**LBA3500** **Oral Abstract Session**

# First-line encorafenib + cetuximab + mFOLFOX6 in BRAF V600E-mutant metastatic colorectal cancer (BREAKWATER): Progression-free survival and updated overall survival analyses.

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# Nivolumab (NIVO) plus ipilimumab (IPI) vs chemotherapy (chemo) or NIVO monotherapy for microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): Expanded analyses from CheckMate 8HW.

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**Background:** In the phase 3 CheckMate 8HW study (NCT04008030), both dual primary endpoints of progression-free survival (PFS) for first-line (1L) NIVO + IPI vs chemo (HR 0.21; $P < 0.0001$) and NIVO + IPI vs NIVO across all lines (HR 0.62; $P = 0.0003$) in patients (pts) with centrally confirmed MSI-H/dMMR mCRC were met. We report expanded analyses of NIVO + IPI vs NIVO (all lines) and longer follow-up results for NIVO + IPI vs chemo (1L). **Methods:** The study design was described previously. Pts with MSI-H/dMMR per local testing were enrolled. After randomization, IHC and PCR based tests were used for central confirmation. PFS2 (time from randomization to progression after subsequent systemic therapy, start of second subsequent systemic therapy, or death) was a key exploratory endpoint. **Results:** In all randomized pts (all lines), 296 of 354 (84%) in the NIVO + IPI arm, 286 of 353 (81%) in the NIVO arm, and 113 of 132 (86%) in the chemo arm had centrally confirmed MSI-H/dMMR. In all randomized 1L pts, 171 of 202 (85%) in the NIVO + IPI arm and 84 of 101 (83%) in the chemo arm had centrally confirmed MSI-H/dMMR. Median follow-up was 47.0 mo (range 16.7–60.5). 1L NIVO + IPI continued to show PFS benefit vs chemo (Table). Subsequent systemic therapy was received by 27 (16%) and 61 (73%) pts after 1L NIVO + IPI and chemo, respectively; 10 (6%) and 21 (25%) received subsequent non-study immunotherapy. In the 1L chemo arm, 39 (46%) pts crossed over to NIVO + IPI on study. PFS2 continued to favor 1L NIVO + IPI vs chemo (Table). Across all lines, NIVO + IPI demonstrated superior PFS vs NIVO (Table). Subsequent systemic therapy was received by 54 (18%) pts in the NIVO + IPI arm and 83 (29%) in the NIVO arm; 20 (7%) and 31 (11%) received subsequent non-study immunotherapy. PFS2 favored NIVO + IPI vs NIVO across all lines of therapy (Table). In all treated pts, grade 3/4 treatment-related adverse events occurred in 78 (22%) and 50 (14%) pts in the NIVO + IPI and NIVO arms, respectively. Additional analyses will be presented. **Conclusions:** NIVO + IPI demonstrated sustained clinical benefit vs chemo (1L) and NIVO (all lines) despite use of subsequent therapy, as shown by improved PFS2 in pts with centrally confirmed MSI-H/dMMR mCRC. No new safety signals were observed. These results support NIVO + IPI as a standard of care treatment for MSI-H/dMMR mCRC. Clinical trial information: NCT04008030. Research Sponsor: Bristol Myers Squibb.

| Centrally confirmed MSI-H/dMMR (1L) | NIVO + IPI (n = 171) | Chemo (n = 84) |
|---|---|---|
| Median PFS (95% CI), mo | 54.1 (54.1–NE) | 5.9 (4.4–7.8) |
| HR (95% CI) | 0.21 (0.14–0.31) | |
| Median PFS2 (95% CI), mo | NR (NE–NE) | 30.3 (15.2–NE) |
| HR (95% CI) | 0.28 (0.18–0.44) | |
| **Centrally confirmed MSI-H/dMMR (all lines)** | **NIVO + IPI (n = 296)** | **NIVO (n = 286)** |
| Median PFS (95% CI), mo | NR (53.8–NE) | 39.3 (22.1–NE) |
| HR (95% CI) | 0.62 (0.48-0.81); $P = 0.0003$ | |
| Median PFS2 (95% CI), mo | NR (NE–NE) | NR (NE–NE) |
| HR (95% CI) | 0.57 (0.42–0.78) | |

NE, not evaluable; NR, not reached.

**LBA3502** **Oral Abstract Session**

# Anlotinib versus bevacizumab added to standard first-line chemotherapy among patients with RAS/BRAF wild-type, unresectable metastatic colorectal cancer: A multicenter, prospective, randomised, phase 3 clinical trial (ANCHOR trial).

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3503 Oral Abstract Session

# ctDNA-guided adjuvant chemotherapy escalation in stage III colon cancer: Primary analysis of the ctDNA-positive cohort from the randomized AGITG dynamic-III trial (intergroup study of AGITG and CCTG).

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**Background:** Despite adjuvant chemotherapy (ACT) a proportion of patients (pts) with stage III colon cancer (CC) will recur. Most at risk are those with detectable ctDNA, whereas those with undetectable ctDNA have a reduced recurrence risk. The DYNAMIC-III study explored the impact of ACT de-escalation or escalation as informed by post-surgery ctDNA results. Here, we report the primary analysis on the impact of treatment escalation in ctDNA-positive pts. Outcome data for treatment de-escalation in ctDNA-negative pts is immature. **Methods:** DYNAMIC-III is a multi-center, randomized, phase II/III trial. Eligible pts had resected stage III CC and were fit for ACT. Pts were randomly assigned 1:1 to ctDNA-informed or standard of care (SOC) management. Clinicians nominated the selected SOC ACT regimen prior to randomization. For ctDNA-informed management, a ctDNA-positive result at 5-6 weeks after surgery with a tumor-informed assay prompted an escalation ACT strategy (from single agent fluoropyrimidine [FP] to oxaliplatin-based doublet, from 3 months doublet to 6 months doublet or FOLFOXIRI [clinician choice], or from 6 months doublet to FOLFOXIRI). The primary efficacy endpoint for the ctDNA-positive cohort was 2-year RFS. The target sample size of 250 provided 80% power with 90% confidence to confirm superiority of ctDNA-informed treatment escalation compared to SOC with a HR of 0.746. **Results:** Of 961 eligible pts randomized between Oct 2017 and Apr 2023, 259 (27%) were ctDNA-positive. Of these, 113 (44%) had clinical low risk disease (non-N2 + non-T4). Median follow-up was 42.2 months (range 0.78 – 63.0). 115 (89%) of 129 ctDNA-informed pts received ACT escalation, with 65 (56%) receiving FOLFOXIRI. Of 130 SOC pts, 14 (11%) and 112 (86%) received single agent FP and oxaliplatin doublet, respectively. 2-year RFS for ctDNA-informed treatment escalation was 52% (90% CI: 44 - 59%) vs 61% (90% CI: 54 - 68%) for SOC (HR 1.11, 90% CI: 0.83 - 1.48; P = 0.6). The 3-year RFS for ctDNA-positive pts receiving FOLFOXIRI and FOLFOX/CAPOX was similar (47% vs 51%, HR 1.09, 90% CI 0.78 to 1.53; P = 0.7). In a pre-specified correlative analysis of all ctDNA positive pts, recurrence risk increased with ctDNA burden, with 3-year RFS of 78%, 63%, 36% and 22% for tumor-derived mutant molecules/mL quartiles $< 0.06$, $0.06 - 0.17$, $0.18 - 1.31$, and $> 1.31$, respectively ($P < 0.01$). Treatment-related hospitalisation was similar for escalated and SOC pts (OR 1.21, P = 0.58). Analysis of post-ACT ctDNA is underway. **Conclusions:** In this first randomised study of ctDNA-informed management in stage III CC, we confirm the prognostic significance of detectable ctDNA, with the novel finding of recurrence risk increasing markedly with ctDNA burden. Treatment escalation, including to FOLFOXIRI, did not improve RFS. Future studies in ctDNA positive pts should explore other escalation strategies. Clinical trial information: ACTRN12617001566325. Research Sponsor: Marcus Foundation; NHMRC; U.S. National Institutes of Health.

# Tissue-free circulating tumor DNA assay and patient outcome in a phase III trial of FOLFOX-based adjuvant chemotherapy (Alliance N0147).

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**Background:** Among patients with resected node-positive colon cancer, nearly 30% will relapse despite standard adjuvant chemotherapy. Analysis of molecular residual disease (MRD) using circulating tumor DNA (ctDNA) may enable risk stratification for tumor recurrence and inform adjuvant treatment decisions. **Methods:** Postsurgical ctDNA was analyzed in patients with stage III colon carcinoma who participated in a phase 3 trial of adjuvant FOLFOX alone or combined with cetuximab (n = 3084) [NCCTG N0147]. We utilized a tissue-free epigenomic assay for ctDNA detection (Guardant Reveal) with sampling prior to start of adjuvant therapy. Among ctDNA positives, epigenomic tumor fraction (TF) was estimated and ctDNA genotyping was done with Guardant360 (panel of 739 genes). Median follow-up was 6.1 years (yr). Study endpoints included time-to-recurrence (TTR), disease-free survival (DFS) and overall survival (OS) analyzed by Kaplan–Meier method. Multivariable Cox proportional hazards models were used to assess prognostic utility of ctDNA status adjusting for confounders. Interaction between ctDNA and clinicopathological features were assessed. **Results:** Among 2260 patients with evaluable ctDNA data, 461 (20.4%) were ctDNA positive.Tumors were significantly associated with higher T, N stage, $BRAF^{V600E}$, high grade, obstruction/perforation, and worse performance status. Positive vs negative ctDNA was significantly associated with shorter TTR (hazard ratio [HR] 4.33, 95% confidence interval [CI] 3.65-5.13, $P < 0.0001$), poorer DFS (HR 3.74, CI 3.18-4.39, $P < 0.0001$] and OS (HR 3.17, CI 2.63-3.83, $P < 0.0001$), adjusting for covariates and tissue MMR, *KRAS* and $BRAF^{V600E}$. ctDNA positive vs negative patients had 3y DFS of 36.4% (95%CI 32.2-41.2%) vs 82.5% (95% CI 80.0-84.4%), respectively. Adverse prognosis was consistent across subgroups (all $P < 0.05$), with stronger detrimental effects for positive ctDNA in N1 (vs. N2), T1/2 (vs T3 or 4), and mismatch repair deficient tumors [interaction P = 0.0002 to 0.041). Among patients with positive ctDNA, TF in those who recurred/died within 3 yr was double of those who remained recurrence-free ($P = 0.0001$). High vs. low ctDNA TF ( $>$ vs $\leq$ median) further stratified TTR (HR 1.48, CI 1.17-1.88, $P = 0.0011$), DFS (HR 1.52, CI 1.21-1.92, $P = 0.0004$) and OS (HR 1.58, CI 1.21-2.07, $P = 0.0009$), adjusting for confounders. ctDNA positive cases, . Analyses of ctDNA detection by site of recurrence, ctDNA clearance, and genomic variant detection are ongoing. **Conclusions:** In the largest study evaluating tissue-free epigenomic-based MRD detection, we demonstrate a robust prognostic utility of postsurgical ctDNA. Tumor fraction provided further patient stratification and analysis is ongoing to identify a subgroup based on TF that may be unlikely to clear ctDNA despite adjuvant chemotherapy. Research Sponsor: National Cancer Institute; U10CA180882.

# Perioperative systemic therapy for resectable colorectal peritoneal metastases: A multicenter randomized phase 3 trial (CAIRO6).

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**Background:** In patients with resectable colorectal peritoneal metastases who qualify for cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC), there is no prospective data comparing the efficacy of perioperative systemic therapy with CRS-HIPEC alone. **Methods:** In this multicenter phase 3 superiority trial, patients with resectable colorectal peritoneal metastases without extraperitoneal metastases who did not receive systemic therapy within six months prior to enrollment were randomly assigned (1:1) to receive perioperative CAPOX, FOLFOX, or FOLFIRI with neoadjuvant addition of bevacizumab (perioperative systemic therapy group) or CRS-HIPEC alone (surgery alone group). The primary outcome was overall survival. Key secondary outcomes were progression-free survival and 90-day major postoperative morbidity and mortality. The trial needed 179 patients in each arm to detect a superior 3-year overall survival of 65% in the perioperative systemic therapy group versus 50% in the surgery alone group (corresponding hazard ratio [HR] for death 0.62) with 80% power, 5% drop-out, and a two-sided log rank test of $p<0.05$. The primary overall survival analysis was done after 171 events (88% power). **Results:** Of 358 randomized patients, 351 were eligible for primary analysis: 173 in the perioperative systemic therapy group and 178 in the surgery alone group. At a median follow-up of 41 months, median and 3-year overall survival were 44 months and 54% in the perioperative systemic therapy group and 39 months and 53% in the surgery alone group, respectively (HR for death 0.85, 95% CI 0.62-1.15, p=0.28). Median and 3-year progression-free survival were 13.5 months and 20% in the perioperative systemic therapy group and 7.0 months and 5% in the surgery alone group, respectively (HR for progression or death 0.51, 95% CI 0.41-0.65). In the per-protocol population of 292 patients who underwent macroscopic complete CRS-HIPEC, median and 3-year overall survival were 54 months and 64% in the perioperative systemic therapy group (138 patients) and 45 months and 59% in the surgery alone group (154 patients), respectively (HR for death 0.73, 95% CI 0.51-1.05). Ninety-day major postoperative morbidity rates were 36% in the perioperative systemic therapy group and 26% in the surgery alone group, with a 90-day postoperative mortality of 1% in both groups. **Conclusions:** Among patients with resectable colorectal peritoneal metastases, perioperative systemic therapy did not result in superior overall survival as compared to CRS-HIPEC alone. Clinical trial information: NCT02758951. Research Sponsor: Dutch Cancer Society; F. Hoffmann-La Roche.

# Long-term safety and efficacy of sotorasib plus panitumumab and FOLFIRI for previously treated *KRAS* G12C-mutated metastatic colorectal cancer (mCRC): CodeBreaK 101 (phase 1b).

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**Background:** In the phase 3 CodeBreaK 300 trial (NCT05198934), the combination of sotorasib ($KRAS^{G12C}$ inhibitor) and panitumumab (monoclonal anti-EGFR antibody) improved clinical outcomes in patients with chemorefractory *KRAS* G12C-mutated mCRC. CodeBreaK 101 is a phase 1b trial where FOLFIRI was added to sotorasib and panitumumab in previously treated patients with *KRAS* G12C-mutated mCRC. For the first time, we report mature overall survival (OS) and progression-free survival (PFS), as well as updated safety and response data. **Methods:** Patients with *KRAS* G12C-mutated mCRC who received ≥1 prior systemic treatment but were $KRAS^{G12C}$ inhibitor-naïve, were enrolled into the expansion cohort of the CodeBreak 101 subprotocol H (NCT04185883) phase 1b trial. As defined from dose exploration cohort, patients received the recommended phase 2 dose (RP2D) of sotorasib (960 mg orally daily) plus panitumumab (6 mg/kg intravenous every 2 weeks [Q2W]) and standard dose FOLFIRI (intravenous Q2W). The primary endpoint was safety and secondary endpoints included confirmed response, OS, and PFS, assessed by investigator per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. **Results:** By November 2024, 40 patients were enrolled (female: 47.5%; median age: 56.0 years; median [range] prior lines of systemic therapy: 2 [1-6]). The most common treatment-related adverse events (TRAEs) were dermatitis acneiform and dry skin (n = 27 [67.5%] each), decreased neutrophil count (n = 20 [50.0%]), and stomatitis (n = 17 [42.5%]). Grade ≥3 TRAEs occurred in 20 (50.0%) patients with no new safety signals. Discontinuation of sotorasib, panitumumab, or FOLFIRI (5-FU, irinotecan, or leucovorin/levoleucovorin) due to AEs was observed in 1 (2.5%), 1 (2.5%), and 16 (40.0%) patients, respectively. A total of 7 patients are still continuing the study, of whom 5 are off-treatment and under follow-up. Updated objective response rate (95% CI) was 57.5% (40.9, 73.0) and disease control rate (95% CI) was 92.5% (79.6, 98.4). Median time to response was 1.6 months and duration of response was 6.6 months. After a median follow-up of 29.2 months, the median (95% CI) PFS was 8.2 (7.0, 10.8) months and median OS was 17.9 (12.9, 25.1) months. **Conclusions:** Sotorasib plus panitumumab and FOLFIRI showed promising long-term safety and efficacy in pretreated *KRAS* G12C-mutated mCRC. AEs were consistent with the safety profile of the drugs administered. The ongoing phase 3 study, CodeBreaK 301 (NCT06252649), aims to evaluate this combination against standard of care in first-line patients with *KRAS* G12C-mutated mCRC. Clinical trial information: NCT05198934. Research Sponsor: Amgen Inc.

