearly communicating the methodology used to define the study population. Higher rates quoted in the lay press and medical publications may be based on mixed populations of average+higher-risk individuals or on study designs that do not represent the full population at risk. Research Sponsor: Exact Sciences Corporation.

Assessment of dietary quality in patients on surveillance for colorectal cancer (CRC) using a computerized food frequency questionnaire (FFQ).

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Background: Poor dietary patterns are clearly implicated in the pathogenesis of CRC and are increasingly associated with worsened CRC outcomes, including a higher risk of cancer recurrence and mortality. We evaluated the use of a novel computerized FFQ technology to assess dietary patterns in patients with CRC who were undergoing cancer surveillance. **Methods:** We recruited patients with stage I-III CRC who had completed curative intent therapy at least 1 year but no more than 5 years prior to enrollment. Dietary assessment was conducted using a computerized FFQ (VioScreen) either in clinic or at home. Dietary quality was defined by the Healthy Eating Index (HEI) 2015 score which was calculated automatically by the FFQ technology. Statistical significance was determined using Pearson correlation and analysis of variance (ANOVA). **Results:** Twenty patients (14 colon, 6 rectal; 12 male, 8 female; median age 66 [49-80]; median 3 years from diagnosis) were recruited between 10/2020-9/2021. Fourteen patients did FFQ remotely and 6 in-person. Nineteen patients were white/non-Hispanic. All received surgery, 20% radiation (all rectal) and 75% chemotherapy. Mean HEI 2015 total and subscores are shown in the table. There were significant differences in dietary quality by age <65 vs ≥ 65 (HEI 58.3 vs. 72.6, p=0.025), body-mass-index (BMI) normal/overweight vs. obese (HEI 72.4 vs. 58.6, p=0.033), and marital status of married vs non-married (HEI 61.7 vs. 76.7, p=0.032). There were no differences in dietary quality by level of education, tumor site (colon vs. rectal) or gender. There was a significant negative correlation with increased time since diagnosis and lower dietary quality ($r= -0.67$, $p<0.001$). **Conclusions:** Dietary patterns can be determined using a computerized FFQ in patients with CRC on surveillance both remotely and in-person. This population has a wide range of dietary patterns with particularly low scores in whole grain, fatty acid, sodium and saturated fat. Patients who are older, non-obese, non-married, and closer to completion of cancer therapy have higher dietary quality scores. Future studies of integrating a computerized FFQ into cancer care will determine whether personalized interventions targeting specific dietary patterns can improve diet quality. Research Sponsor: Supported by grant #15-175-23 from the American Cancer Society, Other Foundation.

HEI Component (Max Score)	Average Score (range)
Adequacy:	
· Total Fruits (5)	3.4 (0.2-5)
· Whole Fruits (5)	3.9 (0.5-5)
· Total Vegetables (5)	4.0 (1.8-5)
· Greens and Beans (5)	3.5 (0.3-5)
· Whole Grains (10)	4.5 (0.9-10)
· Dairy (10)	6.2 (0.5-10)
· Total Protein Foods (5)	4.7 (1.1-5)
· Seafood and Plant Proteins (5)	4.4 (0.1-5)
· Fatty Acids (10)	5.2 (1.4-10)
Moderation (reduced consumption leads to higher score):	
· Refined Grains (10)	8.6 (3.5-10)
· Sodium (10)	4.1 (0-9.4)
· Saturated Fats (10)	5.3 (0-10)
· Added Sugars (10)	8.5 (0-10)
Total Score (100)	66.2 (42.5-84.8)

67 **Poster Session**

Determining frequency and reasons associated to refusal of colorectal cancer screening at a reference center in Mexico.

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Background: in Mexico, Colorectal Cancer (CRC) is a leading cause of cancer death, yet population-based screening programs are lacking. In our center, a cohort was created to validate a risk calculator to detect advanced colorectal neoplasia, and to understand barriers to implement a CRC screening program. We aimed to determine frequency and reasons associated to rejection of CRC screening in our population. **Methods:** from August 2019 to March 2020 (early close owing to COVID-19 pandemic) asymptomatic individuals between 50 and 75 years-old with standard-risk for CRC, without previous screening for CRC, from the outpatient internal medicine clinic at a tertiary care center in Mexico City, received standardized information on the importance of CRC screening and were invited to perform both Fecal Immunochemical Test and a screening colonoscopy within a clinical study at no cost. Individuals who rejected participation were given a 10-item questionnaire to select reasons for refusal, as many items as applied. Here we present two groups: 1) individuals who refused to receive information and to perform screening studies, and 2) individuals who refused to participate after receiving information. **Results:** 162 patients were invited to participate, 77 (47%) refused: 48 rejected immediately (group 1) and provided 51 reasons, and 29 declined after having received standardized information about CRC screening (group 2) and provided 30 reasons. Demographics for 77 patients were: 54 (70.1%) women, median age 66 (IQR 58-71) years. Main reasons for rejection in both groups were: "I do not have time" in 24 (29.6%) times, "I am not interested" in 23 (28.4%) times, and "I am scared" in 14 (17.3%) times (Table). **Conclusions:** in our cohort, we identified that nearly half of the population invited to participate in a CRC screening program refused. Main reasons were lack of time, lack of interest and fear. This may translate poor understanding on the importance of measures to prevent CRC, and absence of education programs to recall its importance. In order to increment participation in CRC screening, education and awareness campaigns should be implemented. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

Reasons for CRC screening refusal before and after receiving standardized information.

Reasons	Group 1 Immediate refusal n=51 n (%)	Group 2 Post-information refusal n=30 n (%)
I do not have time	15 (29.4)	9 (30)
I am not interested	17 (33.3)	6 (20)
I am scared	8 (15.6)	6 (20)
I am healthy	4 (7.5)	1 (3.3)
I prefer not to answer	2 (3.9)	2 (6.7)
Other*	5 (9.9)	6 (20)

Data is shown as the number of times an option was selected, not the number of patients.
* Includes: difficulty with transportation, long distance from home, economic issues.

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The impact of Medicaid expansion on colorectal cancer incidence among vulnerable populations.

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Background: With the Affordable Care Act (ACA), the number of uninsured patients in states that expanded Medicaid decreased more among racial/ethnic minorities and lower income adults. Increased access to care could influence colorectal cancer (CRC) incidence through increased screening. However, we lack research on whether Medicaid expansion differentially influenced CRC incidence among vulnerable patient subgroups. This population-based study examines whether Medicaid expansion with the ACA was associated with decreased CRC incidence among racial/ethnic minorities, and adults with lower income. **Methods:** We queried the Surveillance, Epidemiology, and End Results Program (SEER) database to calculate the age-adjusted incidence rates of CRC among patients under 65 years of age diagnosed between 2010 and 2018. We categorized states into two groups: states that expanded Medicaid on January 1, 2014, and states that did not expand Medicaid over the study period. We determined the change in CRC incidence before Medicaid expansion (2010-2013) and after Medicaid expansion (2014-2018). We used a difference-in-difference approach to determine whether changes in CRC incidence differed by expansion status among all patients and among subgroups stratified by race/ethnicity and other socioeconomic indicators. **Results:** Among the entire study cohort, from 2010-2013 to 2014-2018, rates of CRC (per 100,000) increased from 26.6 to 28.3, and this increasing rate did not differ by ACA expansion status ($p=0.48$). We found that the impact of ACA expansion on CRC incidence varied by race/ethnicity. The increase in CRC rates was higher among non-ACA expansion states compared to ACA expansion states for Hispanics (5.4 vs. 1.6 increase per 100,000; $p=0.002$), and Asian or Pacific Islanders (4.3 vs. 0.4 increase per 100,000; $p=0.02$), but not with Black ($p=0.94$), or non-Hispanic white patients ($p=0.91$). The change in CRC incidence between 2010-2013 and 2014-2018 did not differ by county-level household income, fraction under the federal poverty level, or education level (all $p>0.05$). **Conclusions:** This study found that Medicaid expansion through the ACA might differentially benefit Hispanic and Asian patients with respect to decreases in CRC incidence. This study reports on the first 5 years after the ACA, though the true benefits of increased access to care may take longer to manifest. Additional research with longer follow-up is required to fully understand the influence of Medicaid expansion. Research Sponsor: U.S. National Institutes of Health.

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Pathogenic variants among Mexican patients with colorectal cancer referred for genetic cancer risk assessment.

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Background: Lynch syndrome (LS) is the most frequent hereditary cancer syndrome among patients with colorectal cancer. Screening tests such as immunohistochemistry (IHC) for mismatch repair (MMR) proteins and PREMM5 model help to identify patients at risk of germline pathogenic variants (PVs). However, there has been a disparity in that evaluation of these screening tools and their correlation with pathogenic variants (PVs) has been limited in Hispanic populations. **Methods:** Patients with colorectal cancer referred for genetic cancer risk assessment were enrolled in the Clinical Cancer Genomics Community Research Network (CCGCRN) registry from October 2017 to February 2021 at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. Genetic testing was performed by full sequencing of the MMR genes (*MLH1, PMS2, MSH2, MSH6* and *EPCAM*) and other cancer-associated genes (*APC*, *BRCA1*, *BRCA2*, *TP53*, *NF1*, *ATM*, *CHEK2*, *PALB2*, *BRIP1*) and multiplex ligation dependent probe amplification to detect copy number variants (CNV) was performed for selected genes. Demographic, clinical characteristics and IHC results were obtained from clinical records. MMR PV probability was calculated using PREMM5. **Results:** Sixty-nine patients with colorectal cancer were included; mean age at diagnosis was 50 (26-82) years and 39/69 (56%) were women. A MMR gene PV was identified in 23/69 patients (33%); most frequently in *MLH1* n = 14, followed by *MSH2* n = 2, *MSH6* n = 2 and *PMS2* n = 1. Four recurrent PVs in *MLH1* and *MSH2* represented 22% of PVs. CNVs were identified in 4/23 (17.4%) patients with LS. PVs in other genes were identified in 8.6% of the cases: 2 *ATM*, 1 *APC*, 1 *PALB2*, 1 *BRIP1* and 1 *BRCA1*. IHC results were available in 52/69 cases (75.4%) and MMR protein deficiency was found in 16/17 (94%) carriers and in 14/31 (45%) non-carriers (sensitivity 94.1% and specificity 54.8%). The area under the ROC curve for PREMM5 score was 0.94 (95% CI 0.88-0.99) with a mean score 31.6 (2.4-50) in patients with LS and 4.1 (0.9-50) in non-carriers. The diagnosis of a second primary colon cancer was more frequent among LS (30% vs 2.5%; $p < 0.01$). **Conclusions:** We found a high frequency of MMR gene PVs among patients referred for GCRA with personal history of colon cancer, and only a small proportion with PVs in other genes. Our results showed a good performance of PREMM5 model and a high sensitivity of MMR IHQ in a Mexican population, indicating that these are tools that can be used to prioritize patient selection for germline testing. Research Sponsor: None.

70 **Poster Session**

Biomarker testing in patients (pts) with metastatic colorectal cancer (mCRC): Perspectives from U.S. oncologists (ONC) in rural areas and urban clusters.

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Background: In the US, pts living in rural areas have higher CRC mortality rates than urban areas. Clinical guidelines recommend testing for *BRAF* and *RAS* mutations and deficient mismatch repair/microsatellite instability in pts with mCRC. However, data on biomarker testing rates in rural communities compared with urban areas are limited. We surveyed ONC in the US who practice in rural areas or urban clusters to identify biomarker testing patterns and barriers (data previously reported) and conducted interviews with a select group of respondents to further understand key differences that may contribute to substandard biomarker testing rates in rural areas. **Methods:** A 2-part (quantitative and qualitative) survey was conducted with ONC who spend $>$ 40% of their time providing direct care to pts in rural areas or urban clusters and who had treated $\geq$2 pts with stage IV mCRC in the month prior to the survey. After screening, a subset of those who completed the quantitative survey participated in the qualitative survey (a 30-minute, web-assisted, telephone interview). The interview questions targeted 6 areas: clinical practice description, biomarker and genomic testing patterns, pathology and molecular tumor board, tumor tissue journey, electronic health records, and training/educational opportunities. **Results:** Of the 99 ONC who responded to the quantitative survey, 17 were interviewed for the qualitative survey from June 16–29, 2021. A key finding of the quantitative survey was that although ONC reported being familiar with biomarkers relevant to mCRC, the reported rate of biomarker testing was suboptimal. The interviews probed reasons why testing does not align with current guidelines and found that challenges exist throughout the tumor tissue journey including insufficient tumor tissue available for testing (especially in the relapsed/refractory setting); lack of or limited protocols, clinical decision support systems, reflexive testing, and molecular tumor boards; lengthy and difficult-to-navigate next-generation sequencing reports; and financial toxicity surrounding biomarker tests (especially for underinsured pts), among other barriers. Despite these challenges, ONC reported easy access to third-party reference labs and electronic references, such as NCCN and UpToDate. Although telehealth visits have nearly quadrupled during the COVID pandemic, access to telehealth may be limited for pts living in rural areas or urban clusters. **Conclusions:** The ONC surveyed reported that practicing in rural/urban clusters poses unique challenges related to tissue acquisition, practice resources, pts' ability to pay, and clinical knowledge gaps that may affect biomarker testing rates in pts with mCRC. Addressing these gaps is warranted if optimal utilization of precision medicine tools is to be realized. Research Sponsor: Pfizer.

71 **Poster Session**

Prevalence of information needs among emerging and young adult colorectal cancer survivors.

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Background: The information needs of young adult (YA) cancer survivors have been described, however, the specific needs of YA colorectal cancer (CRC) survivors are not well-documented. Characterizing the distinct unmet needs of YA CRC survivors is important given their unique cancer experience which may include an ostomy, chronic bowel symptoms, and functional deficits. The purpose of this study was to examine CRC survivors' unmet needs across general, clinical, and psychosocial domains. **Methods:** An online, cross-sectional survey was administered via Facebook in collaboration with a national YA CRC patient advocacy organization. Respondents (diagnosed 18-39) endorsed areas in which they required more information on aspects of their lives that may have been affected by their cancer experience. Needs were stratified by life stage (emerging [18-29 years] and young [30-39] adulthood). **Results:** Respondents (n=189) were colon (40.2%) and rectal (59.8%) cancer survivors with a mean current age of 32.2 years (SD=4.6) and a mean age of 30.2 years (SD=4.3) at diagnosis. Most endorsed items per domain included: nutrition and diet (52.1%), complementary and alternative treatments (45.4%), and talking about your cancer experience with family, friends, and co-workers (36.1%). Survivors in emerging adulthood (n=80), compared with those in young adulthood (n=109), endorsed notably greater needs in: staying physically fit (57.5% versus 38.5%), complementary and alternative treatments (57.5% versus 36.7%), and advice/help about dating and intimate relationships (18.8% versus 6.4%). **Conclusions:** Overall, half of respondents endorsed a desire for information on nutrition and diet, staying physically fit, and complementary and alternative treatments. Differing endorsement rates by age group indicate the importance of tailored approaches. Optimal counseling, resources, and referrals specific to life stage can mitigate the unmet needs of YA CRC survivors to improve health outcomes and quality of life. Research Sponsor: The Aflac Archie Bleyer Young Investigator Award in Adolescent and Young Adult Oncology from the Children's Oncology Group and NCI Cancer Center Support Grant P30 CA014089 from the USC Norris Comprehensive Cancer Center.

Information needs endorsed by emerging (N=80) and young adult (N=109) CRC survivors, N (%).

		Emerging Adulthood (18-29)	Young Adulthood (30-39)	Total*
General	Nutrition and diet	44 (55.0)	55 (50.5)	101 (52.1)
	Staying physically fit	46 (57.5)	42 (38.5)	92 (47.4)
	Financial help and counseling for cancer-related costs	26 (32.5)	37 (33.9)	64 (33.0)
Clinical	Complementary and alternative treatments	46 (57.5)	40 (36.7)	88 (45.4)
	Dealing with late and long-term side effects of cancer treatment	35 (43.8)	44 (40.4)	82 (42.3)
	Cancer risks to your family	33 (41.3)	46 (42.2)	80 (41.2)
Psychosocial	Talking about your cancer experience with family, friends, and co-workers	32 (40.0)	36 (33.0)	70 (36.1)
	Managing your anxiety about recurrence (cancer returning)	25 (31.3)	39 (35.8)	65 (33.5)
	Advice/help about dating and intimate relationships	15 (18.8)	7 (6.4)	22 (11.3)

*Column responses may not equal total due to item missingness

Cardiac toxicities of fluoropyrimidine chemotherapy: A literature review and evaluation of current practice at a large U.K. cancer center.

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Background: Fluoropyrimidine chemotherapy is a mainstay of the adjuvant and palliative management of colorectal cancer. Cardiac toxicities—including angina, myocardial infarction and arrhythmias—are uncommon complications thought to be mediated by coronary vasospasm. Although potentially life-threatening, they remain poorly described and consensus guidelines regarding patient selection are lacking. To assess current understanding of this toxicity, we performed a literature review of the topic. We then evaluated fluoropyrimidine use at a large UK cancer center to investigate current practice. **Methods:** MEDLINE, EMBASE and the Cochrane central register of controlled trials were searched to March 1 2021 using the search terms (fluorouracil OR capecitabine) AND—separately—cardiotoxicity, heart disease, and rechallenge*. Original research articles in English were included and their findings summarised. The case notes of all patients who underwent surgery for pathological stage III colon cancer between January 1 2017 and December 31 2019 at Leeds Cancer Centre were reviewed. The proportion of patients who experienced cardiac toxicity during adjuvant chemotherapy was assessed. The proportion of patients who were not offered adjuvant chemotherapy due to cardiac risk was identified. **Results:** The three search strategies identified 582, 55 and 21 citations respectively, of which 28, 7 and 7 full texts were retrieved for further evaluation following review of titles and abstracts. The reported incidence of fluoropyrimidine cardiotoxicity varied widely, as did its definition. Over half of toxicity cases described were ischaemic. Reported risk factors included those for coronary artery disease, although this was not a consistent finding. 125 patients underwent surgery for stage III colon cancer in the study period of whom 81 (65%) received adjuvant chemotherapy. 2 (2.5%) patients failed to complete adjuvant treatment due to cardiac toxicity (angina; cardiac arrest). Pre-existing cardiovascular disease was cited as a reason for not offering adjuvant chemotherapy in 13 of 44 cases (30%). **Conclusions:** Review of the literature revealed a poor evidence base to guide treatment decisions regarding fluoropyrimidine chemotherapy and cardiac risk. Rates of cardiac toxicity at our center were within expected limits. A number of patients were denied adjuvant chemotherapy due to perceived cardiac risk. A clearer understanding of the pathophysiology and management of fluoropyrimidine cardiotoxicity is urgently required to avoid unnecessarily denying patients effective anti-cancer therapy. Research Sponsor: None.

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Utilization of next generation sequencing (NGS) in stage IV gastrointestinal (GI) cancer patients (pts) and efficacy of electronic reminder notification (ERN) in improving utilization of NGS in the private practice community-based setting.

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Background: NGS testing allows for identification of genetic mutations/alterations that can be important in determining treatment options for advanced cancer pts. The National Comprehensive Cancer Network (NCCN) includes NGS testing as part of standard of care for many tumor types including stage IV pancreatic cancer, colon cancer, and rectal cancer and all other GI solid tumor types. Previous reports have described the utilization of NGS in clinical practice at academic centers. To our knowledge this is the first report in the private practice setting. **Methods:** For the historical portion, we established baseline data to quantify NGS testing frequency in stage IV GI tumor pts in our community based oncology practice by performing a retrospective chart review. In the prospective portion, the intervention of an ERN was used to alert treating physicians if NGS had not been done. Primary endpoint is the percent (%) of pts with NGS sent compared to historical control. Secondary endpoint is the % of pts with targeted therapy options made available to them. **Results:** In a private practice multi-office setting, 200 charts of pts with stage IV GI cancer using Flatiron's OncoEMR software were reviewed for the retrospective cohort between July 1 to December 31, 2020. Of the 200, 44.5% (89 pts) had colon cancer, 17.5% (35 pts) had pancreatic cancer, 15% (30 pts) had rectal cancer, and 23% (46 pts) had other types of GI cancer. Of these, 87 (43.5%) pts had NGS testing; of which 41 of 89 (46.0%) are colon pts, 13 of 35 (37.1%) are pancreatic pts and 16 of 30 (53.3%) are rectal pts. For the prospective portion, between July 1 and August 15, 2021 each physician's schedule was evaluated and an ERN was sent shortly before each Stage IV GI pt was to be seen. A total of 114 pts were reviewed, and 92 (79%) had NGS sent. Of these, 47 pts of 54 (87%) are colon pts, 12 of 15 (80%) are pancreatic pts, 16 of 21(76%) are rectal pts, and 17 of 24 (70%) are pts with other GI cancer. 2% of pts with NGS testing had a potentially actionable mutation identified. **Conclusions:** NGS testing is standard of care for pts with stage IV GI cancer that wish to pursue therapy. ERN was minimally helpful in increasing NGS testing. This may be in part due to the effect of the practice's emphasis on NGS testing, which increased its baseline prospective testing rate. Increased use of a team based approach in the office would be a key element to increasing compliance with the current workflow as well as use of pathways which embed the NGS testing into the treatment plan. A more robust EMR would also be vital in increasing NGS testing rates by the use of automatic reminders or order sets. Better support of the physician and use of multiple touch points is necessary until full automation is utilized for NGS testing. Research Sponsor: None.

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Colorectal cancer caregivers demonstrate need for a one-stop comprehensive resource.

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Background: Patients with colorectal cancer often require a caregiver's assistance with daily activities, medical care, social needs, and navigating treatment options. In providing this assistance, caregivers may be at an increased risk for psychological distress. Direct support to manage a caregiver's stress and maintain their well-being is essential. More research is needed to fully understand the challenges caregivers face and to provide solutions. Previous studies have found that caregivers experience high levels of depression and anxiety, and many lack access to resources despite the evidenced need for support. **Methods:** A survey was disseminated via the Colorectal Cancer Alliance's Blue Hope Nation community for two weeks and by email. Forty caregivers of colorectal cancer patients of varying stages and diverse demographic backgrounds completed the survey. **Results:** Half of the respondents have been providing care for 1-3 years, and 63% indicated they were a patient's spouse or partner. Most caregivers were in the 35-40 age group, and 30% were full-time caregivers. A majority reported experiencing anxiety/stress (97.5%), fatigue (80%), poor sleep (77.5%), depression (75%), and feelings of isolation (72.5%). Primary caregiver activities included providing moral support, completing household chores, and researching treatment options. Only 32.5% of caregivers received help or advice from their patient's doctors or medical team on the tasks listed. The survey results suggest the need for a comprehensive resource with information on medications, side effects and treatments; a guide for medical discussions; organization for medical forms and documents; and a tool to connect with peer caregivers. **Conclusions:** Survey themes indicate that caregivers often feel unprepared to provide care, have inadequate knowledge, and receive little guidance from health care providers, so there is continued need to place both the patient and caregiver at the center of care. A comprehensive centralized resource given at diagnosis with vital information and a method for document organization would help reduce caregivers' stress and allow them to share information easily. Such patient and caregiver-directed resources would enable a better quality of care experience, and potentially better mental health outcomes, for patients and their caregivers. Research Sponsor: None.

75 **Poster Session**

Association between environmental quality index and young onset colorectal cancer.

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Background: The factors associated with the rise of young-onset colorectal cancer (YOCRC) remain unclear. In addition to hereditary factors, environmental exposures are believed to be associated with YOCRC. Therefore, we aimed to study the association between the national level Environmental Quality Index (EQI) and YOCRC in the US. **Methods:** We used the SEER database to select the CRC patients diagnosed between 2010-2016. YOCRC was defined based on age at diagnosis $<$ 50 years. EQI (2005-2010) is a measure of county-level cumulative environmental exposures that includes 5 domains: sociodemographic, built, air, land, and water. A higher value represents a lower environmental quality. We distributed the total EQI and each EQI domain into five quintiles. Multivariable logistic regression analysis was used to assess the relationship between YOCRC and quintiles (upper-most vs. lowest) of EQI after adjusting by race (White, Black, and Others), gender, and stage at diagnosis. The age-adjusted incidence rate was also calculated using the SEER*Stat, and correlation efficiency was estimated between EQI domains and incidence rate. **Results:** A total of 261,417 CRC patients were included; 11% were YOCRC. In the adjusted multivariable analysis, poor built EQI (OR 1.15 [1.11-1.20]) and water EQI (OR 1.08 [1.03-1.12]) were more likely to be associated with YOCRC. Poor built EQI was more strongly associated with Black YOCRC (OR 1.21 [1.09-1.35]) as compared to White YOCRC (OR 1.14 [1.09-1.19]). Poor sociodemographic EQI was more strongly associated with Others (OR 1.47 [1.25-1.72]) compared to Black YOCRC (OR 1.14 [1.03-1.25]). In addition, poor built EQI (OR 1.19 [1.12-1.27]) and water EQI (OR 1.12 [1.05-1.19]) were more strongly associated with the metastatic disease among YOCRC patients. However, the total poor EQI was not associated with YOCRC (OR 0.99 [0.95-1.03]). On incidence analysis, there was a positive correlation between the incidence rate of YOCRC and sociodemographic EQI (rho=0.49, $p<0.001$), air EQI (rho=0.30, $p<0.001$), and land EQI (rho=0.18, $p<0.001$). **Conclusions:** This study evaluated a population-based ecological approach and showed that YOCRC was associated with lower environmental quality, including built and water domains. EQI domains were also associated with different racial groups among YOCRC. Research Sponsor: None.

Multivariable logistic regression analysis for the association between 5th quintile of EQI total/domains and YOCRC.

Factors	Odds	Lower	Upper	p-value
5th EQI Overall vs. 1st EQI Overall (Ref)	0.989	0.952	1.028	0.585
5th Sociodemographic quintile vs. 1st Sociodemographic quintile (Ref)	0.952	0.917	0.988	0.010
5th Built quintile vs. 1st Built quintile (Ref)	1.152	1.107	1.198	<0.001
5th Air quintile vs. 1st Air quintile (Ref)	0.949	0.912	0.986	0.008
5th Land quintile vs. 1st Land quintile (Ref)	0.961	0.925	0.999	0.043
5th Water quintile vs. 1st Water quintile (Ref)	1.076	1.034	1.120	<0.001

A survey study of prevention and treatment patterns by academic and community oncologists for cancer therapy-associated diarrhea.

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Background: Chemotherapy and targeted therapies are associated with GI toxicities including diarrhea that affects 50% to 80% of patients. Severe complications include dehydration, malnutrition, fatigue, renal insufficiency, and systemic infection. There are no specific prevention strategies, and treatment options are limited. Dose reduction or interruption of anti-cancer medications may lead to decreased efficacy. This survey was conducted to assess current toxicity management patterns and gaps for cancer therapy-associated diarrhea. **Methods:** An online survey (MedSurvey) with 6 eligibility & 15 practice questions was conducted (April 27 to 30, 2021). Fifty (50) practicing oncologists completed the survey. **Results:** Among the 50 oncologists**,**82% have been practicing ≥ 11 years with 24% from an academic setting and 76% from a community setting. They (percent of respondents) prescribed the following anti-cancer medications more than 10 times per week: cytotoxic chemotherapy (86%), targeted agents (78%), and immuno-oncology therapies (80%). Prevention of chemotherapy-induced diarrhea (CID) with Imodium (loperamide) and Lomotil (diphenoxylate and atropine) were commonly administered (10% always, 60% sometimes) as prophylactic treatment prior to the start of chemotherapy. The majority (60%) would prophylactically use a novel agent for a patient with previous CID, and 38% would use this agent for selected anti-cancer therapies. Many oncologists (5% always, 60% sometimes) start chemotherapy at a lower dose and titrate up to prevent CID. Similar treatment patterns were observed for targeted therapy induced diarrhea (TTID). For Grade 1 CID (multiple choices allowed), 18% used observation only for management, whereas 72% prescribed Imodium, and 22% used Lomotil. For Grade 1 TTID (multiple choices allowed), 26% used observation only, 58% prescribed Imodium, and 26% used Lomotil. Dose reduction was implemented 10% and 6% of the time for CID and TTID, respectively. For Grade 2 CID (multiple choices allowed) 4% used observation only, most started either Imodium (82%) or Lomotil (72%), and 34% considered dose reduction as a treatment strategy. For Imodium or Lomotil non-responders, 50% would dose reduce, and 44% would use an alternate anti-diarrheal treatment (e.g., octreotide). TTID had similar treatment patterns. For immune-oncology agents (e.g., ipilimumab, nivolumab, pembrolizumab) 40% suggested induced GI toxicities (e.g., diarrhea/colitis) require an innovation for managing toxicity. **Conclusions:** Treating cancer therapy-associated diarrhea continues to be a significant challenge with Grade 2/3 often requiring a therapeutic dose reduction or interruption that may impact the efficacy of cancer treatment. Effective management (prevention and treatment) for GI toxicity remains an unmet need for many patients. Research Sponsor: OnQuality Pharmaceuticals (USA) LLC.

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Incidence, severity, and onset of oral mucositis in 5-FU based chemotherapy for gastrointestinal cancer.

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Background: 5-fluorouracil has been used in treatment of gastrointestinal cancers for more than 40 years. Numerous toxicities of 5-FU are known. Little is known about the occurrence, natural course and causes of oral mucositis (OM) of 5-FU in GI tumors. There is little data on the additional toxicity of VEGF and EGFR antibodies together with 5-FU. We followed the occurrence, severity and localization of OM of 5-FU in consecutive patients as part of their cancer treatment. The primary aim of the study was to determine the severity, course and risk factors of OM up to the first six cycles of ctx. OM was evaluated by repeated inspections of the oral cavity and patient questionnaires. **Methods:** Pts who received 5-FU for the first time or who had not received ctx for at least 12 months. 64 consecutive pts were included in the observational study from March 2018 to March 2019. Out of 64 pts a total of 41 (28 m/13f) had complete documentations (inspections of the oral cavity and questionnaires) and were available for the evaluation. **Results:** Mean age 65 ys (range 42-83), 60% were treated for CRC, 22% esophageal/gastric cancer, and 18% other GI-cancers. 13 were non-smokers, 25 former smokers; 7 pts had daily alcohol consumption while 7 pts never consumed alcohol. 10/41 pts wore a dental prosthesis. The mean BMI was 26.5 (range 18.8-41.5). Initial very good/ good oral hygiene was given in 3/ 20 patients. 80% of the pts developed xerostomia after the first cycle, almost every patient needed support for symptoms due to oral problems during ctx. Of 41 pts, an OM could be documented in 38 pts. A total of 93% of the patients developed a mild course of the mucositis with grade 1-2. OM developed between the 2^{nd} and 3^{rd} cyle in the majority of pts. At the third cyle, only 8 pts had OM of grade 0, while 23 pts had grade 1 and 9 pts were grade 2. It was of note here that of these 9 pts with grade 2, 6 had grade 0 in the 2nd cycle. During cycle 5 and 6 only seven pts had a CTC score of 0, but no pat developed a CTC 3 or 4 OM. We could not document a connection between the occurrence of oral mucositis and the oral hygiene measures used, as no severe course of OM CTC Grad 3 or 4 could be detected. We could not find any relation to the type of 5-FU therapy (doublet, triplet +/- monoclonal antibodies). **Conclusions:** The incidence of oral mucositis with CTC score of 1 and 2 was 93%, but serious grade 3 and 4 mucositis rates were not observed. Xerostomia was observed in 80% after the first course of treatment. Symptomatic mucositis occurs early within 4 weeks after starting chemotherapy. Local measures appear suitable for symptom control of OM. Research Sponsor: None.

Adjuvant oxaliplatin and fall-related injury in patients with colorectal cancer.

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Background: Adjuvant oxaliplatin improves colorectal cancer (CRC) survival but causes dose-dependent peripheral neuropathy, possibly increasing the risk of fall-related injuries (FRI) such as fractures. In this retrospective cohort study, we examined the impact of adjuvant oxaliplatin cycles on FRIs. **Methods:** All data were ascertained from linked health administrative and population databases. We included Ontarians aged 18-85 years at CRC diagnosis between January 1 2007 to December 31 2018 who underwent curative resection and received adjuvant oxaliplatin. We excluded those with a prior cancer diagnosis within 5 years, prior CRC diagnosis ever, non-adenocarcinoma histology, prior oxaliplatin, and <2 years of Ontario health insurance prior to CRC diagnosis. Oxaliplatin dose was determined in the 382 days after resection and dichotomized (1-6 vs. 7-12 cycles). The outcome was FRI, defined by ICD10 codes W00-W19 for any injury caused by a fall requiring emergency or inpatient care. Follow-up began at the end of the treatment window and terminated at the first of FRI, death, loss of Ontario health insurance, or March 31 2020. To account for differences between groups, clinical and demographic characteristics at diagnosis (Table) were used to estimate propensity scores for treatment and calculate inverse probability of treatment weights. These weights were applied to a Fine & Gray regression model to determine the subdistribution hazard ratio (sHR) estimating the association between FRI and 1-6 versus 7-12 cycles of oxaliplatin, with death as a competing risk. Standardized differences <0.1 indicated negligible imbalance. An interaction term tested for effect modification by age at diagnosis. **Results:** 9,324 patients were included in the study; 1,870 received 1-6 cycles and 7,454 received 7-12 cycles of oxaliplatin. Those exposed to 1-6 cycles were older (61.0 vs. 59.1 years), had higher comorbidity scores (13.5 vs 12.3), and more often had rectal cancer (27.5 vs. 22.2%). Negligible imbalance remained after weighting. Median follow-up was 50.2 months. Total follow-up was 44,472 person-years. There were 1,223 FRIs and 1,913 deaths. The sHR for FRIs comparing 7-12 cycles against 1-6 cycles of oxaliplatin was 0.98 (95% CI 0.85-1.14). The interaction *p*-value for age and oxaliplatin dose was 0.24. **Conclusions:** In this population-based retrospective cohort study of 9,324 patients with CRC, the risk of FRIs was similar for 7-12 cycles compared with 1-6 cycles of adjuvant oxaliplatin. This finding was consistent across age at diagnosis. Future research should examine the relationship between oxaliplatin dose and falls not resulting in injury. Research Sponsor: PSI Foundation, Other Government Agency.

Measured patient characteristics.

Characteristic	
Age	Stroke
Sex	Alcohol related hospital visit
ADG Comorbidity Score	Neuropathy
Frailty	Material deprivation
Diabetes	Rurality
Dementia	AJCC Stage
Osteoporosis	Colon vs rectal cancer
FRI in prior year	

79 **Poster Session**

Pre-emptive oral clarithromycin to reduce the skin toxicity of panitumumab treatment for metastatic colorectal cancer.

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Background: Chemotherapy with panitumumab is expected to be well tolerated and improve survival in patients with metastatic colorectal cancer (mCRC). However, skin toxicities are its most common adverse events. The aim of this trial was to evaluate the efficacy and safety of pre-emptive antibiotic treatment with clarithromycin (CAM) to prevent panitumumab skin toxicities. **Methods:** We conducted a phase III, multicenter, open-label, randomized clinical trial on mCRC patients treated with pani- tumumab. Eligible patients were randomly assigned 1:1 to pre-emptive antibiotic and control groups. In the pre-emptive group, CAM administration (200 mg twice per day) continued daily through the panitumumab treatment period. The control regimen consisted of skin care only. The primary end point was the incidence of grade $\geq$ 2 skin toxicities during the 6-week skin treatment period. **Results:** Of 156 enrolled patients, 78 received pre-emptive antibiotic treatment, and 78 received reactive treatment. The number and incidence of grade $\geq$ 2 skin toxicities during the 6-week skin treatment period were 16 (21.3%) and 41 (54.7%) for the pre-emptive and control groups, respectively (HR, 0.32; 95% CI, 0.17–0.56). There was almost no difference in the rate of other adverse events between the two groups, but the incidence of grade $\geq$ 3 diarrhea in the pre-emptive group was high, at 8% vs. 1.3% in the control group. There were no treatment-related deaths. **Conclusions:** Prophylactic oral CAM together with relatively simple skin care was found to be effective in suppressing the development of grade $\geq$ 2 skin toxicities induced by panitumumab. Clinical trial information: UMIN000011485. Research Sponsor: None.

Trajectories of body weight change and survival among mCRC patients treated with systemic therapy: Pooled analysis from the ARCAD database.

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Background: Higher baseline body mass index is associated with improved survival in metastatic CRC (mCRC). Whether weight gain or loss after mCRC diagnosis is associated with survival remains largely unknown. **Methods:** We analyzed individual patient data from 3504 patients with previously untreated mCRC enrolled in five phase III randomized trials (AVF2017g, AVF2192g, CRYSTAL, N9741, OPUS) conducted between 2000 and 2006. Weight measurements were prospectively collected at 3 months after diagnosis and then up to 5 years. Patients were categorized into three groups based on the percent weight change at 3 months: stable weight or gain, weight loss up to 5% of baseline weight, and ≥5% weight loss of baseline weight. Cox models were used to assess the prognostic associations of weight change at 3 months with overall survival (OS) and progression-free survival (PFS), adjusting for baseline BMI, age, sex, performance score, chemotherapy backbone (oxaliplatin vs. irinotecan), and biologics type (cetuximab vs. bevacizumab). Sub-analyses included Cox models adjusted for additional clinical-pathological factors (primary tumor sidedness [right colon vs. left colon-rectum], and BRAF status; N=1,511). **Results:** Median percent weight change at 3 months was -0.5% (IQR -4.0 to+1.6%). OS was better in patients with weight stability or gain than in those with weight loss (up to 5% or ≥5%; (Table). Results were consistent for PFS for patients with ≥5% weight loss of baseline weight, as well as for sub-analyses. **Conclusions:** Patients losing weight during the first 3 months of systemic therapy for metastatic colorectal cancer have significantly shorter overall survival than those with stable or increasing weight. Degree of weight loss is proportional to the observed increased risk of death and remains evident among underweight, normal weight and obese individuals. Further studies examining possible usefulness of on-treatment early weight loss as a novel intermediary end-point are needed. Research Sponsor: Aide et Recherche en Canérologie Digestive (ARCAD).

Weight Change (at 3 months)	Events/ N	Adjusted Median OS (in months)	Adjusted Hazard Ratio (95% confidence interval)	Adjusted P-value
Stable weight or gain	723/ 981	23.5	Ref	
weight loss up to 5% of baseline weight	942/ 1295	20.7	1.21 (1.09-1.34)	p<0.001
≥5%weight loss of baseline weight	473/ 563	14.5	1.96 (1.74-2.22)	p<0.001

Survival outcomes associated with chemotherapy-induced neutropenia in the adjuvant treatment of colorectal cancer with FOLFOX.

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Background: Patients undergoing adjuvant treatment with FOLFOX for colorectal cancer (CRC) are at risk of developing chemotherapy-induced neutropenia (CIN). We assessed survival outcomes in patients who develop CIN in this setting. **Methods:** We performed a retrospective chart review of patients with CRC treated with FOLFOX at our institution in Canada from 2013 to 2015. The survival follow-up cut-off date was August 2021. Demographic, treatment, and outcome data were collected. CIN was defined as ANC <1.5, and all episodes of neutropenia were assumed to be the result of chemotherapy. Median OS was calculated using Kaplan-Meier product limit estimates. **Results:** A total of 302 patients were included (baseline demographics in the table). Median follow-up was 110 months. In the overall cohort, 174 patients (58%) had at least one episode of CIN. CIN occurred in 56% of those with stage II cancer, 43% of those with low risk stage III cancer (T1-3 and N1), and 45% of those with high risk stage III cancer (T4 or N2). Median time to first CIN event was 4.3 months. Among patients with at least one episode of CIN, the first CIN event occurred during the first 3 months of treatment in 110 (63%). Among patients with at least one episode of CIN, 79 (45%) received subsequent granulocyte colony-stimulating factor (GCSF). The median OS in the overall cohort was 171 months. For patients with and without CIN the median OS had not been reached, HR 0.84 (95% CI 0.55-1.29, p=0.43). The median OS for patients with CIN treated with and without GCSF had not been reached, HR 1.02 (95% CI 0.57-1.82, p=0.94). The 5-year survival rate for patients with and without CIN was 87% vs 77%. The 10-year survival rate for patients with and without CIN was 70% vs 64%. A trend toward improved survival in those with CIN remained when results were analyzed by cancer stage. **Conclusions:** Patients with CIN had a trend toward improved survival compared to those who did not have CIN. There was no indication that GCSF in the setting of CIN impacted survival. The causes for the potentially protective effect of CIN in the setting of adjuvant CRC treatment require further elucidation. Research Sponsor: None.

Characteristic		Result, n (%)
Age ≥65		99 (33%)
Male		178 (59%)
ECOG PS	0	283 (94%)
	1	19 (6%)
Clinical Stage	II	36 (12%)
	III (Low risk, T1-3, N1)	118 (39%)
	III (High risk, T4 and/or N2)	148 (49%)

Pain among older adults diagnosed with gastrointestinal (GI) malignancies: Results from the cancer and aging resilience evaluation (CARE) registry.

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Background: The impact of pain on functional status and neuropsychological disorders among older adults with cancer is relevant, yet poorly understood. We sought to identify the prevalence of pain at diagnosis in older adults with GI malignancies and evaluate the association between pain and functional status limitations, cognition, and mental health issues. **Methods:** This study included patients diagnosed with cancer at age ≥60 years and enrolled in the CARE Registry at the University of Alabama at Birmingham (UAB). Patients completed a patient-reported geriatric assessment at their initial visit with a medical oncologist. Patients rated pain on a numeric scale from 0-10. We employed the literature-based cut off for moderate-severe pain of ≥4. Logistic regression modeling was used to determine the association between moderate/severe pain and functional status, falls, cognition, and depression/anxiety. We adjusted the models for sex, race, education, race/ethnicity, marital status, cancer type, and cancer stage. **Results:** Our cohort included 714 older adults. Median age at diagnosis was 70y (range 60-96) and 59% were male. Median time between diagnosis and study participation was 37 days. Most prevalent diagnoses included colorectal (27.9%), pancreatic (18%), hepatobiliary (11.5%) and gastroesophageal (6.4%) cancers. Overall, 53.1% of the participants reported none/mild (0-3) pain, 25.6% reported moderate (4-7) pain, and 21.4% reported severe (8-10) pain. In univariate analyses, Black patients, lower education, disabled employment, and pancreatic cancer was associated with moderate/severe pain. After multivariate adjusting for covariates, participants with moderate/severe pain were more likely to report limitations in instrumental activities of daily living (adjusted Odds Ratio [aOR] 4.3, 95% confidence interval [CI] 3.1-6.1, $p < .001$), limitations in activities of daily living (aOR 3.2, 95% CI 2.0-5.1, $p < .001$), falls (aOR 2.4, 95% CI 1.6-3.6, $p < .001$), cognitive complaints (aOR 2.9, 95% CI 1.4-6.0, $p < .004$), anxiety (aOR 2.2, 95% CI 1.4-3.4, $p < 0.01$), and depression (aOR 3.7, 95% CI 2.2-6.5, $p < .001$). **Conclusions:** Pain is common amongst older adults with GI cancers and is associated with functional status limitations, falls, cognitive complaints, and depression/anxiety. Strategies to reduce pain and/or minimize its potential impact on function and mental health warrant future research. Research Sponsor: U.S. National Institutes of Health.

83 **Poster Session**

Preventives for oxaliplatin-induced peripheral neuropathy in colorectal cancer patients.

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Background: For colorectal cancer patients treated with the chemotherapy drug oxaliplatin, oxaliplatin-induced peripheral neuropathy (OIPN) is a serious side effect. We conducted an observational comparative effectiveness study to evaluate whether several potential preventives reduced the rate of OIPN diagnosis in the two years following chemotherapy initiation. **Methods:** This was a retrospective cohort study that utilized the Surveillance, Epidemiology, and End Results database combined with Medicare claims (SEER-Medicare). Eligible patients were diagnosed with colorectal cancer between 2007-2015, 66 years of age or older, and received at least two cycles of oxaliplatin. We used two definitions to denote diagnosis of OIPN: OIPN 1 (diagnosis codes specific to CIPN) and OIPN 2 (additional codes for peripheral neuropathy). Multinomial propensity score weighting was used to balance potential confounders. The Fine-Gray subdistribution hazards model was used to perform a competing risk, time to event analysis for diagnosis of OIPN. **Results:** There were 4,482 subjects analyzed for the outcome of OIPN 1 (n = 477, 10.1%), and 4,561 for OIPN 2 (n = 1,191, 26.1%). Duloxetine, venlafaxine (marginally significant for OIPN 1), opioids, and minocycline were associated with a decreased rate of OIPN according to both definitions. In addition, memantine and neuromuscular therapy were associated with a decreased rate of OIPN 1 but not OIPN 2. Gabapentin and pregabalin exposure was associated with an increased rate of OIPN diagnosis according to both definitions. Mixed results were obtained for nortriptyline and cannabinoids. **Conclusions:** This study revealed several potentially effective preventive options for OIPN in colorectal cancer patients receiving oxaliplatin. A limitation of this study is the observational design which cannot directly inform treatment guidelines. However, evidence from this study may serve as preliminary data to support a future randomized clinical trial. Research Sponsor: U.S. National Institutes of Health.

Relative hazard rate for potential preventives of OIPN.

	OIPN 1			OIPN 2		
	sHR	95% CI	p	sHR	95% CI	p
Duloxetine HCL						
No	Ref			Ref		
Yes	0.36	0.29-0.45	<0.001	0.76	0.69-0.83	<0.001
Memantine						
No	Ref			Ref		
Yes	0.60	0.47-0.78	<0.001	1.02	0.91-1.14	0.774
Nortriptyline						
No	Ref			Ref		
Yes	0.96	0.69-1.33	0.788	0.65	0.52-0.82	<0.001
Venlafaxine						
No	Ref			Ref		
Yes	0.85	0.42-0.56	0.077	0.49	0.42-0.56	<0.001
Gabapentin						
No	Ref			Ref		
Yes	1.81	1.65-1.98	<0.001	1.93	1.83-2.04	<0.001
Pregabalin						
No	Ref			Ref		
Yes	1.21	1.04-1.42	0.015	1.39	1.28-1.51	<0.001
Cannabinoids						
No	Ref			Ref		
Yes	0.78	0.58-1.06	0.117	1.24	1.06-1.45	0.009
Opioids						
No	Ref			Ref		
Yes	0.61	0.56-0.67	<0.001	0.89	0.84-0.94	<0.001
Minocycline						
No	Ref			Ref		
Yes	0.72	0.61-0.86	<0.001	0.88	0.77-0.99	0.034
Neuromuscular therapy						
No	Ref			Ref		
Yes	0.58	0.52-0.64	<0.001	1.27	1.21-1.35	<0.001

Abbreviations: sHR, subdistribution hazard ratio; CI, confidence interval; ref, reference group.

Associations of sarcopenia with hematologic toxicity, treatment intensity, and healthcare utilization in patients with metastatic colorectal cancer.

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Background: We evaluated the impact of baseline sarcopenia on hematologic toxicity, treatment intensity, and healthcare utilization in patients with mCRC receiving FOLFOX or FOLFIRI. **Methods:** We retrospectively analyzed patients with mCRC who received care at our institution from 1/2011-11/2018 and were part of a biobanking protocol. Included adults received either first-line palliative FOLFOX- or FOLFIRI-based regimens and were followed for 6 months. We categorized sarcopenia based on skeletal muscle index measured at diagnosis of metastatic disease and pre-defined sex-specific cutoff values (F $<$ 39 cm2/m2, M $<$ 55cm2/m2). Our primary aim was to evaluate the association of sarcopenia and hematologic toxicity, defined as the incidence of grade ≥3 (G≥3) neutropenia, thrombocytopenia, or anemia (NCI CTCAE v5.0). Secondary endpoints included treatment intensity (dose reductions, treatment delays, relative-dose intensity [RDI]), and healthcare utilization (ED visits and/or hospitalizations). Bivariate analyses were used to evaluate associations between baseline sarcopenia and outcomes. **Results:** 126 of 177 screened patients met inclusion criteria (70 (56%) males, median age 61 yrs (range, 29-85)). 59 (46.8%) patients were sarcopenic. More patients received FOLFOX than FOLFIRI (92 [73.0%] vs. 34 [27.0%]). At baseline, patients had a median weight 76.9kg (IQR, 70.0-90.4 kg), BMI 26.6 kg/m2 (IQR, 24.1-30.5 kg/m2), and BSA 1.90 m2 (IQR, 1.72-2.01 m2). The incidence of G≥3 hematologic toxicity was 39.0% vs. 23.9% in sarcopenic and non-sarcopenic patients, respectively (p = 0.06). Patients with sarcopenia experienced higher incidence of G≥3 neutropenia (30.5% vs. 14.9%, p = 0.03), while G≥3 thrombocytopenia was similar (3.4% vs. 1.5%). The incidence of dose reductions and treatment delays did not differ significantly (86.4% vs. 89.5%, 72.9% vs. 71.6%, respectively). RDI was decreased for the 5FU bolus (52.5% vs. 65.0%, p = 0.02). Rates of ED visits (32.2% vs. 19.4%, p = 0.10) and hospitalizations (32.2% vs. 26.9%, p = 0.51) did not differ compared between patients with and without sarcopenia. **Conclusions:** Patients with mCRC and baseline sarcopenia receiving FOLFOX- or FOLFIRI experienced a higher incidence of G≥3 neutropenia and lower 5FU bolus treatment intensity. Studies are needed to understand how best to adjust treatment according to patients' muscle mass. Research Sponsor: None.

85 **Poster Session**

Predictive factors for renal function deterioration during palliative first-line chemotherapy for metastatic colorectal cancer.

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Background: Effective first-line therapy is a key determinant of treatment outcomes and should be selected after considering both clinical factors and biological markers in metastatic colorectal cancer (mCRC). Considering the increased number of cancer patients with old age and their chronic diseases, it is essential to select a therapeutic agent by evaluating the toxicity that may occur due to long-term chemotherapy. This study assessed changes in renal function for 1 year in patients diagnosed with mCRC during chemotherapy and analyzed the factors and effect of each chemotherapy regimen on renal function. **Methods:** We retrospectively investigated patients with mCRC treated with palliative 1st line chemotherapy at our institution from 2015 to 2020. According to the common 1st line treatment regimen, we divided into 4 groups; FOLFOX/FOLFIRI with bevacizumab/cetuximab. We checked the baseline renal function and 3, 6, 9 and 12 months after the start of chemotherapy. The change in estimated glomerular filtration rate ($\triangle$eGFR) was calculated as [(eGFR at each time point) - (eGFR at baseline)/(eGFR at baseline) X 100]. The clinical factors such as age, gender, chronic disease, BMI (body mass index), disease status, baseline proteinuria, and 1st line chemotherapy regimen were evaluated. Proteinuria was detected on urine dipstick protein $\geq$ 1+. Additionally, predictors for ΔeGFR $\leq -30\%$ at each time points after therapy initiation were evaluated using multivariate logistic regression analysis. **Results:** Among 466 mCRC patients, the median eGFR values at baseline was 95.4 ml/min/1.73m^2. The median eGFR at 6 months after chemotherapy initiation were significantly lower than baseline (88.3 ml/min/1.73m^2, $p < 0.001$). As 1 year, patients with more than 30% worsening of renal function was observed in 27.6 % in FOLFIRI + bevacizumab, 26.3 % in FOLFOX + bevacizumab, 6.6 % in FOLFIRI + cetuximab, and 4.7 % in FOLFOX + cetuximab group. The FOLFIRI + bevacizumab was an independent predictor for ΔeGFR $\leq -30\%$ at 6 months (odds ratio (OR) 1.94, 95% confidence interval (CI) 1.05-3.47, p = 0.034) along with old age ($\geq$ 65 years, OR 2.18, 95% CI 1.29-3.68, p = 0.004) and BMI (p = 0.012). Additionally, FOLFIRI + bevacizumab regimen causes more proteinuria (46.4%) than other chemotherapy regimens. **Conclusions:** Deterioration of renal function was more common with FOLFIRI + bevacizumab than other combination regimen. Old age, BMI were also associated decreasing eGFR. These results will be helpful to be suggested as important consideration when selecting the 1st line chemotherapy regimen for mCRC. Research Sponsor: None.

Second cancer after adjuvant chemotherapy in patients with colon cancer.

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Background: Adjuvant chemotherapeutic treatment of UICC-stage III/IV colon cancer with fluorouracil, leucovorin and oxaliplatin (FOLFOX) is widely accepted as the current standard after R0-resection. However, with continuous improvement of patients´ survival and life expectancy, long-term side effects of chemotherapy such as second cancer development are becoming increasingly important. **Methods:** We performed a retrospective analysis of clinical data derived from the population-based cancer registry at the Regensburg Tumor Center, Germany. Patients who were diagnosed with colon cancer UICC stage III and IV between 2002 and 2018 and underwent R0 surgical resection of primary tumor were included for the study. Second cancer was as defined new tumor occurrence at least 6 months after beginning of chemotherapy and in another localization compared to primary tumor. Second cancer rate was compared between patients with and patients without adjuvant chemotherapy. **Results:** Data of totally 2,856 Patients with UICC-stage III/IV colon cancer were analyzed, 1,520 (53.2%) of whom received adjuvant chemotherapy. Overall, 223 (7.8%) patients developed a subsequent second cancer. Most frequent second cancers were prostate cancer (18.4%), colon cancer (16.1%), breast cancers (8.1%), lung cancer (8.1%), rectal cancer (4.9%) and uterine cancer (4.9%). However, patients treated with adjuvant chemotherapy did not have a significantly increased risk for second cancer development compared to patients without adjuvant chemotherapy (Table). Interestingly, our data suggest a significantly decreased second cancer rate in patients treated with FOLFOX compared to FUFOL for adjuvant treatment. **Conclusions:** Second cancer development was not increased after adjuvant chemotherapy for UICC-stage III/IV colon cancer, which is a novel aspect in the ongoing discussions on reduction of adjuvant treatment to 3 months or treatment of lymph node negative patients. Primary tumor (N) Second tumor (N) Second tumor (%) Cumulative rate 60 months (%) Log-Rank p Chemotherapy Yes 1520 145 9.5% 8.8% No 1336 78 5.8% 9.0% 0.685 Total 2856 223 7.8% 8.9% Research Sponsor: None.

Exploratory analysis of baseline tumor burden in the TRUSTY study: A randomized phase 2/3 study of trifluridine/tipiracil plus bevacizumab versus irinotecan and fluoropyrimidine plus bevacizumab as second-line treatment in patients with metastatic colorectal cancer.