# Efficacy and safety of olomorasib, a second-generation KRAS G12C inhibitor, plus cetuximab in *KRAS* G12C-mutant advanced colorectal cancer.

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**Background:** Olomorasib, a potent and selective second-generation KRAS G12C inhibitor (G12Ci), has demonstrated promising efficacy and a favorable safety profile in *KRAS* G12C-mutant cancers. Based on emerging nonclinical and clinical data, combining a KRAS G12Ci with cetuximab offers a compelling opportunity to improve outcomes in patients (pts) with *KRAS* G12C-mutant colorectal cancer (CRC). Here we report updated results from a phase 1/2 study (NCT04956640) on the safety, tolerability and optimal dose of olomorasib + cetuximab in pts with *KRAS* G12C-mutant CRC. **Methods:** Pts with advanced *KRAS* G12C-mutant CRC (tissue or plasma) previously treated with ≥1 prior oxaliplatin- or irinotecan-containing regimen were eligible and enrolled into dose escalation/expansion or optimization at 2 doses of olomorasib (100 and 150 mg, orally BID). Dose escalation of olomorasib + cetuximab followed a mTPI-2 method. Key objectives were safety and to determine the optimal dose of olomorasib + cetuximab. Antitumor activity per RECIST v1.1 was studied in pts with ≥1 post-baseline response assessment or who discontinued before a first response assessment. **Results:** As of 13 November 2024, 93 pts received olomorasib + cetuximab in dose escalation/expansion (n=49) or optimization (n=44). Median age was 58 yrs (range, 35-82) and median number of prior therapies was 3 (range, 1-8). All grade TRAEs in ≥20% of pts were dermatitis acneiform (58%), diarrhea (38%), dry skin (31%), paronychia (28%), hypomagnesemia (26%), and rash (26%). The majority of TRAEs were grade 1-2, with grade ≥3 observed in 24% of pts. The most common TRAEs grade ≥3 were diarrhea, hypokalemia, and rash, each occurring in 2 pts. TRAEs led to olomorasib dose reduction in 2% of pts, olomorasib dose hold in 22% of pts, and cetuximab dose hold in 16% of pts. Of the 61 pts who discontinued treatment, 57 were due to PD. Two pts discontinued cetuximab due to TRAEs and continued on olomorasib. The AE profile was similar between doses. Median time on combination treatment was 6.5 mo (range, 0.8-24.1) and 32 pts remained on treatment. See Table 1 for efficacy data. Biomarker analysis will be reported. **Conclusions:** Olomorasib + cetuximab demonstrated similar antitumor activity and favorable safety at both dose levels in pts with *KRAS* G12C-mutant CRC, with the optimal dose of olomorasib + cetuximab determined as 100 mg BID. These results further support combining second-generation KRAS G12Ci with other anticancer therapies to improve outcomes in previously treated pts with *KRAS* G12C-mutant CRC. Clinical trial information: NCT04956640. Research Sponsor: Eli Lilly and Company.

| Endpoint | Olomorasib (100 mg BID) + Cetuximab N=64 | Olomorasib (150 mg BID) + CetuximabN=29 | Total N=93 |
|---|---|---|---|
| **ORR, % (n/N)** | 44% (28/64) | 38% (11/29) | 42% (39/93) |
| **BOR, n (%)** | | | |
| **PR** | 28 (44) | 11 (38) | 39 (42) |
| **SD** | 31 (48) | 16 (55) | 47 (51) |
| **PD** | 5 (8) | 2 (7) | 7 (8) |
| **mDOR, mo (95% CI)** | 8.3 (5.6-12.7) | 6.2 (2.8-NE) | 7.6 (6.0-12.2) |
| **mPFS, mo (95% CI)** | 7.5 (6.7-9.7) | 6.6 (4.2-7.6) | 7.5 (6.6-8.8) |

# The KRAS G12C inhibitor MK-1084 for *KRAS* G12C–mutated advanced colorectal cancer (CRC): Results from KANDLELIT-001.

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**Background:** Preliminary data from the phase 1 KANDLELIT-001 trial (NCT05067283) showed a manageable safety profile and preliminary antitumor activity for MK-1084, a next-generation, selective KRAS G12C-GDP covalent inhibitor, in participants (pts) with previously treated, *KRAS* G12C-mutant solid tumors, including non–small-cell lung cancer and CRC. Here, we report data for MK-1084 monotherapy, MK-1084 + cetuximab, and MK-1084 + cetuximab + mFOLFOX6 in pts with advanced *KRAS* G12C-mutant CRC. **Methods:** KANDLELIT-001 enrolled pts with confirmed *KRAS* G12C mutation, RECIST-measurable disease, and ECOG PS 0-1. Pts with any advanced solid tumor and ≥1 prior systemic therapy received MK-1084 monotherapy PO QD or BID (total daily dose, 25-800 mg) in arms 1 and 3. Pts with advanced CRC and 1-2 prior systemic therapies received MK-1084 QD (total daily dose, 25-200 mg) plus cetuximab 500 mg/m$^2$ IV Q2W in arm 5. Pts with advanced CRC and 0-1 prior systemic therapies received MK-1084 QD (total daily dose, 25-100 mg) plus cetuximab 500 mg/m$^2$ Q2W and mFOLFOX6 in arm 6. The primary endpoints were dose-limiting toxicities (DLTs), AEs, and AEs leading to discontinuation. Secondary endpoints included ORR per RECIST v1.1 by investigator review. ORR was assessed in all pts who received their first MK-1084 dose ≥5 wk before the data cutoff date of August 12, 2024, for arms 1 and 3 and November 6, 2024, for arms 5 and 6. **Results:** In arms 1+3, 99 pts, including 53 (54%) with CRC, received MK-1084 alone. In arm 5, 34 pts, including 23 (68%) who had ≥2 prior lines of therapy, received MK-1084 + cetuximab. In arm 6, 20 pts, including 10 (50%) who had no prior therapy, received MK-1084 + cetuximab + mFOLFOX6. Median (range) study follow-up was 14.8 mo (0.2-30.8) in arms 1+3, 5.3 mo (2.6-11.5) in arm 5, and 1.9 mo (0.1-5.4) in arm 6. One pt in arm 6 experienced a DLT (grade 3 febrile neutropenia); there were no DLTs in arms 1, 3, or 5. Treatment-related AEs occurred in 62% of pts in arms 1+3, 97% of pts in arm 5, and 90% of pts in arm 6, were grade ≥3 in 9%, 18%, and 25%, respectively, and led to discontinuation of any drug in 1%, 3%, and 15%, respectively. There were no treatment-related deaths. The two most common treatment-related AEs in each arm were increased AST (17%) and nausea (17%) in arms 1+3, dermatitis acneiform (47%) and rash (24%) in arm 5, and nausea (55%) and rash (50%) in arm 6. ORR (95% CI) was 36% (23-50) in pts with CRC in arms 1+3 (n = 53), 50% (32-68) in arm 5 (n = 34), and 14% (2-43) in arm 6 (n = 14); all responses were partial responses. **Conclusions:** Preliminary data suggest that MK-1084 monotherapy, MK-1084 + cetuximab, and MK-1084 + cetuximab + mFOLFOX6 have manageable safety profiles and show evidence of antitumor activity in pts with advanced, *KRAS* G12C-mutated CRC. Pts continue to be followed, and enrollment continues. Clinical trial information: NCT05067283. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

**LBA3509** **Clinical Science Symposium**

# Association between empirical dietary inflammatory pattern (EDIP) and survival in patients with stage III colon cancer: Findings from CALGB/SWOG 80702 (Alliance).

Sara K. Char, Qian Shi, Tyler Zemla, Chao Ma, En Cheng, Priya Kumthekar, Katherine A. Guthrie, Felix Couture, J. Phillip Kuebler, Pankaj Kumar, Benjamin R. Tan, Smitha S. Krishnamurthi, Brian M. Wolpin, Francois J. Geoffroy, Fred Tabung, Anthony F. Shields, Eileen M. O'Reilly, Jeffrey A. Meyerhardt, Chen Yuan, Kimmie Ng; Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; Alliance Statistics and Data Management Center, Mayo Clinic, Rochester, MN; Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY; Northwestern Memorial Hospital, Chicago, IL; SWOG Statistics and Data Management Center, Fred Hutchinson Cancer Center, Seattle, WA; CHU de Québec, Quebec, QC, Canada; Columbus NCI Community Oncology Research Program, Columbus, OH; Illinois CancerCare, P.C., Peoria, IL; Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO; Department of Hematology and Medical Oncology, Cleveland Clinic, Cleveland, OH; The Ohio State University College of Medicine and Comprehensive Cancer Center, Columbus, OH; Department of Oncology, Karmanos Cancer Institute, Wayne State University, Detroit, MI; Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY

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**LBA3510** **Clinical Science Symposium**

# A randomized phase III trial of the impact of a structured exercise program on disease-free survival (DFS) in stage 3 or high-risk stage 2 colon cancer: Canadian Cancer Trials Group (CCTG) CO.21 (CHALLENGE).

Christopher M. Booth, Janette L. Vardy, Christopher J. O'Callaghan, Sharlene Gill, Christine Friedenreich, Rebecca KS Wong, Haryana M. Dhillon, Victoria Coyle, Neil Sun Chua, Derek J. Jonker, Philip James Beale, Kamal Haider, Patricia A. Tang, Tony Bonaventura, Ralph Wong, Howard J. Lim, Matthew E. Burge, Patti O'Brien, Dongsheng Tu, Kerry S. Courneya; Queen's University, Kingston, ON, Canada; Faculty of Medicine and Health, University of Sydney & Sydney Cancer Survivorship Centre, New South Wales, Australia; Canadian Cancer Trials Group, Queen's University, Kingston, ON, Canada; BC Cancer - Vancouver, Vancouver, BC, Canada; Alberta Health Services - Cancer Care, Calgary, AB, Canada; Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; Faculty of Science, School of Psychology, Centre for Medical Psychology & Evidence-based Decision-making, Psycho-Oncology Cooperative Research Group, The University of Sydney, Sydney, NSW, Australia; Queen's University Belfast, Belfast, United Kingdom; Cross Cancer Institute, University of Alberta, Edmonton, AB, Canada; The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada; Concord Cancer Centre, Concord Hospital, Concord, NSW, Australia; Saskatoon Cancer Centre, University of Saskatchewan, Saskatoon, SK, Canada; Tom Baker Cancer Centre, Calgary, AB, Canada; Newcastle Private Hospital, Waratah, NSW, Australia; CancerCare Manitoba, Winnipeg, MB, Canada; BC Cancer - Vancouver, University of British Columbia, Vancouver, BC, Canada; Royal Brisbane and Women's Hospital, Herston, QLD, Australia; Canadian Cancer Trials Group, Kingston, ON, Canada; Faculty of Kinesiology, Sport, and Recreation, University of Alberta, Edmonton, AB, Canada

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**LBA3511** **Clinical Science Symposium**

# Aspirin as secondary prevention for colorectal cancer liver metastases (ASAC): A multicenter, randomized, double-blind, placebo-controlled, phase 3 trial.

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3512 Rapid Oral Abstract Session

# Upfront modified FOLFOXIRI plus panitumumab (pan) versus FOLFOX/pan for unresectable *RAS* and *BRAF* wild-type (wt) metastatic colorectal cancer (mCRC) patients: Overall survival (OS) results from the phase III TRIPLETE study by GONO.

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**Background:** TRIPLETE (NCT03231722) is a phase III trial where unresectable *RAS/BRAF* wt mCRC patients (pts) were randomized 1:1 to first-line FOLFOX/pan (Arm A) or modified FOLFOXIRI/pan (Arm B). The study failed to demonstrate an improved overall response rate, primary endpoint of the study, in Arm B, and did not show any benefit from the intensification of the chemotherapy also in terms of progression-free survival (PFS), early tumor shrinkage, depth of response, R0 resection rate at the price of increased gastrointestinal toxicity. Here we report OS results. **Methods:** Eligible pts were stratified according to ECOG PS (0-1 vs 2), primary tumor location (right vs left), and liver-only metastases (yes vs no). OS was assessed from randomization to death from any cause. Survival curves were calculated using the Kaplan–Meier method and compared with the log-rank test stratified by the same factors as per randomization. Hazard ratios (HR) with 95% confidence interval (CI) were estimated using Cox regression models. **Results:** 435 pts (A/B: 217/218) were enrolled. Main pts' characteristics were median age 59/59 years, ECOG PS 0 80%/84%, synchronous metastases 88%/86%, liver-only disease 38%/39%, left-sided primary tumour 88%/88%; deficient MMR tumours 1%/3%. At a median follow up of 60.2 months (mos), 292 (67%, arm A/B: 71%/63%) OS events were collected. Significantly longer OS was observed in Arm B with a median OS of 41.1 vs 33.3 mos in Arm A (HR: 0.79; 95%CI: 0.63-0.99; p = 0.049). No molecular or clinical groups of interest emerged from the subgroup analyses. While no significant difference in PFS was confirmed (median PFS Arm A/B: 12.4/12.7 mos, p = 0.606), longer post progression survival (PPS) was reported in Arm B (HR: 0.73; 95%CI: 0.57-0.93; p = 0.012). The proportion of pts receiving subsequent lines of therapy was similar between arms ($2^{nd}$-line Arm A/B: 73%/71%, $3^{rd}$-line: 52%/50%, $4^{th}$-line: 33%/33%), and no differences were evident in the exposure to anti-EGFRs (Arm A/B 35%/38%) and oxaliplatin (26%/33%) after PD, while higher percentages of pts in ARM A received anti-angiogenics (59%/45%) and irinotecan (66%/56%). Similar percentages of pts received locoregional treatments with radical intent after PD (Arm A/B 16%/15%). **Conclusions:** Upfront modified FOLFOXIRI/pan provides a statistically significant and clinically meaningful survival advantage compared to standard FOLFOX/pan in pts with *RAS/BRAF* wt mCRC, with a 7.8 mos difference in median values, though in the absence of any significant difference in treatment activity and PFS. Clinical trial information: NCT03231722. Research Sponsor: GONO Foundation; Amgen.

3513 Rapid Oral Abstract Session

# FIRE-4 (AIO KRK-0114): Randomized study evaluating the efficacy of cetuximab re-challenge in patients with metastatic RAS wild-type colorectal cancer responding to first-line treatment with FOLFIRI plus cetuximab.

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**Background:** Several smaller studies performed in later lines of treatment have suggested a potential benefit from anti-EGFR re-challenge on survival of RAS wild-type (RAS WT) metastatic colorectal cancer (mCRC). FIRE-4 is a randomized phase-III study that prospectively evaluates re-challenge with chemotherapy plus cetuximab as compared to physician's choice. **Methods:** The FIRE-4 study was performed with two steps of randomisation. Within the first randomisation, pts were either attributed to induction therapy with FOLFIRI plus cetuximab continued until disease progression (PD) or intolerable toxicity (arm A) or to a switch maintenance using 5-FU plus bevacizumab (arm B). After first PD, an anti-EGFR-free "window therapy" was recommended. After diagnosis of second PD, RAS WT pts (again selected by liquid- or tumor-biopsy), who had responded to cetuximab-based induction therapy within FIRE-4 (entry 1) or outside of the study (entry 2), could then proceed to 2$^{nd}$ randomization attributing pts either to re-challenge with cetuximab or to physician's choice. Overall survival (OS) after 2$^{nd}$ randomization was evaluated as primary endpoint. **Results:** From August 2015 to February 2021, 672 pts were randomized and 657 pts were assigned to treatment in 120 German and 10 Austrian centers. Within the 2$^{nd}$ randomization, 87 pts (entry 1: N = 62; entry 2: N = 25) were attributed either to physician's choice (A2: N = 42) or (FOLF)IRI plus cetuximab (Arm B2: n = 45). Baseline characteristics were comparable between groups without significant differences regarding parameters such as age, sex, ECOG performance status, or primary tumor sidedness. All pts were RAS WT at the time of randomization. No statistically significant difference between arm A2 and B2 was observed regarding OS (15.1 months vs. 17.6 months; HR 0.84; P = 0.48) or PFS (4.6 months vs. 5.8 months; HR 0.91; P = 0.64). ORR was greater in the experimental arm (11.9% vs. 28.9%; OR 0.33; P = 0.07), while disease control rate was nearly identical (59.5% vs. 60.0%; OR 0.98; P > 0.99). **Conclusions:** FIRE-4 did not meet its primary endpoint. While the control arm using physician's choice exceeded expectations, re-challenge with anti-EGFR therapy in RAS WT pts obtained comparable results in terms of OS. Clinical trial information: NCT02934529. Research Sponsor: MERCK Serono.