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Background: In primary analysis from the TRUSTY study, trifluridine/tipiracil (FTD/TPI) plus bevacizumab (BEV) failed to show non-inferiority to irinotecan and fluoropyrimidine plus BEV in overall survival (OS) as second-line treatment in patients (pts) with metastatic colorectal cancer (mCRC) (median OS, 14.8 vs. 18.1 months: HR, 1.38: 95% CI; 0.99-1.93: p = 0.59 for non-inferiority; Kuboki Y, et al. ASCO 2021). Here we report a *post hoc* efficacy analysis by baseline tumor burden. **Methods:** Pts with histologically confirmed mCRC who failed first-line chemotherapy with fluoropyrimidine and oxaliplatin plus either BEV or an anti-EGFR antibody were eligible. Pts were randomized to receive either FTD/TPI plus BEV (FTD/TPI plus BEV group, FTD/TPI 35 mg/m^2 twice daily on days 1–5 and 8–12 every 28-day cycle, and BEV 5 mg/kg on days 1 and 15) or either FOLFIRI or S-1 and irinotecan combined with BEV (control group). Efficacy measured by OS, progression-free survival (PFS), and disease control rate (DCR) were compared between pts grouped by baseline sum of diameter of target lesions (STL). Survival curves were drawn by direct survival estimation adjusted for stratification factors. **Results:** In the ITT population (N = 396), 60 mm was selected as the optimal cutoff for STL because it produced the most significant difference in OS; 151 pts had high tumor burden with STL $\geq$ 60 mm (FTD/TPI plus BEV, n = 76: control, n = 75), 216 had low tumor burden with STL $<$ 60 mm (n = 107, n = 109), and 29 were excluded due to no measurable lesions. Baseline characteristics in pts with both high and low tumor burden were balanced between treatment groups. In pts with STL $\geq$ 60 mm, FTD/TPI plus BEV was less effective than the control: adjusted median OS was 10.9 versus 16.2 months (HR: 2.32; 95% CI: 1.42-3.79), median PFS was 3.5 versus 6.1 months (HR: 2.32; 95% CI: 1.52-3.53): and DCR was 53.9% versus 72.0% (p = 0.03). In pts with STL $<$ 60 mm, FTD/TPI plus BEV was comparably effective to the control: median OS was 21.4 versus 20.7 months (HR: 0.92; 95% CI: 0.55-1.55), median PFS was 5.6 versus 6.0 months (HR: 1.23; 95% CI: 0.87-1.72), and DCR was 66.4% versus 71.6% (p = 0.46). **Conclusions:** FTD/TPI + BEV might be a second-line treatment option for mCRC pts with low tumor burden (STL $<$ 60 mm). Clinical trial information: jRCTs031180122. Research Sponsor: Taiho Pharmaceutical Co, Ltd.

Phase II single-arm study of palbociclib and cetuximab rechallenge in *KRAS*/*NRAS*/*BRAF* wild-type (*KRAS* WT) metastatic colorectal cancer (mCRC) patients (pts).

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Background: Cetuximab is a monoclonal antibody (mAb) targeting the epidermal growth factor receptor (EGFR) and is given alone or in combination with chemotherapy in the 60% of mCRC that are *KRAS* WT. Unfortunately, resistance inevitably develops, which may be related to downstream upregulation of the extracellular-signal-regulated kinase (ERK) pathway. Rechallenge with anti-EGFR mAb may be effective in patients previously benefiting from anti-EGFR therapy, but median progression-free survival is < 4 months, indicating need for novel more effective combinations for rechallenge. Co-inhibition of EGFR and downstream cyclin-dependent kinases 4/6 (CDK4/6) may overcome ERK pathway reactivation. We hypothesized that the addition of the CDK4/6 inhibitor palbociclib to cetuximab would be effective for anti-EGFR rechallenge in *KRAS*-WT mCRC. **Methods:** LCCC1717 was a multicenter, single-arm, Simon's two stage phase II study of cetuximab and palbociclib in *KRAS* WT mCRC treated with $\geq$2 prior regimens (NCT03446157). Eligible pts were enrolled to one of two cohorts depending on previous anti-EGFR mAb therapy; we report here on cohort B, which enrolled pts who had disease control for at least 4 months with anti-EGFR therapy. Cohort B was designed to initially enroll 10 evaluable pts; if $\geq$ 4 pts had disease control at least 4 months, then 11 more pts would be enrolled. Treatment included cetuximab 400 mg/m^2 followed by 250 mg/m^2 weekly, plus palbociclib 125 mg daily on days 1-21 of a 28-day cycle until progression, toxicity, or withdrawal. Primary endpoint was disease control rate (DCR) at 4 months by RECIST 1.1. Secondary endpoints were overall response rate (ORR), progression free survival (PFS), and overall survival (OS). **Results:** In cohort B, 10 evaluable pts were enrolled from 2/2018-8/2020 (1 additional pt withdrew after an infusion reaction with first dose of cetuximab). Median age 59, 70% male, 90% left-sided primary. The 4-mo DCR was 2/10 (20%; 95% CI 5-52%). Given this, enrollment in this cohort was halted after first stage. Median PFS was 1.8 mo (95% CI: 1.7, NE) and median OS was 6.6 mo (95% CI: 3.6, NE). No pts had a complete or partial response; 3 pts (30%) had stable disease (SD), including 1 patient with SD for 24.7 months. The regimen was well tolerated; most common treatment-related grade 3-4 adverse events were lymphopenia (27%) and leukopenia (18%). While 55% of pts had acneiform rash, none were grade 3-4. **Conclusions:** Selection of patients for anti-EGFR rechallenge using clinical criteria alone was insufficient to identify pts likely to respond to palbociclib + cetuximab rechallenge. This emphasizes the need for screening using circulating tumor (ct) DNA of known resistance mutations to select pts for anti-EGFR rechallenge approaches. Translational work assessing ctDNA in this study is planned. Cohort A with anti-EGFR naïve patients continues enrollment. Clinical trial information: NCT03446157. Research Sponsor: Pfizer.

89 **Poster Session**

Exploratory biomarker analyses of the single-arm, phase 2 study of regorafenib plus nivolumab in patients (pts) with mismatch repair-proficient (pMMR)/microsatellite stable (MSS) colorectal cancer (CRC).

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Background: Combination treatment with regorafenib (80–120 mg/day, PO, 3 wks on/1 wk off) plus nivolumab (480 mg IV Q4W) showed manageable safety but modest efficacy in a phase 2 study of 70 pts from North America with pMMR/MSS chemotherapy-resistant metastatic CRC (mCRC). Five pts had a partial response (PR; objective response rate [ORR]: 7%); all did not have liver metastases at baseline (n = 5/23; ORR: 22%). One pt had a confirmed complete response (CR) after the primary completion analysis of the study (ASCO 2021). This retrospective exploratory analysis investigated the potential association between specific biomarkers and anti-tumor activity, and how those biomarkers are modulated by treatment with regorafenib plus nivolumab. **Methods:** In formalin-fixed paraffin-embedded tumor samples obtained at baseline and Cycle (C) 2 Day (D) 8, immune-related biomarkers were assessed via immunohistochemistry (IHC), and RNA sequencing was used for gene expression profiling/gene signatures. Pre-/on-treatment blood samples were collected to measure circulating tumor DNA (ctDNA) and soluble biomarkers. **Results:** A total of 40 and 27 baseline tumor samples and 14 and 5 paired tumor samples at baseline/C2D8 were available for IHC and RNA sequencing, respectively. Higher baseline protein and mRNA expression of biomarkers for pre-existing immune sensitivity (eg, effector T cells) trended with anti-tumor activity. These biomarkers were expressed at lower levels in pts with liver metastases vs those without liver metastases at baseline. Cytotoxic T cell density was elevated on C2D8 but did not correlate with anti-tumor activity. Increased mean variant allelic frequency in ctDNA at C2D1 predominated in pts with progressive disease (PD), while clearance of ctDNA at C2D1 was only noted for the one pt with a CR. High clonal tumor mutational burden in ctDNA showed a numerical trend with anti-tumor activity (PD vs. SD/PR; P=0.058) and PFS (P = 0.072). Baseline serum levels of select markers related to angiogenesis (eg, vascular endothelial growth factor [VEGF] D) were associated with inferior anti-tumor activity (P = 0.002). Serum levels of immune-related soluble biomarkers (eg, tumor necrosis factor alpha) increased on treatment ($P < 0.005$), while levels of soluble VEGF receptor 2 decreased ($P < 0.001$). **Conclusions:** This study of pts with MSS mCRC treated with regorafenib plus nivolumab suggests that baseline tumor biomarkers for pre-existing immune sensitivity trended with anti-tumor activity, whereas select baseline peripheral biomarkers related to angiogenesis trended with inferior anti-tumor activity. Pharmacodynamics effects were observed, yet no significant correlation with anti-tumor activity was found. Due to the small sample size and retrospective nature, these analyses are hypothesis-generating. Clinical trial information: NCT04126733. Research Sponsor: Bayer, Bristol Myers-Squibb, Ono.

90 **Poster Session**

Survival in total preoperative verus perioperative chemotherapy for patients with metastatic high-grade appendiceal adenocarcinoma undergoing CRS/HIPEC.

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Background: Due to the relative infrequency of high grade appendiceal adenocarcinoma with peritoneal metastases, there is limited data to guide treatment strategies. Current practices for this disease are largely extrapolated from colon cancer patients with peritoneal metastases, who typically undergo six months of systemic chemotherapy in conjunction with cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC). The optimal timing of chemotherapy in relation to CRS/HIPEC remains unknown. In this study, we compare the efficacy of peri-operative chemotherapy to pre-operative chemotherapy alone. **Methods:** This is a retrospective review of patients who underwent CRS/HIPEC for high grade appendiceal cancers from a tertiary referral center from 2014-2020. Outcomes were compared between patients who underwent planned 6 months of chemotherapy followed by CRS/HIPEC (pre-operative group) versus planned 3 months of chemotherapy both pre- and post-operatively (peri-operative group). **Results:** 85 patients were treated for metastatic high-grade appendiceal cancers during the study period, of whom24 were eligible for inclusion. Of those included, 16 were in the peri-operative group and 8 in the pre-operative group. Most patients were white (75%), non-Hispanic (96%) and female (54%). Patients in the pre-operative group tended to be older (65 vs. 56 years, $p = 0.02$). For patients with specified histologic grading, poorly differentiated tumors were common (50%). Signet ring cell histology (42%) and mucinous features (67%) were frequent as well. Median overall survival was similar between the pre-operative and peri-operative groups (32.3 vs. 31.6 months, $p = 0.97$), although patients undergoing peri-operative treatment received fewer total cycles of chemotherapy on average (14.1 vs. 9.5 cycles, $p < 0.01$). Half of the patients in the peri-operative group (8/16) did not complete their chemotherapy regimen, with 75% discontinuing therapy due to chemotherapy-related toxicities. Within the peri-operative group, a non-significant decrease in median survival was observed for those who did not complete chemotherapy (27.8 vs $>$ 53.6 months, $p = 0.22$). **Conclusions:** Peri-operative and total pre-operative chemotherapy strategies are associated with similar survival in patients with high grade appendiceal cancers undergoing CRS/HIPEC. Peri-operative administration may be limited by chemotherapy-related toxicities. Research Sponsor: None.

Changes in prescribing patterns in stage III colon cancer (CC) since the IDEA collaboration.

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Background: Since the publication of the MOSAIC trial, stage III CC has been treated with a six-month (mo) regimen of FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CAPOX (capecitabine and oxaliplatin). Recently, the IDEA collaboration challenged this practice by demonstrating that the 3-year rate of disease-free survival (DFS) was non-inferior to 6mo of treatment (Rx) when given for low risk CC (83.1 vs. 83.3%) and resulted in significantly lower rates of grade 2 and higher neuropathy. In high risk (T4, N2) patients (pts) the DFS of 3mo of CAPOX was equivocal to 6mo (64.1 vs. 64.0%), while 3mo of FOLFOX was inferior to 6mo (61.5 vs. 64.7%). We hypothesized that trends in prescribing would favor shorter courses of Rx with a preference towards CAPOX given its efficacy across both high and low risk CC. **Methods:** We performed a retrospective analysis of stage III CC pts from 4 institutions. We evaluated prescribing patterns of 3mo or 6mo of Rx and CAPOX vs. FOLFOX over a period of 5 years from Jan 2016 to Jan 2021, a time period that traverses before and after the release of IDEA. Logistic and multinomial logistic regression models, with a linear time trend, were used to estimate the percentage of pts receiving CAPOX vs. FOLFOX and the combination of Rx and duration, respectively, while adjusting for baseline characteristics. The prescribing patterns in important subgroups were examined by incorporating the interaction term in the models. **Results:** A total of 366 pts met inclusion criteria. From 2016-2021, there was a significant increase per quarter in patients treated with CAPOX when compared to FOLFOX (OR 1.16 95% CI 1.11 – 1.21, $p < .001$). Prior to IDEA, 78.3% of pts received 6mo FOLFOX and 7.4% received 3mo CAPOX. Two years after IDEA, only 17.3% of pts were on 6mo FOLFOX compared to 67.5% of pts on 3mo CAPOX (Table). At present, high risk pts are more likely to receive 6mo FOLFOX (47.8%) than 3mo of FOLFOX (3.9%), 3mo CAPOX (25.8%), or 6mo CAPOX (22.4%). Low risk pts are more likely to receive 3mo of CAPOX (67.9%) than other Rx. **Conclusions:** Our findings suggest that since IDEA, physician practice has significantly changed in favor of CAPOX and shorter courses of Rx. The use of CAPOX has significantly increased overall, presumably due to its efficacy across all risk groups and relatively reduced toxicity. Research Sponsor: None.

Percentage of pts receiving 3mo vs. 6mo of CAPOX vs. FOLFOX before and after the IDEA collaboration.

%	CAPOX			FOLFOX		
	Any duration	3mo	6mo	Any duration	3mo	6mo
June 2016	16.3	7.4	6.5	83.7	7.9	78.3
June 2020	66.8	67.5	5.9	33.2	9.3	17.3
			Low Risk			
June 2016	—	7.2	5.6	—	8.3	79.0
June 2020	—	67.9	6.6	—	8.7	16.8
			High Risk			
June 2016	—	1.3	11.2	—	0.9	86.6
June 2020	—	25.9	22.4	—	3.9	47.8

93 **Poster Session**

Phase 1/1b trial of fruquintinib in patients with advanced solid tumors: Preliminary results of the dose expansion cohorts in refractory metastatic colorectal cancer.

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Background: Fruquintinib (F) is a highly selective, novel, oral tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor receptors (VEGFR) -1, -2, and -3. The phase (Ph) 3 FRESCO study (NCT02314819) that investigated F (5mg daily, 3 weeks (wks) on 1 wk off) showed improved median overall survival in patients (pts) with metastatic colorectal cancer (mCRC) in third line and beyond when compared to placebo (9.3 vs. 6.6 months); hazard ratio 0.65 ($P < 0.001$) and led to its approval in China. **Methods:** This is an ongoing Ph 1/1b open-label, dose escalation/expansion study conducted in the US. Here we present the preliminary safety and antitumor efficacy data from pts with refractory mCRC in Cohort (Coh) B (progressed on all standard therapies including TAS-102 [TAS] and/or regorafenib [R]) and in Coh C (did not receive TAS or R). **Results:** As of data cutoff on 27 July 2021, 81 mCRC pts had been treated (41 in Coh B and 40 in Coh C); median age of 57 years (range: 3477), Caucasian (81.5%), female (44.4%), and ECOG PS 1 (59.3%). In Coh B, the median number of prior therapies was 5 (range: 3-9), 8 pts (19.5%) received R, 19 (46.3%) received TAS and 14 (34.1%) received both R and TAS. In Coh C, the median number of prior therapies was 4 (range: 1-10). Five pts remain on treatment; reasons for treatment discontinuation included: 56 pts (69.1%) due to progressive disease or death, 8 pts (9.9%) due to adverse events (AE), and 12 pts (14.8%) due to withdrawal of consent or physician decision. The median duration of F treatment was 4.4 months (range: 0.7–20.0) in Coh B and 3.7 months (range: 0.02-14.3) in Coh C. The most frequently reported AEs of any grade in Coh B were fatigue (53.7%), proteinuria (51.2%), and hypertension (HTN; 48.8%). In Coh C the most frequently reported AEs of any grade were HTN (75.0%), proteinuria (40.0%), and myalgia (32.5%). Hand-foot syndrome (HFS) was reported in 29.3% of Coh B pts and 22.5% of Coh C pts. The disease control rate [DCR] was 68.3% in Coh B (1 partial response [PR] and 27 stable disease [SD]) and 59.5% for the 37 patients with at least one post-baseline tumor assessment in Coh C (2 PRs and 20 SDs). **Conclusions:** F is generally well-tolerated in heavily-pretreated pts with refractory mCRC. Evidence of antitumor activity was observed in cohorts B and C. The multi-cohort dose expansion is ongoing. F is being further investigated in refractory mCRC in a global Ph 3 study (NCT04322539). Clinical trial information: NCT03251378. Research Sponsor: HUTCHMED International.

94 **Poster Session**

Outcome of preoperative concurrent radiation and infusional gemcitabine in locally advanced rectal cancer, a phase 2 trial.

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Background: The achievement of a pathological complete response with preoperative concurrent chemoradiotherapy in locally advanced rectal cancer has been found to correlate with a reduced incidence of local and distant recurrences. With the radiosensetizing properties of gemcitabine, we tested the efficacy and toxicity of preoperative concurrent infusional gemcitabine and radiotherapy in locally advanced rectal cancer. **Methods:** This was a phase II, single-arm, single-institution trial. Eligibility included a diagnosis of rectal adenocarcinoma with stage T2–4 and/or nodal involvement by MRI and endoscopic rectal ultrasound, age ≥ 18 years and no prior chemotherapy or radiotherapy. Patients received preoperative radiation at a dose of 50.4–54 Gy over 28 days with concurrent infusional gemcitabine administered at a dose of 100 mg/m2 over the course of 24 hours weekly for 6 weeks. The primary endpoint was a pathological complete response (pCR). The trial was registered at clinicaltrials.gov (NCT02919878). **Results:** Forty patients were enrolled in the study. All of the patients completed the planned therapy, except for one patient who died at the end of his concurrent chemoradiation. Eight patients did not undergo surgery, with 1 patient dying (mentioned above), 2 patients progressing to nonresectable disease and 5 patients withdrawing consent. Six patients progressed prior to or had metastases identified at surgery, with 2 patients having unresectable metastases, 3 patients having resectable liver metastases and 1 patient having a peritoneal metastasis (not resected). Serious adverse events were reported in 8 patients (20%). The most common grade 3–4 toxicities in the preoperative period included lymphopenia (50%), neutropenia (41%), anemia (15%), diarrhea (12%), abdominal pain (12%) and proctitis (8%). Out of the 32 patients who underwent surgery, 7 patients achieved pCR at a rate of 20%. With a median follow-up of 30 months, 4 additional patients relapsed (all of these patients had distant metastases, with one subsequently having a local recurrence). The 3-year event-free and overall survival rates were 70% and 85%, respectively. **Conclusions:** Concurrent preoperative chemoradiotherapy using infusional gemcitabine for locally advanced rectal cancer achieved an encouraging local control. Distant metastasis remains not decreased. Further investigations of a preoperative regimen containing gemcitabine is warranted. Clinical trial information: NCT02919878. Research Sponsor: None.

95 **Poster Session**

Oxaliplatin in metastatic colorectal cancer: Does hepatic arterial infusion reduce sensitive neuropathy compared to the intravenous route?

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Background: Oxaliplatin, a major drug in metastatic colorectal cancer (MCRC), is responsible for a cumulative and limiting peripheral neuropathy (PN). Hepatic arterial infusion (HAI) chemotherapy, which makes sense in cases of exclusive or predominant liver metastases, increases the intratumor concentration of the administered drug(s) to improve efficacy and limit systemic toxicity. **Methods:** We compared the frequency and severity of NP in oxaliplatin-naive patients with MCRC included in trials that evaluated treatment with oxaliplatin administered either by HAI (CHOICE, OSCAR, and PACHA-01 trials) or by intravenous (IV) route (FFCD 2000-05 trial). The primary endpoint was the occurrence of clinically significant NP (grade 2-4) according to the cumulative dose of oxaliplatin received. The secondary endpoints were the occurence of severe NP (grade 3-4) and time to onset of NP. **Results:** 342 patients were included (IV oxaliplatin: 300; HAI: 42). 180 patients in the IV group (60%) and 24 patients in the HAI group (57%) developed clinically significant NP, with no significant difference between the 2 groups ($p = 0.85$). 95 patients in the IV group (32%) and 8 patients in the HAI group (19%) developed severe NP, with no significant difference between the 2 groups ($p = 0.082$). NP appeared earlier in the HAI group, with more treatment discontinuations for neurotoxicity. **Conclusions:** The administration of oxaliplatin HAI rather than IV in the treatment of MCRC does not seem to reduce the incidence, precocity and severity of NP. Research Sponsor: None.

96 **Poster Session**

AB1, a novel protein targeting TP53 mutated GI tumors.

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Background: The tumor suppressor gene *TP53* is one of the most frequently deleted or mutated genes in gastrointestinal cancers. Normal p53 regulates several important proteins that control cell cycle, cell death, DNA damage/repair, stemness, differentiation and other key cellular functions. If the *TP53* gene is damaged, tumor suppression is severely compromised. On the other hand, and downstream of p53, p21 a potent cyclin-dependent kinase inhibitor (CKI) protein binds and inhibitsthe activity of cyclin - CDK2, - CDK1, and - CDK4/6, thus functioning as a regulator ofcell cycle progression at G 1 and S phase. It can act as de facto p53 repair/ replacement mechanism. We have thus hypothesised that, if we were able to deliver wild type p21 into all p53 mutated cancer cells, it would have a possible therapeutic effect. **Methods:** We have constructed recombinantly a new fusion protein, named AB1, composed of a cell penetrating protein (antennapedia) ANTP and wild type p21 and tested it in in vitro and in vivo preclinical models prior to clinical studies. AB1 could also be constructed semi-synthetically by conjugating recombinant ANTP chemically to p21 protein. **Results:** AB1 penetrated and killed p53 mutated cancer cells but did not kill cells that did not have p53 mutations AB1 penetrated but did not kill p53- or p21- wild-type cells. AB1 was not immunogenic in normal New Zealand White rabbits. AB1 was more cytotoxic when administered with conventionally-used chemotherapeutic agents. **Conclusions:** We have generated a selectively cytotoxic fusion protein against p53 mutated GI cancers which is effective when used as a single agent but more so when used in combination with chemotherapy. The phaseI/II clinical trial will include eligible patients who have p53 mutated GI cancers Research Sponsor: Horizon 2020, investors.

97 **Poster Session**

Anti-HER2 therapy with pyrotinib and trastuzumab in refractory HER2-positive metastatic colorectal cancer: A preliminary report from HER2-FUSCC-G study.

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Background: Dual-targeted HER2 therapy has led to a promising antitumor effect in HER2 positive metastatic colorectal cancer. The current study was aimed to evaluate the therapeutic efficacy of pyrotinib and trastuzumab in patients with HER2 positive colorectal cancer. **Methods:** HER2-FUSCC-G is an ongoing, open-label, non-randomised, phase 2a study. Patients in this subset were diagnosed as HER2 positive metastatic colorectal cancer refractory to standard chemotherapies. All the enrolled patients were treated with a loading dose of trastuzumab at 8 mg/kg followed by 6mg/kg once every three weeks, and oral pyrotinib at 400 mg per day until progression. ORR was set as the primary endpoint. Estimates of PFS (progression free survival) and OS (overall survival) were obtained with the Kaplan-Meier method and compared with log-rank test. **Results:** Between January 2020 to June 2021, 11 patients were enrolled in this study. The ORR was 45.5% in whole population, and 55.6% in RAS wild-type patients. At a median follow-up of 17.73 months, median PFS and OS were 7.80 and 14.97 months, respectively. The KRAS wild-type group of patients had prolonged survival (PFS: 9.97 vs. 7.73 months, P = 0.19; OS: 20.67 vs. 12.43 months, P = 0.021) compared with KRAS mutant group. Nine of 11 (81.8%) patients reported≥1 grade treatment-emergent adverse events (TATEs), while 4 (36.4%) patients reported grade 3/4 TATEs. **Conclusions:** The combination of trastuzumab and pyrotinib showed a promising anti-tumor response and prolonged long-term survival benefit in RAS wild-type and HER2 positive mCRC with acceptable tolerance. Clinical trial information: NCT04960943. Research Sponsor: None.

Ezabenlimab (BI 754091), an anti-PD-1 antibody, in combination with BI 836880, a VEGF/Ang2-blocking nanobody, in patients (pts) with advanced colorectal cancer (CRC).

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Background: Anti-PD-1 antibodies may have synergistic effects with other immunomodulatory or targeted agents. This open-label, Phase II platform trial is investigating ezabenlimab, an anti-PD-1 antibody, combined with other agents. Module C of the platform is assessing ezabenlimab plus BI 836880, a humanized bispecific nanobody targeting VEGF/Ang2. Pts are being enrolled into 5 advanced solid tumor cohorts: gastric/gastroesophageal adenocarcinoma; solid tumors (except non-squamous NSCLC or melanoma) with secondary resistance to anti-PD-(L)1 treatment (progression after at least SD for ≥4 months); solid tumors with primary resistance to anti-PD-(L)1 treatment; microsatellite stable (MSS) CRC; mismatch repair-proficient/MSS endometrial carcinoma. Here, we report data from the CRC cohort which has completed recruitment. **Methods:** Pts with locally advanced, unresectable or metastatic, MSS CRC were enrolled. Patients had received ≥1 line of prior systemic therapy for metastatic disease but were anti-PD-(L)-1 therapy-naïve. Prior anti-angiogenic therapy was permitted. Pts received BI 836880 720 mg plus ezabenlimab 240 mg iv q3w for 1 year or until disease progression, consent withdrawal or undue toxicity. Primary endpoint: investigator-assessed OR (CR or PR per RECIST v1.1). Secondary endpoints: duration of response, disease control, and PFS; safety is also being assessed. **Results:** 30 pts have been treated: 57% male; median age 61.5 years. All pts had received prior chemotherapy; most pts (23 [77%]) had received prior bevacizumab. At data cut-off (Sep 2021), median duration (range) of treatment was 115.5 (28–295) days; 6 pts remain on treatment. 1 (3%) pt (who had not received prior bevacizumab) achieved a confirmed PR; 16 (53%) pts had SD. Median duration (range) of SD was 128.5 (42–242) days. 29/17/2 (97/57/7%) pts had an AE (any/G3/G4). The most frequent AEs (any/G3) were nausea (40/10%), fatigue (30/3%), peripheral edema (30/0%), vomiting (27/7%), and hypertension (27/17%). There were two G4 AEs (hypertension; platelet count decreased) and no G5 AEs. 24/10/2 (80/33/7%) pts had a drug-related AE (any/G3/G4); most commonly (any/G3) nausea (33/7%), fatigue (27/3%) and hypertension (27/17%). 3 (10%) pts had an infusion-related reaction (G1, n = 1; G2, n = 2). 2 (7%) pts had an AE leading to discontinuation (G3 bile duct stone and G2 peripheral edema). Immune-related AEs were reported in 6 (20%) pts and serious AEs occurred in 13 (43%) pts. **Conclusions:** BI 836880 plus ezabenlimab had a manageable safety profile in pts with advanced MSS CRC; however, anti-tumor activity was limited in these pts, the majority of whom had received prior bevacizumab. Clinical trial information: NCT03697304. Research Sponsor: Boehringer Ingelheim.

99 **Poster Session**

Phase II study of durvalumab following neoadjuvant chemoRT in operable rectal cancer: NSABP FR-2.

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Background: Although immunotherapy shows no benefit in microsatellite stable (MSS) colorectal cancer, preclinical models suggest that radiotherapy (RT) can enhance neoantigen presentation, modulate the microenvironment, and improve the likelihood of anti-tumor activity with checkpoint inhibitor use. Using a "window-of-opportunity" study design, this prospective phase II trial will determine the safety and activity of this approach with the anti-PD-L1 agent durvalumab (MEDI4736). **Methods:** Stage II/III patients (pts) with MSS rectal cancer undergoing standard NCCN guideline-compliant neoadjuvant chemoradiotherapy (CRT) followed by definitive surgery were eligible. Treatment included durvalumab (750mg IV infusion once every 2 wks) for 4 total doses beginning within 3-7 days after CRT completion followed by surgery within 8-12 wks of the final CRT dose. Primary end point (EP): Improvement in modified neoadjuvant rectal cancer (mNAR) score (goal 10.6) compared to historical controls (15.6) targeting a 20% DFS RR reduction and 3-4% absolute OS improvement. Secondary EPs: toxicity, pCR, cCR, therapy completion, negative surgical margins, sphincter preservation, and exploratory assessments of tumor-infiltrating lymphocytes, tumor Immunoscore, circulating immunologic profiles, and molecular predictors of response. We test H_0: mNAR $\geq$15.6 vs H_A: mNAR $<$15.6 at alpha 0.10 one-sided with statistical significance defined as $p<0.1$. **Results:** From May 2018 to October 2020, 45 pts were enrolled with 40 pts evaluable for mNAR. Mean mNAR was 12.03 (80% CI: 9.29-14.97) (p=0.06 one-sided). pCR=22.2%; cCR=31.1%; R0 resection=81.0%, and sphincter preservation=71.4%. Side effects were consistent with both CRT and durvalumab safety profile. Most common grade 3 AEs included diarrhea, lymphopenia, and back pain. There was one grade 4 AE (elevated amylase/lipase) and no grade 5 AEs. Remaining secondary and correlative immunologic end points are still being assessed. **Conclusions:** Durvalumab immediately following CRT prior to surgery for definitive management of rectal cancer was safe and without unexpected short-term toxicities. The primary end point of mean mNAR score was significantly less than our historical control, warranting further investigation. Correlative analyses for immunologic markers of response including PD-(L)1 expression and Immunoscore are ongoing. NCT 03102047. Support: AstraZeneca-Medimmune, NSABP Foundation. Clinical trial information: NCT03102047. Research Sponsor: AstraZeneca-Medimmune, Pharmaceutical/Biotech Company.

100 **Poster Session**

A phase 1b/2 trial of the PLK1 inhibitor onvansertib in combination with FOLFIRI-bev in 2L treatment of KRAS-mutated (mKRAS) metastatic colorectal carcinoma (mCRC).

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Background: CRC is a common cancer world-wide, accounting for ~10% of cancer cases and mortality. Treatment options are limited, and survival is poor for pts with advanced disease, particularly those with mKRAS. After failure of 1L treatment for mCRC, regardless of KRAS mutation status, the ORR for FOLFIRI-bev is 5-13%, with PFS 4-6 mos, and OS 10-12 mos. Onvansertib is a highly selective, ATP-competitive, orally bioavailable PLK1 inhibitor that is synergistic with irinotecan and with 5FU in xenograft models of mKRAS CRC. We present preliminary safety, efficacy, and biomarker data from an ongoing Ph1b/2 trial of onvansertib + FOLFIRI-bev in pts with mKRAS mCRC progressing after 1L treatment with fluoropyrimidine + oxaliplatin, +/- bev. **Methods:** Pts with mCRC with a KRAS mutation detected by a CLIA-certified lab were eligible. In the Ph1b portion of the study, onvansertib was given on a 3+3 dose escalation at 12, 15 or 18 mg/m^2 on days 1-5 and 15-19 of each 28-day cycle in combination with FOLFIRI-bev. The MTD was 15 mg/m^2 and was chosen as the RP2D. The primary endpoint for the Ph2 was ORR, and radiographic response was assessed every 8 wks per RECIST v1.1. Safety was evaluated continuously, and AEs were recorded using CTCAE v5.0. Baseline and post-treatment blood samples were collected for biomarker analyses, including mutant allele frequency (MAF) of the pt's known KRAS mutation. **Results:** As of 16Sep2021, a total of 50 pts had been treated: 18 on the Ph1b and 32 on the Ph2, including 35 pts at the RP2D, and median follow up was 4.7 mos (range 0.4-18). Of the 50 pts, 26 remain on treatment, as do 24 of 35 RP2D pts. The combination was well-tolerated: fatigue, neutropenia, and nausea were the most common treatment-emergent adverse events (TEAE) and were generally low-grade. Neutropenia was managed by removing the 5FU bolus from subsequent cycles of FOLFIRI and adding growth factor. Of the 50 pts, 44 were evaluable for efficacy, including 31 of 35 RP2D pts. ORR was 36% for the total group (1CR and 15 PR in 44 pts) and 35% for the RP2D group (1 CR and 10 PR in 31 pts). First responses were seen between 2 and 6 months after the start of therapy. Responses were observed across different KRAS variants. Pts achieving a CR or PR showed the greatest decreases in plasma MAF after the first cycle of therapy. Of the 50 pts, 24 pts have discontinued for the following reasons: progressive disease (13), toxicity (4), patient decision (4), proceeding to potentially curative surgery or other localized therapy (3). **Conclusions:** The combination of onvansertib with FOLFIRI-bev was well tolerated: observed TEAEs have been generally low-grade and manageable. The combination has demonstrated a promising ORR in 2L treatment of mCRC pts harboring various KRAS mutations, and efficacy was correlated with early changes in plasma mKRAS. Updated safety, efficacy, and biomarker analyses will be presented. Clinical trial information: NCT03829410. Research Sponsor: Cardiff Oncology.

Efficacy of bevacizumab-based treatment in early-onset treatment-naïve metastatic colorectal cancer patients: An ARCAD database analysis.

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Background: Colorectal cancer (CRC) incidence and mortality have decreased since the 1970s, but the incidence in young adults (20-49 years, named early-onset CRC, eoCRC) has been increasing. eoCRC patients with metastatic disease are treated with the same standard regimens as late-onset CRC (loCRC, age ≥ 50 years) although detailed response data for eoCRC are largely missing. **Methods:** Individual patient data on 7,604 subjects with metastatic eoCRC from 11 first line randomized bevacizumab studies between 2000 and 2012 in the ARCAD advanced colorectal cancer database were pooled. The distributions of demographics, clinicopathological features, biomarkers, and outcome data were summarized by age groups. Progression-free survival (PFS) and overall survival (OS) were assessed by Kaplan-Meier curves and Cox models stratified by treatment arms within studies, adjusting for potential confounders. Predictive value of age group was evaluated by testing interaction effect between treatment and age variables. **Results:** Female eoCRC are more commonly seen compared to loCRC (46.8% vs. 38.7%, $p<0.0001$). Patients with eoCRC (n=1,289) were significantly more likely to have had prior metastasectomy (17.5% vs. 13.5%, p=0.043) and lung metastatic disease (67% vs. 59.8%, $p<0.001$), but less likely to have distant lymph node metastatic disease (58.8 vs. 62.9%, p=0.036) or KRAS mutation (29.2% vs. 34.4%, p=0.042) compared to those with loCRC (n=6,315). eoCRC and loCRC patients had similar distributions according to PS, primary tumor sidedness, prior primary tumor resection, liver involvement, peritoneal involvement, number of metastatic sites, NRAS and BRAF. Age of disease onset was not a statistically significant prognostic factor for PFS in univariate and multivariate analysis (seen in table). Bevacizumab in addition to chemo improved PFS in eoCRC population (9.9 vs. 6.8 months, HR = 0.66, $p<0.001$), which was similar to the findings in loCRC population (9.4 vs. 7.3 months, HR= 0.73, $p<0.001$, interaction p=0.54). By multivariate analysis, a greater improvement in PFS was noted for the addition of bevacizumab in eoCRC relative to LoCRC patients (HR = 0.62 vs. HR = 0.82). **Conclusions:** Treatment naive eoCRC patients with metastatic disease derive similar benefit from bevacizumab relative to their average age counterparts. Research Sponsor: None.

Age Group at Disease Onset (<50 vs. ≥50)	Univariate Analysis	Multivariate Analysis[1]
PFS HR (95% CI, p)	1.04 (0.97-1.11, p=0.31)	0.89 (0.52-1.51, p=0.65)
OS HR (95% CI, p)	0.98 (0.90-1.06, p=0.62)	0.95 (0.51-1.75, p=0.86)

[1]adjusted for PS, primary tumor sidedness, number of metastatic sites, liver/ lung/lymph node/ peritoneal involvement, and KRAS and BRAF mutation status.

QoL analysis: A randomized phase 3 study of sequential versus combination treatment in first-line chemotherapy for metastatic colorectal cancer—The C-cubed study.

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Background: The C-cubed (C3) study demonstrated a sequential approach start from fluoropyrimidines (FP) plus bevacizumab (Bmab) followed by oxaliplatin (OX) adding significantly improved a median Treatment failure of strategy (TFS) for a combination approach start from FP+OX+Bmab [15.2 months vs. 7.6 months, HR, 0.475; 95% CI, 0.362 to 0.623; $p < 0.0001$] in first-line metastatic colorectal cancer (mCRC). In this congress, we focus on the quality of life (QOL) assessments as a pre-planned analysis. (Study information: UMIN000015405). **Methods:** The C3 study was a randomized phase III study which evaluated the time to discontinuation of OX-containing therapy (sequential approach [Capecitabine/5-FU (FP)+Bmab followed by OX-FP+Bmab] vs. combination approach [OX-FP+Bmab]. The primary endpoint was TFS and secondary endpoints were ORR, OS, PFS, Safety and QoL. QOL assessments included European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire for cancer (QLQ-C30) (EORTC QLQ C-30), EuroQol 5D 5L (EQ5D) and the Patient Neurotoxicity Questionnaire (PNQ) in both arm as a pre-planned analysis. Each questionnaire was collected at the time of enrolment, 6, 12, 18 months and end of treatment. QOL scores were compared using a mixed-effects models for repeated measures (MMRM). **Results:** A total 292 patients participated in QoL part (arm A: n =148; arm B: n =144). The returned questionnaire sheets were 292 (reply rate: 97%), 206 (68%), 199 (65%), 61 (20%) at baseline, 6, 12, 18 months, respectively. Sequential approach was statistically improved than combination approach as follows: Physical functioning ($p<0.001$), Cognitive functioning (p=0.012), Social functioning (p=0.0004), and Fatigue (p=0.013) in EORTC QLQ C-30. In addition, at 6 months (after which attrition in the combination arm was more than 50%) after randomization, the mean change rate from baseline of EQ5D score in the sequential approach versus combination approach were: –1.91 (SD 27.57) versus –9.62 (29.60). In contract, PNQ sensory score showed that sequential approach was not statistically improved for combination approach (0.22 [SD: 0.89] vs. 0.61 [SD: 0.95], p=0.115). **Conclusions:** The further clarification of patients' characteristics are needed, but this sequential approach can be advocated as a valuable treatment option in first-line mCRC for current guideline based on these QoLs and main efficacy data. Research Sponsor: This study funded by Chugai Pharmaceutical, Co., Ltd., and was conducted by Japan Southwest Oncology Research Support Organisation (JSWOG), which supported the trial with a research grant.

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Evaluating the technical feasibility of novel salvage endoscopic submucosal dissection after chemoradiotherapy for locally advanced rectal adenocarcinoma.

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Background: According to the National Comprehensive Cancer Network guideline, locally advanced rectal cancer is treated with chemotherapy with or without radiation, followed by transabdominal resection. However, there has been an emerging role for nonoperative management after chemoradiotherapy, and there is significant morbidity and risks associated with surgical resection. Endoscopic submucosal dissection (ESD) after chemoradiotherapy (CRT) for rectal cancer, which is termed "salvage ESD," may be a viable option for patients, in terms of evaluating pathological response and providing potential curative resection. We aim to evaluate the feasibility and safety of salvage ESD. **Methods:** Retrospective chart review of cases of salvage ESD after CRT for locally advanced rectal cancer (salvage group) and standard ESD cases for rectal tumors without prior CRT (standard group) from July 2018 to August 2020 at our institution was performed. Clinical factors, imaging, procedural, and pathology results were collected and compared between the two groups. **Results:** 12 salvage ESD cases were compared to 27 standard ESD cases. 83.3% of the lesions in the salvage ESD group were initially staged as T3 prior to CRT. 100% of the lesions in the salvage ESD group were scarred down, compared to 33.3% in the standard ESD group ($p < 0.01$). Technical outcomes are shown in the table. The en bloc resection rates were 92.7% and 91.7% (p=1.00) and R0 resection rates were 66.7% and 75.0% (p=0.55) for the standard and salvage groups, respectively. In the salvage ESD group, no adverse events were observed. 66.7% of the adenocarcinomas in the salvage ESD group had morphologically changed to hyperplasia or adenoma after CRT and there were no identifiable lesions greater than T1 staging. **Conclusions:** Salvage ESD after CRT for locally advanced rectal cancer is technically feasible and with comparable low complication rates. There may be a diagnostic role in salvage ESD in assessing pathological response to CRT, as well as a possibly therapeutic role in resection of residual lesions with the potential to avoid surgery. Further studies are underway comparing the clinical outcomes of salvage ESD with standard surgical resection after CRT for locally advanced rectal cancer. Research Sponsor: None.

Technical outcomes.

N=33	Standard ESD (N=27)	Salvage ESD (N=12)	p-value
En Bloc Resection Rate	25 (92.7%)	11 (91.7%)	1.00
R0 Resection Rate	18 (66.7%)	9 (75.0%)	0.55
Complication rate	2 (7.4%)	0 (0%)	0.50
Hospital Length of Stay (days), Median (IQR)	2.0 (0.0-3.0)	1.0 (1.0-1.0)	0.05
Histology			
Hyperplasia	0 (0%)	1 (8.3%)	0.14
Tubular Adenoma	5 (18.5%)	5 (41.7%)	
Tubulovillous Adenoma	11 (40.7%)	2 (16.7%)	
Adenocarcinoma	11 (40.7%)	4 (33.3%)	
Post-ESD Tumor Depth			
Tis	2 (7.4%)	1 (8.3%)	
T1	11 (40.7%)	2 (16.7%)	
Missing data	14 (51.8%)	9 (75.0%)	
Residual Lesion or Recurrence Requiring Local Surgery	1 (3.7%)	2 (16.7%)	0.22

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Efficacy and safety of anlotinib plus XELOX regimen as first-line treatment followed by maintenance monotherapy of anlotinib for patients with mCRC: A single-arm, multicenter, phase II clinical trial—Update results from ALTER-C001.

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Background: The combination of anti-VEGF or anti-EGFR targeted drugs with chemotherapy is the standard first-line therapy for metastatic colorectal cancer (mCRC), and the followed maintenance treatment is an optional approach to balance the efficacy and toxicity. However, studies regarding the maintenance strategies based on antiangiogenic TKIs are limited currently. Anlotinib, a novel oral multi-target TKI which can inhibit both tumor angiogenesis and tumor cell proliferation simultaneously, substantially prolonged the PFS with manageable toxicity for refractory mCRC in the phase III ALTER0703 clinical trial (NCT02332499). We present updated data from the study of anlotinib plus XELOX as first-line treatment followed by anlotinib monotherapy for mCRC. **Methods:** In this open label, single-arm, multicenter phase II clinical trial, 29 mCRC patients without prior systemic treated, aged 18-75 and an ECOG performance status of 0 or 1 were planned to recruit. Eligible patients received capecitabine (1000 mg/m^2, po, d1-14, q3w) and oxaliplatin (130 mg/m^2, iv, d1, q3w) plus anlotinib (10mg, po, d1~14, q3w) treatment for 6 cycles. After 6 cycles of inducing therapy, patients would receive anlotinib (12mg, po, d1~14, q3w) as maintenance therapy until disease progression or intolerable adverse events (AEs). The primary endpoint was PFS; Secondary endpoints included ORR, DCR, DOR and safety. **Results:** At updated analysis (cutoff: Sep 10, 2021), a total of 27 patients were enrolled, of which 19 patients were available for efficacy assessment. In best overall response assessment, there were 63.2% PR (12/19), 26.3% SD (5/19) and 10.5% PD (2/19). The ORR was 63.2% (95% CI, 38.4-83.7%) and DCR was 89.5% (95% CI, 66.9-98.7%). One patient experienced the longest duration of treatment which was 17.5 months. The median PFS was not reached. The most common treatment related adverse events (TRAEs) of any grade (≥25%) were leukopenia, nausea/vomiting, hypertension, neutropenia, hypohemoglobinemia, hypertriglyceridemia. Grade 3/4 TRAEs (≥10%) were neutropenia (14.8%), hypertension (14.8%) and hypertriglyceridemia (11.1%). One grade 5 TRAE was pancytopenia that occurred at 2.7 months. **Conclusions:** The update results suggested that anlotinib combined with XELOX as first line regimen followed by anlotinib monotherapy showed promising anti-tumor activity and manageable safety for patients with mCRC. And the conclusions needed to be confirmed in randomized studies. Clinical trial information: ChiCTR1900028417.
Research Sponsor: None.

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Efficacy analysis of regorafenib combined with PD-1 inhibitors in elderly patients with metastatic colorectal cancer.

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Background: Recently, an increasing number of patients (pts) with advanced colorectal cancer tend to receive regorafenib plus PD-1 inhibitors. However, there is a lack of information regarding real world effects of this therapeutic strategy, especially in elderly Chinese pts. We aimed to investigate the treatment patterns, clinical outcomes and prognostic factors of regorafenib plus PD-1 inhibitors therapy to Chinese elderly pts with advanced colorectal cancer. **Methods:** Retrospective analysis of a cohort of pts with advanced colorectal cancer received treatment of regorafenib combined with PD-1 inhibitors enrolled in our institution between January 2019 and January 2021. Among them, pts with 60 years or older were included in our final analysis. Overall survival (OS) and progression free survival (PFS) were estimated by Kaplan Meier curves, and other endpoints included objective response rate, prognostic factors. **Results:** At a median follow-up of 16.2 months, a total of 24 pts were enrolled in a real-world dataset from Henan Cancer Hospital. The median age was 68 years; 62.5% were female. The median OS and PFS were 15.03 months (95% CI 7.0-23.0) and 4.0 months (95% CI 1.8-6.2), respectively. 2/24 partial responses (PR) observed (ORR = 8.3%); Stable disease (SD) was obtained in 15/24. Disease control rate (PR plus SD) was therefore obtained in 17/24 (70.8%). When compared with PFS and OS in different initial daily doses group of regorafenib (such as ≤80, 120 or 160 mg), we concluded that there were no significantly difference between these groups. And similar results were found in final daily doses groups. However, it showed a trend toward better PFS in pts with ≥120 mg final daily doses group compared to <120 mg group (median PFS was 3.5 months in <120mg group versus 10.0 months in ≥120mg group). Median OS of pts for male gender demonstrated increasing trends compared with those female gender (20.2 months in males versus 13.2 months in females). Pts with previous treated with regorafenib had longer median OS than those without it (20.2 months versus 13.2 months). There were no obvious correlation for survival between pts only had liver metastasis and lung metastasis (P>0.05). No significant associations for survival could be seen in other tumor sites, K-RAS status, any kind of PD-1 inhibitors and whether previously treated with bevacizumab (P>0.05). **Conclusions:** This real-world dataset confirms that Chinese elderly pts with advanced colorectal cancer also can benefit from treatment of regorafenib combined with PD-1 inhibitors, similarly with this combination therapy strategies in all age pts. Furthermore, a longer survival time were obtained in pts with prior treated with regorafenib. The result also suggests that pts with ≥120mg final daily doses group had better PFS. However, further larger cohorts research should investigate whether the PFS advantage in high dose group could eventually lead to improved OS outcomes. Research Sponsor: None.

Temsirolimus (T) in patients (pts) with colorectal cancer (CRC) with *PIK3CA* mutation: Results from the Targeted Agent and Profiling Utilization Registry (TAPUR) study.

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Background: TAPUR is a phase II basket study evaluating anti-tumor activity of commercially available targeted agents in pts with advanced cancers with genomic alterations. Results in a cohort of CRC pts with *PIK3CA* mutation treated with T are reported. **Methods:** Eligible pts had advanced CRC with *PIK3CA* mutation reported by a genomic test performed in a CLIA-certified, CAP-accredited site selected lab, no standard treatment options, measurable disease, ECOG performance status (PS) 0-2, and adequate organ function. Use of T was approved by the TAPUR Molecular Tumor Board in each case. After antihistamine pre-treatment, T was administered at 25 mg IV over 30-60 minutes weekly until disease progression. Primary endpoint was disease control (DC), defined as complete (CR) or partial (PR) response per RECIST v. 1.1, or stable disease at 16+ weeks (SD 16+). Simon 2-stage design tested the null DC rate of 15% vs. 35% (power = 0.85; $\alpha = 0.10$). If ≥2 of 10 pts in stage 1 has DC, 18 more pts are enrolled; otherwise, the study stops for futility. If ≥7 of 28 pts has DC, the null DC rate is rejected. Secondary endpoints were progression-free survival (PFS), overall survival (OS) and safety. **Results:** 10 pts (60% male) with CRC with *PIK3CA* mutation were enrolled from November 2017 to May 2020. All were eligible for efficacy and toxicity. Demographics and outcomes are summarized in Table. No objective responses (OR) were observed. 1 pt had SD of 16.1 wks duration for a DC rate of 10% (95% CI: 0%, 45%); the null DC rate of 15% was not rejected (p=0.80). 6 pts had at least one grade 3-4 adverse or serious adverse event (AE/SAE) at least possibly related to T, including acute kidney injury, dehydration, decreased platelet count hypertriglyceridemia, mucositis, neutropenia, and scrotal and penile edema. **Conclusions:** Monotherapy T does not have sufficient clinical activity in CRC pts with *PIK3CA* mutation for continued evaluation in this pt population. Other treatments should be considered for these pts, including treatments offered in clinical trials. Clinical trial information: NCT02693535. Research Sponsor: Pfizer, Pharmaceutical/Biotech Company.

Demographics and efficacy outcomes (N=10).

Median age, yrs (range)		**5**	**2 (47, 64)**
ECOG PS, %	0	4	0
	1	6	0
Prior systemic regimens, %	1-2	2	0
	≥3	8	0
DC rate, % (OR or SD16+) (95% CI)		1	0 (0, 45)
OR rate, % (95% CI)			0 (0, 31)
Median PFS, wks (95% CI)			8.1 (5.0, 15.7)
Median OS, wks (95% CI)		3	8.7 (24.3, 68.3)

Nivolumab plus ipilimumab (N+I) in patients (pts) with colorectal cancer (CRC) with high tumor mutational burden (hTMB): Results from the Targeted Agent and Profiling Utilization Registry (TAPUR) study.

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Background: TAPUR is a phase II basket study evaluating the anti-tumor activity of commercially available targeted agents in pts with advanced cancers with genomic alterations. Results in a cohort of CRC pts with hTMB treated with N+I are reported. **Methods:** Eligible pts had advanced CRC, no available standard treatment options, measurable disease, ECOG performance status (PS) 0-2, adequate organ function and no prior immune checkpoint inhibitor treatment. PDL-1 expression testing was not required. Genomic testing was performed in CLIA-certified, CAP-accredited site selected labs. hTMB was defined *a priori* as ≥9 mutations/megabase (Muts/Mb) reported by a FoundationOne test (n=7) or other tests (n=5) if approved by the Molecular Tumor Board. Pts received N 1 mg/kg IV every 3 weeks (wks) for 4 doses in combination with I 3 mg/kg every 3 wks for 4 doses. N was then continued at 240 mg every 2 wks or 480 mg every 4 wks until disease progression. Primary endpoint was disease control (DC), defined as complete (CR) or partial (PR) response, or stable disease at 16+ wks (SD 16+). Simon 2-stage design tested the null DC rate of 15% vs. 35% (power = 0.85; $\alpha = 0.10$). If ≥2 of 10 pts in stage 1 has DC, 18 more pts are enrolled; otherwise, the study stops for futility. If ≥7 of 28 pts has DC, the null DC rate is rejected. Secondary endpoints were progression-free survival (PFS), overall survival (OS) and safety. **Results:** 12 pts (9 male) with CRC with hTMB in tissue biopsy were enrolled from February 2018 to May 2020; 2 pts were not evaluable and excluded from efficacy analyses. All pts were evaluated for toxicity. TMB ranged from 9 to 233 Muts/Mb (median 13). Demographics and outcomes are summarized in the table below. Tumor microsatellite (MS) status was reported stable for 11 pts and indeterminate for 1 pt. 1 PR (88.1 wks duration, tumor 11 Muts/Mb, MS stable, PDL-1 expression not reported, *KRAS* mutant) and 0 pts with SD16+ were observed for a DC and OR rate of 10% (95% CI: 0%, 45%); the null DC rate of 15% was not rejected (p=0.80) and the cohort closed due to futility. 4 pts had at least one grade 3-4 adverse or serious adverse event (AE/SAE) at least possibly related to N+I including myasthenia gravis, diarrhea, glucose intolerance, hyperglycemia, and small intestinal obstruction. **Conclusions:** Combination therapy with N+I does not have sufficient clinical activity in pts with MS stable, hTMB CRC for further evaluation in this pt population. Other treatments should be considered for these pts, including treatments offered in clinical trials. Clinical trial information: NCT02693535. Research Sponsor: Bristol Myers Squibb, Pharmaceutical/Biotech Company.

Demographics (N=12) and efficacy outcomes (N=10).

Median age, yrs (range)		**58 (43, 69)**
ECOG PS, %	0	33
	1	67
Prior systemic regimens, %	1-2	17
	≥3	83
Median hTMB, Muts/Mb (range)		13 (9, 233)
DC rate, % (OR or SD16+) (95% CI)		10 (0, 45)
OR rate, % (95% CI)		10 (0, 45)
Median PFS, wks (95% CI)		13.6 (5.1, inf)
Median OS, wks (95% CI)		42.9 (13.0, 57.4)

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Modified FOLFIRINOX (mFOLFIRINOX) in high risk locally advanced rectal adenocarcinomas.

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Background: There is limited data with regard to the use of modified 5-fluoroural-leucovorin-irinotecan-oxaliplatin (mFOLFIRINOX) in enabling resection and increasing survival of locally advanced rectal adenocarcinomas (LARC) with high-risk characteristics (T4b status, signet ring histology, etc.) post standard neoadjuvant long course chemoradiation (NACTRT) or short course radiation (SCRT) and chemotherapy. **Methods:** Patients with LARC from January 2018 to December 2020 receiving mFOLFIRINOX (5-Fluorouracil - 1800mg/m2 over 46 hours, Leucovorin 300mg, Irinotecan 135mg/m2, oxaliplatin 65mg/m2) post NACTRT/SCRT to facilitate curative local resection were evaluated. The primary endpoint was event free survival (EFS), where event was defined as disease progression or recurrence post resection after mFOLFIRINOX. Survivals were calculated using Kaplan-Meier analysis. **Results:** Forty-seven patients were evaluated with a median age of 33 years (Range:18-59), 45% T4b status, 94% radiological circumferential margin (CRM) involved (79% CRM positive post NACTRT/SCRT), 43% extramural venous invasion (n=33) and 36% signet ring histology. 62% had received prior NACTRT and 38% had received SCRT with chemotherapy before receiving mFOLFIRINOX. The most common grade 3 and grade 4 treatment related side effects included diarrhoea (7%), anaemia (4%) and infections (4%). Intended duration of mFOLFIRINOX or beyond was completed in 94% of patients. 60% of patients underwent curative local resection with R0 resection rates of 100% (n=28) and pathological complete response rates of 21%. The most common surgeries done were exenterations and abdominoperineal resections in 22% and 17% patients respectively. With a median follow up of 19 months, 25 patients had recurred or progressed for a median EFS of 20 months [95% confidence interval (CI): 15-24] while median overall survival was 55 months (95% CI: 24-86). **Conclusions:** Locally advanced rectal cancers with high-risk characteristics are a niche group of cancers with less-than-optimal outcomes post standard neoadjuvant strategies. mFOLFIRINOX appears to be well tolerated in this cohort of patients and enables conversion to curative local resection and potentially improves survival as well. Research Sponsor: None.