# Longitudinal ctDNA monitoring and prediction of anti-EGFR rechallenge outcomes in RAS/BRAF wild-type metastatic colorectal cancer (mCRC): The REMARRY & PURSUIT trials.

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**Background:** Anti-EGFR monoclonal antibody (mAb) rechallenge involves re-administering EGFR blockade after a treatment-free interval to exploit clonal evolution. Recent evidence suggests that circulating tumor DNA (ctDNA)–based selection may improve outcomes; however, the predictive value of longitudinal ctDNA monitoring remains uncertain. **Methods:** The REMARRY study evaluated plasma *RAS* (p*RAS*) dynamics in patients with *RAS/BRAF* V600E wild-type metastatic colorectal cancer (mCRC), ECOG PS 0–1, who had previously responded to anti-EGFR therapy and experienced progression within two months of the last dose. p*RAS* status was assessed at progression on prior anti-EGFR, before rechallenge, at cycle 3, and at discontinuation using BEAMing digital PCR. Patients meeting additional criteria—namely, p*RAS*-negative, refractory or intolerance to standard chemotherapies, and an anti-EGFR–free interval of at least 4 months—were enrolled in the phase II PURSUIT trial, which administered panitumumab (6 mg/kg) plus irinotecan (150 mg/m$^2$) biweekly. The primary endpoint was confirmed objective response rate (ORR) per RECIST v1.1. In parallel, participants underwent next-generation sequencing (NGS) of ctDNA in the GOZILA trial at corresponding time points to identify resistance alterations in genes including *RAS*, *BRAF*, *EGFR*-ECD, *MAP2K*, ERBB2, and MET. **Results:** Between May 2019 and May 2021, 183 patients were enrolled in REMARRY, and 50 p*RAS*-negative patients before rechallenge were included in PURSUIT. The confirmed ORR was 14.0% (90% CI, 7.0–23.0%), with a median progression-free survival (PFS) of 3.6 months and a median overall survival (OS) of 12.0 months. Although all patients were p*RAS*-negative at baseline, 10.0% converted to p*RAS*-positive by cycle 3 and 36.0% by discontinuation. Patients who were p*RAS*-positive immediately after prior anti-EGFR had higher conversion rates at cycle 3 (42.9% vs. 6.3%, $p = 0.010$) and at discontinuation (85.7% vs. 32.3%, $p < 0.001$) compared with those initially negative. The ORR was 23.8% in patients remaining p*RAS*-negative versus 0% in those converting to p*RAS*-positive ($p = 0.254$). Moreover, NGS-detected resistance alterations after prior anti-EGFR were associated with no responses (0/13) compared to a 27.8% response rate (5/23) in patients without such alterations ($p = 0.038$), and correlated with shorter PFS (HR 3.297, $p = 0.002$) and OS (HR 4.569, $p < 0.001$). In 86% (7/8) of patients who were p*RAS*-positive post–anti-EGFR, the identical p*RAS* codons re-emerged during rechallenge, consistent with NGS findings. **Conclusions:** ctDNA status immediately after progression on prior anti-EGFR therapy predicts subsequent response, thereby supporting clinical decision-making and personalized therapy. Trial Registration: PURSUIT (jRCTs031190096), REMARRY (UMIN000036424), GOZILA (UMIN000029315). Clinical trial information: jRCTs031190096. Research Sponsor: None.

**LBA3515** **Rapid Oral Abstract Session**

# Panitumumab retreatment followed by regorafenib versus the reverse sequence in chemorefractory metastatic colorectal cancer patients with *RAS* and *BRAF* wild-type circulating tumor DNA (ctDNA): Results of the phase II randomized PARERE trial by GONO.

Chiara Cremolini, Paolo Ciracì, Filippo Pietrantonio, Sara Lonardi, Marco Maria Germani, Adele Busico, Paolo Manca, Gianmarco Ricagno, Nicoletta Pella, Vincenzo Formica, Mario Scartozzi, Valentina Burgio, Samantha Di Donato, Roberto Moretto, Iolanda Capone, Federica Palermo, Federica Marmorino, Gianluca Masi, Luca Boni, Daniele Rossini; Unit of Medical Oncology 2, Azienda Ospedaliera Universitaria Pisana and Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Veneto Institute of Oncology IOV, IRCCS, Padua, Italy; Pathology Unit 2, Department of Diagnostic Innovation, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Department of Surgery, Oncology and Gastroenterology, University of Padua and Medical Oncology 1, Veneto Institute of Oncology IOV - IRCCS, Padua, Italy; Department of Oncology, ASUFC University Hospital of Udine, Udine, Italy; Medical Oncology Unit, Department of Systems Medicine, Tor Vergata University Hospital, Rome, Italy; Medical Oncology Unit, University Hospital and University of Cagliari, Cagliari, Italy; Department of Oncology, IRCCS San Raffaele Scientific Institute Hospital, Vita-Salute San Raffaele University, Milan, Italy; Medical Oncology Department ASL Toscana Centro, Santo Stefano Hospital, Prato, Italy; Unit of Medical Oncology 2, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy; Clinical Epidemiology Unit, IRCCS Ospedale Policlinico San Martino, Genoa, Italy; Department of Experimental and Clinical Medicine, University of Florence, Oncology Unit, Careggi University Hospital, Florence, Italy

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**LBA3516** **Rapid Oral Abstract Session**

# JMT101 in combination with irinotecan and SG001 versus regorafenib in patients with metastatic colorectal adenocarcinoma (mCRC): Results of a randomized, controlled, open-label, phase II study.

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3517 Rapid Oral Abstract Session

# Phase 2 dose expansion study of DSP107, a first-in-class bi-specific 4-1BB T-cell engager, with and without atezolizumab in metastatic MSS colorectal cancer patients.

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**Background:** DSP107 is a bi-specific fusion protein composed of sequences from the extracellular domain of SIRP$\alpha$ and 4-1BBL. The SIRP$\alpha$ arm selectively targets CD47 overexpressed on tumor cells, while simultaneously anchoring trimeric 4-1BBL to the tumor, to engage and co-stimulate 4-1BB on activated immune cells in the tumor microenvironment. This results in tumor-localized, conditional activation of innate and adaptive immune responses. Phase 1 data demonstrated an excellent safety profile with no RBC binding and no hematological, hepatic or other dose limiting toxicities (DLTs). Here we describe safety and efficacy data from a Phase 2 microsatellite stable (MSS) colorectal (CRC) expansion cohort in which patients were treated with DSP107 alone or with atezolizumab (NCT04440735). **Methods:** Metastatic/unresectable MSS CRC patients who progressed following 2 lines of therapy including standard chemotherapy $\pm$ targeted antibodies (n = 50), were randomized to receive weekly IV DSP107 infusions (10 mg/kg/dose) alone or with atezolizumab (1200 mg) Q3W during 3-week treatment cycles. The majority (76%) had liver metastases. Study objectives were safety, tolerability and preliminary efficacy. Restaging imaging was performed every 2 months and evaluated by RECIST v1.1 criteria. **Results:** DSP107 monotherapy and with atezolizumab was well tolerated with no DLTs. The most frequent TRAEs were infusion-related reactions (IRR; 38% Grade 1 or 2, 4% Grade 3), fatigue (12% Grade 1 or 2, 4% Grade 3), Grade 1 or 2 nausea (14%) and Grade 1 or 2 anemia (10%). IRRs were managed during subsequent infusions by reducing the infusion rate and administering IV fluids. The median OS from the efficacy-evaluable patients who received DSP107 monotherapy (n = 19) and combination therapy with atezolizumab (n = 21) has not been reached but currently (Dec 2024 cutoff) stands at 7.6 and 14.6 months, respectively. Disease control was demonstrated in 26% (monotherapy) and 62% (combination) of evaluable patients including a patient who achieved complete response ( $>$ 2.5 years) and a patient with a deep (86% target lesion reduction) and durable ( $>$ 16 months) confirmed partial response and disappearance of pulmonary and hepatic metastases. Immunofluorescence analysis of baseline tumor biopsies (n = 16) demonstrated moderate to high levels of CD47 expression in 15/16 biopsies ( $>$ 120 H-Score), and very high levels of CD47 expression ( $>$ 170 H-Score) in all 7 samples collected from liver metastases. **Conclusions:** These data suggest that the combination of DSP107 with PD(L)1 blockade has anti-tumor activity and provides clinical benefit in third line metastatic MSS CRC including in patients with liver metastases. Updated survival data will be presented at the conference. A Phase 2 randomized controlled study is currently in planning to confirm this preliminary efficacy signal. Clinical trial information: NCT04440735. Research Sponsor: KAHR Medical LTD.

# Circulating tumor DNA as an early response indicator in anal squamous cell carcinoma treated with chemoradiation.

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**Background:** Definitive chemoradiation (CRT) is a highly effective, organ-preserving treatment for localized anal squamous cell carcinoma (ASCC). However, a subset of patients experience locoregional failure, leading to unfavorable oncologic outcomes despite salvage surgery. Circulating tumor DNA (ctDNA) has emerged as a promising tool for monitoring treatment efficacy and predicting prognosis; however, there is a paucity of studies evaluating the baseline detectability and kinetics of tumor-informed ctDNA assays in ASCC. **Methods:** Patients with ASCC (*N*=88) undergoing definitive CRT provided prospective consent for longitudinal ctDNA monitoring using a personalized, tumor-informed ctDNA assay (Signatera, Natera, Inc.). ctDNA testing was assessed at three key time points: pre-treatment (any time before CRT to within 5 days after initiation), mid-treatment (from >5 days after initiation to <7 days before completion), and post-treatment (>7 days before completion to 42 days after CRT). Surveillance testing continued every three months. Changes in ctDNA levels were analyzed in relation to clinical outcomes. Locoregional failure (LRF) was assessed using competing risk regression, stratified by ctDNA status (positive vs. negative). ctDNA results were also correlated with progression-free survival (PFS). **Results:** Pre-treatment ctDNA was detected in 79% of patients, with 92% achieving ctDNA-negativity at post-treatment (Table 1). Over a median follow-up of 18 months (IQR 11–26), 7 patients experienced LRF, and 5 experienced distant failure. The cumulative LRF incidence was 0% among patients with ctDNA negativity by mid-treatment. Conversely, 26% of patients with ctDNA positivity at mid-treatment and 61% of patients with ctDNA positivity at post-treatment experienced LRF, respectively. Estimated one-year PFS was 100% for patients who achieved ctDNA negativity by mid-treatment. In contrast, patients who remained ctDNA-positive at mid-treatment and post-treatment had estimated one-year PFS rates of 81% and 44%, respectively, from the date of the corresponding ctDNA test. Among patients who achieved ctDNA negativity but subsequently developed molecular recurrence during the surveillance period (*N*=7), all developed disease recurrence. Molecular recurrence predated clinical or radiographic evidence of recurrence in all instances. **Conclusions:** This tumor-informed ctDNA assay demonstrates high baseline detectability and rapid clearance during CRT, with molecular clearance correlating with favorable outcomes in ASCC. Notably, ctDNA-based detection of molecular recurrence consistently precedes conventional clinical and radiographic indicators of disease recurrence. Further validation in large, prospective cohorts is warranted. Research Sponsor: National Institutes of Health/National Cancer Institute (NIH/NCI); R37 CA248289; National Institutes of Health/National Cancer Institute (NIH/NCI); K08 CA255574; National Institutes of Health/National Cancer Institute (NIH/NCI); 5T32 CA 9501-34; National Institutes of Health/National Cancer Institute (NIH/NCI) Memorial Sloan Kettering Cancer Center (MSK) Support Grant; P30 CA008748.

| | *Pre*-Treatment | *Mid*-Treatment | *Post*-Treatment |
|---|---|---|---|
| **Positive** | 61 (79%) | 29 (47%) | 6 (8%) |
| **Negative** | 16 (21%) | 33 (53%) | 67 (92%) |
| **Unknown** | 11 | 26 | 15 |

# Short-course radiotherapy followed by sintilimab and CAPOX as total neoadjuvant treatment in locally advanced rectal cancer: A prospective, randomized controlled trial (SPRING-01).

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**Background:** Neoadjuvant short-course radiotherapy (SCRT) combined with chemotherapy as total neoadjuvant therapy (TNT) increases the pathological complete response (pCR) rate for locally advanced rectal cancer (LARC). The potential synergistic effects of combining radiotherapy and immunotherapy might benefit patients with LARC. This study aimed to compare the efficacy and safety of SCRT followed by 6 cycles of CAPOX chemotherapy with or without immunotherapy as TNT in LARC patients. **Methods:** In this randomized controlled trial, patients with T3-4, N+, EMVI(+), MRF(+) or lateral lymph node(+) rectal adenocarcinoma were randomly assigned to receive SCRT followed by 6 cycles of CAPOX chemotherapy with or without sintilimab. Total mesorectal excision (TME) was performed 2-3 weeks after the completion of TNT. The primary study endpoint was the pCR rate. **Results:** In this randomized controlled trial, patients with T3-4, N+, EMVI(+), MRF(+) or lateral lymph node(+) rectal adenocarcinoma were randomly assigned to receive SCRT followed by 6 cycles of CAPOX chemotherapy with or without sintilimab. Total mesorectal excision (TME) was performed 2-3 weeks after the completion of TNT. The primary study endpoint was the pCR rate. **Conclusions:** In LARC patients, SCRT combined with sintilimab and CAPOX as a TNT significantly increases the pCR rate while maintaining manageable safety in patients with LARC. SCRT followed by sintilimab and CAPOX can be recommended as a superior neoadjuvant treatment option for these patients. Clinical trial information: ChiCTR2100052288. Research Sponsor: National Natural Science Foundation of China; Special Foundation for Taishan Scholars Program of Shandong Province; Key Research and Development Program of Shandong Province; China Postdoctoral Science Foundation.

**The efficacy of SIN+CAPOX and surgical and pathological results.**

| Intention-to-treat (ITT) population | SIN+CAPOX (N = 49) | CAPOX (N = 49) |
|---|---|---|
| Pathological complete response (ypT0N0, ITT population) — no. (%) | 29 ( 59.2 ) | 16 ( 32.7 ) |
| (% [95% CI]) | (45.4, 72.9) | (19.5, 45.8) |
| Complete response | 30 ( 61.2 ) | 16 ( 32.7 ) |
| Surgical population | SIN+CAPOX (N = 45) | CAPOX (N = 44) |
| Tumor regression grading (AJCC 8th edition) — no. (%) | | |
| 0 | 29 ( 64.4 ) | 16 ( 36.4 ) |
| 1 | 7 ( 15.6 ) | 7 ( 15.9 ) |
| 2 | 5 ( 11.1 ) | 13 ( 29.5 ) |
| 3 | 4 ( 8.9 ) | 8 ( 18.2 ) |

Abbreviations: IQR, interquartile range; N, regional nodal category; T, primary tumor category; yp, pathologic.