Tumor response of FOLFOXIRI plus cetuximab versus bevacizumab in *RAS* wild-type metastatic colorectal cancer: The subgroup-analysis of DEEPER trial (JACCRO CC-13).

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Background: Triplet regimen, FOLFOXIRI, combined with bevacizumab (bev) or panitumumab has been shown to be superior in terms of early tumor shrinkage and depth of response (DpR) compared to doublet combinations in patients with *RAS* wild-type metastatic colorectal cancer (mCRC). We performed a randomized phase II study, DEEPER trial (JACCRO CC-13)[NCT02515734], to investigate the efficacy and safety of cetuximab (cet) vs. bevacizumab (bev) in combination with modified (m)-FOLFOXIRI (irinotecan 150 mg/m^2, oxaliplatin 85 mg/m^2, 5-FU 2400 mg/m^2) in previously untreated mCRC patients with *RAS* wild-type tumors (Tsuji A, et al. ASCO 2021). **Methods:** The primary endpoint was DpR during the entire course. Secondary endpoints included overall response rate (ORR), disease control rate, R0 resection rate, progression-free survival, and overall survival. A post-hoc subgroup analysis by PS, tumor sidedness, age, and location of metastases was performed to evaluate the efficacy of triplet plus cet vs. bev regimen. **Results:** A total of 359 patients were enrolled between July 2015 and June 2019. For the full analysis set (median age 65y, 64% male, PS0/1: 91%/9%, left/right primary: 83%/17%), 173 and 175 patients were randomly assigned to the cet and bev arms, respectively. Median DpR was 57.4% vs. 46.0% (p = 0.001), and the ORR was 69.1% vs. 71.7% (p = 0.60), in cet vs. bev, respectively. The subgroup analysis was present in the table. There was no significant difference in terms of ORR and R0 resection rate between groups according to PS, tumor sidedness, age, and liver metastases (LM). In patients with only LM, the R0 resection rate of cet vs. bev was 25.0% vs. 14.8% (p = 0.21). **Conclusions:** The m-FOLFOXIRI plus cet showed to be significantly superior to the m-FOLFOXIRI plus bev in terms of DpR in first-line treatment for *RAS* wild-type mCRC. The better DpR of m-FOLFOXIRI plus cet was evident for *RAS* wild-type mCRC patients with left-sided tumors, LM or under 70 years old. Clinical trial information: UMIN000018217. Research Sponsor: Merck Biopharma Co., Ltd.

Patient characteristics	median DpR (%)		*p*-value
	mFOLFOXIRI+bev	mFOLFOXIRI+cet	
PS 0 (n = 317)	46.9	55.9	0.0018
PS 1 (n = 31)	40.6	68.2	0.30
Left-sided tumor (n = 287)	46.1	60.3	0.0007
Right-sided tumor (n = 61)	41.2	50.0	0.47
Patients aged < 70-y (n = 265)	47.1	60.3	0.0004
Patients aged ≥70-y (n = 83)	42.9	48.8	0.83
Patients with LM (n = 251)	46.4	60.4	0.0002
Patients without LM (n = 97)	45.8	50.7	0.79

Open-label phase 1/2 study evaluating the tolerability and antitumor activity of selinexor and pembrolizumab in colorectal cancer.

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Background: Single agent selinexor, an oral selective inhibitor of nuclear export (SINE), showed activity against heavily pretreated CRC with *RAS* mutations (mut) or wildtype (wt) in 2 clinical studies. In preclinical studies, selinexor showed superior potency in *KRAS* mut over wt with improved activity in combination with PD-1/PD-L1 blockade. A phase 1b study (NCT02419495) showed the safety and antitumor activity of combined selinexor and a PD-1/PD-L1 inhibitor. This phase 1/2 open-label study is evaluating selinexor with pembrolizumab in patients with microsatellite instability (MSI)-stable CRC. **Methods:** The study enrolled patients with advanced/metastatic CRC who progressed after prior chemotherapy (1-3 lines for *RAS* wt, 1-2 for *RAS* mut) and are ineligible for anti-PD-1/PD-L1 therapy. Patients received weekly oral selinexor 80 mg and pembrolizumab 200 mg IV every 3 weeks. Antitumor activity, safety and tolerability were assessed. **Results:** Thirty-four patients, median age 57.5 years, male 59%, *RAS* mut 53%, median prior lines 2, are enrolled. At data cutoff (1-SEP-21) median treatment duration was 57 days (range: 1-246) and 25 patients were evaluable for response. Best response was stable disease in 8/13 patients with *RAS* mut CRC (62%) and in 3/12 patients with *RAS* wt CRC (25%). Median overall survival (months) has not been reached for the overall population (95% CI: 6.3, NE), for *RAS* mut (95% CI: 7.6, NE), and for the *RAS* wt (95% CI: 6.1, NE). Median progression-free survival is 3.0 and 1.4 months for patients with CRC with *RAS* mut and wt, respectively (p=0.04; HR: 0.43 [959% CI: 0.18, 1.01]). Thirty patients (88%) discontinued therapy, mostly due to progressive disease (44%). The most common treatment-emergent adverse events (TEAEs) (total; Grade ≥3) were nausea (77%; 3%), vomiting (41%; 0%), fatigue (41%; 12%), decreased appetite (35%; 0%), diarrhea (32%; 0%). Nine patients (26%) had serious treatment-emergent adverse events. **Conclusions:** Combined selinexor with pembrolizumab demonstrated higher disease control rates and prolonged overall survival in patients with chemotherapy-refractory advanced/metastatic CRC with *RAS* mut vs *RAS* wt tumors. These patients would not have been eligible for anti-PD-1 mAb therapy because their tumors were not MSI-high, suggesting that the combination may be active in *RAS* mut CRC. Therapy was well tolerated with no unanticipated adverse events. Further investigation of this combined treatment is warranted, particularly in patients with CRC with *RAS* mut. Clinical trial information: NCT04256707. Research Sponsor: Karyopharm Therapeutics Inc.

111 **Poster Session**

Colonic endoscopic submucosal dissection using a novel robotic system.

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Background: Appropriate tissue tension and clear visibility of the dissection area using traction are essential for effective and safe endoscopic submucosal dissection (ESD). We developed a robotic assistive traction device for colonoscopy.This is a preclinical animal study to evaluate the performance of colorectal ESD using novel robotic system. **Methods:** Experienced endoscopist performed ESD on ex vivo porcine colon ten times using a robot and ten times by the conventional method. The outcome measures were operating time (from starting incision to finishing dissection), completeness of resection, procedure-related adverse events, and limitations of arm manipulation in a narrow working space as assessed by counting the frequency of blind cutting.We also conducted an in vivo feasibility study on live pig. **Results:** Total of twenty colonic lesions were resected from ex vivo porcine colon. The submucosal dissection speed was significantly faster in robotic ESD than in conventional ESD ($P = 0.002$). Adverse events such as perforation were also significantly higher in the conventional group. In the in vivo feasibility study, robot was attached to the colonoscope and inserted into the proximal colon. ESD was performed successfully. **Conclusions:** When the robot was assisting in the ESD procedure, the dissection speed improved significantly. Our robotic device can thus provide simple, effective, and safe multidirectional traction during colonic ESD. Research Sponsor: None.

A multicenter phase 2 trial of ramucirumab plus FOLFIRI as second-line treatment for patients with RAS wild-type metastatic colorectal cancer previously treated with combination chemotherapy with anti-EGFR antibody: JACCRO CC-16.

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Background: Ramucirumab (RAM) plus FOLFIRI has been considered as the standard care of second-line treatment in metastatic colorectal cancer (mCRC). However, there have been few data which prospectively evaluated the efficacy and safety of RAM or other anti-VEGF drugs plus FOLFIRI after anti-EGFR antibody therapy in *RAS* wild-type mCRC. We therefore investigated the efficacy and safety of RAM plus FOLFIRI as second-line treatment in patients with *RAS* wild-type mCRC previously treated with oxaliplatin-containing chemotherapy with anti-EGFR antibody. **Methods:** The JACCRO CC-16 was a multicenter, phase 2 trial to evaluate the efficacy and safety of RAM (8 mg/kg) plus FOLFIRI (irinotecan 150 mg/m^2, bolus 5-FU 400 mg/m^2, infusional 5-FU 2400 mg/m^2) in mCRC patients with *RAS* wild-type tumors and ECOG PS 0 or 1, after first-line doublet or triplet plus anti-EGFR antibody therapy. The primary endpoint was 6-month progression-free survival (PFS) rate. The secondary endpoints included PFS, overall survival, objective response rate (ORR), early tumor shrinkage (ETS), and safety. We hypothesized a threshold 6-month PFS rate of 30% and an expected 6-month PFS rate of 45% for the protocol treatment. A sample size of 74 patients was required (one-sided α, 0.05; β, 0.2). **Results:** A total of 92 patients were enrolled between October 2018 and December 2020. Ninety-one patients, excluding one ineligible patient, were analyzed as the full analysis set: median age 66.0-y (range, 29–84), 46% female, 81% ECOG PS 0, 40% with primary tumor, 95% left-sided (rectum, sigmoid or descending colon) primary tumors, 70%/42% with liver/lung metastases. In prior first-line treatment, 19 (21%) patients were treated with triplet plus anti-EGFR antibody. The median number of treatment cycles was 10 (range, 1–56). Primary endpoint was met; at data cut-off, with 76 events, 6-month PFS rate was 58.2% (95% CI; 47.4-67.6). The median PFS was 7.0 months. The ORR, disease control rate, and ETS were 10.7%, 86.9%, and 16.9%, respectively. In the safety population of 92 patients, any grade adverse events (AEs) were neutropenia (75%), hypertension (59%), proteinuria (34%), and diarrhea (33%). Grade 3-4 AEs were neutropenia (48%), hypertension (27%), proteinuria (4%), diarrhea (3%), and febrile neutropenia (3%). No treatment-related death was observed. **Conclusions:** This is the first prospective study to demonstrate that RAM plus FOLFIRI as second-line treatment has favorable PFS rate and tolerability after anti-EGFR antibody containing chemotherapy in *RAS* wild-type mCRC patients. Clinical trial information: jRCTs061180002. Research Sponsor: Eli Lilly Japan K.K.

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A nomogram for predicting cancer specific survival (CSS) in patients with pathological T3N0M0 (pT3N0M0) rectal cancer.

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Background: Preoperative chemoradiotherapy followed by total mesorectal excision (TME) surgery has been widely adopted as the standard treatment for stage II-III rectal cancers. However, the role of adjuvant chemotherapy in pathological T3N0M0 (pT3N0M0) patients remains controversial. A reliable prognostic model is needed to discriminate the high-risk patients from the low-risk patients, and optimize adjuvant chemotherapy treatment decisions by predicting the likelihood of adjuvant chemotherapy benefit for the target population. **Methods:** We gathered and analyzed 276 patients in Sun Yat-Sen University Cancer Center from March 2005 to December 2011. All patients underwent total mesorectal excision, without preoperative therapy, and were pathologically proven pT3N0M0 rectal cancer. LASSO regression model was used for variable selection and risk factor prediction. Multivariable cox regression was used to develop the predicting model. Optimum cut-off values were determined using X-Tile plot analysis. The 10-fold cross validation was adopted to validate the model. The performance of the nomogram was evaluated with its calibration, discrimination and clinical usefulness. **Results:** A total of 188 patients (68.1%) had adjuvant chemotherapy and no patients had adjuvant radiotherapy. Age, carbohydrate antigen 19-9 [CA199], monocyte percentage [MONO%], lymph node dissection numbers [LNDs] and nerve invasion were identified as significantly associated variables that could be combined for an accurate prediction risk of CSS for pT3N0M0 patients. The model adjusted for CSS showed good discrimination with a C-index of 0.723 (95% CI = 0.652 to 0.794). The calibration curves showed that the nomogram adjusted for CSS was able to predict 3-, 5-, and 10-year CSS accurately. The corresponding predicted probability was used to stratify high and low-risk patients. Adjuvant chemotherapy improved survival rate in the low-risk patients (HR = 0.338, 95% CI: 0.135 to 0.848, P = 0.021), while it did not exhibit a significant benefit in the high-risk patients. **Conclusions:** The nomogram effectively predicts CSS in patients with pT3N0M0 rectal cancer, which can be conveniently used in clinical practice. Adjuvant chemotherapy may improve overall survival in the low-risk patients. But the benefit of adjuvant chemotherapy was not seen in the high-risk patients. Research Sponsor: the 5010 Clinical Research Foundation of Sun Yat-sen University.

Radioembolization with chemotherapy for liver-dominant colorectal cancer: Time to subsequent treatment and quality of life in the EPOCH trial.

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Background: The primary objective of the EPOCH trial evaluated potential benefit of adding second-line transarterial radioembolization (TARE) with yttrium-90 glass microspheres to chemotherapy compared to chemotherapy alone in patients with liver-dominant metastatic colorectal disease (mCRC). Secondary endpoints included time to deterioration of quality of life (TTDQoL). **Methods:** EPOCH was a 1:1 randomized, open-label, global, multicenter phase 3 trial. TTDQoL was assessed using the Functional Assessment of Cancer Therapy-colorectal (FACT-c) questionnaire and defined as the time from randomization to the change from baseline in FACT-c total score ≤ -7 points or date of death and was estimated using Kaplan-Meier analysis. Time to subsequent therapy was defined as the time from randomization to the start of subsequent therapy and was estimated using Kaplan-Meier analysis. Restricted mean survival time (RMST) analysis was used to estimate the area under Kaplan-Meier curves (AUC) for progression-free survival (PFS), hepatic PFS (hPFS), and TTDQoL, and the difference in AUC estimates between the two arms were assessed. The use of TheraSphere in the USA in the trial was under Investigational Device Exemption from FDA. **Results:** The EPOCH trial included 428 patients. Both primary endpoints of PFS (HR = 0.69, 95% CI: 0.54, 0.88; 1-sided p=0.0013) and hPFS (HR = 0.59, 95% CI: 0.46, 0.77; 1-sided p<0.0001) were met in the EPOCH study. Median time to subsequent therapy in the TARE plus chemotherapy arm was 21.0 months, compared to 10.1 months in the chemotherapy only arm (HR = 0.49, 95% CI: 0.37, 0.67). TTDQoL before subsequent therapy was reported in 53.5% (115/215) patients in the TARE plus chemotherapy arm, compared to 43.7% of patients in the chemotherapy only arm (93/213). Median TTDQoL was 3.8 months in both the TARE plus chemotherapy arm and the chemotherapy alone arm (1-sided p=0.1513; HR = 0.86, 95% CI: 0.65, 1.14). AUC for PFS until 22.1 months was 9.4 months (95% CI: 8.4, 10.4) for the TARE plus chemotherapy arm, compared to 7.4 months (95% CI: 6.6, 8.1) for the chemotherapy only arm (1-sided p=0.0008). AUC for hPFS until 22.1 months was 10.3 months (95% CI: 9.2, 11.3) for the TARE plus chemotherapy arm, compared to 7.4 months (95% CI: 6.7, 8.2) for the chemotherapy only arm (1-sided p<0.0001). AUC for TTDQoL until 18.5 months was 6.6 (95% CI: 5.6, 7.6) for the TARE plus chemotherapy arm, compared to 5.5 (95% CI: 4.4, 6.5) for the chemotherapy only arm (1-sided p=0.0663). **Conclusions:** These results suggest that the addition of TARE to second-line chemotherapy in patients with liver-dominant mCRC extended PFS, hPFS, and time to subsequent treatment without compromising quality of life. Clinical trial information: NCT01483027. Research Sponsor: Boston Scientific Corporation.

Radioembolization with chemotherapy for liver-dominant colorectal cancer: Analysis of patient subgroups in the EPOCH trial.

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Background: The EPOCH trial evaluated potential benefit of second-line transarterial radioembolization (TARE) plus chemotherapy compared to chemotherapy alone in patients with liver-dominant metastatic colorectal disease (mCRC). Presented here are additional results from EPOCH of depth and duration of response (DoR), and progression-free survival (PFS) and hepatic progression-free survival (hPFS) subgroup analyses. **Methods:** EPOCH was a 1:1 randomized, open-label, global, multicenter phase 3 trial of second-line chemotherapy for liver-dominant mCRC comparing outcomes from chemotherapy with or without unilobar or same-day bilobar TARE treatment using glass microspheres. Primary study endpoints were PFS and hPFS. Pre-specified subgroup analyses of PFS and hPFS were performed. PFS, hPFS, DoR for patients with objective response, and depth of response (percent change from baseline to nadir in sum of longest diameters of target lesions) were based on blinded, independent central review using RECIST 1.1. The use of TheraSphere in the trial in the USA was under Investigational Device Exemption from FDA. **Results:** Both primary endpoints of PFS (HR = 0.69, 95% CI: 0.54, 0.88; 1-sided p=0.0013) and hPFS (HR = 0.59, 95% CI: 0.46, 0.77; 1-sided p<0.0001) were met in the EPOCH study. Median DoR in the 73 responders of the TARE arm was numerically longer, with 7.2 months by Kaplan-Meier analysis; in the 45 responders of the chemotherapy only arm, 6.6 months (HR = 0.79, 95% CI: 0.48, 1.30; 1-sided p = 0.178). Mean depth of response across all patients in the TARE arm with data available (N=196) was -25.6%, compared to -13.0% in the chemotherapy only arm (N=182; mean difference -12.6 percentage points; 95% CI: -18.9, -6.3; 1-sided p = 0.0001). Key subgroups of interest which showed improved PFS and/or hPFS in the TARE arm (ie, 95% CI for the HR entirely below 1) are as follows: **Conclusions:** These data suggest that liver-dominant mCRC patients in this trial benefitted in second-line treatment from a combination of TARE plus chemotherapy based upon improved PFS and hPFS over the full set of patients and in a number of subgroups. The addition of TARE to chemotherapy improves depth of response compared to chemotherapy alone. Clinical trial information: NCT01483027. Research Sponsor: Boston Scientific Corporation.

Subgroup	PFS HR (95% CI)	hPFS HR (95% CI)
Age ≥18 to <65 years	0.65 (0.47, 0.90)	0.56 (0.41, 0.78)
Males	0.66 (0.49, 0.90)	0.58 (0.43, 0.80)
Females	0.74 (0.48, 1.12)*	0.59 (0.38, 0.92)
KRAS mutation	0.57 (0.40-0.80)	0.50 (0.35-0.72)
KRAS wild type	0.79 (0.55, 1.12)*	0.68 (0.47-0.97)
Hepatic tumor burden <10%	0.76 (0.55, 1.05)*	0.62 (0.44-0.86)
Hepatic tumor burden ≥10 - <25%	0.43 (0.26-0.72)	0.43 (0.26-0.72)
Addition of a biological agent	0.58 (0.40-0.84)	0.48 (0.33-0.71)
No addition of a biological agent	0.76 (0.55, 1.06)*	0.67 (0.48-0.94)

*95% CI was not entirely below 1.

A randomized phase II trial of MEK and CDK4/6 inhibitors vesus tipiracil/trifluridine (TAS-102) in metastatic *KRAS*/*NRAS* mutant (mut) colorectal cancer (CRC).

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Background: Constitutively activating *KRAS* or *NRAS* muts occur in ~50% of CRC, increasing RAF-MEK-ERK signaling and causing overexpression of cyclin D1, which binds to cyclin dependent kinase 4/6 (CDK4/6) to drive cell cycle progression. Combination MEK and CDK4/6 inhibitors caused tumor regression in patient-derived xenografts of *KRAS* mut CRC. We hypothesized that binimetinib and palbociclib (B+P) would improve progression-free survival (PFS) compared to TAS-102 in refractory *KRAS/NRAS* mut mCRC. **Methods:** ACCRU-GI-1618 was a multicenter, randomized phase II clinical trial (NCT03981614). Key inclusion criteria were *KRAS/NRAS* mut mCRC, with prior fluoropyrimidine/ oxaliplatin/ irinotecan/ anti-VEGF therapy. There was a 6-patient safety run-in with binimetinib 30 mg po BID D1-28 and palbociclib 100 mg po daily D1-21. After, patients were randomized 1:1 to B+P vs TAS-102 (stratified by *KRAS* mut type and prior regorafenib use), with optional crossover at progression. The primary endpoint was PFS; 73 PFS events (from a sample size of 112) provided 90% power to detect improvement of PFS (hazard ratio = 0.5, i.e. median PFS of 2 vs. 4 months) with 1-sided α = 0.05. A prespecified interim analysis for futility was planned after 37 PFS events were observed, with completion of accrual if 1-sided stratified log-rank p-value $<$ 0.551. Hazard ratios (HR) and 95% confidence intervals (CI) are estimated by stratified Cox proportional hazards models. **Results:** After the safety run-in, 93 patients at 6 sites were randomized; 82 (41 B+P, 41 TAS-102) comprise the primary analysis population (eligible, consented, and started treatment). In this population, median age was 52 years, 50% female, 68% left-sided, 79% with *KRAS* codon 12/13 mut, 12% with prior regorafenib. Enrollment was halted at interim analysis as the futility boundary was crossed (1-sided p = 0.67). At final analysis, 68 subjects had a PFS event (34 in each arm). Median PFS was 2.1 mo (95% CI 2.0-3.0) with B+P vs 2.1 mo (2.0-2.4) with TAS-102; HR 0.86 (0.52-1.44). 4-mo PFS rate was 22.2% (11.9-41.6) with B+P vs 10.6% (3.8-30.0) with TAS-102. With 37 OS events (14 in B+P arm), median OS was 7.7 mo (5.1-NE) with B+P vs 6.6 mo (4.8-8.9) with TAS-102; HR 0.77 (95% CI 0.39-1.51). TAS-102 had greater grade 3-4 hematologic AEs (46% vs 22%), and B+P had more grade 3-4 non-hematologic AEs (47% vs 32%). Grade 3-4 AEs more common with B+P were fatigue (8% vs 0%), oral mucositis (6% vs 0%), and nausea (4% vs 2%). Though 63% of patients on B+P had acneiform rash, only 2% was grade 3-4. Grade 1-2 diarrhea occurred in 35% of B+P and 24% of TAS-102 patients. No new safety signal was observed. **Conclusions:** B+P did not significantly improve median PFS or OS compared to TAS-102 in *KRAS/NRAS* mut mCRC. Subgroup analyses and translational studies are ongoing to determine which subgroups may be more likely to attain 4-mo PFS or identify mechanisms of resistance. Clinical trial information: NCT03981614. Research Sponsor: Pfizer.

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SONCAR study: A prospective randomized controlled study on optimized neoadjuvant chemotherapy-oxaliplatin plus CRT in patients with locally advanced rectal cancer.

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Background: The benefit of adding Oxaliplatin to neoadjuvant chemoradiotherapy in Locally Advanced Rectal Cancer (LARC) patients remains controversial. The present study investigated whether induction chemotherapy (CapOX), 2 cycles of CapOX combined with standard radiation (Oxa-CRT) concurrently and consolidation chemotherapy (CapOX) could improve OS compared with standard treatment (nCRT) for locally advanced rectal cancer. **Methods:** We conducted this randomized, single center, open-label, phase III trial in China. Eligible patients were pathologically confirmed rectal adenocarcinoma, clinical T3-4 with or without regional N + and no sign of distance metastasis determined by pelvic MRI, chest and abdominal CT scan. All patients were randomly allocated to the experimental group: pelvic radiation of 50Gy/25 fractions with 4 cycles of oxaliplatin and capecitabine (1 cycle of CapOX (oxaliplatin: 130mg/$m^{2,}$ cape: 1000mg/m^2, bid, Day 1 to Day 14) administrated before radiotherapy as induction chemotherapy, 2 cycles of CapOX (oxaliplatin: 100mg/m^2, cape: 1000mg/m^2, bid, Day 1 to Day 14) administrated concurrent with RT, and 1 cycle of CapOX (oxaliplatin: 130mg/m^2, cape: 1000mg/m^2, bid, Day 1 to Day 14) conducted as consolidation chemotherapy); or control group: radiation with capecitabine. The primary end point was OS. This trial was registered with ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT02031939). **Results:** From January 2014 to June 2020, 556 patients enrolled in this study (n=278 in both groups), and 536 patients were evaluable (269 in experimental group and 267 patients in control group). Surgery was performed in 235 patients (84.5%) in experimental group and 242 patients (87.1%) in control group. The pCR rates were 27.8% (75 in 269) and 19.4% in control group (52 in 267) (p = 0.025). 16 and 5 patients achieved clinical complete response (cCR) in experimental and control group, respectively. Grade 3-4 toxicities were recorded in 42 (21.8%) and 6 (5.1%) patients in experimental and control group. The most common grade 3-4 toxicities were leukopenia, thrombocytopenia and neutropenia. The overall surgical complication rate was not significantly different between two groups (12.1% vs. 11.9%). **Conclusions:** Four cycles of CapOX combined with RT in LARC significantly increased complete tumor response in Chinese patients with acceptable toxicities. Clinical trial information: NCT02031939. Research Sponsor: Sun Yat-sen 5010 research fund.

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A phase II study of pembrolizumab, binimetinib, and bevacizumab in patients with microsatellite-stable, refractory, metastatic colorectal cancer (mCRC).

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Background: To date, immune-checkpoint inhibition for microsatellite stable (MSS) mCRC has been ineffective, though targeted therapy combination strategies may be promising. This phase II, investigator-initiated trial (NCT03475004) was designed to evaluate the efficacy and safety of the three-drug combination of pembrolizumab (pembro), binimetinib, and bevacizumab in patients with advanced, MSS treatment-refractory colorectal cancer. **Methods:** Patients with mCRC locally determined to be MSS and whom have progressed on two prior lines of therapy were enrolled. Treatment consists of pembro (200 mg every 3 weeks), binimetinib (45 mg BID) and bevacizumab (7.5 mg/kg every 3 weeks) until disease progression or unacceptable toxicity. The primary endpoint is PFS using RECIST v1.1 by investigator review. Additional endpoints include objective response rate, disease control rate at time of first re-staging (2 mo), duration of response, and safety and tolerability. **Results:** 50 patients have been enrolled (accrual is completed). 53% of patients are male and the mean age is 53.6 (range 31-79). The mean number of prior therapies is 5.3. At the time of preliminary data review, 39 patients are evaluable for response data. The median PFS was 5.8 mo (95% CI 4.2 to 8.9). The objective response rate was 13% with 5 partial responses. 24 patients (62%) had stable disease and 10 (26%) had progressive disease as the best response. The disease control rate at the time of first re-staging was 74%. Median duration of response was 6.5 mo. 19 (40%) patients experienced serious adverse events; the most common grade $\geq$3 adverse events included transaminase elevation (15%), diarrhea (11%), acneiform rash (9%), hypertension (9%), and anemia (9%). **Conclusions:** Preliminary results from this phase II study indicate that this regimen of pembrolizumab, binimetinib, and bevacizumab has promising activity and acceptable tolerability in this heavily pre-treated population of patients with MSS metastatic colorectal cancer. Final results will be presented as well as ongoing correlative studies. Clinical trial information: NCT03475004. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

Trastuzumab deruxtecan (T-DXd; DS-8201) in patients (pts) with HER2-expressing metastatic colorectal cancer (mCRC): Final results from a phase 2, multicenter, open-label study (DESTINY-CRC01).

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Background: T-DXd is an antibody-drug conjugate of a humanized anti-HER2 antibody bound to a topoisomerase I inhibitor by a cleavable linker. The primary analysis of DESTINY-CRC01 (DS8201-A-J203; NCT03384940), a phase 2, open-label, multicenter study of T-DXd in pts with HER2-expressing mCRC showed promising antitumor activity and a manageable safety profile (cohort A median follow-up [FU], 27.1 weeks; Siena S, ASCO 2020). We present updated longer-term efficacy and safety data. **Methods:** Pts had centrally confirmed HER2-expressing, *RAS* wild-type mCRC that progressed after ≥2 prior regimens. 6.4 mg/kg of T-DXd was administered every 3 weeks (Q3W) in 3 cohorts (A: HER2 IHC3+ or IHC2+/ISH+; B: IHC2+/ISH−; C: IHC1+). The primary endpoint was confirmed objective response rate (ORR) by independent central review in cohort A. Secondary endpoints were disease control rate (DCR; CR + PR + SD), duration of response (DOR), progression-free survival (PFS), and overall survival (OS). **Results:** At data cutoff (Dec 28, 2020), 86 pts (A, 53; B, 15; C, 18) received T-DXd. Median age was 58.5 y (range, 27-79), 53.5% were male, and 90.7% had left colon or rectum cancer. Median prior regimens for metastatic disease was 4 (range, 2-11). All pts had prior irinotecan; 30.2% in cohort A had prior anti-HER2 therapy. Median (m) treatment duration (all pts) was 3.0 mo (95% CI, 2.1-4.1; cohort A, 5.1 mo [95% CI, 3.9-7.6]). In cohort A (median FU, 62.4 weeks), confirmed ORR was 45.3% (24/53 pts; 95% CI, 31.6-59.6), DCR was 83.0% (44/53 pts; 95% CI, 70.2-91.9), mDOR was 7.0 mo (95% CI, 5.8-9.5), mPFS was 6.9 mo (95% CI, 4.1-8.7) with 37 (69.8%) PFS events, and mOS was 15.5 mo (95% CI, 8.8-20.8) with 36 (67.9%) OS events. These results are consistent with the primary analysis. Confirmed ORR was 43.8% (7/53 pts; 95% CI, 19.8-70.1) for pts with prior anti-HER2 therapy, 57.5% (23/53 pts; 95% CI, 40.9-73.0) for pts with IHC3+ status, and 7.7% (1/53 pts; 95% CI, 0.2-36.0) for pts with IHC2+/ISH+ status. In cohorts B and C, mPFS was 2.1 mo (95% CI, 1.4-4.1) and 1.4 mo (95% CI, 1.3-2.1); mOS was 7.3 mo (95% CI, 3.0-NE) and 7.7 mo (95% CI, 2.2-13.9), respectively. Treatment-emergent adverse events (TEAEs) of grade (G) ≥3 occurred in 65.1% of pts (56/86); the most common TEAEs were hematologic and gastrointestinal. TEAEs leading to drug discontinuation occurred in 13 pts (15.1%). 8 pts (9.3%) had interstitial lung disease (ILD) adjudicated by an independent committee as related to T-DXd (4 G2; 1 G3; 3 G5). **Conclusions:** T-DXd at 6.4 mg/kg Q3W showed promising activity and durability with longer-term FU in pts with HER2-expressing mCRC. The safety profile was consistent with prior results; ILD continues to be an important identified risk that requires careful monitoring and intervention as needed. These results support continued exploration of T-DXd in this patient population. Clinical trial information: NCT03384940. Research Sponsor: Daiichi Sankyo, Pharmaceutical/Biotech Company.

Perioperative and oncologic outcomes of hepatic artery infusion pump therapy at an expanding HAI program.

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Background: Hepatic artery infusion (HAI) is a liver directed therapy to treat unresectable or resected colorectal liver metastases (CRLM) and unresectable intrahepatic cholangiocarcinoma (ICC). Historically, HAI has only been performed at few specialized centers; however, there is increasing expansion to new centers. We previously reported safety outcomes of our index year of HAI therapy. We now report safety, feasibility, efficacy and oncologic outcomes for an expanded cohort of 62 patients in an established HAI program. **Methods:** Patients selected for HAI by multidisciplinary review were evaluated for demographics and perioperative outcomes. Objective hepatic response was calculated according to RECIST 1.1. Overall, hepatic and extrahepatic progression-free survival (PFS) were calculated by the Kaplan-Meier method on an intent-to-treat basis. **Results:** 62 patients were treated with HAI from November 2018-September 2021: 46 for unresectable CRLM, 8 as adjuvant HAI for resected CRLM, and 8 for unresectable ICC. Median age was 54.5 years (range 32-80), 58% were male, and 97% received prior chemotherapy (median 12 cycles, range 0-66). Hepatectomy (18, 29%) and/or colectomy/proctectomy (27, 43.5%) was performed concurrently with pump placement, and 19 (30.6%) were performed robotically. Median operating time was 265 minutes (range 130-526), estimated blood loss was 100 mL (range 22-1000) and length of stay was 5 days (range 1-19). HAI-specific complications occurred in 14% (Table). Floxuridine (FUDR) was initiated in 95% of patients a median of 18.5 days after surgery. Of the 38 patients who received HAI for unresectable CRLM and had measurable disease on imaging, 3- and 6-month hepatic disease control was achieved in 86% (8 partial response [PR], 22 stable disease [SD], 5 progressed [PD]) and 89% (1 complete response, 8 PR, 8 SD, 2 PD), respectively. For patients with at least 3 months follow-up, median PFS, hepatic PFS and extrahepatic PFS were 13 months, 13 months, and 13 months, respectively. **Conclusions:** HAI can be safely and effectively delivered to well-selected patients with CRLM and ICC. Response rates, disease control and PFS in heavily treated patients with unresectable CRLM comparable to high-volume centers can be achieved at new programs with appropriate expertise. These data support the mission of the newly formed HAI Consortium to critically evaluate efficacy and innovation in HAI therapy through multi-institutional collaboration and contemporary prospective trials. Research Sponsor: None.

HAI-Specific Complications	Perioperative Complications < 30 days (n, %)	Late Complications > 30 days (n, %)
None	51 (84%)	49 (79%)
HAI pocket seroma/hematoma	4 (7%)	2 (3%)
HAI pocket infection	1 (2%)	2 (3%)
Pump Migration/Erosion	0	2 (3%)
Arterial thrombosis/dissection	2 (3%)	0
Catheter dislodgement/Separation	0	3 (5%)
Arterial pseudoaneurysm	0	1 (2%)
Extrahepatic perfusion	2 (3%)	0
Biliary Sclerosis	0	4 (7%)

A phase 1b multitumor cohort study of cabozantinib plus atezolizumab in advanced solid tumors (COSMIC-021): Results of the colorectal cancer cohort.

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Background: Cabozantinib, a multiple receptor tyrosine kinase inhibitor, promotes an immune-permissive environment which may enhance the activity of immune checkpoint inhibitors. COSMIC-021 (NCT03170960) is evaluating the combination of cabozantinib with atezolizumab, an anti-PD-L1 inhibitor, in patients with advanced solid tumors. Outcomes in patients (pts) with metastatic colorectal cancer (mCRC) previously treated with fluoropyrimidine-containing therapy are presented. **Methods:** Pts with mCRC and an ECOG PS of 0–1 who progressed during or following systemic chemotherapy including fluoropyrimidine plus oxaliplatin or irinotecan were eligible. Up to 2 prior lines of anti-cancer therapy including EGFR-targeted therapy were allowed. Microsatellite instability high (MSI-H) and/or mismatch repair (MMR)-deficient pts were excluded. Pts received cabozantinib 40 mg PO QD plus atezolizumab 1200 mg IV Q3W. The primary endpoint was objective response rate (ORR) per RECIST 1.1 by investigator. Other endpoints included safety, duration of response (DOR), progression-free survival (PFS), and overall survival (OS). CT/MRI scans were performed Q6W for the first year and Q12W thereafter. **Results:** 31 pts received cabozantinib plus atezolizumab (median age, 60 y [range 31, 79]; male, 58%; ECOG PS 1, 61%; 2 prior lines of therapy, 71%; prior EGFR inhibitor, 16%; ≥3 tumor sites, 52%; tumors in left colorectum, 71%). Median follow-up was 28.1 mo (range, 24.2, 31.3) as of July 21, 2021. Cabozantinib plus atezolizumab demonstrated clinical activity in pts with mCRC (Table). Patients with wild-type RAS (n = 12) had numerically longer PFS and OS and higher ORR vs those with mutations (n = 19) (Table). Treatment-related adverse events (TRAEs) of any grade occurred in 28 (90%); the most common were diarrhea (52%), fatigue (42%), and nausea (35%). Grade 3-4 TRAEs occurred in 16 (52%); the most common were hypertension (10%), fatigue (6%), and lipase increased (6%); no Grade 5 events were reported. **Conclusions:** Cabozantinib plus atezolizumab demonstrated encouraging clinical activity with manageable toxicity in pts with previously treated advanced non-MSI-H/MMR-proficient CRC. Clinical trial information: NCT03170960. Research Sponsor: Exelixis.

End point	All patients (N = 31)	Wild-type RAS (n = 12)	RAS mutant (n = 19)
ORR, % (95% CI)*	9.7 (2.0, 25.8)	25.0 (5.5, 57.2)	0
Disease Control Rate, % (95% CI)†	71.0 (52.0, 85.8)	91.7 (61.5, 99.8)	57.9 (33.5, 79.7)
Median DOR, mo (95% CI)	7.6 (4.2, NE)	7.6 (4.2, NE)	NE (NE, NE)
Median PFS, mo (95% CI)	3.0 (2.7, 5.4)	5.8 (2.8, 11.0)	2.7 (1.6, 4.1)
Median OS, mo (95% CI)	14.0 (5.5, 16.7)	16.7 (8.4, NE)	8.7 (4.7, 15.9)

*Proportion with complete (CR)+ partial (PR) response per RECIST 1.1; †Proportion with best overall response of CR, PR, or stable disease per RECIST 1.1.

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Tumor volume regression of rectal cancer in daily MRI during preoperative chemoradiotherapy with capecitabine.

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Background: Although cone beam computed tomography (CBCT) has been available for over a decade, the pattern of tumor volume change in rectal dancer during preoperative concurrent chemoradiotherapy (CCRT) has been under the veil due to poor soft tissue contrast of registration CBCT. This study was conducted to investigate daily rectal tumor volume change using registration magnetic resonance imaging (MRI). **Methods:** Patients diagnosed with cT3-4 and/or cN+ rectal adenocarcinoma undergoing preoperative CCRT with capecitabine on the pelvis up to 50 Gy in 25 daily fractions from November 2018 to June 2019 were consecutively included. Rectal tumor volume was uniformly measured by single physician (YKK) in daily 0.35T MRI obtained with ViewRay MRIdian Linac (ViewRay Inc., Oakwood, USA). The mean +/- standard deviation (SD) of daily tumor volume (cc), difference of tumor volume between first fraction and daily fraction (daily tumor volume – baseline tumor volume at first fraction), and tumor volume reduction rate (%, (daily tumor volume – baseline tumor volume at first fraction)/baseline tumor volume at first fraction x 100) were calculated. Statistical significance of differences were tested using the Wilcoxon's signed rank test and paired t-test. **Results:** Thirteen patients were included. Median age was 65 and majority of the patients were male (92.3%). Most tumors were T3 (76.9%) and N1-2 (92.3%). Tumors were located median 6 cm (range: 2.4 – 9) above anal verge. Median follow-up was 27.3 months (range: 11.7 – 30.6) and 2 patients had recurred at the time of analysis (1 local and 1 distant). Tumor volume steadily regressed with daily administration of CCRT (mean 2.06 +/-1.73 cc; Figure 1). Significant tumor volume reduction compared to baseline was observed from fourth fraction (mean -12.37 +/- 16.72 cc; $P < 0.0005$). The difference of tumor volume between baseline and the last fraction was mean -49.33 +/- 68.13 cc ($P < 0.0002$). The tumor volume reduction rate was significantly increased since fourth fraction (mean - 17.2 +/- 11.78 %; $P < 0.0002$). The tumor volume reduction rate at the last fraction was - 70.62 +/- 14.01 % ($P < 0.0001$). **Conclusions:** For the first time, this study demonstrated daily tumor volume regression in preoperative rectal CCRT with capecitabine using daily MRI. Steady pattern of tumor regression may be explained in part by daily administration of capecitabine. Based on the hypothesis-generating observation, this study may warrant initiation of further investigations such as analysis and comparison with daily tumor volume regression with CCRT using leucovorin and 5-FU. Research Sponsor: None.

Periop-01: A randomized controlled trial of extended perioperative tinzaparin to improve disease-free survival in patients with resectable colorectal cancer.

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Background: Cancer patients undergoing surgical resection of their tumor are hypercoagulable beyond the period of hospitalization. Preclinical studies demonstrate that the postoperative hypercoagulable state promotes metastases, an effect that is abrogated by administration of perioperative low molecular-weight heparin (LMWH). **Methods:** We conducted a randomized, open label clinical trial to determine if extended duration thromboprophylaxis using subcutaneous LMWH (tinzaparin 4,500 IU daily), beginning at decision to operate and continuing for 56 days postoperatively, compared to inpatient postoperative thromboprophylaxis only, increased the 3-year disease-free survival (DSF) in patients undergoing resection for colorectal cancer. Secondary outcomes included 5-year overall survival (OS), postoperative bleeding and venous thromboembolism (VTE). **Results:** Trial recruitment was stopped prematurely after 614 of the planned 1075 patients were registered, following a pre-defined interim analysis for futility. The intention-to-treat analysis included 602 patients with demographics in the table. The 3-year DFS was 78.9% (63/299 recurrences) in the tinzaparin group and 80.5% (59/303 recurrences) in the control group (hazard ratio (HR) 1.09; [95% CI 0.91,1.31; p=0.3]). The 5-year OS was 91.3% in the tinzaparin group and 92.4% in the control group (HR 1.08; [95% CI 0.66,1.79; p=0.1]). The incidence of postoperative VTE was 1.7% and 1.3% in the tinzaparin and control groups, respectively (HR 1.3; [95% CI 0.30,5.69; p=0.7]. The incidence of major bleeding in the first postoperative week was 0.3% and 2% in the tinzaparin and control groups, respectively (HR 0.16; [95% CI 0.02,1.15; p=0.07]. **Conclusions:** Extended duration perioperative anticoagulation with tinzaparin did not improve DFS or OS in colorectal cancer patients undergoing surgical resection. The incidences of postoperative bleeding and VTE were low. Funded by Canadian Institute of Health Research and Leo Pharma Clinical trial information: NCT01455831. Research Sponsor: Canadian Institute of Health Research, Pharmaceutical/Biotech Company.

Baseline characteristics	Extended duration thromboprophylaxis (n=299)	Standard thromboprophylaxis (n=303)
Age (mean, s.d.)	61.4 (13.2)	60.8 (12.6)
Male (n, %)	179 (58.3)	186 (60.6)
Rectal tumor (n, %)	155 (50.5)	156 (50.8)
Neoadjuvant therapy (n, %)	116 (38.8)	113 (37.3)
Adjuvant therapy (n, %)	144 (54.1)	141 (53.4)
Type of surgery (n, %) Laparoscopy	201 (67.2)	203 (67)
Node positive (n, %)	105 (35.6)	96 (32.1)
Duration of postop thromboprophylaxis (median days, range)	55 (53-56)	5 (3-7)

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Safety and efficacy of pressurized intraperitoneal aerosolized chemotherapy in appendiceal and colorectal cancer patients with peritoneal carcinomatosis: A first-in-US phase I study.

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Background: Pressurized intraperitoneal aerosolized chemotherapy (PIPAC) is being evaluated as a novel minimally invasive palliative treatment of peritoneal metastases (PM). Prior studies have established the feasibility and safety of repeated PIPAC treatments in gastrointestinal and gynecologic cancers. The goal of the present phase 1 trial was to establish the safety and feasibility of PIPAC oxaliplatin in a highly chemotherapy refractory colorectal and appendiceal cancer patient population. **Methods:** Patients with biopsy-proven peritoneal metastases from colorectal or appendiceal cancer underwent up to three PIPAC treatments using oxaliplatin (92 mg/m^2) with a six-week interval at two academic centers. Patients with bowel obstruction, extra-peritoneal metastases, or poor performance status (ECOG$>$2) were excluded. PIPAC was nebulized over 5 min with a 30 min aerosol dwell time. Apart from the first PIPAC cycle, the patients also received a sensitizing dose of 5FU/LV (400mg/m^2) within 24 hours of the procedure. Primary end point was safety as assessed by dose limiting toxicities within 6 weeks of the first PIPAC. Secondary endpoints included safety with the addition of 5FU/LV, efficacy, surgical morbidity, technical failure rate, progression-free and overall survival, pharmacokinetics (PK), and quality of life assessment. **Results:** A total of 8 patients were included: 5 colorectal; and 3 appendiceal. Median number of prior chemotherapy cycles was 2 (Interquartile range – IQR; 1.5-3.5). All patients were refractory to systemic oxaliplatin-based chemotherapy. Median time from diagnosis to PIPAC was 16 months (IQR; 5.6, 17.5) and Peritoneal Carcinomatosis Index was 29 (IQR; 20.5, 31.5). Five (62.5%) patients completed 3 PIPAC cycles while in 3 (37.5%) patients PIPAC was discontinued due to disease progression within the peritoneal cavity. No surgical complication or dose limiting toxicity was observed. Only one patient developed grade 3 treatment-related toxicity after first PIPAC (anemia), and another patient after second PIPAC (abdominal pain and anemia). At the completion of PIPAC treatment 5 patients had stable disease and 3 had disease progression. Pharmacokinetic, histologic response and preliminary survival data will be presented at the meeting. **Conclusions:** PIPAC with oxaliplatin is safe and feasible in a highly chemotherapy refractory cohort of appendiceal and colorectal carcinomatosis patients with or without sensitizing 5-FU/ LV. Clinical trial information: NCT04329494. Research Sponsor: Philanthropic Support and Institutional Funds.

Intensification of local therapy with high-dose rate intraoperative radiation therapy (HDR-IORT) and extended resection for locally advanced and recurrent colorectal cancer.

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Background: This study reports our long-term experience with high dose rate intraoperative radiotherapy (HDR-IORT) in a single, quaternary institution. **Methods:** From 2004-2020, 138 consecutive patients with 141 total resections for locally advanced rectal cancer (LARC) (n=60, 43%) defined as T4Nx or T3N+ or locally recurrent rectal cancer (LRRC) (n=81, 57%) were retrospectively reviewed. The median age was 61 years (range 31-83) with 30 patients aged >70 years during surgery. Most patients had preoperative radiotherapy (RT) +/- concurrent chemotherapy (n=125). Thirty-two recurrent cancers received preoperative pelvic reirradiation to a median dose of 36 Gy (range 34.2 – 41.4). HDR-IORT was delivered using isotope iridium-192 in a remote afterloader, and a Freiburg applicator, after macroscopic resection of the tumour. A single 10 Gy fraction was delivered. Fifty-eight of 84 patients who underwent pelvic exenterations had >3 en bloc organs resected, and 96 patients underwent pelvic sidewall dissections. IORT sites included the primary tumour bed (33%), nodal regions (28%) and wider pelvic areas (70%). Resection margin status were R0 in 76 patients (54%) and R1 in 65 (46%). R1 resection was defined as positive (n=53) or close (n=12). R1 resection patients accounted for 61% of pelvic relapses. **Results:** With a median follow-up time of 4 years, 3-, 5-, and 7- year, overall survival (OS) rates were 75%, 48%, and 45%, respectively (84%,58%, 58% for LARC and 68%,39%, 35% for LRRC). Local progression-free survival (LPFS) of all patients were 88%, 85%, and 85%, respectively (97%, 93%, 93% for LARC and 80%, 80%, 80% for LRRC). On multivariable analysis, an R1 resection was associated with a trend toward poorer OS (p=0.05), while a trend towards worse LPFS (p=0.07) was noted for those without preoperative RT. The most common severe (grade ≥3) adverse events were postoperative abscess (n=25) and bowel obstruction (n=11). Overall, there were 49 (34%) grade 3-4 and no grade 5 adverse events. No intraoperative complications were attributed to IORT. The 30-day mortality rate was 0%. **Conclusions:** Favorable OS and LPFS can be achieved with intensive local therapy. As R1 resection may be associated with worse survival, optimisation of IORT, surgical resection, and systemic therapy are required. Research Sponsor: None.

Overall survival estimates by tumor diagnosis and resection margin status, % (95% CI).

Year	Primary rectal cancer	Recurrent rectal cancer	R0	R1
1	97 (87, 99)	87 (77, 93)	95 (86, 98)	87 (76, 93)
3	84 (70, 92)	68 (55, 78)	85 (73, 92)	61 (46, 73)
5	58 (40, 73)	41 (26, 55)	61 (45, 73)	31 (17, 49)
7	58 (40, 73)	37 (22, 52)	61 (45, 73)	26 (11,44)

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Efficacy of retreatment with oxaliplatin-based regimens in metastatic colorectal cancer patients: The RETROX-CRC retrospective study.

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Background: Oxaliplatin in association with fluoropyrimidines is universally considered one of the most effective drugs for colorectal cancer and the mainstay of front-line treatment of metastatic patients. In contrast the efficacy and safety profile of oxaliplatin based regimens in the late-care treatment space have been poorly and conflictingly reported. **Methods:** We identified a real-world cohort of metastatic colorectal cancer (mCRC) patients undergoing repeated oxaliplatin treatments in a single institution and retrospectively analysed their clinicopathological features to identify potential efficacy-predictive determinants of oxaliplatin response at retreatment (RETROX-CRC Study). **Results:** Out of 2,606 consecutive mCRC patients referred to Niguarda Cancer Center, 119 fulfilled the eligibility criteria of the study. The response rate (RR) and the disease control rate (DCR) after oxaliplatin retreatments were respectively 21.6% (95% CI 14.4-31.0%), and 57.8% (95% CI 47.7-67.4). A trend towards better RR and DCR was observed among patients who were exposed to oxaliplatin in the adjuvant setting, while a significantly poorer outcome was observed when two or more intervening treatments were delivered in between oxaliplatin exposures. Median progression-free survival (PFS) was 5.1 months (95% CI 4.3-6.1), significantly lower if oxaliplatin was re-administered beyond the third line (HR 2.02; 1.25-3.25; p=0.004). Safety data were reliably retrieved in 65 patients (54,6%). Of these 18.5% (12/65) and 7.7% (5/65) of them had G3-4 toxicities. Overall, toxicity was the cause of treatment discontinuation in almost a third of cases (28.6%; 34/119), with hypersensitivity reactions as the most prevalent reason for stopping treatment (58.8%; 20/34). **Conclusions:** In this large real-world series of 2,606 mCRC patients, less than 5% were re-treated with oxaliplatin. A late-disease control was achieved in almost 60% of patients, with a clinically acceptable sustained PFS and safety. Given the low performance of current standard drugs in late care of mCRC, retreatment with oxaliplatin might be considered a viable alternative especially if hopefully biology-based predictive markers for improving patient selection could be found. Research Sponsor: Fondazione Oncologia Niguarda Onlus.

Maintenance therapy following an anti-EGFR-based induction regimen in metastatic colorectal cancer (mCRC): A network meta-analysis of clinical trials.

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Background: A fluoropyrimidine with or without bevacizumab is often used in clinical practice as maintenance therapy after a first-line chemotherapy + bevacizumab induction in mCRC. However, the role of maintenance following an anti-EGFR-based induction and the optimal regimen are not well established. **Methods:** We searched PubMed and conferences' proceedings for clinical trials assessing maintenance therapy after first-line treatment for RAS WT mCRC. Two independent reviewers excluded single-arm studies and retrospective reports from trials that were not designed to assess maintenance therapy. We used the method of Guyot et. al. to obtain the individual patient data, followed by a Cox procedure to derive the survival hazard ratios (HR) from studies that did not report that value. Safety analysis included grade 3-4 asthenia, neuropathy, neutropenia, rash, and diarrhea. We performed a random-effects bayesian network metanalysis using the package "GeMTC R Package" to compare all treatment strategies included (anti-EGFR, anti-EGFR + chemotherapy [CT], CT alone, and observation). The risk of bias was assessed according to the Cochrane Handbook for Systematic Reviews of Interventions. **Results:** The systematic review retrieved 145 studies from which 142 were excluded. Two additional studies were found in the Conferences' Proceedings review. Consequently, 5 studies were included in this NMA. In terms of Progression-Free Survival (PFS), there was a benefit of anti-EGFR and anti-EGFR+CT versus CT alone (HR 0.63 [95%CrI 0.31-1.30] and 0.72 [95%CrI 0.41-1.30], respectively). The rank probability of anti-EGFR being the best option considering PFS was 61%. In terms of Overall Survival (OS), the benefit of anti-EGFR and anti-EGFR+CT versus CT alone was statistically weak (HR 0.92 [95%CrI 0.54-1.50] and 0.84 [95%CrI 0.57-1.20], respectively). The rank probability of anti-EGFR+CT be the best option in terms of OS was 51%. Comparing anti-EGFR versus anti-EGFR+CT resulted in no statistically significant difference. Anti-EGFR-containing regimens increased the rate of rash and diarrhea compared to CT alone (RR 11.23 and 1.23, respectively). The risk of bias was average low, except for the unclear risk of selection bias linked to unpublished studies. **Conclusions:** Anti-EGFR±CT maintenance therapy improves PFS and OS compared to CT alone or observation in RAS WT mCRC, with manageable safety profile. Research Sponsor: None.

Clinical outcomes of concomitant use of proton pump inhibitors and regorafenib in patients with metastatic colorectal cancer: A multicenter study.

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Background: Tyrosine kinase inhibitors (TKI) are the most common oral drugs in cancer patients. Similarly, proton pump inhibitors (PPI) are commonly used to relieve dyspeptic symptoms in patients with cancer. However, gastric pH levels may affect the absorption of TKI through the gastrointestinal system. However, all TKIs do not have the same chemical structure, and the absorption rate of each TKI depends on their solubility in different gastric pH levels. Limited data is available about the clinical outcomes of concomitant use of PPI and regorafenib in patients with metastatic colorectal cancer (mCRC). We present here the results of the multicenter study following the initial results of our single-center experience. **Methods:** Patients with mCRC treated with regorafenib were included in this multicenter and retrospective study. Patients prescribed PPI after initiation of regorafenib were assigned to the PPI user group, and the remaining patients were assigned to the PPI non-user group. To exclude immortal time bias, the log-rank test was performed between PPI non-user and all patients. The primary outcome was overall survival (OS), and secondary outcomes were time to treatment failure (TTF) and adverse events (AEs) profile. **Results:** Two hundred and seventy-two patients from eight cancer centers were included in this study. Most patients were male (59.9%), had liver metastasis (62.1%), and received regorafenib in the third line (52.2%). The median age at the initiation of regorafenib was 60 years (interquartile range (IQR): 51-66)). Eastern Cooperative Oncology Group performance score was 0 or 1 in approximately three out of four patients. The rate of patients with K-RAS mutation was 46.7%. There were 131 (48.2%) and 141 (51.8%) in the PPI user and non-user groups, respectively. The most prescribed PPI was pantoprazole (40.4%). At a median 34.2 months follow-up, the median OS was 6.9 months (95% Confidence Interval (CI): 5.3-8.5) and 7.7 months (95% CI:6.6-8.8) in the PPI non-user and all patients, respectively. No statistical significance was observed between the groups (p = 0.913). The median TTF was 3.3 months (95% CI: 2.6-3.9) and 3.4 months (95% CI:2.9-4.0) in the PPI non-user and all patients, respectively. No statistical significance was observed between the groups (p = 0.651). In the time-dependent covariate Cox regression model, there was no difference between PPI user and non-user groups in OS and TTF (adjusted Hazard Ratio (aHR):0.96, 95% CI:0.74-1.24, p = 0.735 for OS; aHR:0.88, 0.68-1.14, p = 0.354 for TTF). The rates of all AEs were also similar in the PPI user and non-user groups (p = 0.628). **Conclusions:** To our knowledge, this was the first study evaluating the effect of concomitant use of PPI and regorafenib in patients with mCRC, and no adverse survival and safety outcome was observed with the concomitant use of PPI and regorafenib in those patients. Research Sponsor: None.

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Improved organ preservation with dose escalation using contact X-ray brachytherapy for good responders following external beam chemoradio-therapy: Long-term outcomes from a single institution.

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Background: We previously reported the benefit of Contact X-ray Brachytherapy boost (CXB) in achieving a higher clinical complete response (cCR) following partial response to external beam chemoradiotherapy (EBCRT). We now update our report on the organ preservation rate and long-term durability of the cCR in this cohort. **Methods:** Outcome data for rectal cancer patients referred to our institution from 2003 to 2012 were retrieved from an institutional database after an audit approval. These patients were referred after initial local multidisciplinary team discussion. All patients had EBCRT 45Gy/25/5 weeks with capecitabine 825mg/m2 (Mon-Fri). Those who respond well but has a small residual tumour were offered CXB boost of 90Gy in 3 fractions over 4-6 weeks as they were not suitable or unwilling to undergo completion surgery. Following treatment, patients had close 3 monthly follow-ups with DRE, endoscopy, and MRI in the first 2 years, then 6 monthly up to 5 years. **Results:** Of 345 consecutive patients with rectal cancer referred to us, 83 patients who responded well to EBCRT but with small suspicious residual disease (≤3 cm) were offered CXB boost. Median age was 72 years (range 36–87) and 58 (69.9%) were males. Initial MRI tumor stages were cT2 (n = 28), cT3 (n = 55) and 54.2% were node positive. The median follow up of surviving patients was 6.4 years (range 2-11 years). cCR was achieved after CXB boost in 53/83 (64%). After achieving cCR, 8/53 (15%) developed local regrowth. However, all patients successfully underwent curative surgery with R(0) resection rate of 24/30 (80%) and only 21/83 (25%) had stoma. Organ preservation was achieved in 62/83 (75%). 12/53 (14%) patients developed metastatic disease. At the end of the study period, 64/83(77%) were cancer free. **Conclusions:** Our long-term data suggests dose escalation with CXB boost following EBCRT can achieved high organ preservation rate with excellent long-term durable cCR. This approach can provide an alternative treatment option for elderly or comorbid patient patients who are not suitable for surgery. This can also be an option for some patients who wish to avoid surgery upfront after initial diagnosis. Those who needed surgery later for treatment failure can be salvage successfully. A phase 3 European randomised trial OPERA (Organ Preservation in Early Rectal Adenocarcinoma) was set up to evaluate this concept further. Research Sponsor: None.

TACH101, a first-in-class pan-inhibitor of KDM4 for treatment of gastrointestinal cancers.

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Background: TACH101 is a novel, potent small molecule inhibitor of KDM4, a novel epigenetic target for cancer therapy. KDM4 is a family of histone lysine demethylases that, when overexpressed, drives key processes linked to cancer. Validation of KDM4 as a driver gene was confirmed across gastrointestinal tumor types including esophageal, colon and gastric cancers, and is associated with formation of aggressive tumors. **Methods:** TACH101 was evaluated in *in vitro* and *in vivo* studies including cell inhibition assays, patient-derived xenograft (PDX) and organoid models, and bioinformatics analyses studies. **Results:** *In vitro*, TACH101 treatment potently inhibited cell proliferation in cell lines and organoid models representing esophageal, CRC, and gastric cancers. TACH101 induced apoptosis in human CRC (HT-29) and esophageal (KYSE-150) cancer cell lines (EC50s 0.033 - 0.092 μM). Further evaluation using a panel of $>$ 300 cell lines from different tumor types showed potent activity of TACH101 against gastric cancer and CRC. In gastric cancer, 2D cell viability inhibition assays conducted on a panel of 11 gastric cancer cell lines showed 9/11 (82%) were sensitive to TACH101 treatment (IC50 0.004 - 0.072 μM); in PDX models, 4/5 (80%) were sensitive to TACH101 treatment (IC50 0.007 - 0.039 μM). In CRC, bioinformatics analysis indicated increased TACH101 sensitivity in cell lines with MSI-H status (IC50 1-150 nM). Sensitivity of MSI-H CRC to TACH101 was further confirmed in a panel of 14 CRC PDX models and 7 CRC organoid models in culture-based viability inhibition assays. In PDX models, 5/5 (100%) characterized as MSI were sensitive to TACH101 treatment (IC50 0.001 - 0.014 μM), whereas 4/8 (50%) characterized as MSS were sensitive to TACH101 (IC50 0.003 - 0.270 μM). In patient derived CRC organoid models, 3/3 (100%) characterized as MSI were sensitive to TACH101 treatment (IC50 0.022 - 0.149 μM) whereas 0/3 (0%) characterized as MSS were sensitive (IC50 $>$ 10 μM). *In vivo*, TACH101 triggered effective tumor control ($\geq$70%) in xenograft models of CRC (SU60), esophageal (KYSE-150) and gastric (GXA-3036) cancers. Pharmacologic studies showed TACH101 demonstrated favorable cell permeability, good oral bioavailability, and high metabolic stability. **Conclusions:** Preclinical work on TACH101 KDM4 inhibitor demonstrates compelling data and applicability as a potential therapy for gastrointestinal cancers. Preparations to advance TACH101 into clinical trials are underway. Research Sponsor: Tachyon Therapeutics.

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Evaluation of efficacy and tolerance of radical radiotherapy and radiochemotherapy in treatment of locally advanced, unresectable rectal cancer.

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Background: Evaluation of tolerance and efficacy of two schemes of neoadjuvant treatment in patients with unresectable rectal cancer: radiochemotherapy and radiotherapy, including conventional and accelerated hyperfractionation. **Methods:** 145 patients (pts) with unresectable, locally advanced rectal cancer. Schemes used: radiotherapy (RT) in 73 (50%) or radiochemotherapy (CRT) in 72 (50%). In RT group conventional fractionation (CFRT) and hyperfractionated accelerated radiotherapy (HART). In CRT 54 Gy in 1.8 Gy fractions was given with two cycles of 5 Fu-LV chemotherapy in three or five day cycles. **Results:** Objective response (OR) in RT and CRT group was 60% versus 75%. Resection rate (RR) in RT and CRT: 37% versus 65%. Tumor mobility and laparotomy-based unresectability were significant factors for OR. Performance status, tumor mobility, neoadjuvant treatment method were significant for RR. Five-year LC in CRT versus RT: 68% versus 37%. Five-year OS: 52% versus 27%. CRT was independent positive prognostic factor for resection rate, local control. Tumor volume did not reach significance for any of the end points. Lenght of chemotherapy cycles (three or five days) did not reach significance for any of the endpoints. Toxicity was acceptable in both groups. CRT had best outcome in LC: 68% versus 42% in HART; and 25% in CFRT. Five-year OS was much better in CRT than in CFRT: 52% versus 17%. **Conclusions:** The results of treatment depend on performance status, patients age, tumor mobility and unresectability based on earlier laparotomy. The lack of influence of the tumor volume on all endpoints indicates the need for radical neoadjuvant treatment independently of tumor volume and underlines the key role of a proper surgical treatment. In patients not suitable for CRT, HART is optimal strategy for its better efficacy than CFRT. Research Sponsor: None.

BREAKWATER safety lead-in (SLI): Encorafenib + cetuximab (EC) ± chemotherapy for first-line (1L) treatment (tx) of *BRAF* V600E-mutant (*BRAF*^{V600E}) metastatic colorectal cancer (mCRC).

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Background: Currently, there are no 1L tx options indicated specifically for patients (pts) with *BRAF*^{V600E} mCRC. Based on results of BEACON CRC (NCT02928224), BRAF inhibitor encorafenib + EGFR inhibitor cetuximab was approved for tx of previously treated pts with *BRAF*^{V600E} mCRC. BREAKWATER (NCT04607421), an ongoing, open-label, global, multicenter, randomized phase 3 study, evaluates 1L EC ± chemotherapy for tx of pts with *BRAF*^{V600E} mCRC. Here we present preliminary data on safety and pharmacokinetics (PK) from the BREAKWATER SLI, which aimed to identify the chemotherapy backbone for EC for the phase 3 portion of BREAKWATER. **Methods:** SLI inclusion criteria were *BRAF*^{V600E} mCRC (determined using tumor tissue or blood); evaluable disease (RECIST v1.1); ≤1 prior systemic tx for mCRC; European Cooperative Oncology Group performance status (ECOG PS) 0/1; and adequate bone marrow, hepatic, and renal function. Pts previously treated with BRAF/EGFR inhibitors or both oxaliplatin and irinotecan were excluded. Pts received encorafenib 300 mg daily + cetuximab 500 mg/m^2 every 2 weeks (Q2W) + either FOLFIRI Q2W or mFOLFOX6 Q2W in 28-day cycles. The primary endpoint was frequency of dose-limiting toxicities (DLTs). PK were a secondary endpoint. Data cutoff date: Sep 13, 2021. **Results:** 57 pts were enrolled (EC + FOLFIRI, n = 30; EC + mFOLFOX6, n = 27). Median (range) age was 57 (28–78) years; 25% were Asian; 65% had ECOG PS 0; 37% had ≥3 organs involved; 58% were treatment naive. At cutoff date, tx was ongoing in 45 (79%) pts. Median (range) duration of tx for encorafenib in EC + FOLFIRI and EC + mFOLFOX6 was 15 (0–31) and 14 (0–27) weeks, respectively. One DLT was observed: grade 4 neutropenia in 1 pt in EC + FOLFIRI. Tx-emergent all-cause serious adverse events (AEs) occurred in 20% and 19% and grade ≥3 AEs in 33% and 56% of pts in EC + FOLFIRI and EC + mFOLFOX6, respectively. The table shows frequent (all grade in ≥30% pts or grade ≥3 in ≥10% with either tx) tx-emergent all-cause AEs. One pt died due to disease progression. In EC + FOLFIRI, in the presence of steady-state encorafenib, AUC_{inf} of irinotecan and its active metabolite, SN-38, significantly decreased ~25% and ~40%, respectively, compared with values in the absence of encorafenib. In EC + mFOLFOX6, oxaliplatin PK was not significantly altered by steady-state encorafenib. **Conclusions:** Based on these data, BREAKWATER phase 3 will compare EC ± mFOLFOX6 with mFOLFOX6/FOLFOXIRI/CAPOX ± bevacizumab. Clinical trial information: NCT04607421. Research Sponsor: Pfizer.

AE, n (%)	EC + FOLFIRI (n = 30) All grades	Grade ≥3	EC + mFOLFOX6 (n = 27) All grades	Grade ≥3
Nausea	13 (43)	0	19 (70)	0
Peripheral sensory neuropathy	2 (7)	0	10 (37)	0
Pyrexia	3 (10)	0	9 (33)	0
Constipation	10 (33)	0	7 (26)	0
Diarrhea	9 (30)	1 (3)	7 (26)	2 (7)
Fatigue	13 (43)	1 (3)	7 (26)	0
Neutrophil count decreased	2 (7)	1 (3)	6 (22)	6 (22)
Neutropenia	1 (3)	1 (3)	6 (22)	3 (11)
Dermatitis acneiform	9 (30)	1 (3)	5 (19)	0

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Phase II trial of cabozantinib (Cabo) plus durvalumab (Durva) in chemotherapy refractory patients with advanced mismatch repair proficient/microsatellite stable (pMMR/MSS) colorectal cancer (CRC): CAMILLA CRC cohort results.

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Background: Cabo is an anti-VEGFR2/MET/AXL drug with broad multi-kinase inhibitory spectrum. Preclinical and clinical studies in various solid tumors demonstrated favorable immune modulatory activity of Cabo with clinical synergy seen when combined with PD-1/ PD-L1 inhibitors like Durva. Upon completion of phase Ib gastrointestinal (GI) basket CAMILLA trial evaluating Cabo + Durva in 30 patients (pts) demonstrating favorable safety & efficacy, the trial was expanded to phase 2 multi-cohort, multi-center trial of 117 pts. Herein, we report results of the phase 2 CRC cohort, the first evaluation of cabo + IO in this population. **Methods:** Pts enrolled in this cohort were administered Cabo + Durva at the RP2D of 40mg QD and 1500mg IV Q4W respectively. Enrolled pts must have progressed on 2 or more lines of therapy. Primary outcome measure was investigator assessed overall response rate (ORR) and secondary outcomes were rate of treatment related adverse events (TRAE), investigator assessed disease control rate (DCR), progression free survival (PFS), and overall survival (OS). Subgroup analysis was done in pts with RAS wild type tumors. Exploratory analysis of pathogenic molecular tumor alterations using next generation sequencing (NGS) was done in pts who achieved confirmed partial response (PRc)/ stable disease (SD) $>$ 6 months. **Results:** Of the 36 pts enrolled, 29 (16F, 13M) were evaluable for efficacy. Median age 57 years (27-76). 90% (26) had ECOG of 1. All had pMMR/MSS, 41% (12) had RAS wild type tumors, and 6.9% (2) had HER2 amplification. 52% (15) had received $\geq$ 3 lines of therapy. All had metastases at $\geq$ 3 sites and 79% (23) metastases in the liver. Among 36 pts evaluable for safety, treatment related serious adverse events (SAEs) occurred in 31% (11/36). Most common TRAEs were grade 1-2 fatigue (53%), nausea (42%), diarrhea (36%), anorexia (31%), hand-foot syndrome (22%), & hypertension (16%). Grade $\geq$ 3 immune-related adverse events (IRAE) occurred in 16.6% (6/36). Efficacy analysis revealed an ORR 27.6% (8/29); PRc 21% (6/29); DCR 86.2% (25/29); median DOR was not reached (NR); median PFS 4.4 months; 6-month PFS 28% & median OS 9.1 months. In the RAS wild type subgroup, ORR (PRc) was 50.0%; DCR 83.3%; median PFS 6.3 months and median OS was NR. Of the 7 pts who achieved PRc/SD $>$ 6 months, one had KRAS G12V tumor mutation along with mutations in ARID1A & IDH1. Remaining pts had RAS wild type tumors & among those, the following NGS alterations were detected: 1 *HER-2* amplification, 1 *MET* amplification, & 2 alterations in *ATM*. **Conclusions:** Cabo + Durva demonstrated promising efficacy and was fairly tolerated without new safety signals in heavily treated pMMR/MSS CRC pts. These encouraging results warrant further evaluation of this regimen in a randomized setting as salvage therapy in pMMR/MSS CRC. Clinical trial information: NCT03539822. Research Sponsor: AstraZeneca and Exelixis.

Clinical significance and biomarker potential of MGMT protein measurement in colorectal cancer.

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Background: O^6-methylguanine DNA methyltransferase (MGMT) is the principal repair mechanism of DNA damage created by alkylating agents. Approximately 40% of colorectal cancers (CRC) exhibit MGMT promoter hypermethylation, expected to result in gene silencing. The role of MGMT as a biomarker is poorly understood, and quantitative measurement of MGMT protein has not been performed in CRC. We hypothesized that altered tumor MGMT would affect DNA damage response, modulate adaptive anti-tumor immune responses, and influence survival in CRC. **Methods:** We used multiplexed quantitative immunofluorescence (QIF) to study 4 clinically annotated retrospective patient cohorts treated from 2000 to 2017 at Yale, consisting of 400 formalin-fixed paraffin-embedded CRC cases represented in tissue microarray format. These included paired tumors and adjacent non-tumor colonic mucosa (n = 112 pairs in Cohort 1), paired primary CRC and lymph node metastases (n = 31 pairs in Cohort 2), and 2 cohorts with primary stage I-IV tumors (n = 250 in Cohort 3; n = 150 in Cohort 4). We established a QIF panel for simultaneous, localized measurement of DAPI (all cells), cytokeratin (CK; tumor epithelial cells), MGMT, γH2AX (DNA damage response), and CD8. The measurement of fluorescent signals in CK-positive tumor cells or CK-negative stromal cells was achieved using co-localization strategies and the AQUA QIF platform. **Results:** We identified lower MGMT protein levels in CRC cells than in non-tumor colonic epithelium ($p < 0.0001$), and in lymph node metastases compared to paired primary CRC tumors ($p = 0.0411$). Using the visual detection threshold, tumor selective MGMT protein downregulation was identified in 20% of cases in Cohorts 3 and 4. Microsatellite instability-high (MSI-H) cases showed decreased tumoral MGMT protein compared to microsatellite stable (MSS) cases ($p = 0.002$). In Cohorts 3 and 4, low tumoral MGMT was consistently associated with increased CD8+ tumor infiltrating lymphocytes ($p = 0.0472$; $p = 0.0002$). The association between MGMT and γH2AX was inconsistent. The association between MGMT and CD8 was significant only in MSS cases ($p = 0.0001$) but not in MSI-H cases ($p = 0.0979$), supporting that the effect is not driven by MSI-H status. Tumor-selective MGMT downregulation evidenced by a low tumor-to-stroma ratio was associated with improved progression-free survival and overall survival in both Cohorts 3 and 4, but statistical significance was only seen in Cohort 3. **Conclusions:** MGMT protein downregulation occurs in 20% of CRCs and is associated with increased adaptive anti-tumor immune responses, mismatch repair (MMR) deficiency and better prognosis. MGMT deficiency may alter DNA repair in tumor cells and mediate the accumulation of antigenic mutations or neopeptides, independent from MMR status. Our results support a biomarker role of MGMT protein and suggest a role for immunotherapy combinations in MGMT deficient tumors. Research Sponsor: U.S. National Institutes of Health.

137 **Poster Session**

Clinical significance of *Bacteroides fragilis* as potential prognostic factor in colorectal cancer patients.

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Background: *Bacteroides fragilis* (*B. fragilis*) is an obligate anaerobe and generally acts as anti-inflammatory manner on the intestinal tract. Enterotoxigenic *Bacteroides fragilis* (ETBF), a subtype of *B. fragilis*, produces *Bacteroides fragilis* toxin (BFT) leading to either asymptomatic chronic colonic inflammation or colonic tumor formation. However, the impact of *B. fragilis* and ETBF on colorectal cancer (CRC) prognoses still remains unclear. We tested whether the presence of *B. fragilis* and ETBF affect clinical outcome in CRC patients who underwent curative surgery. **Methods:** We obtained 197 pairs of matched FFPE samples from colorectal cancerous and adjusted non-cancerous tissues of patients with stage II and III CRC who underwent curative resection between 2014 and 2016. Quantitative analyses of *B. fragilis* and ETBF in the colon tissues were performed using quantitative PCR with primers, 16S rRNA for B. fragilis and *bft* DNA, respectively. Recurrence-free survival (RFS) and overall survival (OS) were analyzed using Kaplan-Meier curves, log-rank test, and Cox proportional hazards regression. **Results:** Among 197 patients, 16S rRNA for *B. fragilis* DNA and *bft* DNA were detected in 120 patients (60.9%) and 12 patients (6.1%), respectively. *B. fragilis*-positive patients had better RFS (5-y RFS rate: 81.4% vs. 73.4%, HR0.59, 95% CI: 0.31-1.12, p =0.10) and OS (5-y OS rate: 88.9% vs 78.3%, HR0.53, 95% CI: 0.26-1.11, p =0.091) compared with *B. fragilis*-negative patients though statistically not significant. In multivariable analysis for RFS, *B. fragilis*-positive remained as an independent prognostic factor (HR0.53, 95% CI: 0.28-0.99, p =0.049) along with tumor depth T4 and Stage III, while there was no significance in OS. No significant differences were observed between ETBF and nontoxigenic *B. fragilis* in patients' characteristics and clinical outcomes. **Conclusions:** Our findings suggest that the presence of *B. fragilis* may predict outcome especially RFS in patients with curatively resected stage II and III CRC. Further research are warranted to explore whether *B. fragilis* status could be involved in a novel prediction model for outcome in early-stage CRC and develop probiotics treatments to prevent recurrence. Research Sponsor: None.

A pilot study to reliably measure the tissue concentration of mitomycin C after hyperthermic intraperitoneal chemotherapy in patients with gastrointestinal malignancies.

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Background: HIPEC with MMC is a treatment for gastrointestinal cancers metastatic to the peritoneal cavity. The pharmacokinetics of MMC in plasma, peritoneal fluid, and urine are described. The amount of MMC in intraabdominal tissues after HIPEC are not well described. The aim of this study is to evaluate if MMC concentrated in tissue samples after HIPEC by high performance liquid chromatography (HPLC) from patients with gastrointestinal neoplasms. **Methods:** HIPEC was performed at 40°C with 40mg of MMC for 90 minutes, after which the peritoneal cavity was flushed, anastomoses created as needed, and the wound closed. Eligible patients were treated at a single institution, ≥18 years old, and underwent HIPEC with MMC. Samples were taken of the omentum, peritoneum, liver core biopsy, tumor, and mesenteric fat before and after HIPEC. All patients signed informed consent. Samples were frozen in liquid nitrogen, minced, and sonicated in 500μL of phosphate buffered saline. The homogenized samples were centrifuged, and the supernatant was analyzed by HPLC for MMC. The HPLC was performed using a Dionex Ultimate 3000. Analysis was performed with a Kinetex - 5μm Biphenyl 100A 150 x 4.6mm column. MMC was detected with a Diode Array Detector 3000 with fixed UV at 365nm, 280nm, 254nm, and 210nm. The mobile phase used isocratic 40% acetonitrile and 60% water at 0.5 ml/min. The analysis volume was 10μL. Samples were blinded prior to analysis and analyzed in triplicate. **Results:** Thirteen patients were enrolled, 11 were female, the average age was 57 years (range: 30 85). Diagnoses were low-grade appendiceal mucinous neoplasm (7), high-grade appendiceal mucinous neoplasm (1), appendiceal adenocarcinoma (1), colon adenocarcinoma (1), colon mucinous adenocarcinoma (1), peritoneal mesothelioma (1), and small bowel mucinous adenocarcinoma (1). Complete tissue samples were available for 10 patients. Two patients had complete cytoreduction and did not have tumor for analysis after HIPEC. One patient refused liver biopsy. MMC was not detected in any sample prior to HIPEC. After HIPEC, MMC was most often detected in peritoneum (12 of 13 cases) and tumor (9 of 11). MMC was less often detected in omentum (5 of 13), mesenteric fat (2 of 13), or liver (1 of 12). **Conclusions:** MMC concentrated in 92% of peritoneal samples, 82% of tumor samples, and less often in liver tissue. MMC is hydrophilic which may contribute to the low detection rates in omentum and mesenteric fat. A reliable method to measure MMC concentration in normal and malignant tissues is novel and may have clinical implications. Our next steps are to expand the cohort of patients and evaluate whether tissue concentration is associated with clinical outcomes. Research Sponsor: None.

139 **Poster Session**

Deep learning analysis of the adipose tissue and the prediction of prognosis in colorectal cancer.

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Background: Colorectal cancer (CRC) is the third most common type of cancer and has a poor prognosis and high recurrence rate. Research has shown that the lipid microenvironment surrounding tumors is closely associated with the occurrence, development, and metastasis of CRC. Recently, advances in artificial intelligence have greatly improved the accuracy of models for CRC prognosis and survival analysis. **Methods:** According to pathological images from the National Center for Tumor diseases(NCT), the University Medical Center Mannheim(UMM) database and the ImageNet data set, a model called VGG19 was pre-trained. A deep convolutional neural network(CNN), $VGG19_{CRC,}$ was trained by the migration learning method. According to the $VGG19_{CRC}$ model, adipose tissue scores were calculated for TCGA-CRC hematoxylin and eosin(H&E) images and images from patients at Zhujiang Hospital of Southern Medical University and First People's Hospital of Chenzhou. Kaplan-Meier(KM) analysis was used to compare the overall survival(OS) of patients. The XCell and MCP-Counter algorithms were used to evaluate the immune cell scores of the patients. Gene set enrichment analysis(GSEA) and single-sample GSEA(ssGSEA) were used to analyze upregulated and downregulated pathways. **Results:** In TCGA-CRC, patients with high-adipocytes(high-ADI) CRC had significantly shorter OS times than those with low-ADI CRC. In a validation queue from Zhujiang Hospital of Southern Medical University(Local-CRC1), patients with high-ADI had worse OS than CRC patients with low-ADI. In another validation queue from First People's Hospital of Chenzhou(Local-CRC2), patients with low-ADI CRC had significantly longer OS than patients with high-ADI CRC. In subgroup analysis, ADI could be used as a prognostic marker for patients with colon adenocarcinoma(COAD) and rectum adenocarcinoma(READ), as well as male and female CRC patients. Among these subgroups, patients with lower ADI also had significantly improved OS. Compared with the low-ADI group, high-ADI patients had significantly decreased CD8+ T cells, T cells,and monocytes in the tumor immune microenvironment(TIME), while M2 macrophages were significantly increased. According to the GSEA and ssGSEA analyses, pathways mediating anti-tumor immunity were significantly downregulated in the high-ADI group, while some oncogenic signaling pathways were significantly upregulated. **Conclusions:** We developed a deep convolution network to segment various tissues from pathological H&E images of CRC and automatically quantify ADI. This allowed us to further analyze and predict the survival of CRC patients according to information from their segmented pathological tissue images, such as tissue components and the tumor microenvironment. Furthermore, we found that ADI may also predict OS in CRC patients and among the subgroups. Research Sponsor: None.

Association of multiplex-immunofluorescence (m-IF) and gene expression signature with prognosis and bevacizumab (bev) treatment outcomes in NRG oncology/NSABP C-08: Implications for combining immune checkpoint blockade (ICB) and bev.

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Background: NRG Oncology/NSABP C-08 tested the efficacy of adding bev to mFOLFOX in patients (pts) with stage II or III colon cancer. In an unplanned analysis we showed that MMR status was predictive of bev benefit with dMMR pts receiving statistically significant bev benefit. More recently, we showed that immune cells and immune checkpoint proteins have differential effects on prognosis and bev benefit in C-08 (ASCO 2021). As part of a preplanned secondary objective of an NCTN-CCSC approved protocol, we tested the association of VEGFR, VEGFA, and CD31, with clinical outcomes and treatment benefit in dMMR and pMMR pts enrolled in C-08. To determine what subset of pts within C-08 received bev benefit, we tested the 10-gene IFNɣ signature (Ayers et al 2017), which has been shown to associate with response to ICB in other studies. **Methods:** VEGFR, VEGFA, and CD31 were quantitated in tumors from C-08 pts (N=1,485) using m-IF and the Vectra Pathology System and inForm software. Gene expression data of C-08 (n=387) via DASL^{R} microarrays was used to test the IFNɣ signature for association with bev benefit in dMMR and pMMR pts. All markers were tested for associations with prognosis and bev benefit in dMMR and pMMR pts using recurrence-free interval, median cut points, and Cox models. **Results:** VEGFR, VEGFA, and CD31 were not prognostic in the total C-08 cohort nor in dMMR or pMMR subsets. However, high VEGFR was associated with bev benefit in dMMR pts p=0.0012, HR=0.08 [95% CI; 0.025-0.224], n=117) but not in pts with pMMR (n=555) (int p=0.03). Pts whose tumors showed higher expression of the IFNɣ signature had a better prognosis than did pts with a low signature. Importantly, in the entire C-08 cohort with available DASL data, pts with low IFNɣ signatures received bev benefit (p=0.034, HR=0.59 [95% CI: 0.36-0.97], n=211). When low IFNɣ tumors were further split by MMR status both dMMR and pMMR pts showed a trend to receive bev benefit, however, numbers of pts were too small to make firm conclusions (dMMR no bev vs. bev p=0.02, n=11; pMMR no bev vs. bev, p=0.051, n=167). **Conclusions:** High VEGFR is associated with bev benefit in dMMR pts. In agreement with other studies, we observe that the IFNɣ signature is associated with a good prognosis in C-08, however, unique to this study is the observation that IFNɣ low is associated with bev benefit in the entire C-08 cohort. The association of high IFNɣ signature with ICB response seen in several other studies, plus our observation that low IFNɣ is associated with bev benefit in C-08, suggests that bev and ICB are most efficacious on different subsets of pts. Current clinical trial, GI-004, is testing the efficacy of the bev + atezolizumab combination. Examination of these markers may be informative. Support: PA DOH, U10CA-180868, -180822, -196067, Genentech, Sanofi; NSABP Clinical trial information: 00096278. Research Sponsor: U.S. National Institutes of Health, PA DOH; Genentech; Sanofi; NSABP.

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Ensemble voting decreases false positives in AI second-observer reads for detecting colorectal cancer.

Brandon Salinel, Matthew Grudza, Sarah Zeien, Matthew Murphy, Jake Adkins, Corey Jensen, Curt Bay, Vikram Kodibagkar, Phillip Koo, Tomislav Dragovich, Michael A. Choti, Madappa N. Kundranda, Hongzhi Wang, Tanveer Syeda-Mahmood, John Chang, 2022 GI-ASCO; Banner MD Anderson Cancer Center, Gilbert, AZ; Arizona State University, Tempe, AZ; A.T. Still University of Health Sciences, Kirksville, MO; M. D. Anderson Cancer Center, Houston, TX; M.D. Anderson Cancer Center, Houston, TX; The University of Texas Southwestern Medical Center, Dallas, TX; MD Anderson, Phoenix, AZ; IBM Almaden Research Center, San Jose, CA

Background: Colorectal cancer (CRC) is the second leading cause of cancer-related deaths, and survival can be improved if early, suspect imaging features on CT of the abdomen and pelvis (CTAP) can be routinely identified. At present, up to 40% of these features are undiagnosed on routine CTAP, but this can be improved with a second observer. In this study, we developed a deep ensemble learning method for detecting CRC on CTAP to determine if increasing agreement between ensemble models can decrease the false positives detected by artificial intelligence (AI) second-observer. **Methods:** 2D U-Net convolutional neural network (CNN) containing 31 million trainable parameters was trained with 58 CRC CT images from Banner MD Anderson (AZ) and MD Anderson Cancer Center (TX) (51 used for training and 7 for validation) and 59 normal CT scans from Banner MD Anderson Cancer Center. 20 of the 25 CRC cases from public domain data (The Cancer Genome Atlas) were used to evaluate the performance of the models. The CRC was segmented using ITK-SNAP open-source software (v. 3.8). To apply the deep ensemble approach, five CNN models were trained independently with random initialization using the same U-Net architect and the same training data. Given a testing CT scan, each of the five trained CNN models was applied to produce tumor segmentation for the testing CT scan. The tumor segmentation results produced by the trained CNN models were then fused using a simple majority voting rule to produce consensus tumor segmentation results. The segmentation was analyzed by the percentage of correct detection, the number of false positives per case, and the Dice similarity coefficient (DSC). If parts of the CRC were flagged by AI, then it was considered correct. A detection was considered false positive if the marked lesion did not overlap with any CRC; contiguous false positives across different slices of CT image were considered a single false positive. DSC measures the quality of the segmentation by measuring the overlap between the ground-truth and AI detected lesion. **Results:** Our results showed that increasing the agreement between the 5 models dramatically decreases the number of false positives per CT at the expense of slight decrease in accuracy and DSC. This is described in the table. **Conclusions:** Our results show that AI-based second observer can potentially detect CRC on routine CTAP. Although the initial result yields high false positives per case, ensemble voting is an effective method for decreasing the false positives with a slight decrease in accuracy. This technique can be further improved for eventual clinical application. Research Sponsor: None.

Pilot results of AI-second observer for CRC detection.

Voter Agreement	Accuracy	False Positives	DSC Histogram Peak
One-Voter	80%	22	0.25-0.5
Two-Voter	60%	7.6	< 0.25
Three-Voter	30%	3.7	0

Comparison of segmentation methods to improve throughput in annotating AI-observer for detecting colorectal cancer.

Brandon Salinel, Matthew Grudza, Sarah Zeien, Matthew Murphy, Jake Adkins, Corey Jensen, Curt Bay, Vikram Kodibagkar, Phillip Koo, Tomislav Dragovich, Michael A. Choti, Madappa N. Kundranda, Hongzhi Wang, Tanveer Syeda-Mahmood, John Chang; Banner MD Anderson Cancer Center, Gilbert, AZ; Arizona State University, Tempe, AZ; A.T. Still University of Health Sciences, Kirksville, MO; M. D. Anderson Cancer Center, Houston, TX; M.D. Anderson Cancer Center, Houston, TX; The University of Texas Southwestern Medical Center, Dallas, TX; MD Anderson, Phoenix, AZ; IBM Almaden Research Center, San Jose, CA

Background: Colorectal cancer (CRC) is the second leading cause of cancer-related deaths, and its outcome can be improved with better detection of incidental early CRC on routine CT of the abdomen and pelvis (CTAP). AI-second observer (AI) has the potential as shown in our companion abstract. The bottleneck in training AI is the time required for radiologists to segment the CRC. We compared two techniques for accelerating the segmentation process: 1) Sparse annotation (annotating some of the CT slice containing CRC instead of every slice); 2) Allowing AI to perform initial segmentation followed by human adjustment. **Methods:** 2D U-Net convolutional neural network (CNN) containing 31 million trainable parameters was trained with 58 CRC CT images from Banner MD Anderson (AZ) and MD Anderson Cancer Center (TX) (51 used for training and 7 for validation) and 59 normal CT scans from Banner MD Anderson Cancer Center. Twenty of the 25 CRC cases from public domain data (The Cancer Genome Atlas) were used to evaluate the performance of the models. The CRC was segmented using ITK-SNAP open-source software (v. 3.8). For the first objective, 3 separate models were trained (fully annotated CRC, every other slice, and every third slice). The AI-annotation on the TCGA dataset was analyzed by the percentage of correct detection of CRC, the number of false positives, and the Dice similarity coefficient (DSC). If parts of the CRC were flagged by AI, then it was considered correct. A detection was considered false positive if the marked lesion did not overlap with CRC; contiguous false positives across different slices of CT image were considered a single false positive. DSC measures the quality of the segmentation by measuring the overlap between the ground-truth and AI detected lesion. For the second objective, the time required to adjust the AI-produced annotation was compared to the time required for annotating the entire CRC without AI assistance. The AI-models were trained using ensemble learning (see our companion abstract for details of the techniques). **Results:** Our results showed that skipping slices of tumor in training did not alter the accuracy, false positives, or DSC classification of the model. When adjusting the AI-observer segmentation, there was a trend toward decreasing the time required to adjust the annotation compared to full manual segmentation, but the difference was not statistically significant (Table; p=0.121). **Conclusions:** Our results show that both skipping slices of tumor as well as starting with AI-produced annotation can potentially decrease the effort required to produce high-quality ground truth without compromising the performance of AI. These techniques can help improve the throughput to obtain a large volume of cases to train AI for detecting CRC. Research Sponsor: None.

Annotation Technique	Median Time (min:sec)
Manual	13:45
Ensemble 1	8:02
Ensemble 2	7:41

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The role of germline polymorphisms in genes involved in the antioxidant system to predict the efficacy of cetuximab for patients with metastatic colorectal cancer (mCRC) enrolled in FIRE-3 trial.

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Background: Reactive oxygen species activate RAS/MAPK signaling either through inactivation of phosphatases or by direct oxidation of kinases. We hypothesized that functional genetic variants in genes involved in the antioxidant system may be associated with the efficacy of cetuximab in mCRC patients. **Methods:** We analyzed genomic and clinical data from FIRE-3, a phase III trial which compared cetuximab and bevacizumab in combination with FOLFIRI in untreated mCRC patients. Genomic DNA extracted from blood samples was genotyped using an OncoArray (IIlumina, Inc., San Diego, CA, USA). Candidate 13 functional single nucleotide polymorphisms (SNPs) (*TXN* rs2301242, *TXN* rs2301241, *TXN2* rs4821494, *TXN2* rs9619611, *TXN2* rs59841625, *CAT* rs7943316, *CAT* rs564250, *CAT* rs11604331, *CAT* rs1001179, *CAT* rs769217, *GPX4* rs757229, *GPX4* rs4807542, and *GPX4* rs713041) were tested for association with progression-free survival and overall survival (OS), using log-rank test and Cox proportional hazards model. To confirm the predictive value, the treatment-by-SNP interaction was tested. **Results:** A total of 236 patients were available for the SNP analyses (cetuximab arm, $n = 129$; bevacizumab arm, $n = 107$). In the cetuximab arm, two SNPs were significantly associated with clinical outcomes in univariate analyses: *TXN2* rs4821494 (T/T vs any G allele, hazard ratio [HR] on OS = 2.17, 95% confidence interval [CI] = 1.04–4.56, log-rank $p = 0.04$) and *GPX4* rs4807542 (G/G vs any A allele, HR on OS = 2.04, 95% CI = 1.05–3.98, log-rank $p = 0.03$). Multivariate analysis confirmed the significance in *TXN2* rs4821494 (T/T vs any G allele, HR on OS = 2.47, 95% CI = 1.06–5.72, $p = 0.03$). In the bevacizumab arm, univariate analyses did not detect any significant associations between the SNPs and clinical outcomes. Treatment-by-SNP interaction test showed the significant predictive value of *TXN2* rs4821494 in terms of OS ($p = 0.03$). **Conclusions:** *TXN2* rs4821494 involved in the antioxidant system may predict the efficacy of cetuximab, in comparing with bevacizumab, in the first-line treatment of mCRC. Our novel findings warrant further validation studies. Research Sponsor: National Cancer Institute, Gloria Borges WunderGlo Foundation, Dhont Family Foundation, Daniel Butler Memorial Fund, Victoria and Philip Wilson Research Fund, and San Pedro Peninsula Cancer Guild.

Tumor microbiome variation in young versus average onset colorectal cancer.

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Background: The incidence of young onset colorectal cancer (yoCRC) is rising at alarming rates. The gut microbiome may be a factor accounting for the increase. We analyzed differences in the intratumoral microbiome of yoCRC vs average onset CRC (aoCRC) and its clinical impact. **Methods:** We identified 314 histologically confirmed cases of stage I-IV CRC that underwent surgical resection at our institution from 2000-2020, diagnosed $<$50 years of age for yoCRC and $>$60 years for aoCRC, who consented to a prospective biorepository. 36 cases were excluded due to nonmalignant, non-adenocarcinoma or metastatic site specimens. Fresh frozen tissue from the primary tumor with paired adjacent nonmalignant tissue specimens were analyzed. 16S rDNA was isolated and sequence reads were assigned to genus level amplicon sequence variants in DADA2 and analyzed for alpha and beta diversity using Phyloseq. Statistical tests included analysis of variance (ANOVA), permutational multivariate analysis (PERMANOVA), linear regression, and Wilcoxon test. Differential abundance and correlation analysis were adjusted for sex and ethnicity as confounding factors. Correlation analysis was adjusted with Benjamini Hochberg correction. Clinical differences were analyzed using Fisher's exact test. **Results:** Of the cohort of 278 patients, 137 had yoCRC (median age 43 years, range 16-49) and 141 had aoCRC (median age 73 years, range 61-95). yoCRC patients were more likely to have stage III or IV disease at presentation (29% vs 14%, p =0.002; 29% vs 18%, p =0.024 respectively), left sided tumors (74% vs 58%, p =0.003) and receive neoadjuvant therapy (29% vs 15%, p =0.004). yoCRC had significantly higher tumor microbial alpha diversity than aoCRC (p $<$2.22e$-$16, Wilcoxon rank-sum test). Beta diversity analysis demonstrated significantly different diversity of genera between the groups (R2=0.12, p =0.001, PERMANOVA). The prevalent taxa identified in both groups were *Lactobacillus*, *Bacillus* and *Listeria*. Differential abundance analysis (ANOVA, p $<$0.05) revealed a significant variation of intratumoral microbiome (Table). Correlation analysis revealed an association of longer overall survival (OS) with the presence of *Akkermansia* in yoCRC (R2 =0.36, p $<$0.001), but not in aoCRC. **Conclusions:** We found significant differences between the intratumoral microbiome of yoCRC and aoCRC. In particular, *Akkermansia*, considered a healthy gut microbe, was found in greater relative abundance in yoCRC and correlated with improved OS. Further studies are warranted to understand the nature of association of these microbes with the development of and outcomes in yoCRC. Research Sponsor: Sondra and Stephen Hardis.

Relative abundance (%) in yoCRC vs. aoCRC.

Genus	yoCRC	aoCRC	*p*-value
Akkermansia	9.96	7.63	1.05e-12
Bacillus	11.37	13.19	<0.001
Listeria	11.18	12.47	0.003
Enterococcus	6.09	6.69	0.028
Escherichia/Shigella	2.64	3.64	0.029
Pseudomonas	3.98	3.43	0.001

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Encorafenib, cetuximab, and cytotoxic chemotherapy combinations in *BRAF^{V600E}* CRC murine models.

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Background: Based on promising results from latest trials, a crucial point is to evaluate whether encorafenib (E) plus cetuximab (C), alone or in combination with chemotherapy, can improve clinical outcomes relative to current standard of care in previously untreated *BRAF^{V600E}* mutant mCRC. Considering the high number of *BRAF^{V600E}* mutant mCRC patients who will never receive a second-line treatment, the rationale of this strategy is to maximize treatment outcome within the first-line setting. **Methods:** We performed an *in vivo* study using human *BRAF^{V600E}* CRC cell line-derived xenografts in nude mice. We evaluated the efficacy of encorafenib (E) + cetuximab (C), FOLFOX, and FOLFIRI, both as individual regimens and in combinations. Mice were treated for 3 weeks and followed for an additional 8 weeks to evaluate durability of tumor control. Additionally, we validated our findings using 3 *BRAF^{V600E}* mutated patient derived xenografts. Tumors progressing on single agent and combined treatment were profiled by RNA sequencing, protein extraction for RPPA/Western blot, and establishment of in vitro primary cell cultures for further analyses. **Results:** Our study showed across all 4 models both FOLFOX and FOLFIRI, each in combination with encorafenib plus cetuximab, having greater efficacy than encorafenib plus cetuximab or either chemotherapy alone. No significant change in toxicity was seen with the addition of chemotherapy. Interestingly, in the one model with long term treatment, FOLFOX + E +/- C performed greatest over the long-term, with significant endpoint separation against all other treatment arms ($P < 0.05$). **Conclusions:** Taken together, results from our study suggest that the addition of chemotherapy to BRAF+EGFR targeted therapy can further increase the magnitude of response in *BRAF^{V600E}* mCRC and is a promising combination now being explored clinically. Additionally, this research will substantially contribute to our understanding of the genetic and molecular bases of resistance to target therapies and chemo-based approach in *BRAF^{V600E}*context. Research Sponsor: U.S. National Institutes of Health.

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Analysis of tumor-associated macrophages' heterogeneity in colorectal cancer patients using single-cell RNA-seq data.

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Background: Colorectal cancer (CRC) is one of the deadliest malignancies worldwide. Though immune checkpoint inhibition has proven effective for a number of other tumors, it offers benefits in only a small group of CRC. In general, heterogenous cell groups in the tumor microenvironment (TME) are considered as the major barrier for unveiling the causes of low immune response. Therefore, deconvolution of cellular components in highly heterogeneous microenvironments is crucial for understanding those mechanisms. Single cell sequencing technology revolutionized TME research enabling profiling cells in high resolution. **Methods:** We have analyzed scRNA-seq data from 23 CRC patients with pretreatment primary tumors using Seurat V3 pipeline. To investigate intercellular ligand-receptor interactions, we used CellPhoneDB and CellChat methods. The results of two independent analyses showed 4 CRC samples with no SPP1-CD44 interaction. It is known, that OPN which is the protein encoded by SPP1 gene, binds to CD44 and can cause cell survival, proliferation, and angiogenesis. Interestingly, analysis of the cellular composition of all 23 samples did not reveal differences in SPP1+ macrophages' content for those 4 "no SPP1-CD44" samples. To investigate the mechanisms that could cause differences in SPP1-CD44 expression across the samples, we analyzed developmental trajectories of single cells using Slingshot trajectory inference method. **Results:** Ligand-receptor interactions analysis revealed 4 CRC samples that lacked SPP1-CD44 interaction that is known to be responsible for tumor progression in CRC. But the proportion of SPP1+ cells was not significantly different in those 4 samples compared to other samples. Trajectory inference analysis showed that the cells from "no SPP1-CD44" samples had high expression of anti-inflammatory macrophage markers in the end of the trajectory. While cells from "high SPP1-CD44" samples had high expression of pro-inflammatory macrophage markers at the same point. **Conclusions:** Based on our data-driven study, we suggest that SPP1+ macrophages' heterogeneity may affect SPP1-CD44 interaction. Thus, targeting SPP1+ macrophages that have anti-inflammatory phenotype can potentially interrupt SPP1-CD44 interaction and therefore reduce tumor progression and immune suppression. Research Sponsor: Career Development Award #IK2-BX004346-01A1 from the United States (US) Department of Veterans Affairs Biomedical Laboratory Research.

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High-risk gene expression in colorectal liver metastasis: Potential for novel therapies.

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Background: Over half of patients with colorectal cancer (CRC) develop liver metastases. While immunotherapy is an emerging treatment of solid tumors, its use among CRC patients is limited. Furthermore, gene expression patterns of liver-specific CRC metastases remain unclear. The purpose of this study was to identify a high-risk gene expression profile for patients with colorectal liver metastasis (CRLM) to better inform prognosis and development of novel targeted therapies. **Methods:** Fifty-three FFPE CRLM samples from patients who underwent complete metastatectomy from 2009-2017 were examined. Expression profiling of extracted RNA was performed using NanoString Immuno-Oncology (IO360) 750-gene panel. Statistical analyses using cutoffs of absolute log 2-fold change$\geq$1.5 and p-value$\leq$0.05 were performed. Patients were analyzed by extremes of outcomes: survival time in the lowest quartile compared to those still alive at last follow-up. **Results:** Eight differentially expressed genes were associated with poor survival. Overexpressed genes included IL6R, CXCL2, C7, MGMT, PCK2, CSF1 and LILRB4 (Table). PLA2G2A was under-expressed. **Conclusions:** This study demonstrates differential gene expression associated with poor survival among patients with CRLM. Specific genes of interest include IL6R, MGMT, CSF1 and LILRB4. IL6R is a known effector in tumor proliferation via IL-6 signaling from tumor-associated macrophages, myeloid-derived suppressor cells (MDSCs) and T-cells. MGMT repairs alkylating DNA damage and is implicated in carcinogenesis and response to chemotherapy. CSF1 promotes macrophage differentiation to M2 phenotype, suppressing inflammation and anti-tumor defense mechanisms. LILRB4 activation via MDSCs leads to T-cell inhibition. These overall suggest a myeloid-dominant tumor immune microenvironment and represent important potential therapeutic targets. Next steps include performing immunohistochemistry to validate findings at the protein level and investigate the tumor intrinsic role using human cell lines. Research Sponsor: U.S. National Institutes of Health.

Overexpressed genes associated with poor survival (25th Percentile).

Gene	Log 2-Fold Change	*p*-value	Function
IL6R	2.26	0.034	Promotes cellular proliferation
CXCL2	1.89	0.009	Promotes angiogenesis, cancer metastasis
C7	1.76	0.045	Component of membrane attack complex for cell death
MGMT	1.73	0.034	Repair of alkylating DNA damage
PCK2	1.62	0.034	Gluconeogenesis, anabolic metabolism, cellular proliferation
CSF1	1.6	0.028	Regulates macrophage differentiation to M2 phenotype
LILRB4	1.58	0.032	Activates myeloid-derived suppressor cells to inhibit T-cell activation & proliferation

IL6R: Interleukin-6 receptor; CXCL2: Chemokine ligand 2; C7: Complement Component 7; MGMT: O^6-methylguanine-DNA methyltransferase; PCK2: Phosphoenolpyruvate carboxykinase 2; CSF1: Colony Stimulating Factor 1; LILRB4: Leukocyte Immunoglobulin-like Receptor Subfamily B-4.

The association between tumour sidedness, clinicopathological characteristics and outcomes in patients undergoing curative resection for colon cancer.

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Background: Right-sided colon cancer is associated with worse outcomes than left-sided disease, likely due to an association between tumour/host factors and tumour sidedness. The present study analyses the association between tumour sidedness, clinicopathological features and common mutations to better understand this discrepancy in outcomes. **Methods:** The association between tumour sidedness, clinicopathological characteristics and survival was examined within a cohort of patients undergoing curative surgery for TNM I-III colon cancer. **Results:** 3,419 patients were identified. 54% of cases were right-sided and associated with worse 3-year OS/CSS. On multivariate analysis for clinical factors: sex (OR 0.63), Systemic Inflammatory Grade (SIG), anaemia and differentiation (OR 0.80/0.31/0.57) were associated with T3 cancer sidedness and: sex, anaemia and differentiation (OR 0.61/0.46/0.57) were associated with T4 cancer sidedness. On further MVA including mutational factors anaemia/ BRAF status remained significant in T3/T4 cancer respectively (OR 0.08/0.09). BRAF mutant status was associated with SIG in all patients/T3 disease (p=0.046/0.016). **Conclusions:** Worse outcomes seen in right-sided colon cancer are likely explained predominantly by factors including tumour stage, SIG, anaemia and BRAF mutational status. BRAF mutations are associated with the Systemic Inflammatory Response and further research is required to better understand this relationship taking into the tumour microenvironment, microsatellite instability. Research Sponsor: None.

a. Clinical factors only

	T Stage 3 Colon Cancer		T Stage 4 Colon Cancer	
Variable	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**
Age	-	0.652	-	0.118
Sex	0.63 (0.46-0.85)	0.003	0.61 (0.39-0.95)	0.029
SIMD	-	-	-	0.427
Smoking	-	-	0.76 (0.57-1.03)	0.073
SIG	0.80 (0.65-0.98)	0.035	-	0.259
Anaemia	0.31 (0.23-0.42)	<0.001	0.46 (0.29-0.71)	0.001
Differentiation	0.57 (0.38-0.85)	0.006	0.57 (0.34-0.94)	0.029

b. Clinical and Mutational Factors

Variable	**T Stage 3 Colon Cancer**		**T Stage 4 Colon Cancer**	
	OR (95% CI)	P	OR (95% CI)	P
Sex	-	0.629	-	0.555
Smoking	-	-	-	0.239
SIG	-	0.200	-	-
Anaemia	0.08 (0.02-0.30)	<0.001	-	0.080
Differentiation	-	0.993	-	0.822
BRAF	-	0.999	0.09 (0.02-0.52)	0.007
KRAS	-	0.153	-	-

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Microorganospheres as a novel precision oncology platform in colorectal cancer.

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Background: Patient-derived organoids (PDO) have been shown to have a high degree of similarity to the original patient tumors. PDO have also been used to perform high throughput drug screens and shown to correlate with patient response to therapy. Unfortunately, PDO require too much tissue, take too long to establish and are too inefficient and costly for adoption into the clinic. The ideal assay for clinical use would be one that could be performed in less than14 days from a core biopsy to minimize delay in therapy. We have now circumvented these barriers by leveraging recent technological advances in emulsion microfluidics and droplet generators to develop MicroOrganoSpheres (MOS) that can be established and used to predict drug sensitivity within 14 days of obtaining a biopsy. **Methods:** 18-gauge core biopsy specimens from patients with colorectal cancer liver metastasis who subsequently received an oxaliplatin based therapy were first obtained. Biopsy specimens were minced, enzymatically digested and mixed with components necessary to generate MOS. The mixture was then processed through a custom fabricated flow-focusing droplet microfluidic chip in our MOS Generator Device to generate MOS. After culturing for 8-10 days, MOS were then used to perform drug screen with oxaliplatin. **Results:** A total of twelve CRC biopsies from liver metastasis were obtained and processed to generate MOS with a success rate of 12/12 (100%). Furthermore, drug screens with oxaliplatin were performed on all twelve samples with an average time to drug screen of 10.1 days. We next wanted to determine if there was a correlation between MOS drug sensitivity and patient clinical outcome (ie. time on treatment). For the first eight patients, MOS was used to predict sensitivity to oxaliplatin and using a drug sensitivity cut-off of 1 uM, four patients were predicted to be sensitive to oxaliplatin and four patients were predicted to be resistant. Three of the four patients predicted to be sensitive to oxaliplatin continue to be on treatment ($>$ 6 months), whereas 3 of the four patients predicted to be resistant to oxaliplatin progressed on oxaliplatin based therapy within 8 weeks (sensitivity = 80%, specificity = 100%, positive predictive value = 100%, negative predictive value = 75%). **Conclusions:** MOS can be generated from core biopsies and correlates to time on treatment. Although further studies will need to be conducted, the ability to generate MOS and perform a drug screen in $<$ 14 days will allow for the development of a precision oncology platform that can be rapidly used in the clinic to guide therapy. Research Sponsor: discretionary fund.

Effect of fruquintinib on programmed death receptor-1 blockade antitumor immune responses in colorectal cancer.

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Background: Programmed death receptor-1 (PD-1) blockade shows little benefit in the patients with microsatellite-stable colorectal cancer (MSS-CRC).Fruquintinib, a China-made anti-angiogenic drug, applied for third line therapy in mCRC. However, the effects of combination of fruquintinib and PD-1 blockade on MSS-CRC and its relative mechanisms are not well determined. **Methods:** Syngeneic xenograft mouse models were establish using murine MC38 and CT26 colon cancer cells to assess treatment efficacy. The percentages of immune cells were detected in peripheral blood, spleen and tumor tissues in tumor-bearing mice by flow cytometry analysis. Angiogenesis in tumor tissues was detected by immunofluorescence. The safety of drug treatment was evaluated by histopathology analysis in murine main organs. The efficacy of combination of fruquintinib and sintilimab were verified in the treatment of MSS-CRC patients. **Results:** Our results showed the combination of fruquintinib and sintilimab exhibited strongest inhibition of tumor growth and achieved longest survival time in mice bearing MC38 or CT26 xenograft tumors, compared to fruquintinib and sintilimab alone. Mechanistically, the combination of fruquintinib and sintilimab reduced angiogenesis, reprogramed the vascular structure, enhanced the infiltration of $CD8^+$T cells, $CD8^+TNF\alpha^+$T cells and $CD8^+IFN\gamma^+$T cells and reduced the ratios of MDSCs and macrophages in mice. No obvious damage was observed in main organs in tumor-bearing mice with the combined treatment. Moreover, the treatment of combination of fruquintinib and sintilimab anti-PD-1 antibodies achieved effective response in five refractory advanced MSS CRC patients. **Conclusions:** Our results show that combination of fruquintinib and sintilimab synergistically inhibits CRC growth by alterating antitumor immune microenvironment. Research Sponsor: The project was supported by National Science Foundation of China (NSFC 81773259,Chinese Society of Clinical Oncology Foundation (Y-Q201802-073, Y-XD202001-0318), the Science and Technique Foundation of Henan Province (No. 202102310121 for J.-Z. W), Medical.

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Gene expression-based personalized prescription of targeted drugs in colorectal cancer.