# Proposed changes to the pathologic staging for colon cancer (CC): AJCC Colon Cancer Expert Panel (AJCCCCEP).

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**Background:** Recent analyses highlight nonhierarchical outcomes using the 8th Edition AJCC staging system for CC. For instance, the 5-year survival rate for stages I and IIIa patients (pts) closely align. Additionally, tumor deposits (TDs) have been established as significant prognostic indicators. The AJCCCCEP commissioned this study to develop an updated pathological staging system for CC focused specifically on pts without distant metastasis (M0), while retaining the existing stage IV classification. **Methods:** Individual patient data (IPD) from pts diagnosed with cc (2010- 2017) in the NCDB were divided into training (70%) and internal validation (30%) datasets. External validation used IPD from clinical trials. The primary endpoint was overall survival (OS). Risk classification development for M0 pts incorporated ungrouped data on pathologic T categories, the number of involved regional lymph nodes (LN+), and TD counts. Recursive partitioning and regression tree analyses were applied to construct hierarchical staging levels. Pre-specified criteria required survival probabilities to be consecutive and show clear separations using Kaplan-Meier (KM) estimates with pairwise log-rank test P of $< 0.005$ for the training and $< 0.05$ for validation analyses. **Results:** Data from 281,997 pts (median age 67 years, 50% male, 81% white, 55% T3, 19% T4, 44% N+, 26% M+, and 11% with ≥1 TD) were analyzed, with a median follow-up of 7.3 years. The updated staging system (Table) met pre-specified criteria, with all observed pairwise $P < 0.0001$ in the development and internal validation sets. KM OS curves displayed a hierarchical separation across all sub-levels after the 1st year of diagnosis. Consistent results were seen in pts treated with adjuvant chemotherapy in 4 trials (all pair-wise $P < 0.0001$). **Conclusions:** The proposed pathological staging system for M0 pts fulfills pre-specified criteria for hierarchical risk stratification, validated both internally and externally, and provides an evidence-based update. Pending review process, the AJCCCCEP will recommend that these changes be made to the Version 9 staging protocol for colon cancer to improve prognostication for CC pts. Research Sponsor: None.

| Stage | T, # of LN+, # of TD | M | % of pts | 1y OS (CI), % | 3y OS (CI), % | 5y OS (CI), % |
|---|---|---|---|---|---|---|
| I | T1, 0, 0 | 0 | 5 | 96 (95-97) | 91 (90-92) | 84 (83-86) |
| IIa | T2, 0, 0 | 0 | 10 | 95 (94-95) | 88 (88-89) | 80 (79-81) |
| IIb | T1, 0, 1+<br>T1, 1+, 0<br>T2, 0, 1+<br>T2, 1-4, 0<br>T3, 0, 0 | 0 | 27 | 93 (92-93) | 84 (84-85) | 75 (75-76) |
| IIIa | T1, 1+, 1+<br>T2, 1-4, 1+<br>T2, 5+, 0<br>T3, 0, 1+<br>T3, 1-4, 0 | 0 | 14 | 92 (91-92) | 80 (80-81) | 71 (70-72) |
| IIIb | T2, 5+, 1+<br>T3, 1-4, 1+<br>T3, 5+, 0<br>T4a, 0-4, 0<br>T4b, 0-2, 0 | 0 | 13 | 86 (86-87) | 69 (68-70) | 58 (57-59) |
| IIIc | T3, 5+, 1+<br>T4a, 0-4, 1+<br>T4a, 5+, any<br>T4b, 0-2, 1+<br>T4b, 3+, any | 0 | 5 | 78 (77-80) | 53 (51-54) | 40 (38-41) |
| IVa | Any | 1a | 19 | 59 (58-60) | 28 (28-29) | 17 (16-18) |
| IVb | Any | 1b | 7 | 43 (42-44) | 14 (13-14) | 6 (6-7) |

CI: 95% confidence internal; Peritoneum involvement data were not available before 2018 in NCDB. Thus, IVa/b were based on 7th Edition.

# Experience of patients with HIV and squamous cell carcinoma of the anal canal (SCAC) treated with retifanlimab.

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**Background:** People living with HIV (PLHIV) usually have more advanced cancer at diagnosis and a higher cancer-related mortality, posing a significant burden on health care. However, clinical studies often exclude cancer patients with HIV, thereby limiting access to therapies for this patient population. PLHIV have a 25- to 35-fold higher chance of being diagnosed with SCAC than individuals who are HIV negative. We therefore evaluated safety and efficacy of retifanlimab in PLHIV with SCAC. **Methods:** The study designs for POD1UM-202 (NCT03597295) and POD1UM-303/InterAACT-2 (NCT04472429) have previously been described. Both trials permitted PLHIV to enroll if CD4+ count was ≥200/μL with an undetectable viral load per standard of care assay, and who did not experience any HIV-related opportunistic infection for ≥4 weeks prior to study enrollment. Patients continued to receive antiretroviral therapy (ART/HAART) without interruption or dose reduction. HIV viral load and CD4+ cell count was assessed every 8 weeks during the studies and could be reduced to every 6 months during safety and disease follow-up. **Results:** Patient and disease characteristics were similar among PLHIV and the overall study populations. Among the 20 patients with HIV enrolled in these SCAC trials, median age was 58 years, 70% (n = 14) were male, and 80% (n = 16) were White. Forty-five percent (n = 9) of patients received retifanlimab and 30% (n = 6) received retifanlimab with platinum-based chemotherapy, whereas the remaining 5 patients were assigned to placebo plus chemotherapy. During these studies, no patient experienced a sustained drop in CD4+ T-cell counts or increase in HIV viral load of clinical significance. No treatment-emergent opportunistic infections were recorded. Immune-related adverse events (irAEs) and grade ≥3 irAEs were consistent with the non-HIV population. Objective response rates were 22% (2/9) with retifanlimab in second-line and 67% (4/6) with retifanlimab and chemotherapy in first-line (previously untreated). Patient-reported outcomes showed no negative impact and based on Quality-of-Life Questionnaire for Anal Cancer, good scores for bowel function, sexual, and symptom domains were maintained. Retifanlimab pharmacokinetics was independent of HIV status and not impacted by the HAART required for ongoing HIV management. **Conclusions:** Among PLHIV and advanced SCAC who received treatment, retifanlimab showed significant clinical activity with efficacy qualitatively similar to patients without HIV and no excess toxicity or reduced HIV control. The analysis indicates that retifanlimab is generally safe for PLHIV and SCAC and also supports inclusion of HIV-positive patients in other immunotherapy trials. The favorable outcomes in PLHIV are encouraging because infection with HIV is among the most important risk factors for SCAC. Clinical trial information: NCT03597295 and NCT04472429. Research Sponsor: Incyte Corporation.

# Investigating the immunogenomic profile of anal HPV driven disease for novel therapeutic discovery.

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**Background:** Anal squamous cell carcinoma (ASCC) is driven by Human Papilloma Virus and arises from high-grade squamous intraepithelial lesions (HSIL) which, when treated, reduces the risk of cancer progression. However, current treatment options for anal HSIL are limited with considerable morbidity. Although a proportion of patients with localised ASCC can be successfully treated with pelvic chemoradiotherapy, there are significant associated side effects. Given the stepwise evolution of disease, there is an opportunity for the identification of novel therapeutic approaches for cancer prevention. **Methods:** This study investigates the mutational and immune landscape of matched fresh frozen anal cancer and HSIL samples as well as blood samples from 8 patients using multi-omic analysis (WES, RNAseq and FUME-TCRseq). We compared candidate driver mutations and pathways (including known immune escape mechanisms), copy number alterations (CNAs), differential gene expression, predicted neoantigen profiles (using NeoPredPipe) and TCR repertoire composition and diversity. In addition, digital cell classification of H&E stained sections was used to characterise the distribution of 4 immune cell types. **Results:** There was considerable copy number profile overlap between anal HSIL and cancer with 79.2% CNA concordance. Samples clustered by patient rather than pathology on gene expression and few differentially expressed genes were identified. There was no difference in predicted neoantigen burden ($p$= 0.11) nor the proportion of unique or common neoantigens (p = 0.64), illustrating shared immunogenicity between anal cancers with corresponding pre-cancerous lesions. However, we observed a shift in TCR repertoire composition between HSIL and cancer in all patients, with HSIL regions containing larger clusters of related TCR clonotypes (p = 0.02). Driver mutations in *PIK3CA*, *KMT2C*, *PBRM1*, *KLF5*, *STK11* and *CUL1* were shared between matched samples. Enriched GO terms, Kegg pathways and Reactome pathways shared by 2 or more samples included ubiquitination, lipid metabolism and glycosylation. There was higher *PD-L1* and *CTLA4* expression in anal cancer compared with HSIL, suggestive of immune escape at the transition to invasive cancer. Pathogenic mutations in the Endoplasmic reticulum aminopeptidase 1 (*ERAP1*) gene, responsible for modulating the peptide repertoire presented by MHC class I molecules, were found in one HSIL sample and two cancer samples. **Conclusions:** For the first time, this study demonstrates compelling overlap in the immunogenomic profiles of advanced anal HSIL and neighbouring invasive cancer. The shared neoantigen burden and overall immunogenicity supports future vaccine development in the treatment of anal HSIL and subsequent anal cancer prevention. Furthermore, the evidence for immune escape at the transition to invasion could motivate the use of immunotherapy in this setting. Research Sponsor: NIHR Biomedical Research Centre at the Royal Marsden Hospital and Institute of Cancer Research; The Syncona Foundation; The Royal Marsden Cancer Charity.

# Immunotherapy combined with hypofractionated radiotherapy and chemotherapy for locally recurrent rectal cancer (TORCH-R): A prospective, single-arm, two-cohort, phase II trial.

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**Background:** To assess whether the integration of PD-1 inhibitor with hypofractionated radiotherapy and chemotherapy therapy can lead to an improvement in objective responses in patients with proficient mismatch repair or microsatellite stable (pMMR/MSS) locally recurrence rectal cancer (LRRC). **Methods:** We did a prospective, single-arm, two-cohort, phase 2 trial in LRRC patients without or with oligometastases. Eligible patients with previously untreated (cohort A) or progressive disease after first line therapy (cohort B), were assigned received 25-40 Gy/5 Fx irradiation or 15–30 Gy/5 Fx reirradiation for pelvic recurrence, followdd by 18 weeks of chemotherapy, toripalimab, and stereotactic ablative radiotherapy (SABR) for all metastatic lesions between chemoimmunotherapy cycles. The primary endpoint was confirmed local recurrence objective response rate (ORR). The study is registered with ClinicalTrials.gov, NCT05628038. **Results:** Between Oct 15, 2022, and Aug 31, 2024, We enrolled 67 patients: 41 in cohort A and 26 in cohort B. Median follow-up duration was 10.5 months (IQR 7.3-15.5 months). The local recurrence ORR was achieved at 82.9% (34 of 41 patients) in cohort A and 65.4% (17 of 26 patients) in cohort B. Six patients (14.7%) underwent radical resections (R0) in cohort A and two patients (7.7%) in cohort B. The CR rate was 34.1% (12 cCR patients + 2 pCR patients) in cohort A and 11.5% (2 cCR patients + 1 pCR patients) in cohort B. The most frequent grade 3-4 toxicities were neutropenia (10.8% in cohort A and 25.0% in cohort B) and diarrhea (16.2% in cohort A and 20.8% in cohort B). **Conclusions:** The PD-1 inhibitor remarkably improved ORR in pMMR/MSS LRRC compared with historical benchmark with acceptable toxicity. Up-front immunochemotherapy combined with hypofractionated radiotherapy was selected for future definitive study. Clinical trial information: NCT05628038. Research Sponsor: None.

# Harnessing transcriptome signatures and CD103+CD8+ immune infiltration for prognosis and treatment outcomes in anal squamous cell carcinoma.

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**Background:** Anal squamous cell carcinoma (ASCC) is a rare malignancy linked to high-risk HPV, with rising incidence among younger adults. While immunotherapy advances have improved outcomes in metastatic ASCC, treatment for localized disease has remained unchanged for decades, with high recurrence rates. This study investigates molecular biomarkers and immune mechanisms predictive of chemoradiotherapy outcomes in non-metastatic ASCC. **Methods:** This retrospective study analyzed 94 stage I-III non-metastatic anal squamous cell carcinoma (ASCC) patients treated with curative chemoradiotherapy (CRT) at Hôpital Paris Saint Joseph (2010–2017) in France. Treatment response (CR) was assessed at 24 weeks by RECIST v1.1. Molecular analyses included whole-exome and RNA sequencing on FFPE samples to evaluate somatic mutations, tumor mutational burden (TMB), and gene expression profiles. Immunohistochemistry assessed immune markers (CD8, CD103). Statistical analyses identified predictors of CR, progression-free (DFS), and overall survival (OS). **Results:** Complete response (CR) was achieved in 71% of cases, with no significant differences between treatment regimens ($p > 0.05$). Mutational analysis identified 172 alterations in novel (SLAMF7 and GOLGA6L9) and previously described cancer driver genes (KMT2C, KMT2D, and PIK3CA), with higher mutational burdens showing a non-significant trend toward CR. Transcriptomic profiling revealed 350 differentially expressed genes among CR vs. NCR patients (p-value $< 0.01$; FC $> 2$). CR was associated with modulation of immune-related pathways, including TNF$\alpha$/NFkB signaling ($p < 0.01$). Immune infiltrate analysis showed enrichment of CD8+ central memory T cells ($p = 0.008$) and CD4+ resting memory B cells ($p = 0.01$) in CR cases, correlating with improved OS ($p = 0.0026$) and DFS ($p = 0.0098$). CD103+CD8+ tumor-infiltrating lymphocytes emerged as the strongest predictor of survival (OS: $p = 0.011$; DFS: $p = 0.003$), underscoring their potential as prognostic biomarkers and therapeutic targets in ASCC. **Conclusions:** These findings underscore the potential of integrating molecular and immune markers into clinical practice to better predict treatment response and guide personalized therapies for CRT efficacy for ASCC patients. Further validation in independent cohorts is necessary to confirm the clinical relevance of these biomarkers and their application in therapeutic decision-making. Research Sponsor: None.

# POD1UM-303/INTERAACT2 subgroup analyses and impact of delayed retifanlimab treatment on outcomes in patients with squamous cell carcinoma of the anal canal (SCAC).

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**Background:** SCAC is a rare cancer with high unmet medical need and no FDA-approved treatment options. POD1UM-303 is the only phase 3 study of systemic therapy completed to date in advanced SCAC. The study met its primary endpoint of progression-free survival (PFS; 9.3 mo in the retifanlimab group vs 7.4 mo in the placebo group [HR, 0.63; 95% CI, 0.47, 0.84; *P*= 0.0006]) (Rao S, et al. *Ann Oncol*. 2024;35:S1217). Based on these results, retifanlimab combined with carboplatin-paclitaxel represents a new standard of care (SOC) for inoperable locally recurrent/metastatic SCAC. Here, we present outcomes for predefined subgroups of interest in POD1UM-303 and exploratory analyses in patients who received open-label retifanlimab in the crossover phase of the study. **Methods:** The POD1UM-303 study design and methods were previously presented at ESMO 2024. PFS comparisons for predefined subgroups, including PD-L1 expression, region of enrollment, presence of liver metastases, extent of disease, as well as HPV and HIV status, were performed. Exploratory analyses of investigator-assessed response to retifanlimab, overall survival (OS), and safety during crossover treatment were also performed. **Results:** A total of 308 patients were enrolled (1:1) to receive retifanlimab or placebo with chemotherapy; 69 (45%) from the placebo + chemotherapy group received crossover treatment with retifanlimab monotherapy upon confirmed progression. A consistent PFS benefit in favor of retifanlimab + chemotherapy was observed for all predefined subgroups, including tumors with PD-L1 expression $<1\%$, patients with liver metastases, and regardless of HPV or HIV status. Median PFS in the retifanlimab + chemotherapy group was higher in the PD-L1 $\geq 1\%$ vs PD-L1 $<1\%$ groups (9.3 mo; HR, 0.64 vs 7.5 mo; HR, 0.53) but was not impacted by presence of liver metastases. During crossover, investigator-assessed overall response rate was qualitatively similar to that seen in the POD1UM-202 study, which enrolled a similar platinum-refractory population. Median OS for patients receiving crossover treatment with retifanlimab was 24.3 mo, compared with 29.2 mo for patients who were assigned to retifanlimab + chemotherapy at randomization. Safety during crossover was consistent with earlier observations and comparable with experience in POD1UM-202. **Conclusions:** The benefits of retifanlimab combined with carboplatin-paclitaxel extend to the broad population of SCAC, including those with tumors not expressing PD-L1 and liver metastases. Response rate and safety profile of retifanlimab monotherapy in the crossover period were consistent with the previous POD1UM-202 experience; however, exploratory analysis of survival in crossover patients suggests first-line retifanlimab with SOC chemotherapy is preferable to sequential treatment after progression on chemotherapy. Clinical trial information: NCT04472429. Research Sponsor: None.