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Background: Colorectal cancer (CRC) is the fourth most common cancer worldwide with relatively poor patient survival. Transcriptome assay could be used to personalize CRC treatment thus complementing standard mutation analysis. **Methods:** We performed retrospective hybrid experimental and meta-analysis of CRC patient gene expression data with available progression-free survival (PFS) information and/or targeted drug response status. In total we analyzed 243 gene expression profiles from four publicly available (TCGA and three datasets from Gene Expression Omnibus GSE19860, GSE19862, GSE104645), and one experimental (PRJNA663280) patient cohorts. Each gene expression profile was analyzed using bioinformatic second-opinion platform Oncobox to calculate balanced drug efficiency scores (BES) to build personalized ratings of potentially effective targeted drugs. Area under the ROC curve (AUC) metric and Cox regression analysis were used to assess Oncobox capacity to predict tumor response and PFS, respectively. **Results:** Patients from GSE19860 (n = 12), GSE19862 (n = 14), GSE104645 (n = 81) received bevacizumab as monotherapy or in combination with chemotherapy as the nearest line of treatment after biopsy collection. Oncobox correctly classified treatment responders vs non-responders with AUC 0.94, 0.90 and 0.84, respectively. BES value was strongly associated with PFS (HR = 0.53, CI 0.33-0.84, log-rank test p-value 0.0057) in the GSE104645 cohort. However, BES was ineffective for predicting response and PFS after second-line (after biopsy collection) treatment with cetuximab. BES also predicted treatment response with AUC 0.74 in the TCGA cohort (n = 17) treated with 4 different targeted drugs. Thirty clinical outcomes were collected for 14 patients from our experimental cohort PRJNA663280. Patients were treated with 10 different targeted drugs. BES was an effective biomarker that could predict treatment outcomes with AUC 0.74 for all lines of therapy and 0.94 for the first line therapy (after biopsy), and could predict PFS after first-line treatment (HR 0.14, CI 0.027-0.73, log-rank test p-value 0.0091). **Conclusions:** Our results suggest that RNA profiling in tumor samples may be helpful for personalizing prescriptions of targeted therapeutics in CRC. Using recent biopsies is essential to obtain robust estimates of targeted drugs efficacy. Research Sponsor: OmicsWay Corp.

Comprehensive landscape of *BRAF* variant classes, clonalities, and comutations in metastatic colorectal cancer using ctDNA profiling.

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Background: Although *BRAF* V600E accounts for the majority of the *BRAF* mutations in mCRC, non-V600 *BRAF* variants have been shown in recent years to represent a distinct molecular subtype of mCRC. This study provides a comprehensive profile of *BRAF* V600 and non-V600 variants, their clonalities and co-mutations in mCRC using a large genomic database of circulating tumor DNA (ctDNA). **Methods:** A systematic analysis of Guardant360 results was performed among ctDNA samples of mCRC patients from September 2014 to May 2021. A variant was defined as clonal if the mutant allele frequency (MAF) was greater than 50% of the highest somatic MAF in the sample; otherwise it was defined as subclonal. A previously validated anti-EGFR exposure score was applied to predict prior anti-EGFR therapies. Co-mutation analysis was conducted with *BRAF*, *KRAS*, *NRAS*, *NF1*, *ERBB2*, *PIK3CA* and *SMAD4*. **Results:** 1,733 out of 14,742 mCRC patients had at least one *BRAF* variant, including 6.5% of patients with *BRAF* V600 variants, 1.1% with class II variants, 1.9% with class III variants, and 3.2% with unclassified variants. 431 unique BRAF variants were identified in a total of 1,905 BRAF variants. 70.7% of *BRAF* V600 variants were clonal while most (56.0%-78.8%) class II, III and unclassified *BRAF* variants were subclonal (Table). Patients with non-*BRAF* V600 variants tend to be younger and male. The prevalence of *BRAF* class II and III variants were higher (2.1% and 3.7%) in patients with predicted prior anti-EGFR exposure compared with patients predicted to have no prior exposure (0.8% and 1.4%). *BRAF* variants of all classes are more likely to be subclonal in patients predicted to have anti-EGFR exposure than those predicted nonexposed ($p < 0.05$ in all classes, Fisher's exact test). Among patients with non-*BRAF* V600 variants, a greater fraction of co-occurring KRAS and NRAS mutations were detected in those predicted to have prior anti-EGFR exposure. In the patients without predicted EGFR exposure, *BRAF* class II and III variants showed a higher rate of co-occurring *KRAS* mutations (25.6% and 21.5%) and co-occurring *NRAS* mutations (5.8% and 2.7%) compared with *BRAF* V600 variants (2.4% for *KRAS* and 0.1% for *NRAS*); however, co-occurring *KRAS* G12C was only noted in one patient with a *BRAF* class II variant. The analysis of outcome data by variant class will be presented at the meeting. **Conclusions:** We noted significant differences between *BRAF* V600 and class II/III variants using a large genomic database. Within *BRAF* class II and III variants, the enrichment in patients with predicted anti-EGFR exposure and the high fraction of co-mutations in *KRAS*/*NRAS* suggest a unique therapeutic need for these patients. Research Sponsor: None.

% of total BRAF variants (% of the class)	clonal	subclonal
V600	34.3% (70.7%)	14.2% (29.3%)
Class 2	3.2% (37.4%)	5.4% (62.6%)
Class 3	6.6% (44.0%)	8.3% (56.0%)
Unclassified	5.9% (21.2%)	22% (78.8%)

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Serial sampling of rectal tumors during radiotherapy: A proof-of-concept study.

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Background: Treatment response to neoadjuvant therapy in locally advanced rectal cancer (LARC) remains heterogenous. Clinicians are guided by pre-treatment clinical assessment alone in determining neoadjuvant strategy. More must be done to uncover biological mechanisms underpinning response and resistance. We have developed a biospecimen collection protocol in LARC performing serial sampling of tumors and peripheral blood samples prior to, during and after treatment to characterize the biological evolution of this heterogenous response. Here we present early proof of concept results with a focus on the intra-tumoral immune response relating to radiotherapy (RT). **Methods:** Patients receiving standard-of-care neoadjuvant RT were recruited to an ethically approved study between Dec 2018 - Aug 2021. The protocol consisted of a baseline biopsy and blood sample prior to RT followed by repeat sampling at 2, 6 and 12wks after Day 1 of RT. Standard immunohistochemistry (IHC) was performed for markers of immune activity. Target capture sequencing was performed using RNA baits extracted from serial biopsies to target a 276 genes panel. Paired tumor-normal sequencing was performed. Bulk 3' RNA seq (Lexogen Illumina Quantseq) characterized immune and inflammatory gene expression. A multiplex bead array (Luminex xPONENT) of 24 cytokines and chemokines was performed using serial plasma samples. **Results:** 17pts were recruited, 3 with stage IV disease. 14pts received chemoradiation and 3 pts had short-course based regimens. Treatment responses were evaluable in 14pts: graded complete in 2pts; good/ near complete in 7pts and partial/ poor in 5pts. All tumors were MSS, and most frequently mutated genes were *APC* (75%), *KRAS* (38%), *NRAS* (25%), *NOTCH1* (25%) and *PIK3CA (25%)* (n = 8). Quantseq demonstrated that the immune/ inflammatory response, as measured by interferon-gamma response and IL-6/ JAK-STAT signaling, was significantly elevated up to 12wks after Day 1 RT, with a peak at around 6wks (n = 3). Correlative IHC showed an increase in innate immune cells in pts with a favorable response at 6wks (n = 8). Cytokine/ chemokine analysis suggested patients with a favorable response demonstrated strong inflammatory (MCP1 & IL-17a) responses 2 and 6wks post-RT and strong CTL (Granzyme B) and Th1 (GM-CSF & IP-10) responses 12wks post-RT (n = 10). **Conclusions:** We show acquisition of meaningful genomic and transcriptomic material from serial biopsies in rectal cancer is possible. Early data suggest that dynamic profiling of rectal tumors demonstrates transcriptomic evolution during treatment. Specifically, we show that the immune response to radiotherapy peaks at around 6wks after initiation of RT and persists to 12wks. This supports ongoing trials of immunomodulatory treatments in combination with, and following, RT in rectal cancer. Further work is required to define differences between responders and non-responders. Research Sponsor: Beatson Cancer Charity.

The immune impact of PI3K-AKT pathway inhibition in colorectal cancer.

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Background: Our prior work has shown that PI3K-altered colorectal cancer (CRC), with PIK3CA mutation or PTEN loss, has increased expression of key immune checkpoints (including PD-L1) resulting in immune evasion, despite increased immune engagement. Here, we investigated the impact of PI3K-AKT inhibition on the immune repertoire of CRC. **Methods:** Multiplex immunofluorescence was performed using two Vectra panels [1: AE1/AE3, CD3, CD8, PD-1, PD-L1, CD68; and 2: AE1/AE3, CD3, CD8, Granzyme B (GzB), CD45RO, FoxP3] on paired biopsies (baseline and cycle 1 day 15) from 6 patients with PI3K-altered metastatic CRC (mCRC) treated with AKT inhibitor, MK2206 (200 mg oral weekly), on a phase 2 clinical trial. Separately, one million CT26 CRC cells were implanted in BALB/C-e mice. After 48 hours, 10 mice/group were randomized for treatment with pan-PI3K inhibitor copanlisib (C, 10 mg/Kg IV 2x/week), anti-PD-1 (P, 200 μg IP 2x/week), copanlisib + anti-PD-1 (C+P), or control (Ct), for 21 days. Mouse tumors were stained with 6-plex immunohistochemistry (CD3, CD8, PD-L1, Ki67, GzB, AE1/AE3). Data were analyzed using related-samples Wilcoxon Signed-Rank test, Mann-Whitney U test, Kruskal-Wallis test, and Student's t-test, as appropriate. **Results:** In PI3K-altered mCRC patients, AKT inhibition resulted in a trend towards increased median densities of intratumoral $CD8^+$ T cells (0.8 vs 4.8 density/mm^2, P = 0.14) and memory T cells (0 vs 10.3, P = 0.07), and decreased density of macrophages (12.4 vs 0, P = 0.07). No antigen experienced T cells were seen and activated $CD8^+$ T cells were present in 1 patient only. In CT26 mice, PI3K and PD-1 co-inhibition resulted in the smallest mean tumor volumes (C+P 12% of Ct vs C 40% and P 42% of Ct, $P < 0.05$ for both), and the highest median % of intratumoral $CD8^+Ki67^+$ T cells as compared to all other treatment arms (C+P 1.6% vs C 0.5%, P 0.4%, Ct 0.6%, $P < 0.05$ for each pairwise comparison). C+P also increased the % of total $CD3^+$ and $CD8^+$ cells as compared to Ct and C ($P < 0.05$ for all). C alone did not increase immune infiltration in this non-PI3K activated model. **Conclusions:** PI3K-AKT pathway inhibition has the potential to improve effector T cell infiltration in PI3K-altered CRC. PI3K inhibitor synergizes with anti-PD-1 to improve treatment efficacy and $CD8^+$ T cell proliferation. The mechanisms behind this immune repertoire shift are yet to be elucidated, such as via cytokine modulation. Therapeutic approaches to activate the proliferating $CD8^+$ cells would be useful, and may require PI3Kα/β specific inhibitors to allow early T cell activation through PI3Kδ/γ isoforms. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

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Transcriptomic profiling to identify subsets of immune hot locally advanced rectal adenocarcinomas with favorable outcomes after neoadjuvant treatment.

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Background: Understanding the role of the tumor microenvironment in the response to chemotherapy and radiation in patients with locally advanced rectal cancer (LARC, stage II-III) can lead to the identification of novel immunologic biomarkers to preselect patients who can avoid surgery and benefit from watch-and-wait strategies. **Methods:** We performed DNA and RNA sequencing of pre-treatment biopsies from 89 LARC patients who received neoadjuvant therapy, including 5 microsatellite unstable (MSI) and 84 microsatellite stable (MSS) patients. We computed single-sample gene set enrichment analysis (ssGSEA) scores for immune infiltrates and signaling pathways implicated in tumor progression. Immunofluorescence and hematoxylin-eosin staining of tumor slides was performed to confirm significant correlations with RNA-Seq estimates of immune markers. Other genomic variables were also included in the analysis, such as tumor mutational burden (TMB), fraction of genome altered by copy number changes, whole genome duplication events and somatic mutations in rectal cancer driver genes and pathways. Results were largely replicated using an independent cohort of 42 LARC samples with publicly available data from The Cancer Genome Atlas (TCGA). **Results:** Since MSI tumors are known to have a distinct immunologic profile, we separated them into their own group and performed unsupervised hierarchical clustering on the MSS tumors. We identified a set of immune hot MSS tumors (n = 7) with extensive immune infiltration. These tumors had low TMB and were predominantly classified as CMS4 (5/7). None of the 12 patients in the combined MSI and immune hot MSS groups recurred during the length of our study and they had response rates $>$ 50% (vs. $<$ 25% in the rest of MSS patients). MSI and immune hot MSS tumors had lower frequency of TP53 and APC mutations, and they exhibited increased levels of T cell infiltration. In particular, we observed overexpression of markers for Th1 cells, which produce inflammatory cytokines (e.g., IFN-gamma) and are associated with antitumor immunity. Genes encoding protein targets of immune checkpoint blockade, such as PDCD1 (PD-1), CD274 (PD-L1), CTLA4, HAVCR2 (TIM3) and LAG3, were also overexpressed in the immune hot MSS and - to a lesser extent – the MSI tumors, suggesting that these patients might benefit from the use of immune checkpoint inhibitors. **Conclusions:** Our results uncover a unique LARC tumor immune profile evident in the pre-treatment setting that could be used to better prognosticate rectal cancer patients and develop novel therapeutic strategies. Research Sponsor: U.S. National Institutes of Health.

Hippo pathway signaling associated with immune cell trafficking in colorectal cancer.

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Background: Emerging evidence suggests subsets of the Hippo pathway have multiple functions of tumor development and immune response regulation. Increased understanding of the molecular characteristics of its signaling pathways and the impact on immune cell trafficking will be critical to develop colorectal cancer (CRC) therapies. **Methods:** A total of 13,008 CRC tumors were analyzed at Caris Life Sciences (Phoenix, AZ) with whole transcriptome and whole exome sequencing (NovaSeq). MSI-H/dMMR was tested by NGS (next generation sequencing), immunohistochemistry (IHC), and fragment analysis. Tumor mutational burden (TMB)-High was determined with a 10-mt/MB cutoff. RNA-deconvolution using QuantiSEQ was used to assess immune cell infiltration in the tumor microenvironment. Consensus molecular subtypes (CMS) were developed using RNA expression data. Gene expression was reported as transcripts per million. Z-score totals of 6 core Hippo genes were calculated in groups: *MST1+STK3* (G1), *LATS1+LATS2* (G2), *YAP1+WWTR1* (G3), and all 6 genes together (G4). Tumors with bottom quartile (QL) z-scores were compared with the top quartile (QH) using χ^2/Fisher-Exact test and adjusted with the Benjamini-Hochberg method: adjusted $p < .05$ was considered significant; unadjusted $p < .05$ trending. **Results:** Gene expression levels were significantly positively correlated with each other (Spearman rho: 0.30–0.78). Highest expression levels of G1–4 were seen in CMS4 and lowest in CMS3 with significant differences. MSI-H/dMMR were significantly higher in QL than QH in all (G1: 7.4 vs 4.9%, G2: 7.4 vs 4.5, G3: 8.7 vs 4.1, G4: 7.5 vs 4.5). TMB-H prevalence (%) showed inverse relationships with MSI-H significantly in G1–3 (G1: 10.7 vs 7.5, G2: 10.5 vs 7.1, G3: 12.7 vs 6.2) and trending in G4 (11.0 vs 7.0, $p = .006$). Considering only MSS tumors, TMB-H trended more often in QL than QH in G1, 3, and 4 (3.6–3.7 vs 2.2–2.6). PD-L1 expression by IHC was significantly higher in QH than QL in all (5.3 vs 3.3%) and MSS tumors (2.2 vs 4.2) only in G3. Z-scores of G1–4 were all positively correlated with immune cell infiltrations. Significantly higher fractions of B cells, M2 macrophages, myeloid dendritic cells, NK cells, neutrophils, and $CD8^+$ T cells were seen in QH than QL with a median fold change of 1.39. G1–4 z-scores all positively correlated with the expression of the analyzed immune-related genes. The highest Spearman rho averages were in *HAVCR2* (0.54), *CD86* (0.54), *CD80* (0.53), *PD-L2* (0.5), *CD274* (0.46), and *LAG3* (0.36). Significantly different mutation rates were seen in QH compared to QL in G1 (*TP53, KRAS, PIKCA, SMAD2, AMER1*), G2 (*APC*), G3 (*PIK3CA, APC*), and G4 (*TP53, PIK3CA, KRAS*). **Conclusions:** The Hippo pathway correlated with immune cell trafficking suggesting that *YAP1/TAZ* signaling may play a critical role in the immune responses. These findings may help develop novel therapeutic strategies targeting the Hippo pathway combined with immune therapies in CRC. Research Sponsor: None.

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Impact of preoperative chemoradiotherapy (CRT) on the rectal tumor microenvironment (TME) and associated patient outcomes.

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Background: Pembrolizumab did not improve neoadjuvant rectal score when added to neoadjuvant CRT in the NRG-GI002 study. The impact of CRT on TME in patients (pts) with rectal cancer (RC) has not been well characterized. **Methods:** We performed a paired analysis on RC tissue taken pre- and post-CRT from pts undergoing long course CRT with a fluoropyrimidine followed by surgery. Samples underwent next-generation sequencing (NGS) and whole transcriptome RNAseq. Ingenuity Pathway Analysis (IPA), Molecular Signature Database (MSigDB), and xCell algorithm were used to dissect TME changes pre/post-CRT. **Results:** Specimens from 61 pts with MSS-RC were identified: median age, 61y, 75% white, 18% black, and 57% male. Tumor samples from 57 pts underwent NGS: 43 pre-CRT, 48 post-CRT, and 34 paired. A total of 2,642 differentially expressed genes (DEGs) were identified between pre/post CRT tumors and then grouped into 3 main gene sets (GS): "higher eukaryotes transcription factor (E2F) target", "G2/M cell cycle checkpoint", and "Immune/Stress". The 3 GS are mutually exclusive, indicating different cellular processes in response to CRT. E2F and G2/M gene signatures were specifically enriched pre-CRT ($p < 0.0001$), indicating that treatment alters cell survival, proliferation, and tumor growth. Cell death and apoptosis ($p < 0.0001$) and the Immune/Stress set, including stromal stress response ($p = 0.0004$), tissue repair ($p = 0.0025$), and leukocyte production ($p < 0.008$), were significantly enriched post-CRT. The xCell algorithm used to assess alteration stromal vs immune response by CRT; Stromal scores increased by 0.100 ± 0.016-fold, while Immune scores increased by 0.047 ± 0.017 ($P = 0.015$), suggesting a rise in Immune/Stress GS is driven mainly by stromal stress response. The 5 most common gene types upregulated post-CRT were smooth muscle cells, fibroblasts, interstitial dendritic cells, pericytes, and hepatic stellate cells. However, immune alterations trended downward (NK, Th1, and gamma delta T cells) or rose heterogeneously, e.g., a rise in intra-tumoral CD8 T cell subsets (effector, effector memory, or central memory) occurred for 8/35 pts. Fifteen pts (42%) relapsed and/or died after surgery. While CD8 T cell infiltration tends to be associated with better prognosis, it was not statistically significant ($p = 0.2277$; HR 2.709). CD8 T cell infiltrates were associated with higher prevalence of immune checkpoint transcripts LAG3 ($p = < 0.0001$) and to a lesser extend PD1 ($p = 0.0186$) in the tumor, indicating an anergic state of CD8 T cell infiltrates post-CRT. **Conclusions:** TME of RC tumors mainly identified stress/ wound healing response to CRT. Immune response was heterogeneous among pts; a subset showed a significant rise in CD8 T cell infiltration, indicating an anergic state mainly driven by LAG3. The potential of this pt subset to respond to anti-LAG3 immunotherapy is worthy of further study. Research Sponsor: None.

LBX2 expression and outcomes in patients with colon adenocarcinoma.

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Background: Colon adenocarcinoma (COAD) is one of the most common gastrointestinal cancers worldwide. Previous studies found that Ladybird homeobox 1 (LBX1) and Ladybird homeobox 2 (LBX2), were involved in the progress of several types of cancer. However, studies on their roles in cancers, such as COAD, are very limited. Thus, this study was performed to explore their roles in COAD. **Methods:** RNA-sequencing FPKM data and corresponding clinical information of 480 tumor tissues of COAD and 41 normal tissues were obtained from The Cancer Genome Atlas (TCGA). The 'limma' package was used to compare the expression differences of LBX1 and LBX2 between the normal and cancer tissues using Wilcoxon rank-sum test. Analysis of overall survival (OS), disease specific survival (DSS), and progression free interval (PFI) were conducted by Kaplan–Meier (K–M) method via 'survminer' package. Univariate Cox hazard regression analysis of OS was applied to five clinicopathological variables from T stage, N stage, M stage, pathologic stage, CEA level, as well as the expression level of family members of LBX that are overexpressed and associated with worsening survival outcomes, by using 'survival' package. Furthermore, a nomogram was also visualized by the R 'rms' package and 'survival' package to predict the 1-, 3-, and 5-year OS and individual predictors. **Results:** The expression of LBX2 ($p = 8.1e-20$) was upregulated in COAD tissues compared with normal tissues, while no statistically significant difference of expression between normal tissues and tumor was found for LBX1 ($p = 0.06$). Further survival analysis found that higher expression of LBX2 was associate with worse OS (HR = 2.45, 95%CI 1.62-3.71, $p < 0.001$), DSS (HR = 2.34, 95%CI 1.39-3.96, $p = 0.001$), and PFI (HR = 1.48, 95%CI 1.04-2.10, $p = 0.03$). Univariate Cox hazard regression analysis showed that N1, N2, N3, M1, pathologic stage III and IV, CEA level>5, and high expression level of LBX2 were associated with worse OS (all $p < 0.05$). The nomogram based on six clinicopathological variables (T stage, N stage, M stage, pathologic stage, CEA level, and LBX2 expression level) and 1-, 3-, 5-year OS probabilities were developed, with concordance index (C-index) of 0.795(0.755-0.834), indicating its prediction value and sufficient discrimination ability, as C-index was more than 0.7. The calibration curves of 1-, 3-, and 5-year demonstrated the consistency of our results and the predictive values, indicating satisfactory performance for this nomogram. Moreover1-, 3-, 5-year AUCs of LBX2-based nomogram were 0.805, 0.831, and 0.774, showing a moderate accuracy. **Conclusions:** LBX2 are upregulated in COAD tumor samples, and its higher expression is associated with worsening OS, DSS, and PFI. The LBX2-based monogram developed by this study might help predict the OS possibilities for COAD patients. LBX2 can be a potential diagnostic and prognostic marker, and therapeutic marker in COAD. Research Sponsor: None.

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CLK2 upregulation and outcomes for males with colorectal adenocarcinoma.

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Background: Colorectal adenocarcinoma (COAD) is a common cancer in gastrointestinal tract. CDC-like kinase (CLK) family, containing four characterized isoforms (CLK1-4), have been reported for their roles in precursor-mRNA splicing. However, studies on their roles in COAD are limited. Thus, this study was performed to explore the roles of CLK family members in COAD. **Methods:** RNA-sequencing FPKM data and corresponding clinical information of 41 normal tissues and 480 tumor tissues of COAD were obtained from The Cancer Genome Atlas (TCGA). Then expression differences of CLK family between the normal tissues and COAD cancer tissues were compared with Wilcoxon rank-sum test via 'limma' package. Overall survival (OS) of upregulated CLK family members was analyzed by Kaplan–Meier (K–M) method via 'survminer' package. Subgroup analyses of different genders were also conducted. The best discriminate cut-off point between the high and low expression groups was assessed by the receiver operating characteristic (ROC) curve and area under the curve (AUC) values for upregulated CLK family members via 'pROC' package to assess their diagnostic values. **Results:** The expression of CLK1 and CLK2 were upregulated in tumors compared with normal tissues ($p < 0.001$), while CLK3 were downregulated in tumor tissues ($p = 0.02$) and no statically significant difference was found regarding CLK4 ($p = 0.25$). Higher expression of CLK1 was not associated with a change of OS (HR: 1.24, 95%CI: 0.84-1.83, $p = 0.279$), while higher expression of CLK2 is associated with worse OS (HR: 2.03, 95%CI: 1.34-3.06, $p = 0.001$). Subgroup analysis found that higher expression of CLK2 was associated with worse OS (HR: 2.28, 95%CI 1.27-4.08, $p = 0.006$) in males, but not in females (HR: 1.72, 95%CI 0.95-3.10, $P = 0.072$). Further analysis of ROC curve shown that AUC of CLK1 and CLK2 were 0.748 (0.687-0.809) and 0.884 (0.840-0.928), respectively. **Conclusions:** CLK1 and CLK2 are upregulated in COAD tumor samples, and higher expression of CLK2 in male COAD patients is associated worse OS. This demonstrated the potential therapeutic value of CLK2 in male patients with COAD. ROC curve indicated the potential diagnostic value of CLK1 and CLK2. Research Sponsor: None.

Frequency, molecular characteristics, and therapeutic targeting of *ROS1* oncogenic fusions in colorectal cancer.

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Background: c-Ros oncogene 1, receptor tyrosine kinase (*ROS1*) rearrangements have been reported in colorectal cancer (CRC), but little is known about the molecular and clinical features of *ROS1*-driven CRC and the response to *ROS1*-targeted treatment in CRC patients. **Methods:** We report disease course and treatment response of an index patient with chemotherapy-refractory right-sided metastatic CRC, harboring an activating *ROS1* fusion (*GOPC-ROS1*). Moreover, we examined 40,589 patients with CRC who underwent comprehensive genomic profiling as part of routine clinical care at Foundation Medicine (Cambridge, MA); all classes of alterations in at least 324 genes were assessed, including *ROS1*. **Results:** The index patient experienced a rapid and sustained partial response to molecularly targeted treatment with crizotinib. After 15 months on crizotinib, disseminated tumor progression occurred, with KRAS Q61H emerging in tumor tissue (53.7% variant allele frequency (VAF)) and liquid biopsy (13.5% VAF). Within the clinical cohort, *ROS1* genomic rearrangements (*ROS1* RE (+)) were identified in 34 out of 40,589 (0.08%) CRC samples. *GOPC-ROS1* was the most commonly identified *ROS1* fusion (11/34 samples), followed by *TTC28-ROS1* (3/34 samples). All *ROS1*-alterations were found in microsatellite-stable (MSS) CRCs, and *ROS1* genomic alterations were significantly enriched in *KRAS* wild type tumors (*KRAS* mutations in 23.5% of *ROS1* RE(+) vs. 49.8% of *ROS1* RE(-), p=0.003). **Conclusions:** *ROS1* rearrangements represent rare but clinically actionable molecular driver alterations in MSS CRCs. The detection of *ROS1* fusion oncogenes in CRC can pose diagnostic challenges since intrachromosomal *ROS1* fusions including *GOPC-ROS1* and non-canonical *ROS1* fusions such as *TTC28-ROS1* can remain negative on fluorescence in situ hybridization and immunohistochemistry assays, respectively. NGS-based comprehensive molecular profiling may be a useful tool to screen for rare fusion oncogenes. Research Sponsor: None.

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Plasma-informed minimal residual disease (MRD) assay: A multicenter prospective study in Japanese patients with stage II colorectal cancer.

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Background: ~80% of stage II colorectal cancer (CRC) can be cured by surgery alone. However, adjuvant chemotherapy is recommended for patients with high risk features such as bowel obstruction, < 12 lymph nodes examined and T4 tumors. Traditional pathological grading and biomarkers such as carcinoembryonic antigen has limited sensitivity. Several reports indicated circulating tumor DNA (ctDNA) may represent a promising prognostic factor to assess MRD as a factor for prediction of recurrence after surgery. Here, we present a proof-of-concept study for the development of a novel plasma-based highly sensitive Next Generation Sequencing (NGS) panel using SafeSEQ technology in operable CRC Japanese patients. **Methods:** This multicenter prospective study recruited patients diagnosed as operable clinical stage II CRC (n = 46) with pre- and post- (4~6 weeks) operative plasma samples collected between Nov, 2019 and Jan, 2021. ctDNA were extracted and a 14-gene NGS panel was used to analyze single nucleotide variants (SNVs) and Indels covered by gene-specific amplicons. MRD variant was defined as same variant detected in both pre- and post- operative plasma samples. Tissue NGS by a 500-gene panel was also performed in a small number of tissue samples (n = 5) to compare the concordance of plasma and tissue variants. **Results:** Pre- and post-operative ctDNA status of 46 patients were analyzed. ctDNA positive was observed in 69.6% (32/46, 95%CI 55.2, 81.0) pre- and 34.8% (16/46, 95%CI 22.7, 49.3) post- samples. *AKT1, CTNNB1, NRAS, POLE* and *PPP2R1A* mutation were not detected in this study. *TP53* mutation was most frequently detected in both pre- (22/46) and post- (11/46) samples, whereas *APC* mutation was ranked 2nd in pre- (15/46) but none in post- samples. A combined 96 variants were detected in all samples, in which 76 of them were < 0.5% mutant allele frequency (MAF). MRD variants were detected in 17.4% (8/46, 95%CI 8.82, 30.99) post- samples. Evaluation of positive percentage agreement between tissue and pre- plasma samples in three patients show that a total 7 variants detected in plasma, and 3 of them were detected in tissue samples. **Conclusions:** This study assesses the feasibility of a plasma-informed NGS panel by evaluating pre- and post- operative plasma samples. The presence of variants with < 0.5% MAF detected in this study indicate a highly sensitive method is required for accurate MRD detection. Further observation is required to explore the relationship between MRD variant and clinical outcome such as 2-year progression-free survival. Research Sponsor: Sysmex corp.

Evaluation of baseline *BRAF* V600E mutation in circulating tumor DNA and efficacy response from the BEACON study.

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Background: In the randomized phase 3 BEACON study, encorafenib + binimetinib + cetuximab (triplet) and encorafenib + cetuximab (doublet) regimens improved overall survival (OS) and objective response rate (ORR) versus standard of care (control) in patients (pts) with previously treated *BRAF* V600E-mutant metastatic colorectal cancer. To identify whether detection of a *BRAF* V600E mutation in baseline circulating tumor DNA (ctDNA) correlated with response, we evaluated the status and allele frequency of *BRAF* V600E compared with clinical outcomes. **Methods:** Plasma samples were collected at Cycle 1 Day 1 and end of treatment for ctDNA analysis and analyzed using GuardantOMNI. Variant allele frequency (VAF) of *BRAF* V600E was grouped into high ($>$ median) and low ($\leq$median) categories. Low VAF samples included those where *BRAF* V600E mutation was not detected or no ctDNA was detected. ORR, based on blinded independent central review, and OS were compared between treatment arms according to VAF levels. ORR comparisons used Chi-square test and logistic regression. OS was summarized using the Kaplan-Meier method. HRs and 95% CIs were estimated using a Cox model. Additional correlation analyses between *BRAF* V600E status in baseline tumor tissue, as well as clonality, will be presented. **Results:** Baseline plasma samples were analyzed from 544 of 631 pts in the ctDNA analysis: 88.3% (196/222) in the triplet arm, 86.6% (187/216) in the doublet arm, and 83.4% (161/193) in the control arm. *BRAF* V600E mutations were detected in 90.4% (492/544) of pts (90.3% [177/196] triplet, 90.4% [169/187] doublet, and 90.7% [146/161] control). Pts with *BRAF* V600E mutations with high VAF had significantly ($P \leq 0.0001$) increased ORR (95% CI) in the triplet and doublet arms (27.3% [19.5–36.8] and 15.9% [9.7–25.0], respectively) compared with control (0% [0.0–4.3]). Similar response trends were observed in pts with *BRAF* V600E mutations with low VAF (triplet: 28.9% [20.8–38.9]; doublet: 25.3% [17.7–34.6]; control: 5.3% [2.1–12.8]). OS decreased in *BRAF* V600E pts with high VAF (median OS [95% CI]: triplet 7.2 [6.0–8.0] months, n = 99; doublet 5.4 [4.4–6.1] months, n = 88; control 4.2 [3.4–4.8] months, n = 85) compared with pts with low VAF (triplet 14.8 [10.2–19.8] months, n = 97; doublet 14.8 [11.7–23.0] months, n = 99; control 9.3 [7.5–11.3] months, n = 76). **Conclusions:** ctDNA analyses showed the majority of pts in BEACON analyzed at baseline had a detectable *BRAF* V600E mutation. Increased response rates were observed in pts treated with triplet or doublet therapy compared with control, independent of VAF. Pts with a higher VAF for *BRAF* V600E may have a worse prognosis. Clinical trial information: NCT04607421. Research Sponsor: Pfizer.

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Analysis of 16S rRNA sequencing in advanced colorectal cancer tissue samples.

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Background: Changes in the colon's microbiota composition are contributors to the pathogenesis of colorectal cancer (CRC). Features of this microbiome may have prognostic significance. For this study, we analyzed 16S rRNA sequencing data from tumor tissue samples of advanced CRC patients and determined if there were potential correlations between microbiome composition and clinical outcomes. **Methods:** One hundred and thirty three advanced CRC patients in St. Vincent's Hospital in Korea were enrolled. DNA was extracted from collected tissue samples, the V3-V4 regions were amplified, and a 16S rRNA gene amplicon library was prepared using an Illumina protocol. DNA was sequenced on an Illumina MiSeq instrument. We used three different bioinformatic packages to process the sequence data and evaluate the microbiome composition of each tumor. **Results:** The classification performances of three different analytic pipelines (Kraken2, QIIME2, and DADA2) were compared in a microbiome control sample. Among these, DADA2 and QIIME2 were chosen for use in subsequent analysis, due to their lower Chi-square ($\chi 2$) test statistic values on the control data. After excluding samples that retained less than 5% of total reads after merging, 120 samples were analyzed. The median age of the cohort was 63 years, 63.3% were male, and all were Korean. The distribution over primary sites was 27.5% from the right-side colon, 30.8% from the left-side colon, and 41.7% from the rectum. All subjects received the first line of systemic treatment. The median progression-free survival time was 8.9 months. Twenty-nine patients (24.2%) survived more than 24 months. When examining the results from the two bioinformatic packages, pairwise comparisons showed positive correlations in the relative abundances of the top 20 genera. Fusobacterium, a microbe known to relate to pathogenesis and prognosis of CRC, was not detected by QIIME2. Stratifying by primary site, rectal cancers showed higher alpha diversity than left- or right-side colon cancers. Separately, a higher serum CEA level (≥ 8) at diagnosis, and the presence of lung metastasis were both found to be related to higher alpha-diversity, a global indicator of microbiome composition. When excluding minimally abundant ($< 1\%$ per patient) genera, beta-diversity was found to be differentiable by T stage, the presence of lung metastasis, and the presence of liver metastasis. Most notably, beta-diversity differed between patients who survived more than two years and patients who died within 2 years. Using the DADA2 results, we confirmed that the presence of Fusobacterium nucleatum in CRC tissue was found to be a strong predictor of poor overall survival (OS), along with old age and liver metastasis. **Conclusions:** This study suggests potential associations between microbiome composition and clinical parameters of advanced CRC. Microbial biomarkers may be a valuable prognostic tool in this population. Research Sponsor: the Clayville Foundation and the Fund for Innovation in Cancer Informatics.

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Use of ascites CEA as a predictive value for distant metastasis in high-risk stage II and III colorectal cancer.

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Background: Adjuvant chemotherapy in patients with high-risk stage II and III colorectal cancer prevents recurrence by eliminating minimal residual disease. However, patients who are at high risk of recurrence after completing standard adjuvant therapy are currently unknown. Although ascites CEA level has been associated with long-term oncologic outcomes, the clinical significance of ascites CEA in high-risk stage II and stage III colorectal cancer (CRC) has not yet been described. The present study aimed to determine the long-term oncologic impacts of ascites CEA level after curative colorectal cancer. **Methods:** A total of 191 patients with stage II/III CRC were included in this study, between January 2015 and December 2018. CEA of peritoneal fluid sampled at the beginning of each operation was analyzed. long-term oncologic outcomes were analyzed with the known risk factors for recurrence in CRC. **Results:** Multivariate analysis of recurrence revealed that lymphatic invasion (HR 6.0, 95% CI 1.1–32.0, p = 0.04), vascular invasion (HR 2.9, 95%CI 1.0–8.0, p = 0.04), mucinous cancer (HR 5.5, 95% CI 1.6–18.4, p = 0.006), and peritoneal fluid CEA above 5 ng/dl (OR 4.2, 95% CI 1.2–15.0, p = 0.008) were significant risk factors (Table). Peritoneal fluid cytology, microsatellite instability, cancer obstruction did not significantly impact DFS in stage II/III CRC. There were 14 patients with liver metastasis, among them, 11 patients without peritoneal metastasis; they had high ascites CEA level. While 8 patients had lung metastasis, 7 of them confirmed high ascites CEA levels. **Conclusions:** Our results indicate that the ascites CEA may predict as an important biomarker to identify those at risk of distant metastasis in high-risk stage II and stage III CRC patients. We suggest ascites CEA analysis might be included in patient risk assessments and oncologic prediction tools. Research Sponsor: None.

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Spatially resolved transcriptomics deconvolutes histological prognostic subgroups in patients with colorectal cancer and synchronous liver metastases.

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Background: Up to 50% of patients with Colorectal Cancer (CRC) will metastasise to the liver (CRLM). KRAS-mt liver metastases particularly when co-mutated with TP53 are associated with poor prognosis. We have used the Glasgow Microenvironment Score (GMS), a histological score performed on H+E slides utilising immune and stromal components of the microenvironment to robustly stratify outcome in primary CRC. The aim of the current study was firstly to determine the utility of GMS in metastatic CRC and secondly to employ the NanostringTM GeoMx Digital Spatial Profiler (DSP), a state-of-the art analysis platform enabling spatial transcriptomic characterisation while maintaining tumour microenvironment (TME) topographical features, to interrogate the functional biology underlying the GMS. **Methods:** FFPE specimens from primary and metastatic lesions from 44 patients undergoing synchronous resection of CRLM underwent GMS, IHC and panel genomic assessment. Primary endpoints were recurrence-free survival (RFS) and cancer-specific survival (CSS). In addition to bulk transcriptomic assessment, 4 matched pairs from the cohort were selected for GeoMx analysis: 2 samples were GMS0 (high-immune) and 2 were GMS1 (low-immune) with an equal distribution of KRASmt and wt. After multiplex IF staining (PanCK, CD45, DAPI, αSMA), 48 regions of interest were selected and Cancer Transcriptome Atlas Transcriptomic outputs (2000 genes) were analysed using Pathway enrichment analysis with immune deconvolution of the transcriptome performed. **Results:** GMS0 (high-immune) was associated with improved RFS (p=0.0048) and CSS (p=0.0012) remaining an independent predictor of survival on multivariate analysis (HR 2.90, 95% C.I 1.18-7.16 P=0.021). GMS0 lesions were enriched for adaptive immune (NES=2.20 p.adj<0.0005) and IL-10 (NES=1.9 p.adj<0.0005) pathways specifically at the invasive edge. In contrast, a poor prognostic KRAS/TP53 lesion demonstrated profound immunosuppression, upregulated NOTCH signalling (NES=2.13 p.adj<0.0005) and neutrophil degranulation (NES=1.99 p.adj<0.0005). Topographical Immune-cell deconvolution demonstrated significantly higher populations of CD4 (p=0.05) and CD8 (p=0.0003) cells in GMS0 leading edges. **Conclusions:** We have demonstrated that spatial transcriptomic analysis using the Nanostring GeoMx tool can reveal potential novel mechanisms underlying biologically relevant histological and mutational subgroups (KRAS-mt) of CRC, providing potential therapeutic targets requiring further investigation. Future studies will apply this technology to pre and post treatment biopsy samples. Research Sponsor: CRUK grant.

Reproducibility of lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in patients with locally advanced rectal cancer.

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Background: Rectal cancer constitutes over one-third of all colorectal cancers (CRC) and is one of the leading cause of cancer-related death in developed countries. Treatment modalities applied in locally advanced tumors differ substantially among research centers. In order to identify high-risk patients and better adjust the therapy new markers are needed. Systemic inflammatory response (SIR) markers such as LMR, NLR and PLR have been proved highly prognostic in many malignancies, including CRC; however, they lack proper validation. In our study we assessed the reproducibility of LMR, NLR and PLR. **Methods:** Sixty patients with locally advanced rectal cancer treated in Maria-Sklodowska Curie National Institute of Oncology in Warsaw, Poland between 08.2017 and 12.2020 were prospectively enrolled in the study. Three consecutive blood morphology tests of each patient within a median period of 21 days were obtained before start of the treatment. **Results:** LMR, NLR and PLR calculated at two time-points were correlated with the coefficient of 0.776, 0.696 and 0.751 ($p < 0.005$ in all measurements), respectively. Patients were divided into LMR, NLR, PLR-high and low groups. If LMR at the first test was out of the range of 2.2-3.0 (+/- 0.4 from the cut-off) the risk of misclassification in the second measurement defined as an affiliation to a different (high or low) group than initially was 5.0% (95% CI 1.0-13.9%). In case of NLR, when outside of the range of 2.5-3.5 (+/- 0.5) it was 8.3% (95% CI 2.8-18.4%) and PLR outside of the range of 125-175 (+/- 25) 10.0% (95% CI 3.8-20.5%). Mean percentage change between the third and the first measurement of lymphocytes, monocytes, neutrophils and platelets count ranged from -5.59% to 4.76% and the standard error from 2.0 to 3.9. **Conclusions:** In conclusion SIR markers are reproducible, easily obtained biomarkers with potential application in clinical practice. Research Sponsor: None.

Comparison of comprehensive genomic profiles between young-onset and average-onset colorectal cancer.

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Background: The incidence of young-onset colorectal cancer (yoCRC) is rising for unknown reasons. This study assessed for differences in comprehensive genomic profiles between yoCRC and average-onset colorectal cancer (aoCRC). **Methods:** All patients with CRC seen at Cleveland Clinic that had tumor-based next generation sequencing (NGS) performed as part of their care with a clinically available assay between January 2017 and September 2020 were included. The cohort was divided based on age of diagnosis, with yoCRC defined as age of CRC diagnosis $<$50 years old. All clinical data and genomic alterations were included for analysis. We assessed for differences in clinical data and NGS findings between yoCRC and aoCRC using Fisher's exact test, adjusted for primary tumor sidedness. Overall survival (OS) by genomic alteration was estimated by Kaplan-Meier methods and compared using log rank test. **Results:** The study population comprised of 51 yoCRC patients and 211 aoCRC patients. There were no significant differences in sex, race or ethnicity between yoCRC and aoCRC patients. Compared to aoCRC patients, yoCRC patients were more likely to present at diagnosis with stage IV disease (81% vs. 56%, p = 0.02) and have left-sided primary tumors (69% vs. 60%, p = 0.26). YoCRC tumors were more likely to have mutations in APC, KRAS, TP53 and FLT3 compared to aoCRC tumors, independent of tumor sidedness. These data are summarized in Table. Compared to left-sided tumors, right-sided tumors had significantly higher frequency of KRAS (67.7% vs. 48.8%, p = 0.003), BRAF (15.2% vs. 3.1%, p = 0.0006) and PTEN (16.2% vs. 3.1%, p value = 0.0003) alterations. AoCRC patients had significantly longer OS compared to yoCRC patients (median OS: 70.0 months vs. 36.3 months, p=0.004). Black (37.2 months, n=35) and Asian (37.8 months, n=7) patients had significantly worse median OS compared to White patients (67.8 months, n=199), p-value 0.005. In the overall population, patients with APC mutations had significantly better OS compared to those with APC wildtype tumors (median OS: 92.6 months vs. 54.4 months, p=0.001). Patients with FLT3 mutations had worse median OS compared to those with FLT3 wildtype tumors (median OS: 42.0 months vs. 64.8 months, p=0.007). There were no survival differences based on MSI status. **Conclusions:** In this series, yoCRC patients were more likely to present with stage IV disease and experienced worse OS compared to aoCRC patients. YoCRC patients were more likely to have mutations in APC, KRAS, TP53 and FLT3, independent of tumor sidedness. Mutations in FLT3 correlated with worse OS. Research Sponsor: Funding for this research was provided by Sondra and Stephen Hardis. Dr. Khorana acknowledges additional research support from the Sondra and Stephen Hardis Endowed Chair in Oncology Research.

Frequency of key genomic alterations divided by yoCRC and aoCRC. TMB: tumor mutational burden.

Gene	yoCRC (n=51)	aoCRC (n=211)	p value
APC	39 (76%)	122 (58%)	0.03
KRAS	32 (63%)	76 (36%)	0.0005
TP53	38 (75%)	108 (51%)	0.003
MSI-H	3 (6%)	6 (3%)	0.64
FLT3	6 (12%)	8 (4%)	0.004
PIK3CA	11 (22%)	27 (13%)	0.19
PTEN	5 (10%)	11 (5%)	0.33
TMB	2 (4%)	8 (4%)	0.88

Impact of postoperative integrated genomic and epigenomic signatures of circulating tumor DNA (ctDNA) on recurrence in resected colorectal cancer: Initial report of a prospective ctDNA monitoring study COSMOS-CRC-01.

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Background: Identifying molecular residual disease (MRD) using circulating tumor DNA (ctDNA) analysis after curative surgery can potentially stratify the recurrence risk and facilitate personalization of adjuvant treatment in patients with colorectal cancer (CRC). We conducted a prospective study "COSMOS-CRC-01" to evaluate the utility of a plasma-only ctDNA assay integrating genomic and epigenomic signatures. **Methods:** Patients with resectable clinical stage 0–III colorectal cancer were eligible. Plasma samples were collected at structured pre- and post-surgical timepoints and analyzed using Guardant Reveal, a plasma-only ctDNA assay that detects the presence of MRD by identifying somatic alterations and methylation signatures of cell-free DNA associated with colorectal cancer. **Results:** As of April 2021, 501 patients were enrolled in the COSMOS-CRC-01, of which 496 patients had their post-operative 4-week ctDNA status. In this analysis, we included the first 100 patients enrolled with clinical stage II or more CRC. Seven patients were excluded due to non-curative resection or pathological stage (pStage) IV. The assay was able to produce a result for all 93 samples analyzed (failure rate of 0%). MRD was detected in 23 (25%) patients 4 weeks after surgery. The MRD detection rate was 20% in pStage II disease and 29% in pStage III disease. Patients with positive MRD were older than those with negative MRD ($p = 0.0001$). Across all MRD positive samples, 30%, 9%, and 61% were positive by both genomic and epigenomic, only genomic, and only epigenomic calls. Genomic signatures included *APC*, *BRAF*, *KRAS*, and *TP53* mutations with the lowest variant allelic fraction of 0.04%. With a median follow-up time of 12.2 months (range 8-18 months), 9 of 93 patients recurred (9.7%). ctDNA was detected from a single 4-week post-surgical sample in 55% of patients who recurred (5 of 9). 1-year disease-free survival was 81.2% in patients with positive MRD and 93.9% in those with negative MRD (hazard ratio 3.49, 95% CI 0.93–13.10, $p = 0.049$). Multivariate analysis including baseline characteristics associated with recurrence risk showed that MRD status had the strongest association with the recurrence. Post-operative 4-week serum CEA level was not associated with risk for recurrence. **Conclusions:** While follow-up in this cohort is currently limited, the results suggest that a single post-surgery sample run on a plasma-only assay that integrates genomic and epigenomic signatures can more accurately stratify patients with CRC by recurrence risk than previously known clinical factors. Data from baseline and longitudinal timepoints will be reported as available along with longer term clinical follow-up. Clinical trial information: UMIN000037765. Research Sponsor: GUARDANT.

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Circulating nucleosomes for detection of colorectal cancer and high-risk advanced adenomas.

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Background: Detection and treatment of early colorectal cancer (CRC) or advanced adenomas (AA) is the key for superior outcomes and fecal immunochemical testing (FIT)-based screening has proven effective in reducing CRC death and the risk of advanced-stage CRC but the discrepancy in the effectiveness was observed between proximal and distal cancers. On the other hand, false-positive results of FIT with 60 % of negative colonoscopy is another concern, considering the burden to the screening participants and the healthcare providers. A blood-based test as an alternative or supplement to FIT has the potential to concurrently enhance the detection of high-risk neoplasms and identify individuals at risk who should then be referred to colonoscopy. We investigated the levels of circulating free nucleosomes containing different epigenetic modifications in patients referred for colonoscopy. **Methods:** 10mls whole blood was obtained from 520 asymptomatic patients prior to colonoscopy at National Taiwan University Hospital. Patients were classified into 5 groups based on their colonoscopy reports: (i) patient with CRC (n = 33), (ii) patients with AA (n = 123, including 18 with AA $>$ 2cm); (iii) patients with non-AA (n = 168); (iv) patients with non-neoplastic polyps (n = 30); (vi) healthy controls with no endoscopic lesion (n = 166). Plasma samples were analyzed for nucleosome levels using 7 different quantitative immunoassays (Nu.Q assays; Belgian Volition SRL, Belgium) targeting H3.1-nucleosomes or different histone modifications (H3K27Me3-, H3K36Me3-, H3K9Me3-, H3K14Ac-, H3K27Ac- or H3R8Cit-nucleosomes). All study subjects were asked to collect a stool sample at home within 48-hours before the colonoscopy. The fecal samples were assayed with the Eiken OC-SENSOR FIT kit (Eiken Chemical Co., Ltd., Tokyo, Japan) for all study subjects. **Results:** At a cut-off of 20μg/g feces, the FIT test showed a sensitivity of 92,9% at 17.5% specificity for CRC +AA vs. Controls. All the CRC patients and 83.3% of the high-risk AA ($>$ 2cm) patients were FIT positive. A combination of 2 Nu.Q biomarkers: H3K27Me3 and H3R8Cit with FIT in a logistic regression model showed improved sensitivity of 95% at 20.6% specificity allowing the detection of all CRC patients and 94.3% of AA patients including all the high-risk adenomas. The FIT test detected 46 out of 55 proximal adenomas whereas the combined model could detect 50 proximal adenomas including 3 proximal AA $>$ 2cm not being detected by FIT ($p < 0.05$). The same combination would reduce unnecessary colonoscopies by 21.8% of the control and 23.3% of the non-neoplastic polyps subgroups compared to 17.5% and 6.7%, respectively with the FIT test alone. **Conclusions:** Our results indicate that H3K27Me3 and H3R8Cit-nucleosome levels in combination with FIT could improve the detection of proximal high-risk AA and could also provide a non-invasive method to reduce unnecessary colonoscopy. Research Sponsor: Belgian Volition SRL.

Association of circulating nucleosomes levels with FIT performance for advanced adenomas in a symptomatic population.

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Background: The effectiveness of screening using either fecal immunochemical testing (FIT) or colonoscopy in reducing colorectal cancer (CRC) mortality has been demonstrated in previous studies. Nevertheless, the single test sensitivity of FIT for relevant precursor lesions, especially high-risk neoplasms like invasive cancer or advanced adenomas (AA), is a concern. Improving the sensitivity for high-risk neoplasm is critical to improving the effectiveness of screening in reducing CRC incidence and mortality. Dysregulation of histone post-translational modifications (PTMs) has been linked with several cancers including CRC. We investigated the clinical performance of circulating nucleosome levels containing specific histone PTMs in blood, in combination with FIT from symptomatic subjects referred to colonoscopy to evaluate their discriminant power towards CRC and AA. **Methods:** 10mls whole blood was obtained prior to colonoscopy from 476 patients referred to colonoscopy in National Taiwan University Hospital for surveillance or secondary to bowel symptoms. Patients were classified into 5 groups based on their colonoscopy reports: (i) patient with CRC (n = 67), (ii) patients with AA (n = 60, including 22 with AA≥2cm); (iii) patients with non-AA (n = 123); (iv) patients with non-neoplastic polyps (n = 29); (vi) healthy controls with no endoscopic lesion (n = 197). Plasma samples were analyzed for nucleosome levels using 7 different quantitative immunoassays (Nu.Q assays; Belgian Volition SRL, Belgium) targeting H3.1-nucleosomes or different histone modifications (H3K27Me3-, H3K36Me3-, H3K9Me3-, H3K14Ac-, H3K27Ac- or H3R8Cit-nucleosomes). All study subjects were asked to collect a stool sample at home within 48-hours before the colonoscopy. The fecal samples were assayed with the OC-SENSOR FIT kit (Eiken Chemical Co., Ltd., Tokyo, Japan) for all subjects. **Results:** At a cut-off of 20μg/g feces, the FIT test showed a sensitivity of 83.5% at 82.1% specificity for CRC +AA vs. Controls. All the CRC patients were detected but 35% of AA were missed, and 7 of which were high-risk adenomas (AA≥2cm). A combination of 2 Nu.Q biomarkers: H3K36Me3 and H3K9Me3 with FIT in a decision tree model showed an improved sensitivity of 98.4% allowing the detection of all CRC patients and 97% of the patients with AA including all high-risk adenomas. The 2 missed AA were one AA below 1cm and one between 1 and 2cm. Unnecessary colonoscopies could be reduced by 28.9% of the control and 20.7% of the non-neoplastic polyps subgroups as both are found negative with this panel of assays. **Conclusions:** At present, all the symptomatic patients are sent to colonoscopy in clinical practice. Our results indicate that H3K36Me3- and H3K9Me3-nucleosome levels, in combination with FIT in a decision tree model, could detect all CRC patients and all high-risk adenomas and help reduce unnecessary colonoscopies. Research Sponsor: Belgian Volition SRL.

Age-associated mutations in *RAS*-mutated versus *RAS*-nonmutated metastatic colorectal cancer.

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Background: Mutational profiling is recommended for selecting targeted therapy for metastatic colorectal cancer (mCRC). Evidence suggests that among patients with mutations in one of three *RAS* genes who underwent resection of liver metastasis, those with early onset mCRC had worse outcomes compared to those with late onset mCRC. The goal of this study was to explore whether other mutated genes in mCRC exhibit an association between age and wild type versus mutant *RAS* status. **Methods:** Between October 2018 and October 2020, 974 tumor samples from patients with mCRC were identified. Samples meeting requirements were profiled with the Oncotype MAP Pan-Cancer Tissue test, which sequences 257 genes from tumor tissue, including all 3 *RAS* genes (*HRAS*, *KRAS*, *NRAS*). Using the Oncotype MAP assay, single base variants, indels, copy number alterations and structural variants/fusions were identified. Tumor mutational burden (TMB) and microsatellite instability (MSI) were also determined. To identify genes for which there was an association between age group (patients ≤50 years vs >50 years) and *RAS* status we used Fisher's Exact Test. **Results:** Of the 974 samples, 840 met minimum tumor tissue requirements for DNA sequencing (3mm^2 and 15% tumor cellularity). Of these, 759 samples were successfully sequenced for NGS. Median turnaround time from the date of sample accessioning to the date of laboratory report was 5 days (interquartile range, IQR, 4-6 days). TMB varied from 0-227 mutations per megabase (median 6, IQR 4-8), and was high (≥10 mut/Mb) in 117 samples (15%). Of 775 specimens processed for MSI, 714 could be measured and approximately 7% were MSI-high. A total of 496 *RAS* variants were identified, of which 391 were pathogenic, likely pathogenic, or variants of unknown significance (349 *KRAS*, 34 *NRAS*, 8 *HRAS*). Of the 27 genes with at least 78 mutations in the data set, there was an association between *RAS* status and patient age for mutations at *SMAD4*, *ABCC1*, and *RICTOR* (Fisher's Exact test, $P < 0.05$). For all three, mutations at these genes are relatively more prevalent in samples from young *RAS* wild type patients compared to young *RAS* mutant patients (Table). **Conclusions:** The Oncotype MAP Pan-Cancer Tissue test identified numerous genomic changes in mCRC samples. There appears to be an association between age group and RAS status for three mutated genes, *SMAD4*, *ABCC1*, and *RICTOR*. The clinical implication is unclear and warrants further investigation with outcomes data. Research Sponsor: Exact Sciences Corporation.