# Genomic characterization of anal canal squamous cell carcinoma (ASCC) and outcomes on matched targeted therapy.

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**Background:** Anal canal squamous cell carcinoma (ASCC) is uncommon but increasing in incidence. 5-year survival of patients (pts) with metastatic ASCC is only 36%; new therapies are an unmet medical need. Genomic alterations (GA) in phosphoinositol-3-kinase (PI3K) signaling pathway have been reported in small datasets of ASCC. Data on clinical outcomes with therapies targeting these GA in pts with ASCC are lacking. **Methods:** Tumor genomic data of pts with ASCC at Memorial Sloan Kettering Cancer Center (MSK) were obtained using a targeted next generation sequencing assay (MSK IMPACT) from cBioPortal database. GA were annotated for biological significance using the OncoKB database, and only GA with known oncogenic potential were included. GA were categorized as mutations (mut), amplifications (amp), deletions (del) and fusions (fus). Clinical annotations were abstracted from electronic health records and outcomes of pts who participated in clinical trials were assessed. Data were summarized using descriptive statistics and survivals were estimated using Kaplan-Meier method. **Results:** Of 92,711 pts in cBioPortal, 218 (0.2%) pts had ASCC (male n = 65, 30%). Of these 218 pts, 179 (82%) had at least 1 oncogenic GA. Oncogenic GA were most frequently identified in *PIK3CA* 40% (87 pts; mut 67, amp 36, with overlap), *KMT2D* 19% (mut 42), *BCL6* 17% (amp 37), *PTEN* 12% (mut 18, del 9), *EP300* 11% (mut 24), *KMT2C* 11% (mut 20, del 3), and *FBXW7* 10% (mut 20, del 1). Oncogenic GA were most frequent in the PI3K-AKT-mTOR signaling pathway (121 pts, 55%). Amps were also seen in *FGF3*, *FGF4*, *FGF19* and *CCND1* in 4% pts each. Thirteen pts with metastatic treatment refractory ASCC participated in early phase clinical trials; 3 pts enrolled in $>1$ studies (total 18 trial participations). GA-matched targeted therapy was administered to 8 pts: oncogene inhibitors in 6 pts (targeting PIK3CA E545K in 3, PIK3CA Q546K in 1, HER2 I767M in 1, FGFR2 amp in 1), and drugs selected for tumor suppressor gene GA in 3 pts (PTCH1 loss in 1, TP53-wild in 1, FBXW7 in 1). Six pts received immunotherapy and 3 pts were treated with antivirals drugs targeting Human Papillomavirus. Out of 4 pts treated with PI3K signaling inhibitors, 1 had partial response and 2 had stable disease, with median progression free survival of 3.6 (95% CI 0-8.6) months and median overall survival of 9.1 (95% CI 5.7-12.5) months. Two out of four pts treated with PI3K pathway inhibitors were on treatment for $>6$ months. No response was seen in pts treated with drugs targeting GA other than PIK3CA or with immunotherapy; and one of three pts treated with anti-viral agents had best response of stable disease. **Conclusions:** This is the largest characterization of GA with known oncogenic potential in ASCC. The PI3K signaling pathway is altered in over half of ASCC, and PI3K-AKT-MTOR inhibitors have the potential for further investigation in pts with activating GA in *PIK3CA* gene. Research Sponsor: Robert A. Winn Career Development Award.

# Monitoring botensilimab- and balstilimab-induced T-cell dynamics in refractory mismatch repair proficient metastatic colorectal cancer.

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**Background:** Mismatch repair proficient (pMMR) metastatic colorectal cancer (mCRC) responds poorly to immune checkpoint inhibition (ICI). A better understanding of local and systemic immune cell activities is critical for improving ICI treatment efficacy. T cells elicit anti-tumor specificity through their T cell receptors (TCR) and dynamic changes in the TCR repertoire are associated with clinical outcomes. Circulating T cells in the blood provide an accessible liquid biomarker to quantify and track T cell activity at systems level and longitudinally. Here, we present temporal T cell tracking as a correlate of ICI efficacy in refractory pMMR mCRC patients treated with botensilimab (BOT; Fc-enhanced anti-CTLA-4 antibody) with or without balstilimab (BAL; anti-PD-1 antibody). **Methods:** 10 patients from the open-label, phase 2 study (NCT05608044) with BOT in refractory pMMR CRC (without metastatic liver disease) were included. In this trial patients were randomized into BOT (75mg or 150mg Q6W, 4x) monotherapy or in combination with BAL (240mg Q2W, for 2 years), versus standard of care (regorafenib or trifluridine/tipiracil). TCR dynamics were longitudinally assessed (0,2,4,6,12 weeks) from circulating T cells, based on deep TCR sequencing (OS-TCR, Omniscope) and quantified using functional clustering. **Results:** 2 mCRC patients out of 10 (20%) showed partial response (PR) while 8 (80%) had progressive disease (PD), however at variable timepoints. However circulating T cells showed significant expansion of both pre-existing and novel clonotypes in all patients, detectable at conserved frequencies at sequential time points. The magnitude of induced T cell clonotypes varied across treatment cycles, with repeated boosting effects observed in responders. Scoring T cell activity based on quantitative and qualitative TCR repertoire metrics, allowed to rank patients by their response. Intriguingly, TCR repertoire dynamics strongly correlated with clinical outcomes, establishing its potential as a quantitative biomarker for monitoring treatment efficacy. **Conclusions:** Deep T cell repertoire profiling detected dynamics of circulating T cells with quantitative and qualitative difference related to ICI response. Immune cell tracking from liquid biopsies is a powerful tool to quantify ICI efficacy in real time. Research Sponsor: None.

# Predictive role of circulating tumor DNA in pMMR locally advanced rectal cancer patients receiving neoadjuvant chemoradiotherapy combined with sintilimab.

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**Background:** Circulating tumor DNA (ctDNA) has emerged as a potential biomarker for various solid tumors, including colorectal cancer (CRC). It offers the advantage of longitudinal and dynamic surveillance of the tumor-specific genetic characteristics, eliminating the need for repeated invasive biopsies. However, the predictive role of ctDNA in patients with proficient mismatch repair (pMMR) locally advanced rectal cancer (LARC) receiving neoadjuvant chemoradiotherapy (CRT) combined with immunotherapy remains to be explored. **Methods:** In this prospective single-arm, phase II trial, pMMR LARC patients ($cT_{3-4}N_0M_0$ and $cT_{1-4}N_{1-2}M_0$) with an intermediate or high immunoscore ($IS_B$) were enrolled (NCT05450029). Treatment-naïve patients received radiotherapy (50 Gy/25 f) and 6 cycles of mFOLFOX6 plus 5 cycles of sintilimab, followed by total mesorectal excision (TME) 6-8 weeks post-radiotherapy. Baseline tumor tissue DNA and serial ctDNA dynamic changes were evaluated using next-generation sequencing. Baseline (T0) maximal somatic variant allelic frequency (maxVAF) as well as its changes at the first (T1, two cycles after therapy) and the second clinical evaluation (T2, four cycles after therapy) were assessed. **Results:** Tumor somatic mutations and aligned ctDNA analyses were conducted in 43 patients. The most frequently mutated genes in tumor tissue samples were APC (67%, n = 29), TP53 (65%, n = 28), KRAS (47%, n = 20), and FBXW7 (28%, n = 12), which were also observed in plasma. Pathway analysis indicated that mutations in SWI_SNF were more likely to be detected in patients achieving pathological complete response (pCR) (P = 0.02 for tumor tissue, P = 0.08 for plasma), suggesting a potential sensitization to sintilimab combined with CRT. For the dynamic ctDNA analysis, 37 patients were assessed using a 950-gene panel relevant to cancer. A significant decline in maxVAF from T0 to T1 was observed in the pCR group. An optimal cut-off of 0.11 for the maxVAF ratio (T1/T0) was identified to discriminate complete responders from other patients (AUC = 0.768; sensitivity 83.3%; specificity 72.0%; $P < 0.001$; 95% confidence interval [CI] 0.597-939). Patients with a low maxVAF ratio ( $< 0.11$) were more likely to achieve pCR following CRT plus sintilimab therapy (OR = 12.86; 95% CI: 2.23-74.08; P = 0.004). **Conclusions:** ctDNA may serve as a potential biomarker of the response to CRT combined with immunotherapy in pMMR LARC. Further validation is warranted to confirm the predictive value of maxVAF and to identify additional biomarkers with potential predictive significance in pMMR LARC. Clinical trial information: NCT05450029. Research Sponsor: National Natural Science Foundation of China; 82470696 and 82103273; Guangdong Basic and Applied Basic Research Foundation; 2022A1515012498 and 2024A1515010956; the program of Guangdong Provincial Clinical Research Center for Digestive Diseases; 2020B1111170004; Guangzhou Science and Technology Program; 2024A04J6400; Sun Yat-sen University Clinical Research 5010 Program; 2016005.

# Risk factors associated with de novo metastatic colorectal cancer in early onset colorectal cancer.

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**Background:** Early onset colorectal cancer (EO CRC) is rising worldwide. Epidemiologic studies have shown that diets high in sugar and/or processed foods and limited exercise are associated with EO CRC when compared to healthy controls. However, risk factors associated with *de novo* metastatic disease are less well established. Identifying such risk factors may provide insight into modifiable lifestyle variables. **Methods:** All eligible EO CRC patients were enrolled in MSK's Center for Young Onset Colorectal and Gastrointestinal Cancer and completed a risk factor questionnaire (MSK-approved IRB #20-315). We analyzed questionnaire responses and compared risk factors between patients with *de novo* metastatic disease vs localized disease using Wilcoxon rank sum test or Fisher's exact test. Clinical outcomes, including overall survival (OS) from diagnosis and progression free survival (PFS) from 1$^{st}$-line chemotherapy, were estimated using Kaplan-Meier methods. The Cox regression model was used to assess association between risk factors and survival outcomes. Tumors from a subset of patients (n = 206) were sequenced using MSK-IMPACT (MSK-approved IRB #12-245) and underwent genomic analyses. **Results:** 303 patients completed the questionnaire (median age at diagnosis 42; 51% Female; 88% left-sided tumors). 112 had *de novo* stage IV disease and 191 had stage I-III disease. Patients with *de novo* metastatic disease were younger, 40.9 [95%CI: 36.8 - 44.8] vs. 43.0 [95% CI: 38.4 - 46.4] (*P*-value *0.037)*. Analysis of dietary factors showed no association with fruit, vegetable, fish, poultry, red meat, processed meat, or dairy intake. However, high sugar diets were significantly associated with *de novo* metastatic disease, with 30 (45%) vs. 37 (29%) (*P*-value, 0.004) patients reporting daily consumption of high sugar foods. Daily consumption of high calorie foods was also frequently reported in patients with metastatic disease (*P*-value, 0.057). 3-year OS in the metastatic population was 72% [95%CI: 62% - 84%] vs. 99% [95%CI: 98% - 100%]. Within the metastatic group, no association was observed between daily high sugar consumption and non-daily consumption in terms of PFS or OS. 3-year OS in the daily high sugar group was 79 % [95%CI: 62%-100%] vs 74% [95%CI: 57%-95%]. For early stage patients who later progressed (n = 27), median time to progression was not significantly shorter among patients who reported daily high sugar consumption (18 vs. 19 months, *P*-value 0.5). Genomic analyses revealed no significant differences in tumor mutational burden, fraction genome altered, frequency of oncogenic or signaling pathway alterations in *de novo* metastatic vs. non-metastatic patients. **Conclusions:** In a single center study, in EO CRC patients, high sugar diets may be associated with *de novo*metastatic disease. There were no significant genomic differences detected in patients with *de novo* metastatic vs. early stage disease. Research Sponsor: None.

# Survival impact of Neo*RAS* wild-type metastatic colorectal cancer: A SCRUM-Japan GOZILA substudy.

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**Background:** The ''Neo*RAS*'' phenomenon refers to *KRAS* or *NRAS* mutant (MT) metastatic colorectal cancer (mCRC) that becomes *RAS* wild-type (WT) following treatment and may represent a novel indication for anti-epidermal growth factor receptor monoclonal antibodies. We previously described the incidence and clinicopathological characteristics of Neo*RAS* WT mCRC (Osumi et al. *Nat Commun* 2024); here we share the impact of Neo*RAS* WT on survival for patients with mCRC. **Methods:** Patients enrolled in the large-scale nationwide screening platform SCRUM-Japan GOZILA who had mCRC, tumor tissue tested for *RAS* and *BRAF* V600E (MEBGEN RASKET-B), and received systemic therapy were included. Prior to subsequent treatment, all patients underwent next-generation sequencing of circulating tumor DNA (ctDNA) (Guardant360) and were classified into cohorts according to original tissue and subsequent ctDNA genotypes: persistent *RAS/BRAF* V600 WT (*RAS* WT), persistent *RAS* MT, change from *RAS* MT to *RAS* WT (Neo*RAS*WT, including ctDNA not detected), change from *RAS* WT to *RAS* MT (acquired *RAS* MT), persistent *BRAF* V600E (*BRAF* MT). *BRAF* MT outside V600 were not considered. We evaluated the clinicopathological characteristics and overall survival (OS) of patients in each cohort. OS was measured from time of first-line treatment initiation to the date of death. **Results:** The 1,352 patients (median age 61 years) included *RAS* WT: 526 (38.9%), *RAS* MT: 387 (28.7%), acquired *RAS* MT: 223 (16.5%), Neo*RAS* WT: 91 (6.7%), and *BRAF* MT: 125 (9.2%).Median number of therapy lines from tissue assessment to ctDNA testing was 2 (range 1-13). Neo*RAS* WT had low prevalence of liver (23.1%, $P < 0.001$), lymph node (16.5%, $P < 0.001$) and multi-organ metastasis (42.9%, $P < 0.001$), whereas lung (56.0%, $P < 0.001$) and peritoneal metastases (41.8%, $P = 0.004$) were more common in other groups. Left-sided primary tumors were more common with *RAS* WT (80.2%) followed by Neo*RAS* WT (70.3%) and *RAS* MT (67.7%), ($P < 0.001$). Patients with *BRAF* MT had significantly shorter median OS (28.1 months) compared to others ($P_{Log-rank} < 0.001$, hazard ratio (HR), 1.91; 95% confidence interval (CI), 1.52-2.40). Patients with Neo*RAS* WT had median OS (45.6 months) that was between *RAS* WT (51.9 months) and *RAS* MT (41.0 months) ($P_{Log-rank} < 0.001$). On the other hand, patients with acquired *RAS* MT had a significantly shorter median OS (43.3 months) compared to *RAS* WT ($P_{Log-rank} < 0.001$). In multivariate analysis, *BRAF* MT (HR: 2.06, 95%CI, 1.62-2.61, $P < 0.001$), ctDNA fraction (≥1.0%, HR: 1.41, 95%CI, 1.17-1.71, $P = 0.00035$), *RAS* MT (HR: 1.37, 95%CI, 1.17-1.62, $P = 0.0001$), and lymph node metastasis (HR: 0.85, 95%CI, 0.72-0.99, $P = 0.046$) were independent factors associated with shorter OS. **Conclusions:** Patients with Neo*RAS* WT mCRC exhibited distinct characteristics, and intermediate survival between the *RAS* WT and *RAS* MT groups. Research Sponsor: None.

# Revisiting the relevance of sidedness in colonic tumor molecular profiling.

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**Background:** Colorectal cancer (CRC) is a heterogeneous disease with distinct molecular and clinical differences between right- and left-sided tumors. This study analyzes these variations to understand their impact on tumor behavior and treatment strategies. **Methods:** A total of 445 colonic tumor samples (132 right-sided, 313 left-sided) were profiled to assess mutations, amplifications, and fusions in key cancer-related genes along with targeted transcriptome analysis of 20,802 genes in a subset using semiconductor based next-generation sequencing (NGS) platform at Datar Cancer Genetics. Immunotherapy biomarkers (TMB, MSI, and PD-L1 22C3 TPS) were analyzed in a subset. **Results:** Right-sided and left-sided colon cancers exhibit substantial molecular heterogeneity, driven by distinct genetic and epigenetic alterations (Table 1). Right-sided tumors were more frequently associated with MSI and had statistically significant higher incidence of *BRAF* mutations. *KRAS* mutations were frequently observed in both right-sided and left-sided tumors at equal rates. *ERBB2* amplifications were exclusive to left side tumors, whereas oncogenic *ERBB2* mutations were equally distributed. Located around *ERBB2*, *PGAP3* gene co-amplification too was exclusive to left sided tumors. *TFE3* alterations were absent from left sided tumors and common on right side. *TP53* mutations, though more common in left-sided tumors, the difference was not statistically significant. Gene expression profiling of a subset, including 103 left-sided and 41 right-sided colon tumors, revealed activation of the *Wnt/β-catenin* signalling pathway, *RAS/MAPK* pathway, *TGF-β* signalling pathway, and immune-related pathways, though these differences were not statistically significant, suggesting that while specific drivers may differ—such as the predominance of *APC* mutations in left-sided tumors (56.8% vs 37.9%) leading to *WNT* activation and the higher incidence of *RSPO2/3* fusions (7.1% vs 1.7%) in right-sided tumors -eventually some pathways are commonly implicated in colorectal cancer biology. **Conclusions:** Existing therapies like ICIs, *HER2* inhibitors, and emerging molecules such as *RSPO2/RSPO3* inhibitors could have differing impact based on tumor sidedness. Integrating these distinctions into drug development and clinical trials holds potential to optimize treatment outcomes. Research Sponsor: None.

**Molecular profiles of right- and left-sided colon tumors.**

| Gene | Right (%) | Left (%) | p-Value (Chi-square test) |
|---|---|---|---|
| ***TP53*** | 64.5% | 73.2% | 0.075644 |
| ***APC*** | 37.9% | 56.8% | 0.001354 |
| ***KRAS*** | 50.0% | 43.6% | 0.220194 |
| ***BRAF*** | 18.8% | 3.0% | 0.00001 |
| ***TFE3*** | 9.5% | 0% | 0.109087 |
| ***ERBB2* mutation** | 2.3% | 2.0% | 0.80941 |
| ***ERBB2* amplification** | 0% | 5.9% | 0.023006 |
| ***PGAP3* amplification** | 0% | 7.1% | 0.673427 |
| ***RSPO2/3* fusion** | 7.1% | 1.7% | 0.827207 |
| **Immunotherapy Biomarkers** | | | |
| **TMB 10-14** | 24.7% | 29.3% | 0.458066 |
| **TMB ³15** | 15.6% | 7.6% | 0.059925 |
| **MSI-High** | 8.1% | 3.4% | 0.066213 |
| **PD-L1 Positive** | 15% | 5.6% | 0.012571 |

# Predicting pathologic complete response in colorectal cancer patients after immunotherapy based on endoscopic biopsy and deep learning approach.

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**Background:** Immune checkpoint inhibitors (ICIs) have emerged as effective treatments for microsatellite instability-high (MSI-H)/deficient mismatch repair(dMMR) tumors in a select subset of colorectal cancer (CRC) patients. Patients sensitive to preoperative immunotherapy may have the opportunity to be exempted from surgery, while those insensitive may avoid unnecessary treatment. Tumor pathology provides rich biological insights. Several studies have indicated that deep learning algorithms can predict the efficacy of immunotherapy directly from digitized hematoxylin-eosin (H&E) stained Whole Slide Images (WSIs). However, their potential application in CRC immunotherapy remains underexplored. Based on WSIs of endoscopic biopsy, this study aims to construct a predictive model using deep learning approach to identify potential pathological complete response (pCR) in CRC patients after preoperative immunotherapy. **Methods:** This study enrolled CRC patients who received preoperative immunotherapy at West China Hospital, Sichuan University. Stratified randomization based on pathological outcomes was performed, assigning enrolled patients to the training set (70%) and the validation set (30%). WSIs of endoscopic biopsy were used for analysis. A predictive model was developed based on the Swin Transformer architecture, integrating convolutional neural networks (CNNs) with a self-attention mechanism. Pre-trained weights were employed for feature extraction, and the CLAM (Clustering-constrained Attention Multiple Instance Learning) framework was utilized to optimize pathological image analysis. The model's performance was assessed in the validation cohort using the Receiver Operating Characteristic Curve (ROC) and Area Under the Curve (AUC) was calculated. Attention-based visualization analysis was further performed to identify the top patches that contributes to the determination of tumor response to preoperative immunotherapy. **Results:** 96 CRC patients treated with preoperative immunotherapy were included, with 67 in the training set and 29 in the validation set. A total of 278,901 512×512-pixel patches were generated by preprocessing 144 WSIs. A predictive model were established based on the training set and verified in the validation set. The model achieved an AUC of 0.82. Attention-based visualization analysis recognized the top 5% patches contributing to the determination of tumor response to preoperative immunotherapy, with 62.66% identified as tumor tissues and 37.34% identified as non-tumor tissues. **Conclusions:** Endoscopic biopsy based deep learning model, with distinct attention to tumor and non-tumor regions, may provide a novel and effective tool for predicting pCR after preoperative immunotherapy in CRC patients. Research Sponsor: National Natural Science Foundation of China.

# Metastatic site pattern as predictor of outcome of first-line alternating oxaliplatin-based chemotherapy and nivolumab for patients with microsatellite-stable (MSS) colorectal cancer (CRC).

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**Background:** The randomized METIMMOX trial evaluated short-course oxaliplatin-based chemotherapy (FLOX) alternating with nivolumab for previously untreated, unresectable abdominal metastases (mets) from MSS CRC. A subgroup of patients assigned to this experimental (exp) treatment had remarkably extended progression-free survival (PFS) compared to the control group patients given standard FLOX chemotherapy with median PFS 9.3 months. We explored if the extent of involved organs might be decisive for responsiveness to the METIMMOX regimen. **Methods:** Patients with measurable infradiaphragmatic (liver, peritoneal, nodal) mets were randomly assigned to the control group of FLOX (oxaliplatin, 5-fluorouracil, folinic acid) Q2W or the exp group of alternating 2 cycles each of FLOX Q2W and nivolumab Q2W, with prespecified break periods. Radiologic response assessment was done every 8 weeks with PFS as the primary endpoint. For this *post hoc* analysis, at baseline, the principal metastatic site was defined by the 2 largest mets (main lesions) of the dominant infradiaphragmatic organ and the global metastatic pattern by the main and subsidiary lesions of all involved organs. Patients without adverse events leading to treatment discontinuation, thus with conclusive end of treatment (EoT) tumor data, were categorized into discrete outcome groups. **Results:** Of 36 exp group patients reaching the first radiologic reassessment, enabling formal evaluation, 31 proceeded to EoT tumor data. Of these, 6 patients (3 of 25 with liver main lesions, 3 of 4 with lymph node main lesions) had complete response (CR), including 3 of 3 *BRAF*-V600E cases. The remaining 3 CR cases had tumor mutational burden (TMB) 9.4-11.8. Of all 25 patients with liver mets, 13 (52%) had objective response and 5 (20%) stable disease. All 16 patients with objective response had improved PFS (median 15.5 months, 95% CI 12.4-18.5; $p < 0.001$, log-rank test). None of main or subsidiary lesions in peritoneum or lungs responded to the treatment. The 3 outcome groups comprised 7 patients with PFS 19.8-41.6 months (longer than twice the median), 8 with PFS 9.9-16.4 months (above median), and 16 with PFS 1.9-9.2 months (below median). At baseline, the best outcome group cases would have been predicted by the combination of right-sided primary, small main lesions (sum of diameters 42 mm or less), and all mets confined to the liver and/or lymph nodes; the mid group cases by left-sided or rectal primary along with peritoneal or lung subsidiary lesions; and the poor outcome cases by extended organ mets. **Conclusions:** Alternating short-course oxaliplatin-based chemotherapy and nivolumab was particularly efficient in treating unresectable liver or lymph node mets from right-sided MSS CRC with intermediate TMB or the *BRAF* driver mutation, but inefficient at peritoneal and lung mets. Clinical trial information: NCT03388190. Research Sponsor: Norwegian Cancer Society; Bristol-Myers Squibb.

# Open-label phase Ib/II study of cetuximab (CET) plus LY3214996 with or without abemaciclib in patients (pts) with anti-EGFR-refractory metastatic colorectal cancer (mCRC).

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**Background:** Acquired resistance limits the efficacy of anti-EGFR (EGFRi) therapy in RAS wild-type (WT) mCRC, often through MAPK reactivation driven by secondary RAS mutations or other genomic alterations. Preclinical studies on EGFRi-refractory models led by our group showed that LY3214996, a potent ERK1/2 inhibitor, combined with CET suppresses MAPK signaling and reduces tumor growth, while the addition of Abemaciclib further enhances anti-tumor activity by synergistically inhibiting cell cycle and survival pathways. **Methods:** In this open-label, phase Ib/II study, RAS/BRAF/EGFR/MEK1 WT mCRC pts who progressed on prior EGFRi-based therapy and ≥1 chemotherapy were treated with CET + LY3214996 (Arm A) or CET + LY3214996 + Abemaciclib (Arm B). Phase Ib employed a 3 + 3 design to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D). Phase II followed a two-stage design with cohort expansion to assess ORR by RECIST v1.1 as the primary endpoint. Secondary endpoints included PFS and OS. **Results:** Of 44 pts treated on trial, 2 did not meet inclusion criteria; 39 were evaluable for activity, and 34 for efficacy. The RP2D was 200 mg LY3214996 p.o. daily + 500 mg/m$^2$ CET i.v. biweekly in Arm A with the addition of 150 mg Abemaciclib p.o. twice daily in Arm B. Median age was 53.0 years (IQR 47.0 – 63.8), and 59.1% (26/44) were male. Most pts (95.5%, 42/44) had a left-sided or rectal primary, and all were pMMR/MSS. Prior EGFRi-based rechallenge, retreatment/reintroduction, or both were noted in 9.1% (4/44), 25.0% (11/44), and 4.5% (2/44), respectively. ORR, DCR, median PFS and OS were 5.3% (1/19), 36.8% (7/19), 1.8 months (95% CI 1.5 – 4.8) and 7.0 months (95% CI 5.0 – 22.0) for the doublet and 15.0% (3/20), 65.0% (13/20), 3.6 months (95% CI 2.5 – 4.5), and 14.0 months (95% CI 5.9 – 21.0) for the triplet, respectively. Longer time elapsed from last EGFRi was associated with higher predicted probability of response after adjustment for trial regimen (OR 1.35, 95% CI 1.06 – 1.94, $p$ = 0.038). Baseline ctDNA profiling drawn prior to rechallenge revealed acquired RAS mutations in two responders, one per arm. Grade 3 TRAEs occurred in 31.8% (14/44), with acneiform rash (9.1%, 4/44), diarrhea (9.1%, 4/44), thrombocytopenia (6.8%, 3/44), fatigue (4.5%, 2/44), and anemia (4.5%, 2/44) being the most frequent while one Grade 4 TRAE (thrombocytopenia, 2.3%) was reported. **Conclusions:** CET + LY3214996 ± Abemaciclib had a manageable safety profile with no unexpected adverse events. Although activity was modest, this study is the first to report objective responses to an EGFRi-based regimen in pts harboring acquired RAS mutations in pre-rechallenge ctDNA. Translational efforts are ongoing. Clinical trial information: NCT04616183. Research Sponsor: MD Anderson Cancer Center; Jack T. and Lillian S. Clift Fellowship; Andrew Sabin Family Fellowship; NIH GI SPORE; Mr. and Mrs. Jack Lee.

# COPEC trial: Early determination of pathological tumor response to neoadjuvant chemotherapy in low/intermediate risk stage II/II rectal cancer—A multicenter, non-inferiority phase III randomized trial.

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**Background:** Multiple large-scale prospective studies have confirmed that neoadjuvant chemotherapy (NCT) alone can achieve optimal distant and local control in locally advanced rectal cancers (LARC) without high risks. However, due to the potentially lower overall response rate compared to chemo-radiotherapy, it is rational to discontinue ineffective NCT in chemo-resistant patients. In our phase II study, we applied 4 cycles of Capox in LARC patients with low to intermediate risks, observing a considerable patho-clinical response rate and an accuracy of 0.89 in predicting non-responders using MRI features after two cycles of Capox. To determine the optimal number of NCT cycles and prevent unnecessary prolonged treatment, we conducted this phase III trial to assess the non-inferiority of two cycles of NCT compared to four cycles with respect to the final pathological tumor response grade (pTRG) of 3. **Methods:** This multicenter, non-inferiority, phase III randomized controlled trial was conducted at 14 centers across China. Eligible patients with low- to intermediate-risk stage II/III rectal cancer were randomized to receive either 2 or 4 cycles of CAPOX, followed by total mesorectal excision (TME) surgery. The primary endpoint was the proportion of patients with a poor pathological response to NCT (pTRG 3). Secondary outcomes included the accuracy of MRI in predicting tumor response, treatment-related adverse events, and 3-year survival outcomes. **Results:** From August 6, 2021, to May 27, 2024, a total of 573 patients were enrolled. Ultimately, 527 patients (2-cycle group, 266 vs. 4-cycle group, 261) were included in the primary analysis. The pTRG 3 rate in the 2-cycle group (27.8%, 74/266) was non-inferior to that in the 4-cycle group (26.4%, 69/261, p = 0.722). Better lymph node response was observed in the 4-cycle group (pN negative: 83.1%, 217/261 vs. 72.5%, 193/266, p = 0.011). The incidence of major adverse events (grade ≥3, according to CTCAE 5.0) was comparable between the two groups (37.9% vs. 44.8%, p = 0.094). A tumor longitudinal length reduction rate (TLLR) of less than 30% on MRI predicted pathological poor responders with a high positive predictive value of 0.918 after two cycles of NCT in the two-cycle group, 0.864 after two cycles of NCT in the four-cycle group, and 0.841 after four cycles of NCT in the four-cycle group. **Conclusions:** Four cycles of NCT do not result in a greater reduction in poor pathological response compared to two cycles, highlighting the importance of early response assessment. MRI evaluation of tumor response after 2 cycles predict the final pathological results with considerable accuracy. These findings lay the groundwork for future studies exploring response-guided treatment approaches in rectal cancer. Clinical trial information: NCT04922853. Research Sponsor: None.

# Survival of patients (pts) with microsatellite stable/mismatch repair proficient (MSS/pMMR) metastatic colorectal carcinoma (mCRC) treated with EO4010 + nivolumab (EO/N).

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**Background:** EO is designed to expand pre-existing memory CD8 T cells cross-reacting with tumor associated antigens (TAAs). EO is composed of microbial-derived sequences mimicking CD8 T cell HLA-A2 epitopes on 5 TAAs, BIRC5, FOXM1, UBE2C, CDC20 and KIF2C, upregulated in mCRC, and the CD4 peptide UCP2. **Methods:** Pts had MSS/pMMR mCRC, treated with FU, oxaliplatin, irinotecan and anti-VEGF/EGFR. Cohort (C)1 safety lead-in followed by expansion C2; pts received EO (300 μg/peptide in Montanide ISA 51 VG) q2 weeks (w) x4 then q4w + N (240 mg q2w x 3 then 480 mg q4w; C1 omitted 2 first N doses). **Results:** 20 pts (C1 = 3, C2 = 17), 55% female, 70%/30% ECOG 0/1, median age 58 (45-80) years, started EO + N June 2023 to March 2024. Primary tumor right sided 35%/left 35%/rectal 30%, median 2 (1-4) tumor involved organs, 55% liver mets, 65% KRAS mutated, and median 3 (1-5) prior lines of treatments. Any grade related AEs in > 2 pts: local administration site reactions (85%), asthenia (15%), and fatigue (15%); 1 related Gr 3, local administration site ulceration; 1 related SAE, N infusion related reaction. CD8 T cells (EO/TAA peptide specific tetramers staining of PBMC ex vivo) against EO found in 10/11 tested pts, cross-reactivity against TAAs in all 10 positive pts. Best response (RECIST 1.1): 1 partial response (liver mets -47%, lung mets -34%; CEA normalized), 1 stable disease (SD) (lung mets -7%; CEA -68%, CA19-9 -55%; pat died w 17 non-related myocardial infarction), and 1 SD until w 18 (withdrawn consent); 6 (30%) pts had target SD, and unequivocal progression of non-target lesions; 11 pts (55%) had progressive disease. Median PFS 1.8 months (mo) (range 1.4-10.5). 14 pts (70%) received post-study anti-cancer treatment. After a median follow-up of 14.7 mo, median overall survival (OS) 11.2 mo; 80% 6- and 39% 12-mo survival. Immune response assessed using a composite score of EO4010-specific T cell responses, measured by ex vivo tetramer assays weeks 5 to 9 of treatment (best response used), with pts stratified into high and low responders based on median score. Kaplan-Meier analysis with log-rank test showed trend towards better OS in high responders ($p = 0.065$). Median OS low responders 9.6 mo and not reached for high responders. Immune response magnitude showed no correlation with baseline T cell activation potential (by anti-CD3 stimulation/ELISPOT); independence indicates that EO4010-induced CD8 T cell expansion occurs irrespective of baseline T cell status. **Conclusions:** EO4010 + nivolumab promotes expansion of TAA specific CD8 T cells and shows good safety and interesting survival in previously treated MSS/pMMR mCRC. Data suggests a potential survival benefit associated with stronger EO4010-induced immune responses. Continued evaluation of EO is warranted; further immune testing data, and results of addition of bevacizumab to EO + N in a separate cohort are awaited. Clinical trial information: NCT05589597. Research Sponsor: Enterome.

# The prognostic and predictive role of HER2 amplification/overexpression and *HER2* mutations in metastatic colorectal cancer treated with first-line chemotherapy plus bevacizumab/anti-EGFRs: An individual patient data pooled analysis of eight randomized trials.