Three genes appear to exhibit an association between *RAS* status (wild type vs mutant) and age (≤ 50 vs. >50).

GENE (# mutated)	Age ≤ 50	Age > 50
***SMAD4* (N=109)**		
***RAS* Wt**	7 (26.9%)	19 (73.1%)
***RAS* Mt**	6 (7.2%)	77 (92.8%)
***ABCC1* (*MRP1*) (N=85)**		
***RAS* Wt**	7 (21.2%)	26 (78.8%)
***RAS* Mt**	2 (3.8%)	50 (96.2%)
***RICTOR* (N=84)**		
***RAS* Wt**	7 (29.2%)	17 (70.8%)
***RAS* Mt**	5 (8.3%)	55 (91.7%)

Mt = mutated, Wt = wild type.

Rapid point of care NGS in colorectal cancer.

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Background: Next generation sequencing (NGS) is the laboratory cornerstone of precision oncology treatment. In advanced colorectal cancer (CRC), current guidelines recommend testing *RAS*, *BRAF* and MMR biomarkers as standard of care. The added value of comprehensive genomic profiling is so far unclear. Traditional NGS operations are complicated, requiring specialized equipment and personnel. In many jurisdictions, cancer patients are treated in publicly-funded community hospitals, where NGS is not typically utilized and access to testing via send-out services is associated with lengthy turnaround times. Here, we have validated and implemented one of the world's first "point of care" NGS services. Our early experience on NGS implementation and impact in CRC patients is described. **Methods:** All NGS studies were performed using the Oncomine Precision Assay (OPA) on the genexus integrated sequencer. NGS was performed at the request of the treating physician. All NGS was performed in a local community pathology lab by histotechnologists, simultaneously responsible for IHC testing (such as MMR) and interpreted by anatomic pathologists in conjunction with routine diagnostic pathology services. Retrospective chart review was performed for all patients undergoing sequencing studies and key data, including turnaround time and NGS findings were extracted from the electronic medical record for analysis. **Results:** A total of 51 cases with CRC were tested using point of care NGS from November 2020-August 2021, initiated by treating physicians. The median turnaround time for results was 3 days. Oncogenic driver events were identified in 46 (90%) cases, including canonical mutations in *KRAS*, *NRAS* and *BRAF* (Table). Actionable mutations were identified in 13 (25%) samples that would not have been identified with single-gene testing. **Conclusions:** Here, we show that comprehensive NGS can reveal occult resistance mechanisms to standard therapy and identify actionable biomarkers in a substantial proportion of patients with CRC. NGS added valuable information compared to guideline-recommended testing standards. Our study demonstrates that local testing can have rapid turnaround times. To our knowledge, this is the first report of "point of care" NGS in CRC. Further follow up is needed to explore the utility of these expanded roles for NGS testing. Research Sponsor: Eli Lilly, Pfizer, Thermo Fisher, Roche.

Actionable driver mutations identified in CRC cases (N=51).

Driver Mutation	Frequency (%)
KRAS	26 (50.9)
***KRAS* amplification**	5 (9.8)
BRAF	3 (5.9)
ERBB2	3 (5.9)
***ERBB2* amplification**	1 (2.0)
ERBB3	3 (5.9)
***ERBB3* amplification**	1 (2.0)
NRAS	1 (2.0)

The prevalence of common *KRAS* variants and associated outcomes in patients with metastatic colorectal cancer (mCRC).

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Background: *KRAS* is the most common driver oncogene in mCRC. Comprehensive analysis of *KRAS* variants prevalence and the relationship between variants and outcomes are lacking. Herein, we aimed to examine the impact of *KRAS* variants on outcomes in patients (pts) with mCRC. **Methods:** A retrospective review of pts with mCRC with known KRAS mutation status was performed. Fisher's exact test was used to analyze the association between *KRAS* variants. Cox Proportional Hazard modeling was used to study the relationship between *KRAS* variants and overall survival (OS). Kaplan-Meier method was used to assess OS. **Results:** A total of 423 pts diagnosed with mCRC from 2014-2020 with available extended KRAS status were evaluated. Median age at diagnosis was 59.8 yrs (22.3-92 range), 57% were male, 22% were Black, and 75% presented with de novo metastatic disease. A majority (56%) of tumors harbored *KRAS* mutations. The most frequent *KRAS* variants were G12D 47% (111), G12V 12% (28), G12C 13% (31), G13D 9% (21), and 20% (47) were other variants. In univariate analyses, the presence of a *KRAS* mutation, Black race, de novo metastatic disease, age, receipt of chemotherapy, and receipt of surgery were associated with OS. Tumor location was not associated with OS. In multivariable analyses, mutation type was a significant predictor of death and the presence of G12D was associated with an increased risk of death compared to G12V and *KRAS* wildtype. There was no increased risk of death in pairwise comparisons of G12D and G13D or other *KRAS* variants. Black race, de novo metastatic disease, and no receipt of surgery were additional independent predictors of death (Table). With a median follow-up of 25.7 months (mo.), median OS was 35.5 mo. (95% CI 10.5-50.9) with G12C, Not Reached (NR) (95% CI 21-NR) with G12V, 36.2 mo. (95%CI 14.9-58.5) with G13D, 26.2 mo. (95% CI 21.8-37) with G12D, 39.6 mo. (95% CI 22.4-47.9) for other *KRAS* mutations, and 59.6 mo. (95%CI 48.2-NA) for *KRAS* wildtype, respectively (p=0.0003). **Conclusions:** Our findings highlight differences in unadjusted overall survival when comparing G12D to some other *KRAS* variants. Codon and amino acid-specific mutations of *KRAS* should be considered when evaluating prognosis and further study on treatment effects and sequencing is warranted. Research Sponsor: None.

Multivariable analysis of prognostic factors and *KRAS* status in mCRC.

Variable	N, %	Hazard Ratio (95% CI)	*P-value*
***KRAS* G12C vs. G12D**	31, 7%	0.89 (0.52-1.51)	0.65
***KRAS* G12V vs. G12D**	28, 7%	0.48 (0.25-0.94)	0.03
***KRAS* G13D vs. G12D**	21, 5%	0.98 (0.54-1.77)	0.94
Other *KRAS* mutation vs. G12D	47, 11%	0.67 (0.43-1.06)	0.09
***KRAS* Wildtype vs. G12D**	185, 44	0.46 (0.33-0.64)	<0.001
Black vs. White Race	95, 22%	1.69 (1.24-2.31)	0.001
***De novo* vs. recurrent mCRC**	318, 75%	2.22 (1.52-3.24)	<0.001
Age*	60 (50-69)	1.01 (1.00-1.03)	0.010
No surgery vs. surgery	222, 52%	2.63 (1.95-3.54)	<0.001

*Median and interquartile range are reported.

Association of BRAF V600E mutation with survival in patients with metastatic mismatch repair-deficient colorectal cancer.

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Background: Colorectal cancer (CRC), while one of the most common cancer diagnoses, can behave heterogeneously based on molecular characteristics. A subset of patients (pts) with CRC are characterized with mismatch repair deficiency (MMR-d), these pts exhibit encouraging responses to immunotherapy. The predictive nature of various factors, such as BRAF status, age, and MMR-D protein loss type, have been investigated in pts with MMR-d CRC. However, the prognostic role of these factors has not been well established. The purpose of this study was to identify characteristics that influence survival in MMR-d mCRC. **Methods:** This study evaluated pts with MMR-d mCRC in the Flatiron database. Overall survival (OS) was determined from date of diagnosis of stage IV disease to date of death and stratified based on age greater than or less than 50 years, BRAF mutation status, RAS mutation status, and type of MMR gene loss. For statistical analysis, the Chi-Square test was implemented to determine the prognostic significance of clinical and molecular features. Univariate and multivariate analyses were determined through the Cox regression model. **Results:** There were 1,101 pts in the study. The majority of pts were older than 50 (79.7%), Caucasian (75%), and had ECOG 0-1 (83.4%). Among the 803 pts with known BRAF status, 44.3% (n=356) had BRAF V600E mutation and 55.7% (n=447) were BRAF wildtype. Pts with BRAF V600E mutation had OS of 18.9 months vs. 33.2 months for pts with wild type BRAF (HR 1.52, 95% CI: 1.25-1.86, $p<0.001$). Pts older than 50 had a lower median OS vs. those who were ≤ 50 at 21.4 months vs. 38.7 months (HR 1.66, 95% CI: 1.33-2.07, $p<0.001$). When comparing MSH2/MSH6 mutations to MLH1/PMS2, a trend towards improved OS was seen with median survival of 35.2 months vs. 22.7 months, respectively (HR 0.79, 95% CI: 0.61-1.02, p=0.067). On multivariate analysis, BRAF mutation and older age continued to be associated with differences in survival, while KRAS mutation and specific MMR gene loss did not. **Conclusions:** BRAF V600E mutation and age greater than 50 are associated with decreased survival for pts with MMR-D mCRC. KRAS mutations and specific MMR alterations are not associated with differences in survival. Research Sponsor: None.

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ENDOV upregulation and outcomes in females with colorectal adenocarcinoma.

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Background: Colorectal adenocarcinoma (COAD) is a common cancer in gastrointestinal tract. Endonuclease V (ENDOV), an enzyme with specificity for deaminated adenosine (inosine) in nucleic acids, was found to be involved in the development of certain cancers. Thus, this study was performed to explore the effects of ENDOV on the prognosis of COAD. **Methods:** RNA-sequencing FPKM data and corresponding clinical information of 41 normal tissues and 480 tumor tissues of COAD were acquired from The Cancer Genome Atlas (TCGA). Then ENDOV expression differences between the normal and cancer tissues were compared with Wilcoxon rank-sum test via 'limma' package. Overall survival (OS) and disease specific survival (DSS) analyses were conducted by Kaplan–Meier (K–M) method via 'survminer' package. Subgroup analyses of different genders were also performed. **Results:** The expression of ENDOV was downregulated in tumors compared with normal tissues ($p < 0.001$). However, higher expression of ENDOV is associated with worse OS (HR: 1.83, 95%CI: 1.23-2.73, P = 0.003) and DSS (HR: 1.75, 95%CI 1.06-2.91, P = 0.03). Subgroup analysis found that higher expression of ENDOV was associated with worse OS (HR: 2.17, 95%CI 1.18-3.98, P = 0.012) in females, but not in males (HR: 1.48, 95%CI 0.86-2.53, P = 0.158). As for DSS, higher expression of ENDOV was also correlated with worse outcome (HR: 2.36, 95%CI 1.07-5.19, P = 0.033) in females, but not in males (HR: 1.45, 95%CI 0.73-2.86, P = 0.287). **Conclusions:** ENDOV is overall downregulated in COAD tumor samples. However, higher expression of ENDOV in certain COAD patients is associated worse OS and DSS in females but not in males. This indicates the potential role of ENDOV in predicating the prognosis of COAD in female patients. Research Sponsor: None.

Genomic landscape of *ERBB2/3* alterations in colorectal cancer: Comutations, immuno-oncology biomarkers, and consensus molecular subtype.

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Background: *ERBB2* is a rapidly emerging therapeutic target for a subset of colorectal cancer (CRC) harboring oncogenic alterations in this gene. Oncogenic *ERBB3* mutations have been reported in various cancers including CRC, but little is known about its functional impact. Optimal targeting of this pathway requires understanding of the genomic context in which somatic *ERBB2/3* alterations (*ERBB2/3*-alt) occur in a real-world CRC population. **Methods:** We analyzed 7,688 de-identified records from CRC patients that underwent next generation sequencing with the TempuslxT assay (DNA-seq of 648 genes at 500x coverage, full transcriptome RNA-seq). We assessed the prevalence and association of *ERBB2/3*-alt with demographics, co-occurring alterations, immuno-oncology biomarkers (microsatellite instability [MSI], tumor mutational burden [TMB], PD-L1 expression), and consensus molecular subtype (CMS, available for the subgroup with primary biopsies and RNA data [n = 2,686]). **Results:** Overall, 5% (376/7688) of tumors harbored an *ERBB2* or *ERBB3*-alt. 1.9% (n = 143) *ERBB2*-amplified, 1.3% (n = 97) *ERBB2*-mutated, 0.9% (n = 72) *ERBB3*-mutated, < 1% other combinations (excluded from analyses). There were no significant differences in baseline demographics (e.g., age of onset, race and gender) between groups. Patients with *ERBB2/3*-alt were more likely to be MSI-high and TMB-high (Table). There was a trend towards higher prevalence of positive PD-L1 in *ERBB3*-alt vs *ERBB3*-WT tumors. We observed significant differences in co-occurring alterations among *ERBB2/3*-alt and WT groups (Table). CMS classification did not identify significant differences by *ERBB2*-alt or *ERBB3*-alt; *ERBB2*-alt compared to WT (CMS1: 8.6% vs 13%; CMS2: 24% vs 26%; CMS3: 20% vs 17%; CMS4: 30% vs 34%; $p = 0.12$) and *ERBB3*-alt compared to WT (CMS1: 24% vs 13%; CMS2: 12% vs 26%; CMS3: 16% vs 17%; CMS4: 40% vs 34%; $p = 0.3$). **Conclusions:** *ERBB2/3* mutated CRC are more frequently MSI-H, TMB-high and *KRAS* mutated than *ERBB2/3*-WT tumors. Correlation of *ERBB2/3* alterations with other genomic alterations including *BRAF*, *TP53*, *CDK12, PIK3CA, and TOP2A* will help advance the clinical development of HER2-targeted therapies. Research Sponsor: None.

	ERBB2 amplified (n = 143)	*ERBB2* mutated (n = 97)	*ERBB3* mutated (n = 72)	*ERBB2/3* WT (n = 7,312)	*p-value*
Immuno-biomarkers					
MSI-H	0 (0%)	12 (12%)	15 (21%)	404 (5.6%)	< 0.001
TMB ≥10	4 (3.0%)	17 (18%)	20 (28%)	675 (9.4%)	< 0.001
PD-L1+	4 (6.6%)	1 (3.3%)	3 (10%)	205 (7.5%)	0.8
Co-mutated Genes					
TP53	115 (80%)	59 (61%)	42 (58%)	4,234 (58%)	< 0.001
CDK12	101 (71%)	1 (1.0%)	0 (0%)	37 (0.5%)	< 0.001
KRAS	15 (10%)	48 (49%)	41 (57%)	2,764 (38%)	< 0.001
PIK3CA	12 (8.4%)	16 (16%)	20 (28%)	950 (13%)	< 0.001
BRAF	1 (0.7%)	5 (5.2%)	2 (2.8%)	525 (7.2%)	0.010
TOP2A	39 (27%)	0 (0%)	0 (0%)	5 (< 0.1%)	< 0.001

LRP1B and GRM3 expression in colorectal cancer.

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Background: LRP1B is a member of the low-density lipoprotein receptor family and a tumor suppressor found to be downregulated in colon cancer (CRC). GRM3 is a receptor of glutamate, an amino acid and neurotransmitter. Inhibition of GRM3 reduces CRC cell growth. Recent data from CALGB/SWOG 80405 suggests that mutations (MT) of either LRP1B or GRM3 are associated with better and worse overall survival (OS) in patients treated with bevacizumab (Bev), respectively. We investigate the association of LRP1B or GRM3 mRNA levels with outcomes. **Methods:** A total of 13,780 CRC tumors (male 7,497, female 6,283) underwent comprehensive molecular profiling (Caris Life Sciences). Analyses included next-generation sequencing of DNA (592 genes, NextSeq, WES, NovaSEQ) and RNA (NovaSeq). Significance with multiple correction was indicated with q, otherwise p value. Gene Set Enrichment Analyses (GSEA) were performed (significance $p < .05$). A Consensus Molecular Subtype (CMS) calling algorithm was developed using mRNA levels (transcripts per million; TPM). Time on treatment (TOT) with Bev was extracted from insurance claims. **Results:** Male patients had higher GRM3 expression (median TPM.55 vs..52, $p < .001$). GRM3 and LRP1B were both elevated in brain metastases (1.95 vs..40, $q < .01$;.53 vs..16, $q < .01$) and enriched in CMS4 subtype (both $p < .001$). Overexpression of GRM3 and LRP1B were significantly associated with MSS (.11 vs..07, $p < .0001$;.54 vs..39, $p < .0001$) and TMB low status (.11 vs..08, $p < .0001$;.54 vs..40, $p < .0001$). For MSS tumors, high LRP1B was associated with lower MT rates of *APC* (76% vs. 78%), *KRAS* (49% vs. 51%) and *PIK3CA* (15% vs. 17%). For MSI tumors, high LRP1B correlated with higher MT of *MSH6* (41% vs. 32%), *BRCA2* (28% vs. 20%) and *PMS2* (12% vs. 6%). MSS tumors with high GRM3 had more *APC* (79% vs. 75%), less *KRAS* (47% vs. 52%) and *SMAD4* (12% vs. 16%) MT and MSI with high GRM3 carried more *APC* (42% vs. 35%) and *RAD50* (18% vs. 8%) MT. MSS tumors with low LRP1B showed upregulation of the EIF2 pathway while MTOR, RAB, and CDC42 pathways were enriched in MSI with low LRP1B. CDC42 and MTOR pathways were enriched in MSS tumors with low GRM3, and MSI with low GRM3 displayed enrichment of EIF2 and Notch pathways. In MSS tumors, both LRP1B and GRM3 were prognostic and associated with better survival (HR.66, 95% CI [.56-.78], $p < .0001$ for LRP1B; HR.79, 95% CI [.68-.92], $p < .01$ for GRM3) and high expression of either one was also associated with better prognosis for patients treated with Bev (HR.85, 95% CI [.70-.92], $p < .01$ for LRP1B; HR 0.88, 95% CI [.77-.99], $p < .05$ for GRM3). **Conclusions:** LRP1B and GRM3 appear to be important regulators in CRC because of their prognostic value and association with response to bevacizumab treatment. Both LRP1B and GRM3 are associated with pathways of cell cycle progression, cell migration, and DNA repair. A better understanding of their role in angiogenic signaling is critical to develop more effective strategies to improve response to bevacizumab or immunotherapy. Research Sponsor: None.

Clinical usefulness of postoperative serum carcinoembryonic antigen in colorectal cancer patients with liver metastases.

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Background: Colorectal cancer with liver metastases (CLM) has high post operative recurrence rates, and optimizing the perioperative treatment is imperative. Post operative carcinoembryonic antigen (CEA) can help detecting minimal residual disease in colon cancer after curative resection. **Methods:** The aim of this study was to identify the potential role of serum CEA after liver resection in patients with CLM. This study was conducted at the Cancer Institute Hospital, Japanese Foundation for Cancer Research from 2004 to 2018. Patients with CLM who underwent complete resection of primary tumors and liver metastases were enrolled in this study. We studied the associations between the perioperative CEA levels and characteristics of recurrence. **Results:** Recurrence was detected during the median follow-up time of 50.9 months in 343 (54.1%) of the total 633 patients analyzed. Patients with postoperative CEA (>5) group had a significantly higher recurrence rate (75.7% vs 50.0%, $p < 0.01$), with a shorter time until recurrence (4.4 months vs 36.9 months, $p < 0.01$) than those with a postoperative CEA level (≤5) group. In multivariate analysis, a postoperative CEA level >5 ng/ ml was an independent predictor, with the highest hazard ratio for both recurrence free survival (RFS) and overall survival (OS) (RFS: 2.77, 95% confidence interval [CI] 2.14–3.60, $p < 0.01$, OS: 3.18, 95% CI 2.41–4.19, $p < 0.01$). In addition, there was a significantly shorter RFS in the postoperative CEA level (>5) group who did not have normalized CEA levels after adjuvant chemotherapy compared to normalized CEA group (3.3 months vs 18.5 months, $p = 0.008$). **Conclusions:** The postoperative CEA and postadjuvant chemotherapy CEA level in the CEA level (>5) group after surgery may be a predictor of RFS and OS. Research Sponsor: None.

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Clinical implication of *KRAS* mutation variants in patients with resected colon cancer.

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Background: This study evaluated the clinical implication of *KRAS* mutation variants in patients with resected colon cancer (CC). **Methods:** We retrospectively reviewed 482 patients diagnosed with CC and underwent curative surgical resection at Kyungpook National University Chilgok Hospital. The inclusion criteria were: pathologically diagnosed with primary CC; stage I–III CC according to the 7th edition of American Joint Committee on Cancer staging system; and with available test results for *KRAS* mutation status. In total, 345 patients met these criteria and were included in this study. **Results:** Among the 345 patients, 140 (40.6%) exhibited *KRAS* mutations, with their incidences as follows: 90/140 (64.3%) in Exon 2 Codon 12, 37/140 (26.4%) in Exon 2 Codon 13, 1/140 (0.1%) in Exon 3 Codon 59, 7/140 (5.0%) in Exon 3 Codon 61, and 5/140 (3.6%) in Exon 4 Codon 146. *KRAS* mutation status was not a significant prognostic factor for disease-free survival (DFS) or overall survival (OS). Although, there were no significant differences in survival between patients with Exon 2 Codon 12 and Exon 2 Codon 13 mutations, poorer DFS ($p = 0.085$) and OS ($p = 0.005$) were seen in those with Exon 3 Codon 61 mutation than in others. **Conclusions:** *KRAS* mutation status was not correlated with survival, but Exon 3 Codon 61 mutation might be a poor prognostic factor in resected CC patients. Research Sponsor: None.

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Medullary carcinoma of the colon: A comprehensive analysis of a large cancer database.

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Background: Medullary carcinoma (MC) of the colon was described first in 1999 and is characterized by undifferentiated sheets of epithelial cells in a solid growth pattern with pushing borders and prominent lymphoplasmacytic infiltrates. It frequently shows microsatellite instability (MSI). However, the clinicopathological and survival outcomes between MC and the more common adenocarcinoma of the colon (AC) are not well defined in a large database. Therefore, we used a large national registry to explore the association of survival characteristics with sociodemographic, geographic, and disease variables in this cohort of patients. **Methods:** We sampled the National Cancer Database (NCDB) for colon cancer patients diagnosed with MC from 2004-2018. Multivariate cox regression models were used to compare hazard ratios for demographic, geographic, and disease characteristics. In addition, Kaplan-Meier survival plots were utilized to assess survival rate differences between MC and AC tumors located in the ascending, transverse, or descending colon. A p-value$<$0.05 was considered statistically significant. **Results:** Only 2,709 (0.29%) of the 922,667 patients with AC had MC. MC was seen in older patients than AC (76 vs. 69 years). MC was also more common in females than AC (72.5 vs. 49%). The most striking finding in our analysis was the predominance of poorly differentiated (63%) and undifferentiated (21.7%) pathologies in MC. This was in sharp contrast to AC, where 15.8% of patients were poorly differentiated, and only 2% were undifferentiated. Furthermore, undifferentiated and poorly differentiated MC tumors had a poor prognosis (HR 1.45, 95% CI 1.26-1.68, p$<$0.001 and HR 1.44, 95% CI 1.29-1.62, p$<$0.001 respectively) as compared to the other histological grades. Another notable finding in our analysis was the high prevalence of MSI in MC vs. AC (82.4% vs. 25.9%). Cecal MC (HR 1) had the worst prognosis of any colonic site. Left-sided MC tumors also had an inferior prognosis compared to AC (63.21 vs. 87.72 months), although not statistically significant (p=0.217). **Conclusions:** Colon cancer presenting as undifferentiated or poorly differentiated with associated MSI should raise the possibility of a medullary carcinoma diagnosis. However, given the rarity and difficulty in its pathological delineation, MC may remain underdiagnosed. In the modern treatment era, with the approval of immunotherapy for metastatic MSI colon cancer patients, survival and outcomes for metastatic MC may be improved. Research Sponsor: None.

Clinicopathological characteristics and outcomes of patients with deficient mismatch repair colorectal cancer.

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Background: Patients with microsatellite-instability–high (MSI-H) or deficient mismatch repair (dMMR) colorectal cancer (CRC) represent a unique subgroup of patients with evolving treatment opportunities. **Methods:** We included all of the patients with pathologically confirmed diagnosis of CRC at Hospital Universitario La Paz from October 2016 to September 2020. **Results:** A total of 1,152 patients were diagnosed with CRC. IHC for MMR was available in 1,014 patients. Of those, 100 (9,8%) patients were deficient for MLH1 and PSM2 (n = 78), MSH2 and MSH6 (n = 12), PMS2 (n =5), MSH6 (n = 4), or MSH2 (n = 1). Baseline characteristics are depicted in the table. Female sex (55% vs. 38%; p = 0,001), right primary tumor location (75% vs. 29%; p = 0,001), histological grade 3 (20% vs. 8%; p <0,001), and mucinous component (39% vs. 10%; p < 0,001), and localized disease at diagnosis (97% vs. 79% p < 0,001), were more frequent in dMMR group. Among patients with dMMR CRC, 53% were ≥75 years old. The prevalence of BRAF V600E mutation was 56%. More female sex (67% vs. 40%; p = 0,006) and BRAFV600E mutation (66% vs. 48%; p = 0,06) were found in older vs. younger dMMR patients. Six patients were diagnosed with Lynch syndrome. After a median follow-up of 24 months, 279 patients have died. Median overall survival (OS) was not reached in either group (p = 0,327). Three-year OS was 75% (95% CI: 70-80) and 69 (95% CI: 67-71) in the dMMR and pMMR, respectively. In patients with localized disease that underwent antineoplastic treatment (n = 856), median disease-free survival (DFS) and OS were not reached in either group (p =0,403 and p = 0,232). Three-year DFS in patients with stage I (n = 216) was 64% (95% CI: 46-82) and 85% (95%CI: 80-90), p = 0,055; in patients with stage II (n = 274) was 84% (95% CI: 77-91) and 70% (95% CI: 66-74), p = 0,588; and in patients with stage III (n = 366) was 79 (95% CI: 71-87) and 66% (95% CI: 62-70%), p = 0,322; in dMMR and pMMR, respectively. No baseline characteristics were associated with recurrence in patients with localized dMMR CRC. **Conclusions:** Patients with MSI-High/dMMR CRC display distinctive clinical and pathological features. Overall prognosis does not differ in our series, but older age of dMMR patients may have influenced the outcomes. Research Sponsor: None.

	pMMR (n = 914)	dMMR (n = 100)	P value
Sex (female)	351 (38)	55 (55)	0,001
Age	70,6	72,1	0,001
Primary tumor location			0,001
• **Right colon**	• 267 (29)	75 (75)	
• **Left colon**	• 363 (39)	19 (19)	
• **Rectum**	• 284 (31)	6 (6)	
Stage			<0,001
• **I**	• 172 (18)	• 19 (19)	
• **II**	• 230 (25)	• 41 (41)	
• **III**	• 318 (34)	• 37 (37)	
• **IV**	• 194 (21)	• 3 (3)	
Lymphovascular invasion (n = 805)	273 (37)	27 (31)	0,27
Perineural invasion (n = 803)	148 (20)	11 (12)	0,09
Histological grade 3 (n = 856)	61 (8)	17 (20)	<0,001
Mucinous (n = 917)	84 (10)	35 (39)	<0,001
Budding (n = 567)			0,003
• **Low**	• 263 (51)	• 43 (72)	
• **Medium**	• 129 (25)	• 12 (20)	
• **High**	• 116 (22)	• 4 (6)	
BRAF V600E mutation (n = 309)	16 (6)	41 (56)	<0,001

Mismatch repair proteins (MMR) expression as predictive factor in locally advanced rectal cancer.

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Background: Only few data on microsatellite instability in rectal cancer are available in literature, and dMMR role in pre-operative chemoradiotherapy response is under debate. The aim of our study was to evaluate the frequency and therapeutic implications of dMMR status in patients (pts) with locally advanced rectal cancer belonging to our Center. **Methods:** Data were retrospectively collected from 231 patients belonging to the Medical Oncology Unit of the University Hospital of Cagliari from 2011 to 2021. All patients were affected by locally advanced rectal adenocarcinoma (cT3-4 +/- N1-2). All patients included in the study underwent neoadjuvant chemoradiotherapy treatment with capecitabine and RT long course (total dose of Gy 50.4) and subsequently underwent total mesorectal excision (TME) followed by adjuvant chemotherapy. Mismatch repair (MMR) expression was evaluated through immunohistochemistry on surgical samples. **Results:** Of the 231 patients, 213 were suitable for final analyzes. Patients median age was 68 years (range 34-89). 145/201 were male and 68 were female. 66 (31%) had stage II disease and 147 (69%) had stage III disease. Considering MMR, 205/213 (96%) patients had proficient mismatch repair (pMMR), while 8/213 (4%) had dMMR. In dMMR patients defective proteins were: MSH2 in 4 patients, MLH1 and PMS2 combined in 2 patients and MSH6 in 2 patient. dMMR patients showed, unlike pMMR patients, poor or no response to chemoradiotherapy. Responses were assessed through TRG evaluation (Ryan and Dworak scoring systems) on the primary tumour. 5 patients presented a TRG-3 and 3 patients showed a TRG-4, according to Ryan score. All of them had a grade 1 regression, according to Dworak. **Conclusions:** The results of our study, albeit with limitations related to the retrospective nature and the limited number of dMMR cases, might indicate a correlation between microsatellite instability and little or no response to preoperative chemo-radiotherapy. It would be useful to analyze the data prospectively and further evaluate MMR as a predictor of response to combined chemo-radiotherapy. Research Sponsor: None.

Patients characteristics.

	pMMR	dMMR
N. of patients	205	8
Stage II	64	2
Stage III	141	6
Ryan score*[1]		
TRG-1	86	-
TRG-2	110	-
TRG-3	9	5
TRG-4	-	3
TRG-5	-	-
Dworak score*[2]		
Grade 0	-	-
Grade 1	9	8
Grade 2	110	-
Grade 3	74	-
Grade 4	12	-

*[1]Ryan tumor regression (TRG) score: TRG-1 no visible cancer cells; TRG2 single cells or small group of cancer cells; TRG3 residual cancer outgrown by fibrosis; TRG4 significant fibrosis outgrown by cancer; TRG5 no fibrosis with extensive residual cancer.
*[2]Dworak regression score: grade 0, no response; grade 1, minimal response; grade 2, moderate response; grade 3, near complete response; grade 4, complete response.

183 **Poster Session**

Circulating microRNA: Searching for new players in assessment of therapy response in colorectal cancer patients.

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Background: The identification of clinicopathological and molecular predictive and/or prognostic factors represents currently one the most challenging tasks in oncology. Significant efforts are currently being dedicated to identify patients who will or will not benefit from chemotherapy. In fact, drug resistance is a limiting factor of the efficacy of chemotherapy in colorectal cancer (CRC) treatment. However, despite modern surgical techniques and adjuvant systemic therapy, only 20% of patients with distant metastasis achieve long-term remission, while 60–70% of patients develop local or distant recurrence. **Methods:** Recently, we have identified by high-throughput approach that circulating microRNAs (miRNAs), namely, miR-122-5p and miR-142-5p show a high potential for CRC screening and early detection as well as for the assessment of patients' outcomes and the effectiveness of treatment schedule. **Results:** In detail, the expression levels of these miRNAs were significantly different between CRC patients and controls. A year after diagnosis, miRNA expression profiles were significantly modified in patients responding to treatment and were no longer different from those measured in controls. On the other hand, patients not responding to therapy maintained low expression levels in their second sampling. As selection during metastasizing may shift molecular patterns by which CRC liver metastases retain their unique molecular profile, we thus elaborated our results on CRC patients with liver metastasis and measured these circulating miRNAs repeatedly over two years. The first sampling was performed at the time of post therapy developed liver metastasis (i.e., recurrence), and every 3 months depending on patients` conditions (i.e., covering the liver resection, administration of chemotherapy etc). Detailed results of the study will be presented during the meeting. **Conclusions:** The present study aimed to explain why patients with the same cancer stage may differ in treatment susceptibility and long-term outcomes. Research Sponsor: Czech health research council of the Ministry of Health of the Czech Republic.

High immunoscore as a predictor of outcome in patients who underwent chemoimmuno-therapy in locally advanced rectal cancer: A post-hoc analysis of the correlation between immunoscore and pCR in the Averectal study.

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Background: The immunoscore (IS), a prognostic score, was first validated in early colon cancer reflecting the immune response against the tumor. It showed potential in its ability to downstage patients with pathologic complete response (pCR) who would potentially benefit from organ-sparing therapies in locally advanced rectal cancer (LARC). We first presented our initial outcome with 37.8% pCR in patients with LARC treated with short course radiation therapy (SCRT) followed by 6 cycles of mFOLFOX plus Avelumab followed by total mesorectal excision (TME) in the ESMO 23rd World Congress on Gastrointestinal Cancer 2021 Conference (presentation # SO-30). Here we are reporting the post-hoc analysis of the correlation between pCR and pre-treatment biopsy IS to further establish the IS as a prognostic score in patients with LARC. **Methods:** In this Phase II study, 44 patients were accrued from three centers, of whom 40 completed radiotherapy followed by chemoimmunotherapy then TME. 39 patients with available tissue samples, containing tumor cells and its margins, were collected at baseline. CD3 and CD8 cells were counted, and the IS is then derived from the mean density percentiles of CD3 and CD8 positive T cells infiltrating the tumor and in the invasive margin of the tumor. Cutoff for a high IS was established at 62%. We then compared the tumor regression grade (TRG) with the means of IS, using the student t-test. **Results:** 15 patients with pCR had a mean IS of 68 +/- 22 SD as opposed to a mean IS of 52 +/- 22 SD in 24 patients without pCR ($p = 0.036$). **Conclusions:** High IS correlates with TRG as pCR and successfully predicted clinical outcome in LARC patients who underwent chemoimmuno-therapy. It is a promising potential prognostic tool in stratifying patients who would benefit from specific modalities to augment pCR and subsequent organ preservation strategy. Clinical trial information: NCT03503630. Research Sponsor: Merck KGaA, Darmstadt, Germany.

Evaluation of SN-38 PK profile in patients with RAS wild-type metastatic colorectal cancer treated with a combination of SCO-101 and FOLFIRI.

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Background: The FOLFIRI regimen (5-fluorouracil, leucovorin and irinotecan) is a predominant treatment regimen for metastatic colorectal cancer. To optimize the benefit for the patients, it would be desirable to increase the efficacy of irinotecan by increasing the exposure of SN-38 (the active metabolite of irinotecan) to the cancer cells, while maintaining a good safety profile. The oral drug SCO-101, that is currently being developed by Scandion Oncology A/S, was tested in an early clinical trial (CORIST-trial, ClinicalTrials.gov identifier: NCT04247256). SCO-101 is an inhibitor of ABCG2, UGT1A1 and SRPK1. The CORIST trial was set up to address the safety, tolerability, and efficacy of SCO-101 given orally for 6 days followed by FOLFIRI at varying doses from day 5 to 7, in a biweekly schedule, in patients with metastatic colorectal cancer who have formerly been treated with FOLFIRI and afterwards progressed. The first part of the study was a dose-finding study, where the impact of SCO-101 on the pharmacokinetics (PK) of SN-38 was studied. **Methods:** 12 patients from the dose-finding part of the CORIST study received 150 mg SCO-101 for 6 days and 45 – 80% of the recommended dose of FOLFIRI. 6 of the patients had RAS wild-type tumors and these patients are the subject of the current analysis. Blood for PK analysis was sampled from the patients at 1, 2, 4, 8, 24, 48, and 96 hours after treatment with FOLFIRI and SCO-101. The blood samples were analyzed for Cmax, $T^1/_2$ and AUC (0-24h) of SCO-101, irinotecan and SN-38. **Results:** The PK of SN-38 from the patients in the study, normalized to a dose of irinotecan of 90 mg/m2 showed a $T^1/_2$ day 5 of 19 hours (SD 5,7) a Cmax of 60 ng/ml (SD 20,6) and an AUC_0-24h of 1415 hxng/ml (SD: 670). The results were compared to SN-38 data from treatment with irinotecan at 180 mg/m2, which is used in standard doses of FOLFIRI and the data is presented in the table. The data analysis showed an increased $T^1/_2$, increased Cmax and increased AUC of SN-38 when combining SCO-101 with 90 mg/m2 irinotecan, compared to SN-38 PK data from standard irinotecan treatment of 180 mg/m2. The toxicity profile of the patients treated with 90 mg irinotecan/m2 (50% FOLFIRI) showed only grade 1 and 2 adverse events. **Conclusions:** SCO-101 in combination with FOLFIRI has demonstrated the ability to modulate the PK profile of SN-38 in mCRC patients with RAS wild-type tumors, by significantly increasing the half-life, the peak plasma concentration, and area under the curve of SN-38. The combined treatment was well tolerated, and the drug is now being tested for efficacy in the CORIST trial. Research Sponsor: Scandion Oncology A/S.

Comparison of SN-38 PK data between standard irinotecan and data from CORIST study.

	Dose irinotecan/m2	$T^1/_2$ hours (SD)	Cmax ng/ml (SD)	AUC_0-24 hxng/ml (SD)
SN-38 Standard	180 mg	11,7 (4,3)	40 (11,6)	385 (115)
SN-38 CORIST	90 mg	19 (5,7)	60 (20,6)	1415 (670)
Fold increase (CORIST vs Standard)	0,5	1,6	1,5	3,7

Metastatic bulk to predict subclonal heterogeneity by ctDNA in RAS/RAF-wildtype colorectal cancer.

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Background: Distinct molecular subgroups of colorectal cancer (CRC) have been afforded with use of next-generation sequencing (NGS) as standard in clinical practice for advanced disease. We have previously demonstrated that disease bulk predicts clinical resistance to EGFR inhibition in RAS/RAF-wildtype (WT) CRC. We hypothesized bulky disease would predict advanced subclonal heterogeneity by circulating tumor DNA (ctDNA) in RAS/RAF^{WT} CRC. **Methods:** Following IRB-approval, a retrospective review of molecular profiles in advanced CRC (n = 965) were compiled from the Veteran Administration's (VA) National Precision Oncology Program (NPOP) and University of Wisconsin Precision Medicine Molecular Tumor Board (MTB). Disease bulk was defined as the longest diameter of metastatic disease or short axis for advanced lymphadenopathy. Molecular profiling was performed using commercially available platforms including Strata Oncology (MTB) and FoundationOne (NPOP). Bulky was compared as categorical ($>$ 35 cm) and continuous variable against the count of pathologic variants. **Results:** The population was largely representative of advanced CRC with alterations in *TP53* (80.5%), *KRAS* (44.8%), *PIK3CA* (22.0%) and *BRAF* (12.8%). Veterans had increased frequency of alterations in *PIK3CA* (22.7% v. 13.0%, $p < 0.02$) and BRAF (13.3% v. 6.9%, $p < 0.05$). There was no difference in metastatic bulk at the time of NGS for tissue biopsy between MTB and NPOP populations ($t = 0.80$). Disease bulk did not predict the number of pathologic variants from tissue sampling in RAS/RAF^{WT} CRC ($n = 96$, $t = 0.24$). RAS/RAF^{MT} cancers had increased frequency of subclonal alterations by ctDNA (9.1±4.0) v. RAS/RAF^{WT} (4.5±3.4, $p < 0.0001$). Using ctDNA, bulky disease in RAS/RAF^{MT} CRC was not predictive of increased pathologic variants (8.8±3.5 v. 9.5±4.8, $t = 0.62$). Bulky disease ($>$ 35mm) in RAS/RAF^{WT} CRC predicted increased subclonal variants (6.2±3.6 v. 3.5±2.9, $p < 0.02$). As a continuous variable, disease bulk predicted the number of pathologic variants in RAS/RAF^{WT} CRC ($R = 0.51$). **Conclusions:** These data indicate that metastatic bulk is a predictor of subclonal heterogeneity by ctDNA in RAS/RAF^{WT} CRC. Molecular profiling of tissue alone did not predict differences in subclonal heterogeneity when stratified by disease bulk in RAS/RAF^{WT} CRC. Limited subclonal heterogeneity in non-bulky cancers support ongoing prospective investigations to select non-bulky cancers for early incorporation of anti-EGFR inhibition (NCT04587128). Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

187 **Poster Session**

Comprehensive genomic profiling (CGP)-informed personalized molecular residual disease (MRD) detection: An exploratory analysis from the PREDATOR study of metastatic colorectal cancer (mCRC) patients undergoing surgical resection.

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Background: Detection of MRD following metastatic liver resection in advanced CRC patients is associated with poor prognosis with high rate of relapse. Nevertheless, there is currently no standard of care to guide further therapy after curative intent surgery. MRD detection has the promise to be implemented into standard of care and guide treatment decision making. Here we establish feasibility of MRD detection using Foundation Medicine's novel tissue-informed personalized monitoring assay, FoundationOne Tracker (F1T), in mCRC patients undergoing surgical resection with curative intent. **Methods:** Tissue-based CGP was performed retrospectively on a cohort of 72 patients from the PREDATOR trial. Trackable patient-specific single nucleotide variants were selected using a novel computational approach negating the need for buffy coat sequencing to filter germline variants. Personalized multiplex PCR was used to detect and evaluate prognostic value of ctDNA from plasma collected at MRD timepoint post-surgery (median 27 days, range 8-99.5). Median follow-up of patients in the overall population was 10.7 months (range: 0.9-53.8 months). Survival analyses were performed using the Kaplan-Meier Estimator and Cox regression. **Results:** Post-surgical F1T analysis was successful on 96% of cases (69/72). CGP analysis revealed at least one driver mutation in 57% of samples (41/72) including *KRAS/NRAS* (46%) and *BRAF* mutations (3%). MRD was detected in 45% (31/69) of patients, of which 94% (29/31) had progressed at the time of the data cut. Median progression -free survival (PFS) was 3.2 months (2.1-7.1) in ctDNA-positive vs 28 months (20.9-NA) in ctDNA-negative population (HR 5, CI 2.7-9.3, $p<0.001$). Median overall survival (OS) was 31.6 months in ctDNA-positive vs not reached in ctDNA-negative group (HR 27, CI 3.6-205, $p<0.001$). **Conclusions:** CGP-informed post-operative MRD detection is a strong prognostic biomarker and correlates with survival outcomes in patients with resected mCRC. F1T is a novel and convenient technological approach to MRD detection utilizing highly validated FMI testing to reveal potentially targetable mutations and inform personalized ctDNA monitoring. These results demonstrate the ability of F1T to accurately detect MRD in mCRC patients following surgical resection, without the need for germline sequencing. Research Sponsor: Foundation Medicine, Inc.

188 **Poster Session**

Clinical evolution after surgery of hepatic metastases of colorectal cancer according to genomic profile.

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Background: Hepatic metastatic disease from colorectal cancer (CRC) is a significant clinical problem, as the liver is the dominant metastatic site for patients with CRC and 25% of patients will have liver affection at diagnosis. Due to improvement in systemic therapy and locoregional treatments in the last decade, survival has increased significantly. In this regard, it is key to be able to establish several prognostic factors that significantly influence survival. **Methods:** We carried out a retrospective analysis of 554 patients with mCRC treated at the Gregorio Marañon Hospital (Madrid, Spain) between January 2010 and 2021. We analyzed the clinical and molecular characteristics of patients undergoing liver metastasis surgery as first metastasis surgery together with relapse patterns to progression. **Results:** Out of our cohort of 554 patients with mCRC we identified 169 patients that underwent liver metastasis surgery as 1st surgery, achieving a media of survival of 56.38 months [95% CI, 44.21-73.78 months]. Regarding the clinical characteristics of the population, the majority were men (63,91%) and had a PS 0-1 (90,5%); and 46 patients (27,2%) were more than 70 years old. In relation to the location of the primary tumour, 46 patients (27,2%) had it n the right colon and 120 in the left colon (71,0%). And 43 patients (25,4%) had extrahepatic disease at the time of surgery. Regarding the biomakers, we indentified the following mutations: 68 mutated KRAS (40,2%), 5 mutated NRAS (2,9%), 9 mutated BRAF (5,3%), 13 mutated PI3K (7,6%), 1 HER2 amplification (0,5%) and 4 with IMS phenotype (2,3%). After the metastasis surgery, progression was mainly hepatic (50,3%), followed by pulmonary (24,8%), peritoneal (11,8%), lymph node (12%), bones (4,7%) and cerebral (1,1%), without having significant differences in relapse patterns at the statistics when analyzed by genomic profile. When analyzing progression-free survival (PFS) and overall survival (OS) according to the genomic profile, in the BRAF mutated vs BRAF WT population, no statistically significant differences were found, obtaining therefore an evident benefit. Furthermore, we found significant differences in OS for patients with right vs left primary tumour as well as for patients with extrahepatic involvement at the time of surgery. **Conclusions:** Patients undergoing sequential metastatic surgery have a long survival, so it is important to analyse patterns of relapse and clinical course. There is no evidence of significant differences in the progression patterns according to the mutational status of the mCRC; but selected patients with BRAF mutations may obtain benefit in PFS and OS with locoregional approaches to their liver disease. Research Sponsor: None.

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Longitudinal monitoring of circulating tumor DNA (ctDNA) during disease course of metastatic colorectal cancer (mCRC).

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Background: ctDNA is an attractive alternative to tissue for its easy accessibility and real time representation of systemic tumor profile. We explored the utility of ctDNA profiling during the course of mCRC treatment. **Methods:** Serial blood samples were obtained from mCRC patients before and during first-line palliative chemotherapy at fixed intervals (after every four cycles) until confirmed disease progression. ctDNA was sequenced using targeted next-generation sequencing (NGS) platform with 106 genes. Changes of ctDNA profile and treatment outcome were comprehensively analyzed. **Results:** A total of 272 samples from 62 patients were analyzed. In the pre-treatment blood samples, 56 (90.3%) of patients had detectable ctDNA mutations including single nucleotide variants, short insertions/deletions and copy number changes (median 4.5 mutations/ patient, range 0 - 133). In 31 (50.0%) patients who had tissue NGS panel results performed in the clinic, overall concordance between mutations from ctDNA and tissue was 86.5%. In three patients, ctDNA mutational profiles were found to be completely different from tissue profiles. At further investigation, these patients were found to have a separate primary cancer in their colon. At the time of the first follow-up, most (98.0%) patients showed decrease of ctDNA from baseline, represented by average variant allele frequency (VAF) changes of all ctDNA mutations found. Clearance of ctDNA was achieved in 40 (78.4%) patients and was associated with longer progression-free survival (median PFS 11.8 moths in ctDNA clearance (+) vs. 4.7 months in ctDNA clearance (-), $p < 0.001$). The ctDNA clearance at the same time point was able to further discriminate the patients in same category by RECIST 1.1. Serial follow-up monitoring revealed three patterns of ctDNA changes at the time of clinical progressive disease (PD): 1) re-emergence or re-increase of baseline ctDNA mutations, 2) emergence of new resistance mutations, 3) radiologic PD without evidence of ctDNA progression. In the patients with detectable ctDNA at PD, the ctDNA progression preceded radiologic progression in 25 (58.1%) patients by median of 3.3 months. The patients in clinical PD without ctDNA progression showed different patterns of metastasis having mainly extrahepatic spread, while 77.8% of the patients with ctDNA progression had their progression confirmed in liver metastasis. Diverse resistant mutations and gene amplifications in PD patients were discovered by ctDNA sequencing. For seven (16.3%) of the PD patients, the newly identified mutations could be potential candidates of targeted therapy or clinical trial. **Conclusions:** ctDNA profile provided additional information to conventional evaluation methods and reflected dynamic changes. ctDNA monitoring may improve precise treatment decision-making for individual patients. Research Sponsor: None.

Next generation sequencing (NGS) to identify relapsed gastrointestinal (GI) solid tumor patients with human leukocyte antigen (HLA) loss of heterozygosity (LOH) for future logic-gated CAR T therapy to reduce on target off tumor toxicity.

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Background: Metastatic colorectal (CRC), pancreatic (PANC), and gastroesophageal (GE) cancers are the leading causes of GI cancer–related mortality (5-yr survival rate, 14%, 3% and ~5-6%, respectively). T-cell immunotherapy targeting GI-associated tumor antigens has been attempted, but efficacy has been constrained by on-target off-tumor toxicity, limiting the therapeutic window. The Tmod (TM) platform is an AND-NOT logic-gated CAR T modular system, versions of which have a CEA- or MSLN-targeting CAR activator and a separate HLA-A*02-targeting blocker receptor to protect normal cells. Tmod CAR T exploits HLA LOH, common in GI malignancies (10-33% in primary solid tumors [TCGA]) and can kill tumor cells without harming healthy cells in vitro and in vivo. However, the prevalence of HLA LOH across GI tumors is unknown in the real-world setting. We utilized the Tempus xT oncology NGS database of patients with multiple GI tumors. From a standard-of-care NGS assay, GI cancer patients can be readily identified for HLA LOH and future treatment with Tmod CAR T therapy. **Methods:** The occurrence of HLA LOH in GI tumors of 1439 patients was assessed using paired germline and somatic DNA sequencing using a research assay [6]. CRC, PANC and GE patients with ≥ stage 3 were then extracted, and rates of HLA LOH were identified (ie, whether loss occurred across high-frequency HLA-A alleles). In addition, mutations in *KRAS* and *BRAF*, as well as MSI status were stratified to determine any association with HLA-A LOH. **Results:** HLA-A LOH was detected in 830 (17.3%) of all solid tumor records, and a similar proportion when all GI cancer records were analyzed (17.0%). For GI subtypes, these values ranged from 13.5% to 23.1% (Table). No high-frequency HLA-A allele (A*01, A*02, A*03, A*11) was more likely to be lost. Clinical biomarkers (*KRAS*, *BRAF* and MSI status) were not associated with HLA-LOH. **Conclusions:** The frequency of HLA LOH among advanced solid tumor cancers in this dataset is 17.3%, with a range of 13.5-23% between CRC, PANC and GE. The HLA LOH frequency observed in these GI tumors is consistent with that in primary tumors from TCGA, which also used germline-matched and tumor samples. Clinical biomarkers were not associated with HLA LOH. Tempus NGS was able to identify HLA LOH, which can be used for Tmod CAR T therapy to an enhanced therapeutic window. Identification of these patients in BASECAMP-1 (NCT04981119) will enable novel Tmod CAR T therapy. Research Sponsor: A2 Biotherapeutics.

Frequency of HLA LOH for advanced GI tumors.

	Tempus HLA-A LOH advanced disease real-world	TCGA HLA-A LOH primary tumors
Average	17.3% (n=4796)	12.6% (n=10,844)
Range in GI cancers	13.5-23.1% (n=1439)	9.6-33.1% (n=1424)
CRC	13.5% (n=880)	9.6% (n=615)
PANC	21.8% (n=325)	33.1% (n=184)
GE	23.1% (n=234)	16.2% (n=625)

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

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Background: Somatic alterations in *KRAS* and *BRAF* have prognostic as well as predictive impact in pts with mCRC; however, the differential impact of various somatic alterations in these genes need further characterization. We analyzed the prognostic impact of specific somatic mutations in K*RAS* and *BRAF* in mCRC pts. **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. Prevalence of genetic alterations was estimated using proportions and compared between groups using a chi-squared test. Patients were followed for survival from metastatic diagnosis until death or last follow-up, with left truncation at the time of CGP. Kaplan-Meier estimates were used to estimate overall survival, and groups were compared using a Cox-regression based likelihood ratio test. **Results:** 192 pts were identified - median age at diagnosis was 55 years, 62% (119/192) presented with metachronous metastatic disease, and 28% (54/192) had a rectal primary. Somatic mutations in *KRAS* were found in 49% (95/192) pts, and 53% (50/95) had a left sided primary ($p = 0.3$). Majority of the *KRAS* mutations localized to codon 12 (72/95 -76%), *KRAS* G12C comprised 12% (11/95). Median Overall Survival (mOS) of *KRAS* mutated pts was 3.0 years compared to 3.5 years for *KRAS* wild type (WT) pts ($p = 0.5$). Median OS of pts with different *KRAS* mutations were as follows: codon 12 mutations (excluding G12C) - 2.7 years; *KRAS* G12C – 5.2 years; non-codon 12 *KRAS* mutations - 4.8 years. *BRAF* mutations were identified in 7.8% (15/192) pts, and 67% (10/15) had a right sided primary ($p = 0.062$). *BRAF* V600E represented the most common alteration in *BRAF* – 87% (13/15). Patients with *BRAF* mutation had a mOS of 1.8 years compared to 3.1 years for *BRAF* WT pts ($p = 0.2$). Median OS of pts with different *BRA*F mutations were as follows: *BRA*F V600E – 1.8 years and *BRAF* non V600E - 2.1 years ($p = 0.4$). **Conclusions:** The numerically higher mOS in pts with *KRAS* G12C and non-codon 12 KRAS 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.

Clinical outcomes of neoadjuvant treatment strategies in localized mismatch repair-deficient rectal cancer.

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Background: Rectal cancer treatment paradigm has been evolving over time. Historically, for locally advanced rectal cancer, standard therapy (ST) consisted of neoadjuvant chemoradiation followed by surgery and adjuvant chemotherapy. Recently, total neoadjuvant treatment (TNT) approach that delivers both neoadjuvant chemotherapy (CAPOX or FOLFOX) and chemoradiation (or radiation only) prior to surgery is increasingly being utilized. The prognostic and predictive values of mismatch repair deficient (dMMR) in rectal cancer is not well characterized. Most dMMR patients receive the same treatment as MMR proficient (pMMR) patients although there is limited data that dMMR rectal cancer patients may not have the same level of benefits from neoadjuvant treatment. This retrospective study aims to evaluate the clinicopathological/molecular characteristics, disease response, and clinical outcomes in dMMR localized rectal cancer patients. **Methods:** A retrospective analysis was conducted on consecutive adult patients with a diagnosis of dMMR rectal cancer who were treated at Mayo Clinic between January 2000 to September 2021. Patients who presented with concurrent primary non-colorectal malignancies were excluded. The distributions of demographics, clinicopathological features, biomarkers, and outcome data were collected. Survival was assessed using Kaplan-Meier curves and Cox models were stratified by treatment arms to determine significance of treatment strategies. **Results:** Forty-one patients were identified with a median age of 45.3 years. Thirty (73.2%) pts were male. The most common MMR were loss of MSH2 and MSH6 (12/42; 29.3%) followed by loss of MLH1 and PMS2 (10/42; 24.4%) and solitary loss of MSH2 (4/42; 9.8%). The treatment, pathological response, and clinical outcomes are listed in table. With a median follow up of 101 months, only 6 patients (14.3%) died and median overall survival was not reached. **Conclusions:** Our findings showed dMMR localized rectal cancer responded to both ST and TNT with good clinical outcomes. Research Sponsor: None.

	Total Neoadjuvant Therapy	Standard Therapy	No Neoadjuvant Therapy
Patients (number)	8	21	12
Gender (number, %)			
Male	6 (75%)	18 (85.7%)	7 (58.3%)
Female	2 (25%)	3 (14.3%)	5 (41.7%)
Disease stage change after neoadjuvant treatment:			N/A
- Down-staged (complete response)	5 (3)	14 (6)	
- Stable	1	5	
- Progression	2	2	
Number of patients with recurrence or cancer related death	2 (25.00%)	4 (19.05%)	5 (41.67%)

Circulating tumor DNA dynamics on front-line chemotherapy with bevacizumab or cetuximab in metastatic colorectal cancer: A biomarker analysis for acquired genomic alterations in CALGB/SWOG 80405 (Alliance) randomized trial.

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Background: Enhanced understanding of the evolving clonal architecture under treatment stress is crucial to optimizing care and developing effective therapies in metastatic colorectal cancer (mCRC). Emergence of genomic alterations (GAs) [mutations (muts) and amplifications (amps)] in *RAS*, *BRAF*, *EGFR, ERBB2, and MET* have been recognized as key resistance mechanisms to anti-EGFR therapy in later lines in mCRC. Data regarding occurrence of these GAs under selective pressure in the first line setting is lacking. **Methods:** CALGB/SWOG 80405 was a randomized trial of bevacizumab (bev) vs cetuximab (cet) in first line mCRC. Patients (pts) with paired plasma samples (pre-treatment and post-progression) available for circulating tumor DNA (ctDNA) testing were included in this substudy. Sequencing of ctDNA was performed by Guardant360 assay in a CLIA-certified environment to detect GAs in 73 genes. *RAS/BRAF* status [mut vs. wild type (wt)] was based on clonal muts [pre-defined cut-off of relative MAF (rMAF) $\geq$ 25%] in ctDNA. Only samples with $\geq$1 GA were analyzed to minimize false negatives. The primary objective was to determine and compare prevalence of acquired GAs between study arms: bev (anti-VEGF) and cet (anti-EGFR). Descriptive statistics and Fisher's exact test were used. **Results:** Baseline characteristics of ctDNA cohort were similar to the 80405 population. Among 133 randomized *RAS/BRAF* wt pts, 11 (15.3%) and 5 (8.2%) developed acquired GAs (OR 2.0, P = 0.29), in bev and cet arm, respectively. Key comparative data for pts with regard to acquired pathogenic GAs are shown in the table. **Conclusions:** In this randomized mCRC cohort, the ctDNA profile of acquired GAs with front line anti-EGFR chemotherapy appears to be strikingly distinct from that seen with later lines of therapy. Acquisition of GAs, classically associated with EGFR resistance in later line, was not only rare with upfront cet-chemotherapy but also comparable to bev-containing (anti-VEGF) regimen. The mechanisms of acquired resistance appear to differ when anti-EGFR therapy is administered in combination with highly active first line chemotherapy. Our findings have critical translational relevance to the timing and value of ctDNA-guided anti-EGFR rechallenge in mCRC pts, especially in those treated with anti-EGFR therapy upfront. Research Sponsor: U.S. National Institutes of Health.

Treatment Arm	Bev (N = 72)	Cet (N = 61)	P
Any acquired mutations	26 (36.1)	20 (32.8)	0.72
Any acquired amplifications	9 (12.5)	5 (8.2)	0.57
Anti-EGFR Resistance GAs	**11 (15.3)**	**5 (8.2)**	**0.29**
Mutations	9 (12.5)	5 (8.2)	0.57
RAS	4 (5.6)	3 (4.9)	0.99
BRAF	2 (2.8)	2 (3.3)	0.99
EGFR	4 (5.6)	1 (1.6)	0.37
Amplifications	3 (4.2)	1 (1.6)	0.62
ERBB2	2 (2.8)	1 (1.6)	0.99
MET	1 (1.4)	-	0.99

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Characteristics and outcomes of patients with multiple synchronous colon cancer primaries.

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Background: Patients (pts) with multiple synchronous colon cancer primaries (MCPs) constitute a unique subset of pts with colon cancer. However, there are limited published studies about these pts. The objective of this study is to compare the characteristics and outcomes of pts with MCPs to those with single colon cancer primaries (SCPs) using the largest study population to date. **Methods:** Data was obtained from the Surveillance, Epidemiology, and End Results (SEER) database between 2004 and 2015. Pts with synchronous MCPs were included and were matched 1:3 with pts with SCPs based on the Coarsened Exact Matching method for age, gender, and race. Only patients with multiple synchronous primaries were included (time since index = 0 months). We excluded pts with a lag time since diagnosis of index primary of 1 month or more. Univariate (UNA) and multivariable (MVA) analyses were performed to identify factors associated with patient outcomes. Kaplan-Meier analyses and Cox proportional hazards models were used to assess the association between tumor/patient characteristics and overall survival (OS). **Results:** A total of 3322 pts with MCPs and 9966 pts with SCPs were identified. Median age was 71 years. Majority were male (51.5%) and White (80.1%). 73.4% and 69.6% of pts had 12 or more lymph nodes examined for the MCPs and SCPs cohorts, respectively. The SCPs cohort included more T4 stage and more well- and moderately-differentiated histology. OS was significantly shorter in MCPs compared to SCPs (HR 1.29; 1.22-1.36; $p < 0.001$), with a 5- and 10-year OS rate of 47.8% and 28.2% for the MCPs and 56.4% and 41.6% for the SCPs, respectively, for all stages combined. In the MCPs cohort, the use of adjuvant chemotherapy was associated with an improved survival in AJCC stages II, III, and IV but not stage I. **Conclusions:** This is the largest study evaluating the impact of MCPs on outcomes. Across stages II to IV, pts with MCPs have a shorter survival than those with SCPs. Pts with stage II MCPs who receive adjuvant chemotherapy derive a survival benefit. Current guidelines do not list multiple synchronous primaries as a high-risk feature for stage II. Research Sponsor: None.

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Effect of primary tumor location on second- or later-line treatment with anti-epidermal growth factor receptor antibodies in patients with metastatic colorectal cancer: A retrospective multicenter study.

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Background: Currently, there are no guideline recommendations of anti-EGFR Ab specific to tumor sidedness in subsequent-line treatment in patients with metastatic colorectal cancer (mCRC). We previously reported the effect of primary tumor location on subsequent-line treatment with anti-EGFR Ab from a single center. Here we presented the outcome from a multi-center study. **Methods:** Medical records of patients diagnosed with mCRC at 3 academic centers in Thailand (Siriraj, Chulalongkorn, and Ramathibodi hospital) between 2008 and 2019 were retrospectively reviewed. Patients with *KRAS*wt mCRC who received anti-EGFR Ab in second- or later-line treatment were included. The impact of tumor sidedness on progression-free survival (PFS) was determined using Kaplan-Meier method, and those results were compared using log-rank test. **Results:** Among the 2,102 patients who had *KRAS* analysis data, 1,130 (54%) patients had *KRASwt*. Of those, 413 patients received anti-EGFR Ab in second- or later-line treatment. One hundred and sixty-two of 413 (39%) patients had extended *RAS* analysis. Seventy (17%) patients had right-sided tumors. Two hundred and thirty-eight (58%) patients received anti-EGFR Ab in the third line, and 132 (32%) patients and 43 (10%) patients were treated in the second and more than third line, respectively. Single-agent irinotecan was the most commonly used backbone chemotherapy (303/413, 73%). Patients with right-sided tumors had non-significantly inferior PFS compared to patients with left-sided tumors (median PFS: 5.7 months (mo), 95% confidence interval [CI]: 3.9-7.5 vs. 7.5 mo, 95% CI 6.5-8.5; p =0.17). Subgroup analysis showed no difference in PFS when stratified by treatment lines. Patient with right-sided tumors had significantly inferior OS compared to patients with left-sided tumors (median OS: 23.3 mo vs. 29.9 mo; p =0.005). **Conclusions:** To date, this is the largest real world data of the effect of primary tumor location on anti-EGFR Ab which demonstrated that tumor sidedness has no significant impact on treatment outcomes in *KRASwt* mCRC patients receiving second- or later-line therapy. Our findings do not support the utility of tumor sidedness for treatment selection in these settings. We confirmed that patients with right-sided tumors had significantly worse survival. Research Sponsor: None.

Clinical performance of Immunoscore in stage III colorectal cancer patients in the SCOT and IDEA-HORG cohorts.

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Background: The ESMO clinical practice guidelines recommend consideration of Immunoscore (IS) for risk assessment of early colon cancer patients. IS clinical performance was assessed in the SCOT and IDEA-HORG trials evaluating 3 vs. 6 months (3m vs. 6m) of mFOLFOX6 adjuvant chemotherapy in stage III colorectal cancer (CRC). **Methods:** 1,002 formalin-fixed paraffin-embedded (FFPE) tumor samples (762 from SCOT;240 from HORG) were collected, of which 851 were eligible for biomarker analysis. Eligible samples were classified into 2 groups using pre-defined cut-offs (IS-Low, IS- High) and the performance of IS to predict 3 year disease-free survival (3y-DFS) was evaluated. **Results:** IS was successfully assessed in 846 cases (99%). 615 (72.7%) samples were classified as IS-High (311 and 304 in 3m and 6m arm, respectively). No significant association between IS and patients' gender, age, PS, BMI or primary tumour location was observed. However, a significant difference between IS-High (43.7%) and IS Low (57.1%) was observed in the proportion of high risk (T4 and/or N2) tumours (p=0.001). Patients with IS-High tumors had significantly longer 3y-DFS (79.4%, 95%CI: 75.9%-82.4%) compared to those with IS-Low tumors (65.0%, 95%CI: 58.3%-70.9%); adjusted hazard ratio (HR) 1.9 (95%CI: 1.46-2.46; $p<0.0001$). Similarly, IS-High was significantly correlated with longer 3y-DFS in both treatment arms: 78.5% (95% CI 73.4%-82.7%) for IS-High and 65.8% (95% CI 56.1%-73.9%) for IS-Low in 3m arm; 80.3% (95% CI 75.3%-84.5%) for IS-High and 64.4% (95% CI 54.8%-72.6%) for IS-Low in 6m arm. The estimated HRs according to treatment duration and IS classification were 1.80 (95% CI 1.25-2.60) in 3m arm, 2.00 (95% CI 1.38-2.92) in 6m arm and 1.89 (95% CI 1.46-2.47) in the total study population; interaction $p = 0.687$. **Conclusions:** The results of this study confirm the prognostic value of IS observed in the IDEA-France trial (Pagès F et al 2020). However, this analysis was not powered to determine the predictive value of IS for treatment duration. Similar analysis of patients treated with CAPOX is warranted. Research Sponsor: Halio Dx.

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The role of genetic variants involved with ferroptosis regulator genes in predicting outcomes in patients (pts) with RAS-mutant metastatic colorectal cancer (mCRC): Data from MAVERICC and TRIBE trials.

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Background: Ferroptosis, an iron-dependent programmed cell death, is one of the anti-tumor mechanisms of anti-angiogenesis drugs. RAS mutation can confer ferroptosis in colorectal cancer (CRC). Previous studies suggested that polymorphisms of ferroptosis regulator genes are associated with the increased risk of CRC. Therefore, we hypothesized that genetic variants in the ferroptosis regulator genes may predict first-line treatment outcome in RAS-mutant mCRC pts treated with bevacizumab (bev)-based chemotherapy. **Methods:** Genomic DNA from blood samples of mCRC pts enrolled in two independent randomized trials, MAVERICC (FOLFIRI+bev arm: discovery cohort, RAS-mutant, n = 56; control-1: RAS-wildtype, n = 87) and TRIBE (FOLFOXIRI+bev arm: validation cohort, RAS-mutant, n = 57; control-2: RAS-wildtype, n = 34), was genotyped through the OncoArray, a customized array manufactured by Illumina including approximately 530K SNP markers. The impact on outcome of 13 selected SNPs in 5 main ferroptosis regulator genes (ACSL4, LPCAT3, SLC3A2, SLC7A11, ALOX15) was analyzed. **Results:** In the MAVERICC bev cohort, pts with RAS-mutant tumors carrying ALOX15 rs7217186 any C allele (n = 35) showed significant longer overall survival (OS) than carrier of T/T allele (n = 5) in both univariate (24.97 vs. 12.22 months, hazard ratio [HR] = 0.23; 95% confidence interval [CI]: 0.06-0.9; p = 0.02) and multivariate (HR = 0.06; 95%CI 0.007-0.5; p = 0.009) analysis. In the TRIBE bev cohort, RAS-mutant carriers of any C allele (n = 30) showed numerically longer progression-free survival (PFS), compared to carriers of T/T allele (n = 13) in both univariate (11.91 vs. 9.47 months, HR = 0.45; 95%CI 0.2-1.02; p = 0.05) and multivariate (HR = 0.42; 95%CI 0.16-1.1; p = 0.09) analysis. Conversely, RAS-wildtype carriers of any C allele (n = 17) showed significant shorter PFS than T/T carriers in the TRIBE bev cohort (8.91 vs. 15.59 months, univariate HR = 3.39, 95%CI: 1.03-11.18, p = 0.04). **Conclusions:** Our study demonstrated for the first time that ALOX15 polymorphisms may have different predictive values for the bev-based treatment in mCRC patients based on RAS mutational status. These findings may provide novel insights for the combination of ferroptosis inducers and anti-VEGF treatment. Research Sponsor: None.

Early-onset colorectal cancer: Real-world genomic data from the community-based Sarah Cannon Cancer Centers Network.

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Background: Rising incidence in early-onset colorectal cancer (EO-CRC) is a recent phenomenon observed especially in the US. We exploited Sarah Cannon's web-based analytics platform, to compare the genomic profiles of EO-CRC to late-onset colorectal cancer (LO-CRC). **Methods:** Commercial NGS testing performed in oncology practices are routinely extracted and harmonized into the Genospace database. Data from CRC adenocarcinomas were selected; patients (pts) with unknown microsatellite instability (MSI) status were excluded. To reduce the confounding effect of MSI-high hypermutated tumors, only MSI-stable (MSS) tumors were analyzed. Reports generated from archival tissue samples were analyzed separately from those generated from plasma, since liquid biopsies were more likely to be post-treatment. **Results:** NGS reports from 1,477 MSS CRC pts were analysed. Compared to LO, EO pts had same sex distribution and significantly lower prevalence of Caucasian ethnicity (53% LO vs. 43% EO, $p < 0.01$). 1029 were tissue (18.7% EO) and 448 plasma (17.8% EO) tests. Of 68 CRC-related genes assessed in tissue, 2 were significantly enriched in EO: BRCA1 mutation (3% LO vs. 7.3% EO p 0.01); PTEN mutation (3% LO vs. 6.2% EO p 0.05). Looking at panel-wide gene association, 19 genes (tissue) were enriched in EO, though none were significant after multiple testing correction. In plasma, ATM alterations were significantly higher in LO (17.3% LO vs. 3.8% EO p <0.001, FDR 0.16), (likely clonal haematopoiesis). No difference in tissue nor plasma TMB were observed [tissue: median (IQ): LO 5.04 (3.5 - 7); EO 4.39 (2.5 – 6.1); TMB >10: 7% LO vs. 6% EO; plasma: median (IQ): LO 8.73 (5.7 – 13.4); EO 7.19 (2.9 – 12.6); TMB >10: 12% LO vs. 14% EO]. Overall, tissue and plasma genomic profiles were concordant, except for EGFR alterations (4.5% tissue, 21.6% plasma, possibly acquired amplification post-EGFR therapy). **Conclusions:** Here we provide real-world insight from pts across the US. In MSS CRC, tissue and plasma genomic profiles of EO pts do not significantly differ from LO pts. Epigenetic and transcriptional events should be investigated. Enrichment for BRCA1 and PTEN mutations in EO pts may have important screening and therapeutic implications; germline status will be further investigated. Research Sponsor: None.

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Safety and efficacy of encorafenib, binimetinib, plus cetuximab for BRAF V600E-mutant metastatic colorectal cancer: Results of a prospective study as an expanded access program.

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Background: The encorafenib, binimetinib, and cetuximab (triplet) regimen showed survival benefit and a higher response rate over standard chemotherapy among pretreated patients (pts) with BRAF V600E-mutant metastatic colorectal cancer (mCRC) in the phase III BEACON trial. Herein, we report the safety and efficacy of the triplet regimen in a prospective study (JapicCTI-205146) as a Japanese expanded access program (EAP). **Methods:** The key eligibility criteria were age ≥18 years and a diagnosis of BRAF V600E-mutant mCRC with progression observed after one or two prior systemic chemotherapy. Encorafenib (300 mg QD), binimetinib (45 mg BID), and weekly cetuximab (400 mg/m^2, followed by 250 mg/m^2) were administered. Patients who had received at least one dose of any study drug were included in this analysis. Adverse events were evaluated using CTCAE v4.0. The objective response rate (ORR) was evaluated using RECIST Guideline Version 1.1. **Results:** A total of 86 pts were enrolled from 10 Japanese institutions from February to December 2020. Safety and efficacy were evaluated in 81 pts. The median age was 60 years. Fifty-four pts (67%) had ECOG PS 0 and 50 pts (62%) received one prior chemotherapy. Treatment-related serious adverse events and grade 3 or higher treatment-related adverse events were observed in 14 (17%) and 24 (30%) pts, respectively. Treatment-related death occurred in one pts. Among the 76 pts with target lesions, 21 pts were responders, and the confirmed ORR was 27.6%. Stable disease was observed in 42 pts, resulting in a disease control rate of 82.9%. The ORR was consistent regardless of ECOG PS status, the number of prior chemotherapy lines, and the number of metastatic organs. **Conclusions:** The safety and efficacy of the triplet regimen in the Japanese EAP were comparable to those in the BEACON trial. These results support the triplet regimen as a new standard-of-care treatment option in the second- or third-line treatment of pts with BRAF V600E-mutant mCRC in the Japanese population, as there was a promising response without any new safety signals. Clinical trial information: JapicCTI-205146. Research Sponsor: Ono Pharmaceutical.

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A single-center comparative surveillance strategies of ctDNA (Signatera), imaging, and CEA in the surveillance of resected colorectal cancer.

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Background: Signatera (S) assay is a CLIA certified minimal residual disease ctDNA assay that has become widely used for monitoring of disease relapse in patients (pts) with resected colorectal cancer. In a longitudinal study, S+ recurrence (SR) occurred at median $>$ 10 months (mo) prior to radiographic disease recurrence (RDR) in a prospective clinical trial. However, the radiographic surveillance frequency in that study was inadequate by US standard practices. **Methods:** We retrospectively evaluated, in a single center, the sensitivity (ss), specificity (sp), positive predictive value (ppv) and negative predictive value (npv) of S, CT/MRI imaging (Im), and CEA in curatively resected stage II, III, IV pts against True Disease Recurrence (TDR). We considered TDR as any SR, RDR confirmed by pathology, RDR associated with CEA elevation, or RDR with sequential growth on imaging or regression with chemo. S and CEA were performed Q3 mo x 2 yrs and then Q6 mo x 3 yrs. Im was performed Q3 mo x 2 yrs and then Q6 mo x 3 yrs in resected stage IV, Q6 mo x 2 yrs and then Q yr x 3 in stage III/high-risk stage II, and Q yr x 5 yrs in low-risk stage II. **Results:** 48 pts underwent curative resection (31 stage II-III, 17 stage IV). 15 patients recurred during surveillance (6 stage II-III, 9 stage IV). The ss, sp, ppv, and npv of S, Im, CEA, and (Im and/or CEA) are tabulated below. S, Im, CEA, and Im or CEA were positive for recurrence at the diagnosis of TDR in 8, 9, 4, and 12, respectively. S sensitivity was poor for lung recurrence with 5/6 pts with lung-only mets (3 confirmed by path) being negative by S at the time of Im relapse. S was negative at the time of CNS recurrence and liver recurrence in 2 pts. 2 Pts with negative imaging at SR developed subsequent liver metastases. 2 Pts, counted as TDR, were SR and remain NED without any therapy, by CEA and Im $>$ 1.5 years from S positivity. **Conclusions:** S does not appear to provide definitive advantages as a surveillance strategy over standard Im frequency- when performed as per NCCN guidelines. Sensitivity of S is particularly poor for low volume lung-only disease recurrence. Research Sponsor: None.

	S %			Im %			CEA %			Im or CEA %		
Stage	II-III	IV	II-IV	II-III	IV	II-IV	II-III	IV	II-IV	II-III	IV	II-IV
ss	66.7	44.4	53.3	33.3	77.8%	60	50	11.1	26.7	83.3	77.8	80
sp	100	100	100	96	100	96.9	88	100	90.9	84	100	87.8
ppv	100	100	100	66.7	100	90	50	100	57.1	55.6	100	75
npv	92.6	61.5	82.5	85.7	80	84.2	88	50	73.2	95.5	80	90.6

201 **Poster Session**

Antitumor activity and safety of dostarlimab monotherapy in patients with mismatch repair deficient non-endometrial solid tumors: A post-hoc subgroup analysis of patients with colorectal cancer.

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Background: Dostarlimab is a programmed death receptor-1 (PD-1) blocking antibody that is approved in the US as a monotherapy in adult patients (pts) with mismatch repair deficient (dMMR) recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen or dMMR recurrent or advanced solid tumors that have progressed on or following prior treatment and who have no satisfactory alternative treatment options. Here, we report on the antitumor activity and safety of dostarlimab monotherapy in pts with dMMR colorectal cancer (CRC), a post-hoc subgroup analysis of cohort F of the GARNET trial. **Methods:** GARNET is a phase 1, multicenter, open-label, single-arm study of dostarlimab monotherapy in pts with advanced or recurrent solid tumors. Cohort F of the GARNET expansion cohorts enrolled pts with dMMR/MSI-H or POLε mutated non-endometrial solid tumors, including pts with CRC. Pts must have progressed per blinded independent central review (BICR) following prior systemic therapy for advanced disease. Pts with CRC were required to have progressive disease after or been intolerant to fluoropyrimidine, oxaliplatin, and irinotecan. Pts received 500 mg intravenous dostarlimab every 3 weeks for 4 cycles, followed by 1000 mg every 6 weeks until discontinuation. Primary endpoints were objective response rate (ORR) and duration of response by BICR per RECIST v1.1. Pts were included in the efficacy analysis if they received $\geq$1 dose of dostarlimab, had measurable disease at baseline, and had $\geq$24 weeks of follow-up. All pts who received $\geq$1 dose of dostarlimab were included in the safety analysis. **Results:** As of the March 01, 2020 interim analysis data cut, 141 pts with dMMR non-endometrial solid tumors were included in the safety analysis, with 106 in the efficacy analysis. Of the pts in the efficacy analysis, 69 (65.1%) had CRC. Confirmed ORR by BICR per RECIST v1.1 in pts with dMMR CRC was 36.2% (95% CI, 25.0%–48.7%). There were 3 complete responses and 22 partial responses. At the data cut, 23 pts (92%) were still on treatment. Median duration of response had not been reached for pts with CRC. In the overall dMMR non-endometrial solid tumor population, treatment-related adverse events (TRAEs) were reported in 68.1% of pts, with 8.5% of pts experiencing at least 1 grade $\geq$3 TRAE. The most common grade $\geq$3 TRAE was lipase increased in 2 (1.4%) of pts. Only 5 pts (3.5%) discontinued dostarlimab due to at TRAE. Treatment-related serious AEs were reported in 9 (6.4%) pts. **Conclusions:** Dostarlimab demonstrated durable clinically meaningful antitumor activity in pts with dMMR CRC, which was consistent with that seen in patients with dMMR non-CRC solid tumors. No new safety signals were detected in patients with dMMR non-endometrial solid tumors. Clinical trial information: NCT02715284. Research Sponsor: GlaxoSmithKline.

Efficacy of regorafenib and 5-fluorouracil-based rechallenge treatment in the third-line treatment of metastatic colorectal cancer: A Turkish oncology group study.

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Background: The optimal treatment for metastatic colorectal cancer (mCRC) after the second line is still controversial. Regorafenib (Reg) revealed promising results by improving overall survival compared to best supportive care. However, in real-world practice rechallenge chemotherapy (CTr) is often preferred even though supporting evidence is not enough. We aim to compare the efficacy of regorafenib and 5-fluorouracil-based (5-FU) rechallenge treatment in the third line setting of mCRC. **Methods:** In this retrospective multi-institutional trial, mCRC patients from 21 centers in Turkey progressing after 2 lines of chemotherapy between 2012-2020 were analyzed. Patients who were treated with Reg or rechallenge therapy in the third-line setting were eligible. Rechallenge chemotherapy was identified as the re-use of the 5-FU based regimen which was administered in one of the previous treatment lines. Overall survival (OS), objective response rate (ORR), progression free survival (PFS) and toxicity were analyzed. Chi-square, Kaplan-Meier method and Cox regression analysis were used for analysis. **Results:** The clinical data of 441 mCRC patients were analyzed. Of these, 284 received regorafenib while 156 received rechallenge chemotherapy. The mean age was 57 and 56% was male. Median OS since the diagnosis was better with CTr than with Reg (48 months (95% CI, 43.4–52.6) vs. 39 months (95% CI, 35.4–42.5), $p<0.001$). Median OS after the third-line treatment was 12.0 (95% CI, 9.9–14) and 9.0 months (95% CI, 7.5–10.4) for CTr and Reg groups, respectively ($p<0.001$). PFS was 6 months for patients receiving CTr and 4 months for those treated with Reg ($p = 0.139$). ORR was significantly higher in CTr group than Reg ($p<0.001$). BRAF status, MSI status and treatment type (CTr vs. Reg) are factors found associated with OS in Cox regression analysis ($p<0.001$, $p=0.021$ and $p<0.001$, respectively). Adverse effects were seen in 82% and 68.2% of patients receiving Reg and CTr, respectively. Discontinuation of treatment due to adverse effects was higher in patients treated with Reg (10% vs. 2.5%). **Conclusions:** Our analysis revealed that rechallenge is an appreciated option, in both efficacy and toxicity, when the limited treatment options for mCRC is considered. Although regorafenib treatment contributes to survival, CTr shows better disease control. Our study has the highest number of patients in the literature. Still, prospective studies are mandatory for validation of CTr in the third-line treatment of mCRC. Research Sponsor: None.

203 **Poster Session**

Adverse event management costs for first-line treatment with cetuximab or panitumumab of RAS wild-type metastatic colorectal cancer patients in Latin America.

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Background: Anti-EGFR treatment of *RAS* wild-type metastatic colorectal cancer (mCRC) in Latin America includes cetuximab or panitumumab, added to chemotherapy (cet+CT and pan+CT, respectively). Adverse event (AE) profiles for each regimen may influence the treatment decision. This study aimed to estimate the associated financial impact of AE management in three countries: Argentina (AR), Brazil (BR) and Panama (PA) from a healthcare payer perspective. **Methods:** We revised a published Microsoft Excel-based economic model to calculate average patient- and population-level costs from a payer perspective of mCRC AE management for first-line cet+CT and pan+CT treatment, using AE frequency and severity data derived from the authorization relevant FDA prescribing information (PI), multiplied by the country-specific unit costs of managing AEs. Costs of AE management were obtained from publicly available sources in each country and converted to US dollars (USD). Country-specific market research data were applied to calculate costs at the eligible mCRC population level. The model structure and input parameters were endorsed by local practising oncologists. **Results:** A 17.5% (all-grade) and 31.6% (grade 3-4) lower average per patient AE frequency were estimated from the PI, for cet+CT vs pan+CT. Cost results are presented in the table. Projected AE management costs of cet+CT for the eligible mCRC population are $297,643 (AR), $124,981 (BR) and $65,895 (PA), annually, reducing current annual estimated AE costs by $42,181 (AR), $8,548 (BR) and $4,691 (PA). **Conclusions:** According to the average estimated AE frequencies, patients treated with cet+CT are expected to experience fewer AEs than with pan+CT. According to our analyses, the lower frequency rates could result in lower overall and severe AEs' management costs, resulting in 12.4% (AR), 6.4% (BR) and 6.6% (PA) lower costs of AE management for cet+CT versus pan+CT. Research Sponsor: The healthcare bussiness of Merck KGaA, Darmstadt, Germany.

Results.

	Per patient cost estimate (USD)		Estimated eligible mCRC patients per year		mCRC population AE management cost (USD)	
Country	Cet+CT	Pan+CT	Cet+CT	Pan+CT	Cet+CT	Pan+CT
AR	311	389	411	545	127,962	211,862
BR	169	194	384	354	65,031	68,499
PA	709	876	65	28	46,056	24,531

204 **Poster Session**

Survival of stage III colon cancer patients with adjuvant chemotherapy: Experience from a specialized cancer institute in Latinoamerica - Peru.

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Background: In Peru, colon cancer is the 5th most common cause of cancer and the sixth most deadly. Currently, surgery remains as the only curative therapy, however, there is risk of recurrence. Adjuvant chemotherapy has become a useful tool to improve progression-free survival (PFS) and overall survival (OS). In this study, we determine the current survival of our stage III colon cancer patients, submitted to adjuvant chemotherapy, and if this is similar to the evidence seen in large international studies; also, we analyze if delay of adjuvant chemotherapy has impact on survival. **Methods:** This descriptive cross-sectional study involved 162 patients with stage III colon cancer who underwent a resection surgery and received adjuvant fluoropyrimidine-based chemotherapy. They were evaluated, according to the TNM classification (tumor, nodule), as low risk (T1-T3, N1) and high risk (T4, N2). We also classified patients, according to the weeks of delay from surgery to adjuvant chemotherapy, into subgroups of 6, 8 and 10 weeks. **Results:** The mean age was 63.7 years, 63 patients were women (38.9%), 99 patients (61.1%) were men. Only 38.3% of patients started adjuvant chemotherapy in the first 6 weeks after surgery, and 85.8% of patients, in the first 10 weeks; the median time from surgery to initiation of adjuvant chemotherapy was 7.0 weeks. We estimated that, at 3 years, the median PFS is 73.5% (95% CI: 65.8-82.1). The 3-year PFS in the low-risk group was 82.9% (95% CI: 72.3-95.0) and 67.3% (95% CI: 57.2-79.2) in the high-risk group. It was estimated that at 3 years, the median OS is 81.1% (95% CI: 75.2-87.5). The 3-year OS in the low-risk group was 87.9% (95% CI: 80.4-96.2) and 76.0% (95% CI: 67.8-85.3) in the high-risk group. **Conclusions:** The PFS and OS in Peruvian population is similar to data evidenced in international historical studies such as the IDEA trial. This study, also, suggests that starting adjuvant treatment within 10 weeks does not present an impact on OS and PFS in our population. Research Sponsor: None.

205 **Poster Session**

Colontown University: Patient-created disease education.

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Background: PALTOWN's Facebook community, COLONTOWN, serves over 6,000 colorectal cancer (CRC) patients and caregivers. 81% of members are late stage patients (or late stage caregivers), and 85% are under the age of 60. They are highly motivated to find reliable information about treatment options as quickly as possible. Many arrive with little prior CRC education. Here we illustrate the creation of a patient-centric disease education program, COLONTOWN University (CTU), developed from the conversations and information journeys in COLONTOWN. **Methods:** CTU is a unique model for disseminating patient-facing disease education. CTU's patient and caregiver staff develop original resources from a patient perspective, and work with principal investigators, testing companies, and other partners to create content specifically designed for the Learning Centers. Each Center provides resources to address the information needs of patients across both the spectrum of disease education and of CRC disease experience. Within the University's online platform, self-contained Learning Centers offer structured resource libraries on topics of high interest to patients. **Results:** CTU creates patient-centric disease education that is accessible and more sophisticated than typical patient education materials. The discussions in COLONTOWN, in groups focused on specific biomarkers, metastases locations, and treatment modalities, provide members with the framework for understanding their disease. CTU gives them the resources they need to have informed discussions with their care teams. The CTU platform provides insight into what resources are most utilized. Survey tools facilitate an understanding of whether patients feel they have access to more treatment options, and have more productive interactions with their care teams, as a result of the education provided by CTU and the conversations with their peers in COLONTOWN. **Conclusions:** In its first year, CTU has become the education resource of choice for the thousands of members of COLONTOWN. Clinicians, principal investigators, and industry have all been enthusiastic partners in the development of resources. The positive response to CTU demonstrates the value of this model of patient-driven disease education. Research Sponsor: Various companies such as Natera Oncology, Guardant Health, Seagen, Taiho, and Thermo Fisher.

Learning Center	Focus	Scope
CRC 101	What do newly diagnosed late-stage patients need to know?	Understanding diagnosis and first line treatment options
Diagnostic and Surveillance Tests	What are current biomarker testing options for CRC?	Role of biomarkers in treatment, new testing options
Clinical Trials Basics	How to navigate the clinical trials ecosystem	Understanding clinical trials, and identifying trial options to discuss with care team
Precision Medicine	How is precision medicine used in CRC	Understanding precision medicine and its current application in CRC
The Lecture Hall	CRC education directly from clinicians and researchers	Video library from immunotherapy to liver transplants

Deviation from the precisely timed age-associated patterns revealed by blood metabolomics to find CRC patients at risk of relapse at the CRC diagnosis.

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Background: Human serum metabolome profiles have been analyzed to explore the molecular changes that occur with aging. We hypothesized that deep metabolic profiling of sera with different ages would allow the identification of distinct metabolic chronologic patterns as a normal biological baseline to study personal aging. We further hypothesized that metabolic assessment of this chronologic deviation, resulting from advanced precancerous lesion (APL) and stage I/II/III CRC, from the normal reference baseline, would be instrumental for prognosis of relapse revealing underlying pathophysiology. **Methods:** A cohort of normal (n=3,616, training; n=1,170, testing), 631 advanced adenoma, 1,019 stage I, 404 stage II and 417 stage III serum samples were assembled. Innovative global LCMS metabolomic production were applied to deep profile these subjects. Identification of the age-associated molecular patterns in normal subjects, modeled with an elastic net algorithm, established the reference baseline to mirror a metabolic clock. CRC associated deviation from the precise chronologically paced metabolic patterns was quantified to associate the clinical endpoints of relapse, OSF and PFS, and to identify the tightly associated metabolic pathways. **Results:** We observed that for those CRCs, the predicted metabolic age can differ from the chronological age with consistent variations, resulting "older" or "younger" metabolic age subgroup in reference to the chronological age. Significant disruptions from the normal baseline were observed in CRCs patients, and consistent stage specific patterns were observed. Outlier, "Older" or "younger" metabolic age subgroup, CRC patients were found with significant future relapse enrichment. Predictive models were derived to case find the patients at risk of future relapse at the CRC diagnosis timepoint. **Conclusions:** Deviations from the meticulously timed metabolic aging patterns may provide utility to allow prognosis of future clinical endpoints of relapse and overall survival. Close examination of the underlying metabolic pathways, associated with CRC stage specific metabolic patterns, disrupting the baseline ageotypes, not only may improve the sensitivity and specificity of prognostic tests of CRC relapse, but also shed new insights into CRC therapeutics. Research Sponsor: None.

TPS207 **Trials in Progress Poster Session**

A proof-of-concept formative trial evaluating the interest of multiple connected devices for the early detection of hand-foot skin reactions in patients treated with regorafenib therapy (FACET).

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Background: Hand-foot skin reaction (HFSR) is a common skin toxicity associated with regorafenib that may lead to drug withdrawal, dose reduction, or drug interruption. Predicting or recognizing early symptoms of HFSR could allow for better care. Digital solutions for ambulatory monitoring of patients provide an opportunity for monitoring and early detection of HFSR in home conditions. **Methods:** FACET is a phase 4, prospective, open-label, multicenter, interventional trial designed to assess the clinical utility, technical feasibility and usability of a system including a camera, FeetMe Connected insoles for gait assessment, ePRO questionnaires (HFS-14, EQ-5D-5L, FAS and VAS), and educational materials to detect and grade the severity of HFSR. During the study, enrolled patients developing an HFSR will be assigned to the HFSR group and patients without any sign of HFSR, they will be assigned to non-HFSR group. Study registration number at ANSM (French Authority): ID-RCB 2020-A03080-39. Patients will have metastatic colorectal cancer requiring initiation of regorafenib in accordance with clinical practice standard. Other key inclusion criteria are ECOG Performance Status 0-2, ability to understand the instructions and complete the ePRO questionnaires, ability to understand and communicate in French language, familiarity in using mobile communication devices and mobile application software, no previous episode of HFSR or HFS. The primary objective is to explore fit-for-purpose, and usability of the ePRO instruments and the data collecting devices. The primary endpoint is participants' compliance with data collection measured by ePRO questionnaires completion, use of camera to take images vs expected and number of device days of insoles usage vs expected. Secondary objectives are to characterize variables exhibiting significant associations with development of HFSR. Secondary endpoints include summary statistics of ePRO questionnaires scores at the HFSR worst grade event in the HFSR group vs at 3 weeks in the non-HFSR group; Summary statistics for Feetme Connected insoles variables; Regorafenib dose modifications and treatment discontinuation; Participant's device daily use to generate data; Participants ability to reach a hotline for technical issues or usability complaints. For HFSR related secondary endpoints, a blinded and independent Preliminary Adjudication Committee (PAC) will retrospectively assign participants to two groups (HFSR vs. no-HFSR) based on a case-by-case blinded assessment. An independent Final Adjudication Committee will compare the PAC assessment and investigators' assessments done on site. It is planned to include a total of 38 participants from 4 centers. As of September 2021, all sites are open and ready to enroll. Study funded by Bayer. Research Sponsor: Bayer.

TPS208 **Trials in Progress Poster Session**

Prevention of colorectal cancer through multiomics blood testing: The PREEMPT CRC study.

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Background: The USPSTF recently recommended colorectal cancer (CRC) screening for adults aged 45 to 49 years in addition to those aged 50 to 75 years. This guideline update, which increases the number of screen-eligible individuals by ~19 million, is similar to the recommendation in 2018 by the American Cancer Society (ACS) and is based on the modeling studies that reflect rising CRC incidence rates in younger adults. Currently, only 67% of average-risk individuals over the age of 50 years are up-to-date on CRC screening, and adherence to screening is lower in younger individuals (e.g., 50-54 years). Despite the non-invasive nature of existing stool-based CRC tests, barriers remain to adoption, including a dislike for manipulating stool and a requirement for substantial navigational support. Blood tests may overcome these barriers through ease of sample collection and integration into routine blood work. **Methods:** Here we describe our prospective, multi-center registrational study for validating a blood-based multiomics test for average-risk CRC screening: PREEMPT CRC. Eligible participants include those aged 45-85 with no known history of CRC or colorectal adenomas who are undergoing CRC screening by colonoscopy. The target enrollment is 25,000 participants, and primary outcome measures are sensitivity for CRC and specificity for advanced colorectal neoplasia, which includes CRC and advanced adenomas. Secondary outcome measures include positive predictive value for CRC, negative predictive value for advanced colorectal neoplasia, and sensitivity for advanced adenomas. Novel recruitment methods have been implemented by combining traditional, site-based recruitment and virtual recruitment using an online web portal, coupled with mobile phlebotomy, to make participation broadly accessible, especially during the COVID-19 pandemic. Participants have been enrolled from 40 states as of August 2021, and virtual recruitment has enabled widespread participation, potentially from any zip code in the continental US. To ensure adequate representation of the intended use population, community organizations, federally qualified health centers (FQHCs), and universities have been engaged to reach underserved and minority patient populations. The study was initiated in May 2020 and to our knowledge will be the largest prospective, multi-center registrational validation study of an average-risk CRC screening test to date. Clinical trial information: NCT04369053. Research Sponsor: None.

TPS209 **Trials in Progress Poster Session**

Phase II trial of moderate dose omega-3 acid ethyl esters for colorectal cancer prevention in patients with lynch syndrome (COLYNE).

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Background: Lynch syndrome (LS) is the most common inherited colorectal cancer (CRC) syndrome and is responsible for about 3% of newly diagnosed CRC. It is caused by germline mutations in one of the DNA mismatch repair (MMR) genes, and patients with LS carry a lifetime risk of CRC ranging between 10% and 70%. The role of inflammation in driving this malignant transformation is now well established and retrospective studies have revealed a potential chemo-preventative role for omega-3 (ω-3) polyunsaturated fatty acids (PUFAs), possibly via inhibition of inflammatory pathways associated with the development of defective MMR CRC tumors. While patients with LS have the highest risk of developing CRC, the majority of chemoprevention trials are focused on sporadic CRC. Effective interventions to reduce the risk of developing CRC in this population are limited to close surveillance and surgical prophylaxis. There is an unmet need for safe, effective, and non-invasive chemo-preventive interventions in patients with LS. **Methods:** This pilot study is a single-arm, open-label, phase 2 clinical trial of omega-3 acid ethyl esters (generic Lovasa; 2 grams orally once daily) for adult patients ($\geq$ 18 years of age) with confirmed LS (based on germline testing of the MMR genes panel: *MLH1*, *MSH2*, *MSHS6*, *PMS2* or deletion in *EPCAM* gene). Patients who are not candidate for elective endoscopy and/or with prior history of right sided or pan-colectomy are excluded. Thirty-four patients are expected to enroll, with a primary objective to determine the feasibility (defined as 80% retention rate) of 12 months of treatment with 2 grams capsules of omega-3 acid ethyl esters daily. Secondary endpoints include safety and tolerability of the intervention. Correlative aims include pre and post treatment assessment of colon mucosal tissue proliferation (right sided colon specimens will be evaluated for markers of proliferation (Ki-67) and apoptosis (Caspase-3)), the effect of omega-3 acid ethyl esters on inflammatory markers in serum, urine and feces (PGE-2, COX-2, β-catenin levels, and EPA:AA ratios), and gene expression related to proliferation, apoptosis and cell survival in colon tissue (NF-κB/Wnt pathways). The impact of omega-3 acid ethyl esters on intestinal microbiota will also be assessed (16S rRNA-based profiling). Correlative Colon tissue, serum, urine and feces samples are collected at baseline and at 12 months. The study is actively enrolling with 20 patients enrolled at the time of submission. Clinical trial information: NCT03831698. Research Sponsor: Kansas University Institutional funding.

TPS210 **Trials in Progress Poster Session**

Neoadjuvant chemoradiotherapy with or without Pd-1 antibody sintilimab for pMMR/MSS/MSI-L locally advanced rectal cancer: A randomized controlled study (cohort B).

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Background: Neoadjuvant chemoradiotherapy (NACRT) could bring tumor downstaging and pathological response (pCR), and also survival benefit for locally advanced rectal cancer (LARC) patients. Several single arm prospective clinical trials have investigated combination effect of immunotherapy (PD-1 or PD-L1 antibody) and NACRT in LARC patients, such as the VOLTAGE clinical trial. A randomized trial is needed to confirm the benefit of immunotherapy in this setting and explore predictive biomarkers. This is a clinical trial with two cohorts according the MMR/MSI status (clinicalTrials.gov, NCT04304209). **Methods:** In this study, LARC patients with pMMR/MSS/MSI-L tumor will enter cohort B and be randomized into two arms. Main inclusion criteria include: cT3-4N0M0 or cTxN+M0 rectal adenocarcinoma, pMMR/MSS/MSI-L confirmed by immunohistochemistry or gene test, aged 18-75y; ECOG performance 0-1; no previous anti-tumor treatment for rectal adenocarcinoma. Main exclusion criteria include: active autoimmune diseases or a history of autoimmune diseases, and inadequate main organ functions. Patients in the experimental arm will receive four cycles of neoadjuvant PD1 antibody Sintilimab, Capeox chemotherapy and concurrent radiotherapy, followed by curative surgery or watch and wait, then four cycles of adjuvant Capeox chemotherapy. Patients in the control arm will receive four cycles of neoadjuvant Capeox chemotherapy and concurrent radiotherapy, followed by curative surgery or watch and wait, then four cycles of adjuvant Capeox chemotherapy Primary outcome measure is pCR rate. Secondary outcome measures include acute toxicity, tumor regression grade, R0 resection rate, local recurrence, distant metastasis. Sample size for this cohort is 134. Whole exome sequencing, RNA sequencing and immunohistochemistry of the rectal primary tumor are planned for biomarker searching and synergy effect mechanism investigation. The first patient has been enrolled in June, 2020. Clinical trial information: NCT04304209. Research Sponsor: None.

TPS211 **Trials in Progress Poster Session**

BREAKWATER: Randomized phase 3 study of encorafenib (enco) + cetuximab (cet) ± chemotherapy for first-line treatment (tx) of *BRAF* V600E-mutant (BRAFV600) metastatic colorectal cancer (mCRC).

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Background: Approximately 10% of patients (pts) with mCRC have *BRAF* mutations (mostly V600E). First-line tx options for $BRAF^{V600E}$ mCRC are limited to cytotoxic chemotherapy ± anti-VEGF or anti-EGFR; or immune checkpoint inhibitors in pts with MSI-H tumors. In Europe, Japan, and USA, the combination of BRAF inhibitor enco + EGFR inhibitor cet is approved for tx of $BRAF^{V600E}$ mCRC after prior therapy. In BEACON CRC, enco + cet resulted in a median overall survival (OS) of 9.3 months (95% confidence interval [CI]: 8.0–11.3) and an objective response rate (ORR) of 19.5% (95% CI: 14.5%–25.4%) in previously treated pts with $BRAF^{V600E}$ mCRC (median follow-up: 12.8 months); 57.4% of pts had grade 3/4 adverse events (AEs), and 9% discontinued due to AEs. Given the poor prognosis of pts with $BRAF^{V600E}$ mCRC and based on the efficacy and tolerability of enco + cet from BEACON CRC, the BREAKWATER study will evaluate the efficacy and safety of enco + cet ± chemotherapy in tx-naive pts with $BRAF^{V600E}$ mCRC. **Methods:** BREAKWATER is an open-label, global, multicenter, randomized, phase 3 study with a safety lead-in (SLI). Approximately 60 and 870 pts will be enrolled in the SLI and phase 3 parts of the study, respectively. Pts must have mCRC with *BRAF* V600E-mutation (determined using tumor tissue or blood); ECOG performance status 0/1; and adequate bone marrow, hepatic, and renal function. Pts in the SLI must have evaluable disease (RECIST v1.1) and have received ≤ 1 prior tx regimen; those previously treated with a BRAF or EGFR inhibitor, or both oxaliplatin and irinotecan, will be excluded. Pts in the phase 3 study must have measurable disease and be tx naive for metastatic disease. Study tx and endpoints are shown in the table. Enrollment began on 06-Jan-2021. Clinical trial information: NCT04607421. Research Sponsor: Pfizer.

	SLI	Phase 3
Tx*	Enco 300 mg QD + cet 500 mg/m^{2†} + mFOLFOX6† or Enco 300 mg QD + cet 500 mg/m^{2†} + FOLFIRI†	Arm A Enco 300 mg QD + cet 500 mg/m^{2†} Arm B Enco 300 mg QD + cet 500 mg/m^{2†} + mFOLFOX6† or FOLFIRI† (depending on SLI) Control (± bevacizumab) mFOLFOX6† or FOLFOXIRI† or FOLFIRI† or CAPOX (21-day cycle; oxaliplatin, Q3W; capecitabine, BID Day 1–14)
Endpoints		
Primary	Incidence of dose-limiting toxicities	Progression-free survival (PFS; by blinded independent central review [BICR]) (arm A vs control; arm B vs control)
Secondary	Incidence/severity of AEs, ORR, duration of response (DOR), PFS, time to response (TTR), OS, pharmacokinetic (PK) parameters, drug–drug interaction of enco with irinotecan/oxaliplatin	**Key:** OS (arm A vs control; arm B vs control) **Other:** ORR, DOR, PFS (arm A vs arm B by BICR; arm A vs control, arm B vs control, and arm A vs arm B by investigator), OS (arm A vs arm B), TTR, progression after next tx line, incidence/severity of AEs, patient-reported outcomes, PK parameters, MSI status, *BRAF* V600E variant allele fraction

* All 28-day cycles except CAPOX; † Q2W.

TPS212 **Trials in Progress Poster Session**

NRG-GI008: Colon adjuvant chemotherapy based on evaluation of residual disease (CIRCULATE-US).

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Background: Currently, there are no biomarkers validated prospectively in randomized studies for resected colon cancer (CC) to determine need for adjuvant chemotherapy (AC). However, circulating tumor DNA (ctDNA) shed into the bloodstream represents a highly specific and sensitive approach (especially with serial monitoring) for identifying microscopic or residual tumor cells in CC patients (pts) and may outperform traditional clinical and pathological features in prognosticating risk for recurrence. CC pts who do not have detectable ctDNA (ctDNA-) are at a much lower risk of recurrence and may not need AC. Furthermore, for CC pts with detectable ctDNA (ctDNA+) who are at a very high risk of recurrence, the optimal AC regimen has not been established. We hypothesize that for pts whose colon cancer has been resected, ctDNA status may be used to risk stratify for making decisions about AC. **Methods:** In this prospective phase II/III trial, up to 1,912 pts with resected stage III A, B (all pts) and stage II, IIIC (ctDNA+ only) CC will be enrolled. Based on the post-operative ctDNA status using Natera's Signatera assay, those who are ctDNA- (Cohort A) will be randomized to immediate AC with fluoropyrimidine (FP) + oxaliplatin (Ox) for 3-6 mos per established guidelines vs serial ctDNA monitoring. Patients who are ctDNA+ post-operatively or with serial monitoring (Cohort B) will be randomized to FP + Ox vs more intensive AC with addition of irinotecan (I) for 6 mos. The primary objectives for Cohort A are time to ctDNA+ status (phase II) and disease-free survival (DFS) in phase III in the immediate vs delayed AC arms. The primary objective for Cohort B is DFS in the FP + Ox vs FP + Ox + I arms for both phase II and phase III portions of the trial. Secondary objectives include prevalence of detectable ctDNA post-operatively, time-to event outcomes (overall survival & time to recurrence) by ctDNA status, and the assessment of compliance to adjuvant therapy. Biospecimens including archival tumor tissue, post-operative and serial matched/ normal blood samples will be collected for exploratory correlative research. Study will activate in early 2022 across the NCTN. NCT#: Pending. Support: U10-CA-180868, -180822; UG1CA-189867; Natera. Research Sponsor: U.S. National Institutes of Health, Natera.

TPS213 **Trials in Progress Poster Session**

REVERCEII (ACCRU-GI-1809): A randomized phase II study of regorafenib followed by anti-EGFR monoclonal antibody therapy versus the reverse sequencing for metastatic colorectal cancer patients previously treated with fluoropyrimidine, oxaliplatin and irinotecan.

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Background: Regorafenib (R) is an oral multikinase inhibitor that blocks several protein kinases involved in angiogenesis and oncogenesis; it has a survival benefit in refractory metastatic colorectal cancer (mCRC). The current standard (std) treatment in patients (pts) with RAS wildtype (WT) mCRC is sequential treatment with an anti-EGFR antibody (AEA) followed by R. However, R, which is orally administered once daily, may be more convenient and thus preferable for pts than AEA. REVERCE, a Japanese trial, demonstrated a significant 5.8 month (mo.) survival benefit with regorafenib administered prior to AEA compared to the std sequence. Based off these findings, the proposed phase II trial is to confirm the observed survival benefit from regorafenib sequencing prior to anti-EGFR monoclonal antibody therapy in REVERCE in a US patient population. **Methods:** REVERCEII is an Academic and Community Cancer Research United (ACCRU) network-led randomized phase II study of R (dose escalation from 80mg to 160mg based on tolerance) prior to AEA (R+AEA) compared to standard sequencing (AEA+R) in pts with refractory RAS WT mCRC. Patients are randomized 1:1 to receive R (Arm A) vs. AEA (with or without irinotecan per investigator choice) (Arm B). At the time of disease progression or intolerance, patients will receive sequential treatment until disease progression. Eligibility criteria include histologically confirmed mCRC, ECOG $\leq$ 2, acceptable organ function, and patients must have had prior fluoropyrimidine, oxaliplatin and irinotecan, and no prior AEA nor R. The primary objective is to compare the overall survival (OS), the primary endpoint, between evaluable patients (eligible, consented, started protocol treatment) who were randomized to R+AEA (arm A) and AEA+R (arm B). With 83 OS events, we have 87% power to detect an improvement in median OS from 9 months to 14.5 mo., assuming 1-sided significance level of 0.15, and exponential distribution. The total sample size is 124 patients. Secondary endpoints include progression-free survival, objective response, and adverse events. The total study duration is expected to be 3 years. Clinical trial information: NCT04117945. Clinical trial information: 04117945. Research Sponsor: Bayer.

TPS214 **Trials in Progress Poster Session**

A phase 1b study of sotorasib, a specific and irreversible KRAS^{G12C} inhibitor, in combination with other anticancer therapies in advanced colorectal cancer (CRC) and other solid tumors (CodeBreaK 101).

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Background: Approximately 3% of patients (pts) with CRC have the oncogenic *Kirsten rat sarcoma viral oncogene homolog (KRAS)* p.G12C mutation. Sotorasib, a small molecule that specifically and irreversibly inhibits the KRAS G12C mutant protein, has demonstrated modest clinical activity and no dose-limiting toxicities as a single agent in heavily pretreated pts with *KRAS* p.G12C-mutated CRC. The combination of sotorasib with other anticancer therapies, such as EGFR or MEK inhibitors, may enhance antitumor efficacy and counteract potential escape mechanisms. Other attractive partners for sotorasib in CRC include biologics and chemotherapy combinations. The CodeBreaK 101 master protocol is designed to evaluate safety, tolerability, pharmacokinetics (PK), and efficacy of multiple sotorasib-based combinations in pts with *KRAS* p.G12C mutated solid tumors. Key subprotocols with CRC combination treatment arms are highlighted here. **Methods:** This is a phase 1b, open-label study evaluating sotorasib alone and in combination regimens in pts with advanced *KRAS* p.G12C mutated CRC, NSCLC, and other solid tumors. Key regimens being explored in CRC include (1) Subprotocol A: Sotorasib + trametinib (MEK inhibitor) +/- panitumumab (EGFR inhibitor), (2) Subprotocol H: Sotorasib + panitumumab and sotorasib + panitumumab + FOLFIRI, and (3) Subprotocol M: Sotorasib + bevacizumab-awwb + FOLFIRI or FOLFOX. Key eligibility criteria include advanced or metastatic solid tumor with *KRAS* p.G12C mutation identified through molecular testing in treatment-naïve and pretreated patients depending on cohort. Primary endpoints include dose-limiting toxicities and treatment-emergent or treatment-related adverse events. Secondary endpoints include PK profile of combination regimens and efficacy (objective response, disease control, duration of response, time to response, and progression-free survival assessed per RECIST 1.1, and overall survival). Enrollment is ongoing. Contact Amgen Medical Information for more information: medinfo@amgen.com (NCT04185883). Abbreviations: EGFR = epidermal growth factor receptor; FOLFIRI = 5-fluorouracil + leucovorin + irinotecan; FOLFOX = 5-fluorouracil + leucovorin + oxaliplatin; MEK = mitogen-activated protein kinase. Clinical trial information: NCT04185883. Research Sponsor: Amgen Inc.

TPS215 **Trials in Progress Poster Session**

A randomized, double-blind, phase III study comparing trifluridine/tipiracil hydrochloride therapy versus placebo in resected colorectal cancer patients who are positive for blood circulating tumor DNA after standard adjuvant therapy (EPOC 1905): ALTAIR trial in CIRCULATE-Japan (trial in progress).