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**Background:** HER2 amplification/overxpression (HER2-pos) is detected in the 5% of *RAS/BRAF* wild-type (wt) metastatic colorectal cancers (mCRC) and is associated with poor efficacy of EGFR blockade in preclinical models. Whether HER2-pos is a prognostic and/or predictive biomarker of benefit from anti-EGFRs/bevacizumab (bev) in mCRC patients (pts) is still debated. Similarly, the role of activating *HER2* mutations (mut) is unclear. **Methods:** We collected individual patient data from 8 randomized clinical trials (RCTs) in the first-line treatment of mCRC: TRIBE2, TRIPLETE, VALENTINO, ATEZOTRIBE, PANDA, PANAMA, PARADIGM and CALGB/SWOG80405. Only pts with *RAS/BRAF* wt pMMR mCRC with available HER2 *status* by means of immunohistochemistry ± *in situ hybridization* and/or Next-generation sequencing on tumor or circulating DNA and treated with triplet or doublets + bev or an anti-EGFR were included. The prognostic and predictive impact of HER2-pos and *HER2* mut was assessed in terms of PFS, OS and ORR. **Results:** 1604 pts were eligible. 81 (5%) tumours were HER2-pos. HER2-pos was associated with shorter PFS (mPFS: 9.8 vs 12.2 months (mos), HR: 1.31, p = 0.02) and OS (mOS: 28.0 vs 34.9 mos, HR: 1.37, p = 0.01), and similar ORR (77 vs 72%, p = 0.47) compared to HER2-neg pts. P-values adjusted for clinically meaningful covariates ($p_{adj}$) were $p_{adj}$PFS = 0.075 and $p_{adj}$OS = 0.036. We found no interaction between HER2-pos and treatment effect according to the use of bev vs anti-EGFRs in terms of PFS ($p_{int}$= 0.76), OS ($p_{int}$= 0.76) and ORR ($p_{int}$= 0.64). Similar findings were reported restricting the analysis to pts treated with doublets (N = 1465), and to those with left-sided tumors (N = 1315). In the HER2-pos subgroup (N = 69) of pts with left-sided *RAS/BRAF* wild-type pMMR tumors no difference between chemotherapy/bev and chemotherapy/anti-EGFR was reported in terms of PFS (mPFS: 9.8 vs 9.3 mos, HR: 0.73, p = 0.30), OS (mOS: 29.8 vs 28.0 mos, HR: 1.29, p = 0.40), and ORR (59% vs 79%, p = 0.10). Activating *HER2* mut were found in 27 (2%) out of 1408 HER2-neg tumors with *HER2* mutational *status* available. Pts with *HER2* mut tumors had a shorter OS (median: 23.7 vs 34.4 mos, HR: 1.56, p = 0.04) than *HER2* wt. No interaction between *HER2* mutational status and treatment effect was evident, with no significantly different PFS (mPFS: 9.4 vs 5.7 mos, HR: 0.88, p = 0.76) and OS (mOS: 20.9 vs 23.7 mos, HR: 1.04, p = 0.93) in the *HER2* mut subgroup between bev and anti-EGFRs. **Conclusions:** This is the largest analysis of HER2 *status* in untreated mCRC pts enrolled in RCTs. Waiting for targeted approaches, HER2-pos is an independent negative prognostic factor and does not predict benefit between bev/anti-EGFRs also in left-sided tumors. *HER2* mut may exert a negative prognostic impact in HER2-neg *RAS/BRAF* wt pMMR mCRC. Research Sponsor: Gruppo Oncologico del Nord Ovest (GONO); Arbeitsgemeinschaft Internistische Onkologie (AIO); Hoffman - La Roche; Amgen; Genentech; National Cancer Institute (HHS - NIH); National Cancer Institute (HHS - NIH); National Cancer Institute (HHS - NIH).

# Assessing the predictive role of tumor sidedness in *RAS* and *BRAF* wild-type metastatic colorectal cancer (mCRC) treated with first-line doublets + anti-EGFRs/bevacizumab (bev) or triplet + bev: An individual patient data pooled analysis of 10 randomized clinical trials.

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**Background:** Chemotherapy (chemo) + an anti-EGFR and chemo + bev are currently regarded as preferred upfront options for left- and right-sided pMMR *RAS/BRAF* wild-type (wt) mCRC patients (pts), respectively. This recommendation is mainly based on trial-level pooled analyses of *RAS* wt pts' cohorts, thus including also *BRAF* mutant cases. **Methods:** We collected individual patient data from 10 randomized clinical trials (RCT) in first-line mCRC: TRIBE, TRIBE2, TRIPLETE, VALENTINO, ATEZOTRIBE, PANAMA, FIRE-3, FIRE-4, PARADIGM and CALGB/SWOG80405. *RAS* and *BRAF* wt mCRC pts treated with doublets + anti-EGFR/bev or triplet + bev were included. **Results:** 2178 pts were eligible. Left- and right-sided tumors were 1780 (82%) and 398 (18%), respectively. As reported in the table, among 2051 pts treated with doublets/bev or doublets/anti-EGFR, no significant interaction effect between primary sidedness and treatment arm was reported in terms of ORR ($p_{int}$: 0.27) and PFS ($p_{int}$: 0.32), with a p-value for interaction for OS of 0.13. Anti-EGFR-based doublets were associated with higher ORR and longer OS among pts with left-sided tumors, while similar outcomes were reported in right-sided ones. Among 339 pts enrolled in trials where triplet was included as a treatment arm, a potential interaction effect between primary sidedness and treatment (triplet/bev or doublet/anti-EGFR) was evident in terms of PFS ($p_{int}$: 0.14) and OS ($p_{int}$: 0.08) but not ORR ($p_{int}$: 0.42). Triplet/bev was associated with longer PFS and OS among pts with right-sided tumors. **Conclusions:** This is the largest analysis assessing the differential effect of biologic agents and chemo intensification according to primary tumor origin in pts with untreated *RAS* and *BRAF* wt mCRC enrolled in RCTs. Doublets/anti-EGFR is superior to doublets/bev in left-sided tumors, with no significant differences in right-sided tumors, where triplet + bev appears as the most efficacious regimen for fit pts. Further analyses assessing the role of molecular hyperselection beyond *RAS* and *BRAF* are ongoing. Research Sponsor: Gruppo Oncologico del Nord Ovest (GONO); Merck KGaA; Arbeitsgemeinschaft Internistische Onkologie (AIO); Hoffman - La Roche; Amgen; Genentech; National Cancer Institute (HHS - NIH); National Cancer Institute (HHS - NIH); National Cancer Institute (HHS - NIH); National Cancer Center.

| | Right | | Left | | $P_{int}$ | Right | | Left | | $P_{int}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| | Doublets/ antiEGFR N=209 | Doublets/ bev N=157 | Doublets/ antiEGFR N=1120 | Doublets/ bev N=565 | | Triplet/ bev N=95 | Doublets/ antiEGFR N=189 | Triplet/ bev N=32 | Doublets/ antiEGFR N=23 | |
| **ORR (%)** | 65 | 62 | 74 | 66 | | 66 | 83 | 72 | 78 | |
| **OR [95% CI]** | 1.13 [0.73-1.73] | | 1.48 [1.19-1.84] | | 0.27 | 0.42 [0.10-1.48] | | 0.72 [0.41-1.27] | | 0.42 |
| ***p*** | 0.58 | | < 0.001 | | | 0.16 | | 0.25 | | |
| **mPFS*** | 9.6 | 10.6 | 12.6 | 12.6 | | 12.4 | 10.1 | 12.2 | 13.8 | |
| **HR [95% CI]** | 1.12 [0.90-1.40] | | 0.99 [0.89-1.10] | | 0.32 | 0.62 [0.35-1.09] | | 0.98 [0.75-1.27] | | 0.14 |
| ***p*** | 0.32 | | 0.84 | | | 0.09 | | 0.88 | | |
| **mOS*** | 25.1 | 29.1 | 36.4 | 33.6 | | 37.2 | 23.8 | 37.7 | 35.5 | |
| **HR [95% CI]** | 1.05 [0.83-1.32] | | 0.85 [0.76-0.96] | | 0.13 | 0.55 [0.30-1.01] | | 0.95 [0.70-1.30] | | 0.08 |
| ***p*** | 0.69 | | 0.007 | | | 0.05 | | 0.76 | | |

*Months.

# Drug-eluting beads loaded with irinotecan-transarterial chemoembolization (DEBIRI-TACE) combined with hepatic artery infusion chemotherapy and regorafenib in colorectal liver metastases refractory to second-line and above standard systemic therapy: A single-center, phase II clinical trial (DREAM).

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**Background:** For patients with colorectal liver metastasis (CRLM) who have failed in first-line or second-line systemic treatment, the prognosis is extremely poor. Regorafenib is the standard third line treatment regimen. We aim to explore the safety and clinical efficacy of added drug eluting beads loaded with irinotecan (DEBIRI) plus hepatic arterial infusion chemotherapy (HAIC) to regorafenib in the combination treatment of second-line and above in patients with CRLM. **Methods:** For this single-center, single-arm, prospective, phase II trial, patients with unresectable progression of CRLM after previously receiving at least six cycles of standard systemic chemotherapy above the second line were enrolled. All of the patients received at least once DEBIRI-TACE and FOLFOX-HAIC (Oxaliplatin 85mg/m$^2$ 2h + Calcium Levofolinate 200mg/m$^2$ 2h + Fluorouracil 2400mg/m$^2$ 46h) plus oral regorafenib 80/120/160 mg once daily during weeks 1-3 of each 4-week cycle until disease progression or unacceptable toxicity. The primary endpoint of this study was the best objective response rate (ORR) per RECIST 1.1, the secondary endpoints include progression-free survival (PFS), overall survival (OS), safety and tolerability assessments. **Results:** By the cutoff date of 17 November 2023, 21 patients were enrolled, with the median age of 61 (ranges, 38-71 years old), 14 (66.7%) of whom were male. 17(81.0%) patients had more than one tumor and 13(61.9%) patients had major tumor larger than 5cm. The most frequent primary cancer localization was colon (81.0%) and the primary had been resected in 14(66.7%) patients. Somatic mutation status was available for 15 patients: KRAS mutation was found in 7 patients. The ORR was 33.3% and the DCR was 100%. The median PFS was 7.8 months (95% CI: 5.8—NA), the median OS was 17.6 months (95% CI: 9.3—NA), the 1-year and 2-year OS rate were 54.6% (30.7%-73.4%) and 23.9% (4.6%-51.3%), respectively, and the 1-year PFS rate was 36.4% (15.7%-57.5%). The most common TRAEs were AST/ALT increase (81.8%), abdominal pain (63.6%), hyperbilirubinemia (63.6%), hand-foot skin reaction (59.1%), diarrhea (40.9%), etc. 9 patients presented with grade 3 or 4 TRAEs, which were the transient liver function injury and abdominal pain caused by TACE and HAIC. **Conclusions:** DEBIRI-TACE combined with HAIC and regorafenib is feasible, safe and shows promising efficacy in treating the patients with CRLM, even after second-line and above systemic chemotherapy. Clinical trial information: NCT06071052. Research Sponsor: None.

# Biomarkers of emergent resistance to sotorasib plus panitumumab in *KRAS* G12C-mutated metastatic colorectal cancer (mCRC) from the randomized, phase 3 CodeBreaK 300 study.

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**Background:** The use of sotorasib (soto; $KRAS^{G12C}$ inhibitor) alone in patients with *KRAS* G12C-mutated mCRC gives rise to several receptor tyrosine kinase (RTK) alterations, resulting in treatment resistance. In CodeBreaK 300 trial, the addition of panitumumab (pani; monoclonal anti-EGFR antibody) counters this resistance and significantly improves clinical outcomes compared with standard of care (SoC; trifluridine-tipiracil or regorafenib). Over time this combination (soto+pani) may lead to the emergence of new resistance patterns. This study reports the distribution, patterns, and prevalence of genetic alterations that arise after treatment with soto+pani. **Methods:** Patients from the phase 3 CodeBreaK 300 trial with chemo-refractory *KRAS* G12C-mutated mCRC who had paired plasma samples at baseline and at progression, were included in the analysis. The samples were evaluated using the 753-gene Guardant Infinity ctDNA test. Gene alterations that were absent at baseline but present at progression were considered. **Results:** By December 2024, 99 patients (median age: 62 years, female: 48%) were evaluated (soto 960 mg-pani: 32 [60% of ITT population], soto 240 mg-pani: 33 [62% of ITT population], SoC: 34 [63% of ITT population]). Overall, 90% of patients had at least 1 emergent, likely pathogenic, genomic alteration at progression. Median time to progression in biomarker-evaluable patients was 3.8 months for soto 960 mg-pani arm, 3.6 months for soto 240 mg-pani arm, and 2.0 months for SoC arm. Overall, the distribution, patterns, and prevalence of pathogenic emergent alterations were similar across all treatment arms. The most common pathogenic emergent alterations included *TP53* (34%), *DNMT3A* (17%), *ERBB2* (12%), and *LRP1B* (11%), generally associated with the RTK, cell cycle control, DNA methylation, and DNA damage response pathways. The median copy number of emergent *KRAS* copy number variations (CNVs) was higher (p = 0.007) in the soto 960 mg-pani (4.18) and soto 240 mg-pani (4.24) arms compared with the SoC arm (2.05). Emergent *KRAS* CNVs were primarily present in the soto+pani arms (soto 960 mg-pani: 40.6% [n = 13], soto 240 mg-pani: 36.4% [n = 12], and SoC: 14.7% [n = 5]). The presence of emergent pathogenic variants in *ALK* (n = 7) and *KMT2D* (n = 4) was observed exclusively among patients treated with soto+pani. *DNMT3A* mutations, along with other diverse emergent alterations, were observed in all three evaluable patients with partial response in the soto 960 mg-pani arm. **Conclusions:** Dysregulation of the DNA methylation and RTK pathways and *KRAS* amplifications may contribute to the development of resistance to soto+pani combination. Further characterization of these acquired alterations, can help inform future therapeutic strategies. Clinical trial information: NCT05198934. Research Sponsor: Amgen Inc.

# Safety and efficacy of anti-CEA CAR-T cells to prolong relapse-free survival of colorectal cancer liver metastases patients after radical resection.

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**Background:** Approximately 75% of colorectal cancer liver metastasis patients relapse within two years after surgery due to circulating tumor cells and microscopic residual disease. Specific chimeric antigen receptor (CAR) T-cell therapy, effective for hematological tumors, may also treat recurrent colorectal cancer liver metastases. Carcinoembryonic antigen (CEA) is a glycoprotein which is highly expressed in colorectal tumor. Therefore, this study aimed to evaluate the safety and efficacy of this therapy in postoperative colorectal cancer liver metastasis patients. **Methods:** We conducted a single-arm, dose-escalating phase I clinical trial (NCT05240950). Key eligibility criteria were achieving no evidence of disease status after treatment and had CEA positivity of 30% or greater. Three dose levels of 1, 3, and 6 (10^6/kg) Anti-CEA CAR-T cells were administered in a dose-escalating manner. The primary endpoint is safety which measures are incidence and severity of adverse events within 28 days and relapse-free survival at 24 months. **Results:** From December 2021 to December 2024, 48 subjects were screened, and 12 received CAR-T cell infusion (2 in the 1 and 3×10^6/kg group, and 8 in the 6×10^6/kg group). Three subjects who had relapsed before the infusion still asked for the infusion, so we proceeded to infuse after fully informing about the benefits and risks of the infusion. 8 subjects experienced adverse events during treatment, including lymphopenia (5 subjects), arthralgia (1 subject), fever (1 subject), and rash (1 subject). No severe adverse events occurred. The median follow-up time for the 9 pre-infusion relapse-free subjects was 23 months, of which 5 relapsed after infusion. In the 6×10^6/kg dose group, 4 subjects remained relapse-free survival of 5, 7, 10 and 15 months after infusion, and their follow-up is ongoing. By infusing CAR-T cell, 57.14% of the subjects in the 6×10^6/kg dose group were free of recurrence within two years after radical resection. **Conclusions:** This is the first clinical trial of Anti-CEA CAR-T therapy for prolonging relapse-free survival of postoperative colorectal cancer liver metastases patients, showing no serious adverse events and significant reduced risk of recurrence with high doses. Clinical trial information: NCT05240950. Research Sponsor: National Natural Science Foundation of China; 82072750, 82203137, 82473479; Shanghai Shenkang Hospital Development Center; SHDC2022CRT007; Natural Science Fund of Shanghai; 20ZR1457200; Shanghai Sailing Program; 21YF1459300; Health Care Research Project 2024; 24BJZ10; Commission Health Industry Clinical Research Project; 20224Y0348.

**Clinical information of 9 pre-infusion relapse-free subjects.**

| Subhects number | TNM Stage | Infusion dose (×10^6/Kg)[1] | Current NED status | Post-infusion relapse-free survival time (months)[2] | Post-infusion survival time (months)[2] | Overall survival time (months)[3] |
|---|---|---|---|---|---|---|
| **S01002** | T3N0M1a | 1 | No | 3 | 27 | 33 |
| **S01037** | T2N1bM1a | 3 | No | 12 | 12 | 26 |
| **S01008** | T3N0M1a | 6 | Yes | 10 | 10 | 25 |
| **S01010** | T3N1M1a | 6 | No | 10 | 10 | 26 |
| **S01015** | T3N0M1a | 6 | Yes | 15 | 15 | 21 |
| **S01023** | T3N0M1a | 6 | No | 12 | 14 | 23 |
| **S01042** | T3N2aM1a | 6 | No | 3 | 10 | 16 |
| **S01033** | T3N1bM1a | 6 | Yes | 7 | 7 | 18 |
| **S01043** | T3N1bM1a | 6 | Yes | 5 | 5 | 14 |

[1]One subject in each of the 1, 3, and 6 dose groups relapsed before infusion.
[2]From the day of infusion.
[3]From the day of radical resection.