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Background: Circulating tumor DNA (ctDNA) can be used to predict the risk of recurrence by detecting molecular residual disease (MRD) in patients with colorectal cancer (CRC). Although patients with MRD positive status have extremely high risk of relapse, no standard treatment has been established for these patients after adjuvant chemotherapy. Trifluridine/tipiracil hydrochloride (FTD/TPI) is an oral anti-tumor agent combining thymidine-based nucleoside analogue with a thymidine phosphorylase inhibitor, which presents improved survival in patients with metastatic CRC refractory to fluoropyrimidines. **Methods:** The ALTAIR trial is a randomized, double-blind, phase III study designed to establish the superiority of FTD/TPI as compared with placebo in patients with resected CRC who show MRD positive status at any time after curative resection. ctDNA testing for screening patients with MRD positive is performed in the observational GALAXY study (UMIN000039205) that is a prospectively conducted large-scale nationwide registry designed to monitor ctDNA status for patient who can undergo curative resection. A personalized tumor-informed assay (Signatera bespoke multiplex-PCR NGS assay) is used for the detection and quantification of ctDNA-based postsurgical MRD. Key eligibility criteria are (a) having undergone radical resection of primary and/or metastatic tumors, (b) a history of standard adjuvant chemotherapy, (c) positive ctDNA status within the previous 3 months at any time postoperatively, and (d) no obvious relapse confirmed by chest, abdominal, and pelvic CT scans. Patients will be randomly assigned in a 1:1 ratio to receive either 6 months of oral FTD/TPI or a matching course of placebo. Randomization is stratified by age ($<$70 vs. $\geq$70 years), stage (stage II or lower vs stage III vs. stage IV or M1), primary tumor location (right-sided vs left-sided colon vs rectum), ctDNA status at 1 month (positive vs negative or unmeasurable), and institution. The primary endpoint is disease free survival (DFS). Key secondary endpoints include rate of conversion from positive to negative ctDNA status, overall survival, adverse events, and quality of life. Assuming that the median DFS in the placebo group is approximately 8 months, a total of 240 patients (120 per arm) will provide 80% power to detect an expected DFS hazard ratio of 0.667 at two-sided significance level of 0.05, with an enrollment period of 2 years and a follow-up period of 1 year. This trial is actively accruing across 39 institutions in Japan and Taiwan and opened to recruitment in August 2018. By October 2021, a total of 67 patients have been enrolled. Clinical trial information: JapicCTI-205363/NCT04457297. Research Sponsor: Taiho Pharmaceutical Co., Ltd.

TPS216 **Trials in Progress Poster Session**

GOBLET: A phase 1/2 multiple-indication biomarker, safety, and efficacy study in advanced or metastatic gastrointestinal cancers exploring treatment combinations with pelareorep and atezolizumab.

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Background: Checkpoint blockade therapy only benefits a small subset of GI cancer patients (approximately 4%) with microsatellite instability-high (MSI-H) tumors, which are characterized as immunologically 'hot' (Bonneville et al., 2017). Most GI cancers, however, have microsatellite stable (MSS) tumors, which have an immunologically "cold" phenotype with fewer genetic mutations, reduced immune cell infiltration, and downregulated immune checkpoint proteins. These attributes make MSS tumors resistant to conventional immunotherapy including checkpoint blockade therapy (Ooki et al., 2021). Pelareorep is a naturally occurring, non-genetically modified reovirus. Upon intravenous administration, pelareorep selectively kills tumor cells and promotes several immunologic effects that prime tumors to respond to checkpoint blockade. These include the stimulation of tumor-directed innate and adaptive immune responses, increased T cell infiltration, expansion of new T cell clones, and increased PD-L1 expression in tumors (Samson et al., 2018, Manso et al. 2021 AACR). Given its expected synergy with checkpoint blockade, as well as its encouraging efficacy in prior GI cancer studies (Mahalingam et al. 2020), the GOBLET study is designed to evaluate pelareorep plus atezolizumab in multiple GI cancer indications. **Methods:** GOBLET is an open-label, non-randomized, multiple-cohort, phase 1/2 study in patients with advanced or metastatic GI cancers. This study employs a Simon two-stage design. Stage 1 comprises four treatment groups: Cohort 1 – First-line pancreatic cancer treated with pelareorep plus atezolizumab and chemotherapy (gemcitabine and nab-paclitaxel) (N = 12); Cohort 2 – First-line MSI-H colorectal cancer (CRC) treated with pelareorep plus atezolizumab (N = 19); Cohort 3 – Third-line CRC treated with pelareorep plus atezolizumab and chemotherapy (trifluridine/tipiracil) (N = 14); and Cohort 4 – Second-line or later squamous cell carcinoma of the anal canal treated with pelareorep plus atezolizumab (N = 10). The first 3-6 patients enrolled into the chemotherapy-containing cohorts (Cohorts 1 and 3) comprise a safety run-in that must be successfully concluded prior to enrolling additional patients into these cohorts. The primary objectives are safety and efficacy based on objective response rate (ORR) at week 16. Any cohort showing a promising ORR in Stage 1, based on pre-specified criteria, may be advanced to Stage 2 and enroll additional patients. Clinical trial information: 2020-003996-16. Research Sponsor: Oncolytics Biotech Inc.

TPS218 **Trials in Progress Poster Session**

Phase II trial of organ preservation program using short-course radiation and folfoxiri for rectal cancer (SHORT-FOX).

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Background: Locally advanced rectal cancer is treated with preoperative chemoradiotherapy followed by total mesorectal excision (TME). While this trimodal approach achieves low rates of local recurrences, distant metastasis rates can exceed 25%. Total neoadjuvant therapy (TNT) has been shown in OPRA, RAPIDO, and PRODIGE23 to reduce risk of distant metastasis and improve rates of pathological complete response compared to standard preoperative chemoradiotherapy. Thus, TNT not only addresses distant disease, but gives opportunity to reduce locoregional morbidity through organ preservation. We propose a treatment approach that incorporates TNT with FOLFOXIRI and up-front short-course radiation with the goal of increasing clinical complete response (cCR) rates and thereby eligibility for organ preservation. Currently, clinical response following neoadjuvant therapy is best assessed by a multidisciplinary team and includes flexible endoscopy and MRI. Circulating tumor DNA (ctDNA) analysis can be used as a noninvasive method for tumor monitoring. Biomarker development is essential to better select patients for treatment de-escalation and monitor for recurrence in order not to jeopardize the excellent cure rates following standard of care therapy. **Methods:** This is a single-arm, open-label, non-randomized study of an organ preservation approach using short-course radiation followed by FOLFOXIRI for patients with $>$ T2N0 or low T2N0, M0 rectal adenocarcinoma (NCT04380337). Patients undergo radiation (25 Gy/5 fractions + 5 Gy/1 fraction boost) followed by 8 cycles of FOLFOXIRI. Patients are assessed for response at 8 weeks following chemotherapy completion using pelvic MRI (MRI Tumor Regression Grading), flexible sigmoidoscopy, and digital rectal exam. Those who achieve a cCR can defer TME and be surveilled. The primary objective is to assess cCR, with the hypothesis that this approach will achieve higher cCR rates than historical controls (40 versus 20%). Secondary objectives include assessing toxicity, local regrowth rate, disease-free survival, colostomy-free survival, overall survival, and longitudinal health-related quality of life. ctDNA will be collected throughout treatment and surveillance, and correlative studies will assess the association between ctDNA levels and cCR, local regrowth, and disease-free survival. A Simon 2-stage design addressed our primary objective. Assuming a one-sided type 1 error of 0.1, power of 0.9, a null cCR of 0.2 versus an alternate cCR of 0.4, we plan to enroll 37 patients. The null hypothesis will be rejected if $>=$ 11 patients have cCR. Seventeen patients have been enrolled and the trial is currently on hold for planned interim analysis for futility and safety. If $<=$ 3 patients have cCR or if $>=$ 7 patients have non-hematologic grade 4+ toxicity, the study will be stopped. Otherwise, we will continue to enroll 20 more patients. Clinical trial information: NCT04380337. Research Sponsor: None.

TPS219 **Trials in Progress Poster Session**

A phase 1b/2 study of VS-6766 in combination cetuximab in patients (pts) with advanced KRAS mt colorectal cancer (CRC).

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Background: *KRAS* mutations (mts) are present in about 45% of CRC and predict lack of response to anti-EGFR therapy like cetuximab. Limited therapy options exist for pts after prior 5-FU based regimens. Regorafenib or TAS-102 is commonly used however, the modest clinical benefit, and toxicity limit their use. Novel therapies are needed for pts at this point in their disease course. *KRAS G12D* and *G12V* mts occur in 11-12% and 9-10% of CRC, respectively, whereas G12C mts occur in 3-4% of CRCs. *KRAS G12C* mts occur in 3-4% of CRCs. Recently, results of phase 1/2 KRYSTAL-1 study were reported. Adagrasib (a *KRAS G12C* inhibitor) was used with/without cetuximab in heavily pretreated CRC pts harboring *KRAS G12C* mts. The objective response rate (ORR) and disease control rate (DCR) was 43% and 100% (resp.) in pts receiving cetuximab and adagrasib (28 evaluable pts), and 22% and 87%, resp., in those receiving adagrasib alone (42 evaluable pts). Phase 1b CodeBreaK101 study evaluating sotorasib (*KRAS G12C* inhibitor) and panitumumab (anti-EGFR) combination in *KRAS G12C* mt CRC showed 15.4% confirmed ORR and 26.9% unconfirmed ORR. These data are encouraging, suggesting EGFR inhibition in combination with downstream *KRAS* inhibition may represent important therapeutic strategy for this disease. *KRAS* mts lead to constitutive activation of the MAPK pathway signaling and cell activation. VS-6766 is a novel dual RAF/MEK inhibitor which has shown activity in *KRAS* mutated tumors. Combination of EGFR inhibition and VS-6766 may overcome resistance of *KRAS* mt CRC cancers to EGFR inhibition alone. Preclinically, VS-6766 and EGFR inhibition showed synergy in *KRAS* mt CRC cell lines, including cell lines harboring *KRAS G12D* and *G12V* mts, and CRC PDX of *KRAS G12V* mt CRC showed tumor regression with this combination. These data support the development of VS-6766 with anti-EGFR therapy in KRAS mt CRC warranting this phase 1 study to evaluate safety and efficacy of this combination in clinical settings. **Methods:** This is an open label, single arm study evaluating VS-6766 with cetuximab in pts with *KRAS* mt advanced CRC. Phase 1b primary endpoints include safety and tolerability, and maximum tolerated dose and recommended phase 2 dose determination. ORR is the primary endpoint of the Phase 2 study. Secondary endpoints include OS and PFS. There will be upto 4 dose levels tested. Three de-escalation doses to find the optimal cetuximab dose, and one dose escalation of VS-6766, are planned. Eligible pts include those with metastatic CRC and progression after 5-FU, oxaliplatin, irinotecan and VEGFi therapy. Based on prior studies, dermatologic, gastrointestinal, ocular and CPK elevation have been the main toxicities noted with VS-6766. The study is funded by research grants from Verastem Oncology. Cetuximab will be supplied by Eli Lilly. Research Sponsor: Verastem Oncology.

TPS220 **Trials in Progress Poster Session**

Anlotinib combined with mXELIRI as second-line treatment in advanced colorectal cancer pretreated with bevacizumab plus standard chemotherapy: A single-arm, phase IB/II study.

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Background: For advanced colorectal cancer (CRC), fluoropyrimidine-based chemotherapy (5-FU or capecitabine combined with oxaliplatin) with VEGF inhibitors (bevacizumab) is standard first-line treatment. However, once this treatment had been used, the second line treatment is limited. Although continuation of bevacizumab after first progression can improve PFS and OS, the benefit of bevacizumab may be reduced compared with who never pre-treated with bevacizumab (the ML18147 study). Anlotinib is an oral small molecule tyrosine kinases inhibitor, targeting VEGF receptors 1/2/3, FGF receptors 1-4, PDGF receptors α/β and c-kit. mXELIRI is a chemotherapy regimen consisting of irinotecan and capecitabine. The trial is to investigate the efficacy and safety of anlotinib combined with mXELIRI as second-line treatment in advanced colorectal cancer pre-treated with bevacizumab plus standard chemotherapy. **Methods:** This is a multi-center, prospective, single-arm, 2-part, phase Ib/II study. Eligible pts are aged 18-75 years with histologically and radiographically confirmed mCRC who had progressed or intolerant with bevacizumab plus FOLFOX or CAPEOX regimen chemotherapy treatment. ECOG performance status 0 - 1, and adequate organ function. Treatment: anlotinib (8mg, 10mg or 12mg), po, qd, on days 1-14 every 3 weeks; irinotecan 180-200 mg/m^2, iv, on day 1 every 3 weeks; capecitabine, 800 mg/m^2, po, bid, on days 1-14 every 3 weeks. 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 anlotinib. 3 patients are enrolled and treated per dose level (8mg,10mg,12mg). If no DLT, dose is escalated for the next cohort of 3 patients; If 1 DLT, 3 additional patients are treated at this level with dose escalation only if no additional DLTs; If $\geq$ 2 DLTs, prior dose level is defined as MTD. MTD decided when 6 patients are treated at a dose level with $<$ 2 DLTs. Primary endpoint is objective response rate (ORR) according to RECIST v1.1. Secondary endpoints are progression-free survival (PFS), overall survival (OS), disease control rate (DCR), duration of response (DOR) and quality of life (QoL). Based on a one-sided one sample log-rank test with 2.5% Type I error, 80% power to detect an improvement in ORR from 5.4% to 15%, there will be 94 patients consider 20% of patients fall off. Research Sponsor: Guangdong Provincial Hospital of Chinese Medicine Clinical trial information: NCT05035914. Research Sponsor: Chia Tai Tianqing Pharmaceutical Group Co.,Ltd.

TPS221 **Trials in Progress Poster Session**

A multi-modular phase I/II study of UCB6114, a first-in-class, fully human IgG4P anti-Gremlin-1 monoclonal antibody, as monotherapy and in combination with mFOLFOX6 or trifluridine/tipiracil, for patients with advanced gastrointestinal (GI) tumors.

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Background: Despite recent advances, effective treatment for GI cancers remains a significant unmet medical need. Gremlin-1 is secreted by the peri-tumoral stroma and down-regulates bone morphogenetic proteins (BMP) -2, -4, and -7 (members of the transforming growth factor-β superfamily), thereby allowing malignant cell expansion, renewal, and a more treatment-resistant mesenchymal phenotype. Gremlin-1 mRNA is highly expressed in multiple solid tumors including $>$60% of colorectal, pancreatic and esophageal cancers. UCB6114 is a first-in-class, fully human IgG4P monoclonal antibody optimized for neutralizing the activity of human Gremlin-1 thereby restoring BMP signaling. Preclinical studies have demonstrated that UCB6114 binds to Gremlin-1, inhibits its pharmacological activity, and has antitumor activity in several *in vivo* mouse models (including several GI cancers). **Methods:** ONC001 (clinicaltrials.gov: NCT04393298) is an ongoing multi-part, multicenter, nonrandomized, open-label, Phase I/II study evaluating the safety, pharmacokinetics (PK) and antitumor activity of UCB6114 administered intravenously as monotherapy or in combination with selected standard of care (SOC) regimens. Eligible patients (pts) are: aged $\geq$18 years; resistant or refractory to standard therapy; ECOG performance status 0/1; and have adequate renal, hepatic and bone marrow function. In the Phase I monotherapy dose escalation and adaption part (part A and A1; modified rolling 6 design), up to 66 pts with advanced solid tumors associated with high levels of Gremlin-1 mRNA expression will be recruited. In parts B and C (modified toxicity probability interval design), up to 54 pts with locally advanced or metastatic colorectal, gastric or gastroesophageal junction adenocarcinomas will receive UCB6114 in escalating doses in combination with either mFOLFOX6 (5-fluorouracil, leucovorin and oxaliplatin) or trifluridine/tipiracil, given at SOC dosing and schedules. The overarching objective of the phase I parts of the study (Parts A–C) is to identify the recommended phase II dose of UCB6114 either as monotherapy or in combination. The primary objective is to characterize the safety profile of UCB6114; secondary and exploratory objectives include PK, antitumor activity (RECIST v1.1), and pharmacodynamics (including circulating Gremlin-1). Enrollment in ONC001 began in July 2020; as of Sept 2021, four dose escalation levels in the monotherapy dose-escalation module (Part A) have been completed without DLT. Recruitment to parts B and C is due to commence in Q4 2021. Clinical trial information: NCT04393298. Research Sponsor: UCB Pharma.

TPS222 **Trials in Progress Poster Session**

A first-in-human phase Ia/b, open-label, multicenter study of the TRAILR2 agonist BI 905711 in patients (pts) with advanced gastrointestinal (GI) cancers.

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Background: Activation of the tumor necrosis factor-related apoptosis-inducing ligand receptor 2 (TRAILR2) induces apoptosis via caspase activation. Targeting TRAILR2 is an attractive therapeutic strategy, but some early TRAILR2 agonists were associated with severe hepatotoxicity. Cadherin 17 (CDH17), a membrane protein highly expressed in GI cancers, is not expressed in normal hepatocytes so using CDH17 as a liver-sparing anchor may avoid hepatotoxicity. BI 905711 is a tetravalent bispecific antibody that cross-links TRAILR2 with CDH17 to induce CDH17-dependent TRAILR2 oligomerisation. In preclinical assays, BI 905711 demonstrated a potency shift of ~1000 fold versus the 1st-generation TRAILR2 agonist lexatumumab. BI 905711 induced apoptosis in CDH17-positive tumor cells *in vitro*, impaired tumor growth in pt-derived colorectal cancer (CRC) xenografts, and no hepatotoxicity was observed. **Methods:** This phase Ia/Ib study (NCT04137289) aims to determine the safety, maximum tolerated dose (MTD), pharmacokinetics (PK), pharmacodynamics, and preliminary efficacy of BI 905711 in pts with advanced, refractory GI cancers. Up to 140 adult pts with histologically confirmed, advanced unresectable/metastatic colorectal, gastric, esophageal or pancreatic adenocarcinoma, cholangiocarcinoma, or gallbladder or small intestine carcinoma, who have progressed on standard-of-care therapies, will be enrolled. In phase Ia, pts will receive intravenous BI 905711 at escalating doses (range 0.02–4.8 mg/kg) every 14 days, until disease progression or unacceptable toxicities. Dose escalation will be guided by a Bayesian logistic regression model with overdose control based on dose-limiting toxicities (DLTs) in the first 28 days. In phase Ia, a minimum number of CRC pts will be enrolled to each cohort: ≥1 CRC pt at each of the 2 lowest dose levels (0.02/0.06 mg/kg) and 4 pts at each subsequent dose level (0.2/0.6/1.2/2.4/3.6/4.8 mg/kg). In parallel to dose escalation in CRC pts, up to 4 pts with non-CRC GI cancers will be included at the dose level below that of the CRC cohort. If an objective response (OR) per RECIST v1.1 is observed in CRC or non-CRC GI pts at a safe dose level, up to 10 additional pts with the same tumor type will be recruited at that dose level. In phase Ib, CRC pts will be randomized into up to 4 dose cohorts (as determined in phase Ia; n=20 each) to define the recommended phase II dose. The primary endpoints are determination of the MTD based on the proportion of pts with DLTs (phase Ia) and OR rate based on RECIST v1.1 (phase Ib). Secondary endpoints include PK parameters and OR in pts with measurable disease (phase Ia), and disease control, tumor shrinkage, duration of response, and progression-free survival (phase Ib). Trial enrollment is ongoing, with 33 pts enrolled to date. Clinical trial information: NCT04137289. Research Sponsor: Boehringer Ingelheim.

TPS223 **Trials in Progress Poster Session**

A phase II randomized therapeutic optimization trial for subjects with refractory metastatic colorectal cancer using circulating tumor DNA (ctDNA): Rapid 1 trial.

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Background: Patients with advanced colorectal cancer after progressing through first line therapy, have several FDA-approved systemic therapies that are associated with clinical benefit for a substantive minority of patients. Current clinical practice is to trial these various treatments in a step-wise fashion using CT scans every 3 months to evaluate effectiveness. This process requires 3-4 months between therapeutic interventions from which the patient may ultimately derive no clinical benefit, may have a performance status decline; limiting the number of possible interventions and increases risk for physical and financial toxicity. An alternative to the traditional CT-scan guided approach for disease assessment is a circulating tumor DNA (ctDNA) intervention. The Signatera ctDNA assay which utilizes 16 truncal mutations derived from a patient's tumor, can be assessed every 2 weeks for a rapid determination of the effectiveness of a systemic therapy. This may allow patients to be exposed to many treatments during a short time, limiting toxicity, allowing for a quicker determination of clinical benefit and personalization of treatment. The aim of this study will be to compare the traditional scan-driven approach vs an intervention guided by ctDNA assessments, both arms using a pre-specified order of chemotherapy treatments. **Methods:** This is a phase 2 randomized study of patients with refractory metastatic adenocarcinoma of the colon or rectum. Participants are eligible after progression or intolerance to first line chemotherapy or recurrence within 6 months of adjuvant oxaliplatin based chemotherapy. They must have RECIST measurable metastatic disease that is not eligible for definitive management. Tissue from the primary and/or metastatic deposit is required for Signatera NGS analysis and subjects must have measurable ctDNA at sampling. Participants must be $\geq$18 years old without major organ dysfunction and have an ECOG performance status of 0 to 2. Subjects with Microsatellite High, deficient in DNA mismatch repair genes, or BRAF V600E mutations are excluded. Subjects will be randomized 1:1 to Arm A (ctDNA guided intervention) or Arm B (scan-guided control group). Patients in both arms will undergo systemic treatments in a standardized pre-specified order. Arm A will have ctDNA assessments every 2 weeks until an intervention shows a significant decrease, then every 4 weeks until Progressive Disease (PD) by scan or significant ctDNA increase. CT imaging will be performed every 12 weeks. Those in Arm B, will have CT imaging every 12 weeks and blood collected for post-hoc analysis every 4 weeks until PD by scan. The primary endpoint is overall survival. Secondary endpoints include progression free survival and overall response. Exploratory analysis with be performed of the microbiome. Enrollment continues to a maximum of 78 patients. Clinical trial information: NCT04786600. Research Sponsor: University of Florida.

TPS224 **Trials in Progress Poster Session**

Trastuzumab deruxtecan in patients with HER2-overexpressing locally advanced, unresectable, or metastatic colorectal cancer (mCRC): A randomized, multicenter, phase 2 study (DESTINY-CRC02).

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Background: Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate comprising an anti-HER2 antibody (trastuzumab) linked to a potent topoisomerase I inhibitor (DXd). T-DXd has been approved to treat HER2-positive metastatic breast cancer (United States [US], Japan, Europe, Israel) and advanced gastric cancer (US, Japan, Israel). It is currently being evaluated in other solid tumor types including colorectal cancer. The phase 2 DESTINY-CRC01 study included patients with *RAS* wild-type mCRC, with a median 4 (range, 2-11) prior lines of therapy. Preliminary results in patients with HER2-overexpressing (IHC 3+ or IHC 2+/ISH+) mCRC showed T-DXd treatment (6.4-mg/kg intravenously [IV] every 3 weeks [Q3W]) resulted in a confirmed objective response rate (ORR) of 45.3% (24/53; 95% CI, 31.6-59.6%) and a median progression-free survival (PFS) of 6.9 months (95% CI, 4.1-not estimable; Siena *J Clin Oncol*. 2020). Activity was also seen in patients treated with prior anti-HER2 therapy. Although 5.4-mg/kg and 6.4-mg/kg doses of T-DXd have shown clinical efficacy in multiple cancer indications, the lower dose has not yet been tested in patients with HER2-overexpressing mCRC. Preliminary data also suggest T-DXd may be active in *RAS* mutant mCRC, unlike other anti-HER2 therapies. The DESTINY-CRC02 study aims to determine efficacy and safety of T-DXd in patients with HER2-overexpressing, *RAS* wild-type or mutant mCRC at 5.4-mg/kg and 6.4-mg/kg doses.
Methods: DESTINY-CRC02 (NCT04744831) is a multicenter, randomized, double-blind, 2-arm, parallel phase 2 study that will be conducted in 2 stages. Eligible patients (≥18 years; ≥20 years in Japan, Taiwan, and Korea) will have HER2-overexpressing (IHC 3+ or IHC 2+/ISH+) locally advanced, unresectable or metastatic CRC and have previously received chemotherapy, anti-EGFR therapy, anti-VEGF treatment, and/or anti–PD-1/PD-L1 therapy, as clinically indicated. Prior anti-HER2 therapy will be allowed. In stage 1, patients will be randomly assigned 1:1 to receive T-DXd IV Q3W at a dose of 5.4-mg/kg (n = 40; arm 1) or 6.4-mg/kg (n = 40; arm 2). Randomization will be stratified by ECOG PS (0 or 1), HER2 status (IHC 3+ or IHC 2+/ISH+), and *RAS* status (wild-type or mutant). After stage 1 enrollment is complete, eligible patients in stage 2 (n = 40) will receive T-DXd 5.4 mg/kg until disease progression or other treatment discontinuation criteria are met. The study is actively enrolling and aims to enroll 120 patients across 60 sites. The primary objective is to assess efficacy of T-DXd at the 5.4-mg/kg and 6.4-mg/kg doses, with a primary endpoint of confirmed ORR by blinded independent central review. Secondary endpoints include investigator-assessed ORR, PFS, duration of response, disease control rate, clinical benefit rate, overall survival, pharmacokinetics, and safety. Clinical trial information: NCT04744831. Research Sponsor: Daiichi Sankyo, Pharmaceutical/Biotech Company.

TPS225 **Trials in Progress Poster Session**

An open-label, single-center, phase II study of exploration on optimizing the administration time of fruquintinib combined with camrelizumab in the third-line treatment of MSS advanced colorectal cancer.

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Background: Immune checkpoint inhibitors monotherapy has limited clinical benefits in patients with MSS or pMMR metastatic colorectal cancer (CRC), which may be attributed to low level of tumor-infiltrating lymphocytes in MSS advanced CRC. Combination immunotherapy is changing the landscape of cancer treatment, especially combination of immunotherapy with small molecule angiogenesis inhibitors. Preclinical studies have shown that there is a time window from anti-angiogenesis to vascular normalization and this has been initially demonstrated in the clinical study of breast cancer. However, the time window is rarely considered in clinical practice. It is necessary to explore the optimal administration timing of angiogenesis inhibitors when combined with immunotherapy. Here, we conduct an open-label, single-center, phase II study to explore the issue. **Methods:** Patients eligible for the trial are included: 1) pathologically confirmed advanced colon or rectal adenocarcinoma, MSS or pMMR; 2) previously received only 2 standard regimens after recurrence or metastasis; 3) aged 18-70 years (boundary value included); 4) ECOG performance status of 0 or 1; 5) at least 3 months of survival expectations; 6) patient must present with measurable lesions according to the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST version 1.1; 7) patients with asymptomatic central nervous system metastases or asymptomatic brain metastases after treatment, with stable disease for at least 3 months, and need not be treated with steroids for at least 4 weeks; 8) had adequate organ function before the enrollment; 9) patients of reproductive age should agree to use effective contraceptive measures from the time of signing the informed form until 3 months after the last dose; 10) sign an informed consent form voluntarily, and be willing to and be able to follow and complete all experimental procedures. The patients enrolled were given oral fruquintinib (3 mg, qd, for 2 consecutive weeks, and then discontinued for 1 week, in 3 weeks [21 days] cycle); on the day 5, administered with intravenous camrelizumab (200mg, once every 3 weeks). The treatment was administered continuously until disease progression, unacceptable toxicity, or required withdrawal from patients. The primary endpoint is progression free survival (PFS), and the secondary endpoints are overall survival (OS), objective response rate (ORR), disease control rate (DCR) and drug safety. As of September 23, 2021, a total of 21 patients have been enrolled. Clinical trial information: ChiCTR2100048528. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd, Shanghai, China.

TPS226 **Trials in Progress Poster Session**

REGINA: A phase II trial of neoadjuvant regorafenib (Rego) in combination with nivolumab (Nivo) and short-course radiotherapy (SCRT) in intermediate-risk, stage II-III rectal cancer (RC).

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Background: Despite recent improvements, management of locally advanced rectal cancer (LARC) remains challenging, and many patients (pts) still experience recurrence. In preclinical models, combining Rego with an anti-PD-1 inhibitor led to superior tumour growth suppression as compared with either treatment alone. In a phase I clinical trial, remarkable results were reported for the combination of Rego and Nivo in advanced MSS colorectal cancer. This synergistic effect is thought to be secondary to the anti-angiogenic effects of Rego and its potential to reduce TAMs, promote M1 macrophage conversion, and down-regulate expression of immunosuppressive factors. Building on these data, we designed a trial of Rego-Nivo with standard SCRT in the neoadjuvant setting of RC. **Methods:** REGINA is an academic, multicentre, single-arm, phase II trial sponsored by Institut Jules Bordet. Eligible patients are treated according to the following plan: induction phase (Nivo 240 mg IV D1&15, and Rego 80 mg PO D1-14), SCRT (D22-26), consolidation phase (Nivo 240 mg IV D29,43&57, and Rego 80 mg PO D29-49), and surgery (7-8 weeks after SCRT). Key eligibility criteria include age $\geq$18 years, ECOG PS $\leq$1, adenocarcinomas below the peritoneal reflection, intermediate-risk, stage II-III tumour (ie, cT3/T4aNany or cT1-2N+, no involvement/threatening of the mesorectal fascia, no involvement of lateral pelvic lymph nodes) irrespective of microsatellite instability status. The primary endpoint is pathological complete response (pCR). Secondary endpoints include, among others, toxicity, compliance to treatment, pathological tumour regression grade, event-free survival, and overall survival. Subjects will be followed for recurrence and survival for 5 years after end of treatment visit. The study follows a Simon's two-stage design (null hypothesis pCR = 12%, alternative hypothesis pCR = 24%; α= 5%, β= 20%) with a maximum of 60 pts to be enrolled. A safety interim analysis is planned after the first 6 pts have completed treatment. Serial collection of tumour, blood, and stool samples is mandatory at pre-specified time points for exploratory correlative biomarker analyses. The trial is planned to be run at 8-10 centres across Belgium. Study recruitment started in Q1 2021 and is anticipated to complete in Q3 2023. The study is funded by Bayer. Clinical trial information: NCT04503694. Research Sponsor: Bayer.

TPS227 **Trials in Progress Poster Session**

KEYNOTE-B79 phase 1b trial to evaluate the allogeneic CAR T-cells CYAD-101 and pembrolizumab in refractory metastatic colorectal cancer patients.

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Background: The allogeneic chimeric antigen receptor (CAR) T-cell treatment CYAD-101 utilizes the NKG2D receptor that targets eight ligands expressed on tumor cells and also on stromal and immunosuppressive immune cells of the tumor microenvironment. CYAD-101 co-expresses a T-cell receptor (TCR) inhibitory peptide with the aim to eliminate the potential of graft versus host disease (GvHD), the main safety risk associated with engineered cells of allogeneic origin. In the previous alloSHRINK trial (NCT03692429), CYAD-101 was administered post FOLFOX preconditioning chemotherapy to 15 patients with progressive metastatic colorectal cancer (mCRC) who were previously treated with FOLFOX. Overall, the treatment was well tolerated with no evidence of GvHD. The disease control rate was 73.3% with two patients presenting a confirmed partial response per RECIST's criteria (4 months and 8 months of duration from first CYAD-101 infusion) and nine had stable disease with a median duration of 4.6 months. Evidence of increase in the TCR repertoire and modulation of the cytokine profile post-treatment with CYAD-101 were observed implying that CYAD-101 may also be modulating the immune suppressive environment in patients mirroring what was demonstrated in pre-clinical models. We considered that a sequential therapy with the anti-PD1 monoclonal antibody pembrolizumab to further release the anti-tumor potential of this expanded T-cell population may drive deeper, more durable and new clinical responses beyond that currently demonstrated with the CAR T-cells alone. **Methods:** The phase 1b KEYNOTE-B79 trial (NCT04991948) will evaluate, according to a Simon's two stage study design, the safety and clinical activity of three consecutive infusions of CYAD-101 ($1x10^9$ cells per infusion) post FOLFOX preconditioning chemotherapy with two-week interval between cycles, followed by pembrolizumab treatment (200 mg administered every three weeks for up to two years) in microsatellite stable/mismatch-repair proficient mCRC patients with recurrent/progressing disease after at least one metastatic line of therapy, which must include FOLFOX chemotherapy. The pembrolizumab treatment will be initiated 3 weeks after the last CYAD-101 infusion to fall outside the classical time window of potential CAR T-cell toxicities (e.g., cytokine release syndrome). The co-primary endpoints of the trial are the occurrence of dose-limiting toxicities (DLTs) at any time from the first FOLFOX preconditioning treatment up to 3 weeks after the first pembrolizumab treatment and the objective response rate (ORR) at the tumor assessment planned 6 weeks after the first pembrolizumab treatment administration. The KEYNOTE-B79 study will be initiated in Q4-2021 in five sites in USA and Europe. Clinical trial information: NCT04991948. Research Sponsor: Celyad Oncology.

TPS228 **Trials in Progress Poster Session**

mFOLFOXIRI+Bev vs. mFOLFOX6+Bev for RAS mutant unresectable colorectal liver-limited metastases: A study protocol of a multicenter randomized controlled phase 3 (BECOME2) trial.

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Background: Colorectal cancer patients with initially unresectable liver-only metastases may be cured after downsizing of metastases by conversion therapy. However, the optimal regimen of conversion therapy for RAS mutant patients has not been defined. **Methods:** BECOME2 is a multicenter, randomized, phase 3 clinical study. RAS mutant and BRAF wild type colorectal cancer patients with initially unresectable liver-limited metastases are eligible. The (un)resectability status is prospectively assessed by a central multidisciplinary team (MDT) consisting of at least one radiologist and three liver surgeons, according to predefined criteria. RAS and BRAF mutation status were evaluated according to primary tumor. Patients with RAS mutant and BRAF wild type will be randomized between modified FOLFOXIRI (IRI, 165mg/m2; Oxa, 85mg/m2; LV, 400mg/m2; 5-FU 2400mg/m2) plus bevacizumab (5mg/kg) and modified FOLFOX6 (mFOLFOX6) plus bevacizumab. Radiological evaluation to assess conversion to resectability will be performed by the central MDT every eight weeks. The primary study endpoint is conversion resection rate. Secondary endpoints are the ETS, DpR, ORR, PFS, OS, toxicity, perioperative complication, and the proportion of no evidence of disease. Clinical trial information: NCT04781270. Research Sponsor: None.

TPS229 **Trials in Progress Poster Session**

Anlotinib plus chemotherapy as first-line therapy for gastrointestinal tumor patients with unresectable liver metastasis: A multicenter, multicohort clinical trial (ALTER-G-001).

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Background: Liver metastases (LMs) are usually found in gastrointestinal tumors, such as colorectal cancer (mCRC), esophageal squamous cell carcinoma (ESCC) and gastric cancer. Currently, there is no formal option for such patients (pts) due to the different pathological characteristics, and more effective treatment regimens are needed. Anlotinib is an oral multi-targeted tyrosine kinase inhibitor targeting VEGFR1/2/3, FGFR1-4, PDGFRα/β and c-Kit, which effectively blocks tumor neovascularization and growth. Previous phase II clinical trials suggested that anlotinib plus chemotherapy as first-line therapy were well tolerated and showed clinical anti-tumor activity in mCRC and ESCC. It was demonstrated an objective response rate (ORR) of 76.7%, a disease control rate (DCR) of 93.3% and a median progression-free survival (mPFS) of 11.4 months in RAS/BRAF wild-type unresectable mCRC pts using anlotinib plus CAPEOX (ALTER-C002 trial, NCT04080843). Additionally, preliminary encouraging ORR (78.3%), DCR (93.5%) and mPFS (8.38 months) was observed in advanced ESCC pts treated with anlotinib plus cisplatin and paclitaxel (ALTER-E002 trial, NCT04063683). Based on these results, this multicohort, multicenter phase II ALTER-G-001 trial was launched to evaluate efficacy and safety of anlotinib plus chemotherapy as first-line therapy in gastrointestinal tumor pts with unresectable LMs. **Methods:** Previously untreated and histologically or cytologically confirmed gastrointestinal tumor pts with unresectable LMs were eligible, who will be divided into 3 cohorts, including mCRC (n = 45), ESCC (n = 31) and others (n = 25). Pts must be aged 18-75 years, with an ECOG PS of 0/1, adequate organ function, and at least one measurable LMs lesion according to RECIST v1.1. HER2-positive gastric adenocarcinoma, and pts with a high risk of bleeding, perforation or fistulas will be excluded. During first 6 cycles (3 weeks per cycle) of inducing treatment, mCRC pts will receive anlotinib (12mg, po, qd, d1-d14), oxaliplatin (130 mg/m^2, iv, d1) and capecitabine (850 mg/m^2, po, bid, d1-d14). ESCC pts will be treated with anlotinib, cisplatin (60-750 mg/m^2, i.v., d1/d1-3) along with paclitaxel (135 mg/m^2, i.v., d1) or docetaxel (75 mg/m^2, i.v., d1). And pts in others cohort will receive anlotinib plus standard first-line chemotherapy. Then, pts without PD and LMs resection, will receive anlotinib and metronomic capecitabine (500mg, po. bid, d1-21, q3w) until PD or unacceptable toxicity. Primary endpoint is investigator-assessed ORR (RECIST 1.1). Secondary endpoints include duration of response (DoR), PFS, overall survival, DCR, radical resection rate for LMs and safety (NCI-CTCAE v5.0). Research sponsor: Chia Tai Tianqing Pharmaceutical Group Co., Ltd. Clinical trial information: ChiCTR2100050872. Research Sponsor: None.

TPS230 **Trials in Progress Poster Session**

An observational study to evaluate *RAS* mutations in circulating tumor DNA after standard chemotherapies for metastatic colorectal cancer patients with tumors harboring *RAS* mutation: RASMEX study (JACCRO CC-17).

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Background: *RAS* status in tumor tissue is a predictive factor for the efficacy of anti-epidermal growth factor receptor (EGFR) antibodies therapy in patients (pts) with metastatic colorectal cancer (mCRC). In mCRC pts with tumors harboring *RAS* mutation, anti-EGFR antibodies therapy has the lack of clinical benefit; thus, the survival of *RAS* mutant mCRC pts is shorter compared to *RAS* wild mCRC pts. Recently, several studies have shown that colorectal cancer tissue had heterogeneity of gene profiling, and the analysis of circulating tumor DNA (ctDNA) in blood samples could detect the change of gene alterations in tumors which were caused by chemotherapy. Bouchahda et al., demonstrated that nearly half of the pts with *RAS* mutant mCRC had no detectable *RAS* mutation in ctDNA after first-line chemotherapy; moreover, some of the pts had clinical benefits from post-anti-EGFR antibodies therapy. Therefore, anti-EGFR antibodies therapy might become a novel treatment option for *RAS* mutant mCRC pts without *RAS* mutations in ctDNA after chemotherapies. Other report also showed the frequency of no *RAS* mutations in ctDNA was about 1%. There have been few studies to prospectively evaluate the *RAS* status in ctDNA for mCRC pts with *RAS* mutant tumors treated with standard chemotherapies. We, therefore, conducted an observational study to evaluate *RAS* mutations and the mutation allele frequency in ctDNA for mCRC pts with *RAS* mutant tumors who were treated with first- or second-line chemotherapy. **Methods:** This study is a multi-center observational/translational study in 67 facilities. The key eligibility criteria are as follows: 1) Eastern Cooperative Oncology Group Performance status 0-1, 2) histologically proven unresectable mCRC, 3) *RAS* mutation in tumor tissue, 4) refractory or intolerable after response to prior fluoropyrimidine-containing regimen. OncoBEAM RAS CRC kit is used to investigate *RAS* status in ctDNA just after first- or second-line treatment in enrolled pts. The primary endpoint is the frequency of pts without *RAS* mutations in ctDNA. Secondary endpoints include mutation allele frequency of *RAS* in ctDNA and clinical outcomes of pre- and post-treatments (overall response rate, disease control rate, overall survival, and progression-free survival). As the exploratory analysis, gene alterations related to the resistant mechanism of anti-EGFR antibodies *(BRAF*, *PIK3CA*, *ERBB2*, *MET*) are analyzed in pts without *RAS* mutations in ctDNA. We assume that no *RAS* mutations are observed in ctDNA in at least 1 % pts. We expect that one patient with no *RAS* mutations in ctDNA is detected in 100 pts; thus, the sample size of 300 pts is set for our study. Accrual is starting in April 2021. Clinical trial information: UMIN000043442. Research Sponsor: Sysmex.

TPS231 **Trials in Progress Poster Session**

Durvalumab (MEDI 4736) with extended neoadjuvant regimens in rectal cancer: A randomized phase II trial (PRIME-RT).

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Background: Advances in multi-modality treatment of locally advanced rectal cancer (LARC) have resulted in low local recurrence rates, but many patients still die from distant disease. There is increasing recognition that with neoadjuvant treatment some patients achieve a complete response and may avoid surgical resection. The PRIME-RT trial tests the inclusion of neoadjuvant immunotherapy with the aim of enhancing complete response rates, improving stoma-free survival and reducing distant relapse. **Methods:** PRIME-RT is a multi-centre, open label, phase II, randomised trial for patients with newly diagnosed LARC. Eligible patients are randomised to Arm A: short course radiotherapy (25 Gray in 5 fractions) with concomitant durvalumab, followed by durvalumab and FOLFOX chemotherapy, or Arm B: long course chemoradiotherapy (50 Gray to primary tumour, 45 Gray to elective nodes, in 25 fractions with capecitabine) with concomitant durvalumab followed by FOLFOX and durvalumab. The primary endpoint is complete response rate in each arm. Bio-specimens including serial tumour biopsies and peripheral blood samples are collected prior to, during, and following treatment to explore the molecular and immunological factors underpinning treatment response. The main trial will recruit up to 42 patients and commence after a safety run-in ($n \geq 6$) which is recruiting patients with metastatic disease. After opening in January 2021, three patients have been treated within the safety run-in; 2 in Arm A and 1 in Arm B. Early recruitment to PRIME-RT has shown that adding immunotherapy in the neoadjuvant setting for LARC is feasible. The expectation is that the trial will provide efficacy and safety information which allows the optimal treatment approach to be tested within a larger phase clinical trial. Funding information Core funding (Glasgow CRUK CTU) and trial specific funding (Astrazeneca). Trial registration Clinicaltrials.gov NCT04621370 (Registered 9 Nov 2020) ISRCTN18138369 (Registered 27 October 2020) Clinical trial information: NCT04621370. Research Sponsor: Astrazeneca, Cancer Research UK.

TPS232 **Trials in Progress Poster Session**

NRG-GI004/SWOG-S1610: Colorectal cancer metastatic dMMR immuno-therapy (COMMIT) study—A randomized phase III study of atezolizumab (atezo) monotherapy versus mFOLFOX6/bevacizumab/atezo in the first-line treatment of patients (pts) with deficient DNA mismatch repair (dMMR) or microsatellite instability high (MSI-H) metastatic colorectal cancer (mCRC).

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Background: Despite the superiority in progression-free survival (PFS) of inhibition of programmed cell death-1 (PD-1) pathway in dMMR/MSI-H as compared to chemotherapy with either anti-vascular endothelial growth factor receptor (VEGFr) or anti-epithelial growth factor receptor (EGFr) antibodies in mCRC, more pts had progressive disease as the best response in the anti-PD1 monotherapy arm (29.4% vs. 12.3%) with mean PFS of 13.7 months (*N Engl J Med* 2020; 383:2207). We hypothesize that the dMMR/MSI-H mCRC pts may be more effectively treated by the combination of PD-1 pathway blockade and mFOLFOX6/bevacizumab (bev) rather than with anti-PD-1 therapy (atezo) alone. Preclinical work demonstrated synergistic effects between anti-PD-1/anti-VEGF and between oxaliplatin/anti-PD-1 in murine CRC models and phase II data showed activity of anti-PD-1/anti-VEGF in chemotherapy refractory colon cancer. Additionally, in other solid tumor malignancies, anti-PD1 plus anti-VEGFr (i.e., HCC and RCC) as well as anti-PD1 plus chemotherapy (i.e., gastric and esophageal cancers) combinations are standard first-line treatments. **Methods:** The redesigned COMMIT study was reactivated on 1/29/2021 as a two-arm prospective phase III open-label trial randomizing (1:1) mCRC dMMR/MSI-H (211 pts) to atezo monotherapy versus mFOLFOX6/bev+atezo combination. Assuming our control arm, atezo monotherapy, 48% PFS at 24 months, as assessed by site investigator, we have 80% power to detect a hazard ratio of 0.6 (equivalent to 64.4% PFS at 24 months) with alpha 0.025 one-sided. Stratification factors include BRAFV600E status, metastatic site, and prior adjuvant CRC therapy. Secondary endpoints include OS, objective response rate, safety profile, disease control rate, duration of response, and centrally-reviewed PFS. Health-related quality of life is an exploratory objective. Archived tumor tissue and blood samples will be collected for correlative studies. Key inclusion criteria are: mCRC without prior chemotherapy for advanced disease; dMMR tumor determined by local CLIA-certified IHC assay (MLH1/MSH2/MSH6/PMS2) or MSI-H by local CLIA-certified PCR or NGS panel; and measurable disease per RECIST. Enrollment actively continues to the target accrual of 211 patients randomized between the two immunotherapy arms. Support: U10CA180868, -180822, -180888, UG1CA189867, U24CA196067; Genentech, Inc. Clinical trial information: NCT02997228. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

TPS233 **Trials in Progress Poster Session**

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).

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Background: There are currently no validated predictive biomarkers for stage II resected colon cancer (CC) after adjuvant chemotherapy. However, circulating tumor DNA (ctDNA) 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 in prognosticating 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 active surveillance (i.e., not needing 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 Guardant Reveal assay, 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. Enrollment continues across North America to the 540-patient phase II endpoint. Support: U10-CA-180868, -180822; UG1CA-189867; GuardantHealth. Clinical trial information: NCT04068103. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

TPS234 **Trials in Progress Poster Session**

A prospective observational study to determine the feasibility of tumor response assessment by circulating tumor DNA (ctDNA) in patients with locally advanced rectal cancer (LARC) undergoing total neoadjuvant therapy (TNT).

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Background: Total neoadjuvant therapy (TNT) followed by total mesorectal excision (TME) is one of the standard treatment options for patients with locally advanced rectal cancer (LARC). A commonly employed TNT protocol consists of 8 biweekly cycles of oxaliplatin-based chemotherapy (CT) followed by radiation concurrent with fluoropyrimidine-based chemotherapy (CRT) for about 6 weeks. During the TNT, patients undergo tumor response assessments periodically with standard modalities (SM) consisting of pelvic magnetic resonance imaging (MRI) and proctoscopic/endoscopic examination. The objective of the current protocol is to evaluate the feasibility of tumor response assessment by ctDNA in patients with LARC undergoing TNT. The present feasibility study is designed to collect preliminary data to evaluate if a subsequent larger validation study is justified. If ctDNA-based response assessment is validated, ctDNA can potentially replace at least some components of the SM (for example, MRI) as tumor response assessment by SM is often time-consuming, expensive, and poses logistical challenges. **Methods:** Patients with LARC undergoing TNT will be enrolled. After obtaining informed consent, venous blood samples will be obtained for ctDNA level measurements at the following time points: baseline (within 1 week before the CT begins), after 4 cycles of CT within +/- 5 days of the MRI study, after 8 cycles of CT within +/- 5 days of the MRI study, and 1 to 14 days before TME. ctDNA levels will be measured by a commercially available ctDNA assay (Signatera by Natera), and ctDNA response is defined as $>$90% drop in the ctDNA level after treatment compared to the baseline level. Tumor response will be evaluated after 4 and 8 cycles of CT by SM. Primary endpoint: correlation between the response rate (RR) assessed by ctDNA and by SM after 4 cycles of CT. Secondary endpoints: 1) correlation between the RR assessed by ctDNA and by SM after 8 cycles of CT, and 2) correlation between the ctDNA defined RR and the complete pathological response (pCR) rate. The trial will enroll 30 patients. To evaluate the primary endpoint, differences in ctDNA levels between the baseline and 4-cycles post-CT will be computed. The differences will then be expressed as a proportion of each patient's baseline level, D. This relative change, D, will be compared between the responder and non-responder groups using a two-sample Welch's t-test. Similar methods will be applied for the secondary endpoints. All analyses will use the nominal type I error level of 0.05 and two-sided tests. Clinical trial information: NCT04670588. Research Sponsor: Natera Inc.

TPS235 **Trials in Progress Poster Session**

Prospective study of the co-relation of ctDNA with pathologic complete remission (pCR) and other efficacy outcomes in rectal cancer patients undergoing neoadjuvant chemotherapy and radiation.

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Background: Circulating tumor DNA (ctDNA) has emerged as a biomarker for non-invasive longitudinal monitoring of tumor progression in cancer management. Through the recent advances in next generation sequencing (NGS) technologies and personalized assays, ctDNA has been heralded as a promising tool to detect residual disease, relapse, and monitor treatment response in hematologic malignancies and solid tumors. Our study aims to determine whether treatment related ctDNA dynamics can be used as a reliable indicator to predict pathologic complete response (pCR) in patients with rectal cancer receiving neoadjuvant treatment. **Methods:** This is a prospective observational cohort study. The primary aim is to estimate the sensitivity and specificity of ctDNA clearance in predicting pCR in patients undergoing neoadjuvant therapy. The secondary aim is to evaluate the feasibility of using ctDNA as a surveillance method to detect progression of rectal cancer during neoadjuvant therapy and relapse in the subsequent follow up period. ctDNA levels are collected from newly diagnosed rectal cancer patients at 7 discrete time points: at diagnosis or screening, during neoadjuvant therapy, after completion of neoadjuvant therapy and 1 month, 2 months, 4 months, 6 months after surgery. This will be followed by every 3 months ctDNA testing for surveillance for up to 2 years. We expect to enroll approximately 30 patients at our institution. The subjects will be sorted into two groups: responders and non-responders based on whether they achieve pCR. ctDNA level between two groups will subsequently be compared. The use of ctDNA to predict pCR in rectal cancer patients may allow for many of these patients to safely avoid surgery if undetectable ctDNA at the end of neoadjuvant therapy strongly correlates with pCR. We are actively enrolling patients into this prospective observational study and expect to report the data in the near future. The data we obtain will be combined with those from several institutions around the US doing similar studies with the same test. Data analysis will subsequently be conducted. Research Sponsor: Signatera, Natera.

Study Schema:

Patient screening (inclusion and exclusion criteria) and enrollment

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First ctDNA testing at the time of study enrollment
Second ctDNA test during neoadjuvant chemotherapy and radiation (chemoRT)

↓

Third ctDNA test 8 weeks after completion of chemoRT

↓

Fourth ctDNA test 4 weeks after surgery

Fifth ctDNA test 2 months after surgery

↓

Sixth ctDNA test 4 months after surgery

↓

Seventh ctDNA test 6 months after surgery

↓

Surveillance ctDNA tests Q 3 months x 2 years

TPS236 **Trials in Progress Poster Session**

Minimal residual disease assessment in colorectal cancer (MiRDA-C).

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Background: Detection of circulating tumor DNA (ctDNA) in the bloodstream is emerging as a novel marker for identifying of radiographically occult microscopic or minimal residual disease (MRD) in colorectal cancer (CRC) patients (pts) after curative intent treatments. Accumulating data suggest that ct-DNA defined MRD is a highly specific prognostic biomarker for future recurrences with a lead time of several months and prospective clinical trials are being conducted using ct-DNA defined MRD as an integral biomarker for improving risk stratification for adjuvant chemotherapy decision making. However, large scale, prospective data regarding kinetics of ctDNA-defined MRD with accurate pre-analytical methodology for plasma isolation and paired clinical data are limited. **Methods:** In this multi-center, prospective observational study, 1,000 pts with resectable CRC (stages II – IV) without other active malignancies undergoing therapy with curative intent will be enrolled any time from time of diagnosis up to start of adjuvant therapy (or ≤ 3 months post curative surgery, whichever is earlier). All therapeutic and surveillance visits decisions are at the discretion of the treating physicians. Serial biospecimens including blood (in Cell-Free DNA BCT tubes) to be processed to plasma and buffy coat in ≤ 2 days and formalin fixed tumor tissue will be collected at key time points until the time of radiographic recurrence or up to 5 years of surveillance. Blood draws will be at study entry, after each line of neoadjuvant therapy, post-surgery, during and after adjuvant therapy in addition to each surveillance visit. These blood draws will be coordinated with pts' standard of care visits in order to minimize additional venipunctures. Relevant clinical data including demographics, cancer history, treatment details and outcomes, serum tumor markers and genomic data will be collected at each time point. Samples will be evaluated retrospectively with a primary objective of evaluating sensitivity and specificity of post-operative MRD for radiographic recurrences utilizing Guardant Health's Reveal assay. Other key objectives include evaluating ctDNA kinetics with neoadjuvant and adjuvant therapies and to correlate with outcomes. The study is active, and enrollment is ongoing. Clinical trial information: NCT04739072. Research Sponsor: Guardant Health, Other Government Agency.

TPS237 **Trials in Progress Poster Session**

Examination of the functional and diagnostic potential of methylation-sensitive enhancers in metastatic colorectal cancer.

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Background: Molecular characterisation of colorectal cancer (CRC) has demonstrated the regulatory role of epigenetic alterations, such as DNA methylation, in CRC tumorigenesis(1). Robust molecular profiling of CRC has the potential to provide critical diagnostic and prognostic information. The establishment of 4 consensus molecular subtypes (CMSs), developed initially for primary CRC tumours, resulted in the evolving framework for molecularly targeted interventions; the molecular genetic profile characterising mCRC is less well defined(3, 4). Previous pilot work identified a unique tumour-specific methylation sequence, at 376 sites within the DNA of mCRC cells(5). This study will assess whether this methylation sequence drives mCRC pathogenesis and underpins disease phenotype. The primary aim of this study is validation of the diagnostic utility of this novel enhancer signature and identification of key enhancers with the potential to direct targeted treatment development. Secondary aims include CRISPR knockdown library development targeting the enhancers in CRC cells in vitro, evaluating the impact of the knockdown on phenotype in vitro, and identifying the mechanisms by which methylation-sensitive enhancers regulate the mCRC phenotype. **Methods:** This is a retrospective, non-interventional, single-centre clinical study, including patients $>$ 18 years, with (group A) de novo mCRC (n = 100), (group B) stage III colorectal cancer that subsequently relapsed (n = 100) or (group C) stage III colorectal cancer without radiological evidence of relapse at study enrolment (n = 100). Formalin-fixed, paraffin-embedded (*FFPE*) tissue obtained at diagnosis will be analysed. Additionally, 50 stage III patients who have relapsed (group B) will have blood samples collected prospectively at time of consent to enable assessment for the presence of the methylation signature on ctDNA. The presence or absence of the novel methylation signature will be evaluated via the application of a targeted bisulfite sequencing panel consisting of the previously identified differentially methylated enhancer (DME) signature to both tissue and plasma samples; results will be correlated with conventional histological parameters, systemic therapy, and overall survival. Quantitative statistical analysis will be performed using SPSS with linear regression analysis for survival data. Ethical approval was obtained from the MMUH Institutional Review Board; reference 1/378/2188. This study is open and recruiting. Clinical trial information: 1/378/2188. Research Sponsor: Royal College of Surgeons in Ireland StAR programme.