# Preliminary safety, pharmacokinetics, and clinical activity of RG6344 in patients with BRAF V600E-mutant metastatic colorectal cancer (mCRC).

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**Background:** RG6344 (RO7276389) is a novel paradox breaker and brain penetrant BRAF inhibitor (BRAFi) designed to overcome the MAPK paradoxical activity, a well-established liability of the first generation BRAF inhibitors. The BRAF V600E mutation, present in about 10% of mCRC patients, negatively impacts prognosis and response to standard therapies. **Methods:** Dose escalation of RG6344 is being conducted in participants with solid tumors harboring BRAF V600E mutation up to the protocol specified maximum daily dose, to define the maximum tolerated dose (MTD) and/or recommended Phase 2 dose and characterize safety, PK/PD, and clinical outcomes (ISRCTN13713551). **Results:** As of September 25, 2024, 51 patients with mCRC (27, 53% with prior BRAFi treatment; median number of treatments 3 [2-6]), including 4 patients with non-measurable brain lesions, have been treated with RG6344 in the monotherapy dose escalation part of the study. Patients received at least one dose of study drug as a single agent. MTD has not been reached up to the highest dose of 3600 mg/d. Of the 51 treated patients, Grade 3 treatment-related AEs (TRAEs) occurred in 8 patients (14.5 %), grade 4 TRAEs in 2 patients (3.6%; both laboratory findings) and no grade 5 TRAEs were reported. The most commonly reported TRAEs included diarrhoea (23.6%), nausea (21.8%) and fatigue (12.7%). 3 patients (5.5%) discontinued study treatment due to TRAEs. None of the typical BRAFi class toxicities, such as cutaneous squamous cell carcinomas (cSCCs), Palmar-Plantar Erythrodysesthesia (PPE) and keratoacanthoma, have been observed to date, highlighting the paradox breaking properties of this BRAF inhibitor. Linear and time-independent PK was demonstrated across the tested dose range, reaching Ctrough levels exceeding pERK inhibition $>$ 80%. Strong and early ( i.e. FDG PET at 15 days) metabolic response of 74% (6 CMR, 30 PMR out of 49 evaluable patients) was observed on FDG PET. Association between metabolic responses and exposure was observed. Observed ORR (RECIST v1.1) was 25% in BRAFi-naive mCRC patients and 14.8% in BRAFi-experienced patients, DCR was 100% for BRAFi-naive patients and 62.9% for BRAFi-experienced patients, mPFS was 7.3 months and 3.6 months, respectively, in the ongoing study. **Conclusions:** RG6344 is well tolerated allowing unprecedented exposure for pERK inhibition and shows promising preliminary single-agent activity. Clinical trial information: ISRCTN13713551. Research Sponsor: None.

# Impact of anti-EGFR and anti-VEGF antibodies on survival in BRAF$^{V600E}$ mutated metastatic colorectal cancer: A pooled analysis of eight clinical trials performed in the first-line treatment of mCRC (German AIO Study Group).

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**Background:** BRAF$^{V600E}$ mutation in metastatic colorectal cancer (mCRC) is associated with poor prognosis. Registrational approval of anti-EGFR antibodies does not exclude their use in BRAF$^{V600E}$ mutated (mut) mCRC, while current guidelines explicitly advise against the use of anti-EGFR-directed therapy and recommend the use of chemotherapy plus anti-VEGF antibodies. The present analysis of single-patient data evaluates the therapeutic benefit from anti-EGFR- vs. anti-VEGF-directed therapy in BRAF$^{V600E}$ mut mCRC. **Methods:** We conducted a pooled analysis of eight first-line AIO-studies (FIRE-1, FIRE-3, FIRE-4, FIRE-4.5, CIOX, XELAVIRI, PANAMA, VOLFI) including 251 evaluable pts with BRAF$^{V600E}$ mut and RAS wild-type mCRC. Right-sided primary tumors (RSPT) included tumors from the caecum to the colon transversum, while left-sided tumors (LSPT) included the splenic flexure to the rectum. **Results:** Of 251 BRAF$^{V600E}$ mut pts, exact primary tumor location was available in 230 pts. In this cohort, 117 were male (50.9%) and 113 female (49.1%). LSPT was observed in 106 (46.1%) pts compared to 124 (53.9%) with RSPT. In the entire cohort, median OS (mOS) of LSPT vs. RSPT did not differ significantly (15.2 months vs. 13.4 months; HR 0.96; 95% CI, 0.70–1.29; P=0.77). Pts with LSPT showed a numerical survival benefit with anti-EGFR therapy compared to anti-VEGF therapy (17.8 months vs. 11.8 months; HR 0.71; 95% CI, 0.45–1.14; P=0.16). This effect was observed independent of sex. In contrast, pts with RSPT showed a trend towards inferior outcome with anti-EGFR vs. anti-VEGF therapy (11.6 months vs. 17.1 months; HR 1.31; 95% CI, 0.84–2.05; P=0.23). This effect was primarily driven by females, who experienced a significant survival disadvantage with anti-EGFR therapy (10.2 months vs. 17.1 months; HR 1.85; 95% CI, 1.05–3.25; P=0.031). For males, however, both anti-VEGF and anti-EGFR antibodies were associated with comparable outcome. **Conclusions:** The present analysis performed in the first-line treatment of BRAF$^{V600E}$ mut mCRC suggests a survival benefit from anti-EGFR antibodies in pts with LSPT, independent of gender. Male pts with RSPT appear to derive comparable benefit from anti-EGFR and anti-VEGF antibodies, while female pts exhibit a survival disadvantage from anti-EGFR antibodies. Clinical trial information: NCT00433927 (FIRE-3), NCT02934529 (FIRE-4), NCT04034459 (FIRE-4.5), NCT01249638 (ML22011), NCT00254137 (CIOX), NCT01991873 (PANAMA), NCT01328171 (VOLFI). [clinicaltrials.gov].
Research Sponsor: None.

# Circulating tumor DNA (ctDNA) dynamics in liver-limited metastatic colorectal cancer (mCRC) patients resected after first-line systemic treatment.

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**Background:** Liver-limited disease (LLD) occurs in 20-30% of metastatic colorectal cancer (mCRC) patients. Although 20-30% of patients who undergo resection can achieve a long-term overall survival benefit from liver surgery, most patients relapse during the first two years after hepatectomy. ctDNA is a promising tool in detecting the presence of minimal residual disease (MRD) after resection of colorectal liver metastases and a reliable prognostic tool for recurrence. ctDNA and its dynamics may also serve as a prognostic tool in patients candidate to liver resection following upfront chemotherapy. **Methods:** mCRC patients (N = 116) with initially unresectable LLD and R0/R1 resected after upfront chemotherapy were selected from 3 Italian academic centers. Blood samples were collected prospectively at baseline (T0), pre-surgery (TPrS) and post-surgery (TPoS). T0 samples were evaluable for 82 patients, TPrS for 116 and TPoS for 60. Biobanked plasma samples were analyzed with the Tempus xM MRD assay (xM), a tumor-naïve ctDNA MRD assay that integrates methylation and genomic variant classifiers to deliver a binary MRD call blinded to clinical outcomes. The methylation classifier detects fragments with CRC methylation signatures in differentially methylated regions trained by sequencing CRC and presumed-healthy samples on a 6 Mbp panel. The variant classifier detects highly prevalent CRC variants. **Results:** Methylation results were available for 60 TPoS patients with a clinical sensitivity of 56.4% and specificity of 100%. TPoS ctDNA status was associated with relapse-free survival (RFS) with the ctDNA- group experiencing longer median RFS (mRFS) than ctDNA+ (HR = 6.7, mRFS $>$ 24 mos vs. 5.5 mos, $p < 0.001$). Patients who were persistently ctDNA- by methylation calls (n = 20) or converted to negative (n = 13) from TPrS to TPoS experienced longer RFS (mRFS 16.3 mos and $>$ 24 mos respectively). Those who remained persistently ctDNA+ (n = 9) or converted to ctDNA+ (n = 12) had a mRFS of 5.3 and 5.9 mos respectively. Patients with variant allele fraction (VAF) reduction of $\geq$50% from T0 to TPrS (N = 53) experienced longer RFS than those who had $<$ 50% reduction or increase in VAF (N = 18) (HR 2.21, mRFS 18.8 mos vs. 9.8 mos, p = 0.012). Lastly, patients that remained positive from T0 to TPrS (N = 23) experienced a numerically shorter RFS compared to those who converted to negative (N = 47) (median RFS 10.4 and 15.1 mos, HR 1.65, p = 0.10). **Conclusions:** xM demonstrates remarkable performance in predicting clinical recurrence and correlation to RFS at TPoS in LLD mCRC patients resected after upfront systemic therapy. Interestingly, patients with a VAF reduction $\geq$ 50% experience longer RFS following surgery, suggesting a potential role for this tool in multidisciplinary decision making in this setting. Research Sponsor: None.

3545 Poster Session

# Tumour microbiome and immune dysregulation in early-onset colorectal cancer.

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**Background:** Early-onset colorectal cancer (EOCRC) in patients under 50 years is increasing incidence in many countries worldwide, including New Zealand. The reason for this trend is yet unclear, but is associated with such risk factors as obesity, alcohol intake, lifestyle and diet. This suggests a multi-factorial exposome-related aetiology, with changes to the gut microbiome likely to play a role. **Methods:** In this study, we investigated differences in the tumour-resident microbiome and molecular characteristics between patient cohorts of EOCRC and late-onset CRC (LOCRC). Transcriptomic analysis was carried out on pre-treatment tumours from a cohort of 19 EOCRC patients and compared to a control group of 196 LOCRC aged over 65 years. Bioinformatics analysis of RNA sequencing data was used to analyse tumour microbial abundance and taxonomy, differential gene expression and gene-set enrichment between the two groups, as well as assign consensus molecular subtypes (CMS) . **Results:** We found an increase in expression of genes involved in the cell cycle in the EOCRC cohort, and of specific genes (e.g. HOXA11-AS, STMN2) involved in cell proliferation and metastasis. Converesly, enriched gene sets in the late-onset category were predominantly related to immune function. When grouping CMS subtypes as immune-rich (CMS1/CMS4) versus immune-depleted (CMS2/CMS3), there was a significant difference between the two groups with 94% of EOCRC tumours being immune-depleted, compared to 67% of late-onset tumours ($p = < 0.05$). Meanwhile, we found an increase in bacterial richness (observed alpha diversity) in the late-onset tumours compared to early-onset, while there were no differences in the Shannon alpha diversity measures (richness and evenness), and in beta diversity between the groups. We also found a depletion of the bacteria *Helicobacter canadensis* and *Campylobacteria ureolyticus* in the early-onset cohort, while there was an increase in *Lachnospiraceae* species. **Conclusions:** Our results add to the growing body of evidence that EOCRC is a distinct disease from LOCRC. EOCRC shows lower tumour-immune activation compared to LOCRC and very low rates of CMS1 and CMS4 subtypes, which is associated with a distinct tumour-resident microbiome. This may have implications for prognosis and targeted treatments. Research Sponsor: None.

# Prognostic and predictive impact of the baseline systemic proteome in patients with *RAS* wild-type metastatic colorectal cancer: Analysis from the randomized phase II PanaMa (AIO KRK0212) trial.

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**Background:** Systemic proteomics offers a minimally invasive approach to identifying biomarkers in metastatic colorectal cancer (mCRC). This study analyzed the prognostic and predictive potential of the systemic proteome in *RAS* wild-type (wt) mCRC patients from the PanaMa trial, which investigated maintenance therapy with fluorouracil/folinic acid (FU/FA) ± panitumumab (Pmab) following induction with FU/FA plus oxaliplatin and Pmab. **Methods:** Baseline serum samples were analyzed using liquid chromatography-mass spectrometry to identify protein markers. Their impact on overall survival (OS) and progression-free survival (PFS) was evaluated using Kaplan-Meier estimates and Cox regression. Prognostic analyses utilized hierarchical clustering and random forest models to delineate protein groups associated with survival outcomes, enhanced by sparse partial least squares discriminant analysis for feature selection. Gene ontology analysis was used to identify biological functions of these markers. ROC analysis was performed to evaluate the accuracy of prognostic protein signatures. For predictive analysis, PFS outcomes of maintenance with FU/FA ± Pmab were assessed using Kaplan-Meier estimates and Cox regression. Hazard ratios (HR), differences in hazard ratios (delta HR), and statistical significance (p-values) were used to differentiate patient outcomes based on protein marker expression. **Results:** Of 378 patients treated in the trial, 231 had baseline serum samples. Proteomic clustering identified two survival clusters: the high-survivability cluster showed significantly longer induction PFS (HR 0.75, 95% CI 0.56–1.00, P = 0.05) and OS (HR 0.63, 95% CI 0.45–0.88, P = 0.01). Hierarchical clustering revealed 470 proteins, with specific proteins enriched in high-survivability (e.g., ALB, APOA2) and low-survivability (e.g., SERPINA3, CRP) clusters. Gene ontology analysis highlighted distinct pathways, such as enzyme inhibitor activity in low-survivability clusters and peptidase regulator activity in high-survivability clusters. For maintenance, prognostic arm-specific proteomic signatures linked to improved PFS with strong accuracy in the FU/FA + Pmab arm (AUC 0.99), and FU/FA arm (AUC 1.00). Predictive analysis revealed a total of eight proteins that predicted benefit of Pmab addition to maintenance. A positive combined proteomic biomarker including these proteins (ITIH4, FLNC, HP, CTPS1, SERPINA1, HRG, MAN1C1, C4A) predicted significant benefit of addition of Pmab to FU/FA maintenance (PFS: HR 0.68, 95% CI 0.49–0.95, P = 6.4e-09). **Conclusions:** Proteomic profiling identified prognostic clusters linked to distinct survival outcomes and predictive signatures for FU/FA ± Pmab maintenance, supporting its utility in guiding personalized treatment strategies for *RAS* wt mCRC. Research Sponsor: AIO-Studien gGmbH; Amgen Inc.

# Prognostic and predictive role of HLA supertypes in pMMR mCRC patients receiving FOLFOXIRI/bev ± atezolizumab in the AtezoTRIBE study.

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**Background:** The HLA system plays a crucial role in the development of the adaptive immune response, influencing antigen presentation and T-cell-mediated tumour recognition. Emerging evidence suggests that specific HLA allele groups named supertypes may influence the efficacy of immune-checkpoint inhibitors (ICIs). We investigated the impact of HLA supertypes in the pMMR cohort of mCRC patients (pts) treated with FOLFOXIRI/bev ± atezolizumab in the AtezoTRIBE study. **Methods:** Genomic DNA from blood samples was genotyped using Oncoarray, a custom array manufactured by Illumina including approximately 530K SNP markers. HLA class I and II alleles were characterized with minimac3 algorithm using the Four-digit Multi-ethnic HLA v2 (2022) reference panel. The presence of 22 HLA supertypes were assigned based on the imputed dosages across relevant alleles. The effects of HLA supertypes on survival were evaluated with Cox proportional hazard models. Given the exploratory nature of the analysis, no adjustments for multiple comparisons were applied. **Results:** Among 153 assessed pts (102 and 51 treated with FOLFOXIRI/bev/atezo and FOLFOXIRI/bev, respectively), B44 and DR9 supertypes were associated with worse prognosis in terms of both PFS (mPFS 11.4 months (mos) for B44 pos vs 13.9 mos for B44 neg; HR 1.74; 95% CI 1.19–2.52; p = 0.004, and mPFS 11.4 mos for DR9 pos vs 13.2 mos for DR9 neg; HR 2.37; 95% CI 1.01–5.60; p = 0.04, respectively) and OS (mOS 29.6 mos for B44 pos vs 36.6 mos for B44 neg; HR 1.59; 95% CI 1.03–2.45; p = 0.038, and mOS 26.6 for DR9 pos vs 33.9 mos for DR9 neg; HR 3.22; 95% CI 1.24–8.38; p = 0.017, respectively) in multivariable analysis. As summarized in the Table, PFS and OS benefit from the addition of atezolizumab to FOLFOXIRI/bev was reported among A3 neg but not A3 pos patients, and B8 pos patients derived higher benefit than B8 neg. **Conclusions:** Our exploratory findings suggest that HLA supertypes could influence prognosis and ICIs-based treatment efficacy in pMMR mCRC pts. In particular, B8 and A3 supertypes could identify patients more likely to benefit from the addition of ICIs to FOLFOXIRI/bev. These findings highlight the potential of HLA profiling to optimize the use of immunotherapy in pMMR mCRC pts. Research Sponsor: GONO Foundation.

| | Median PFS | | | | Median OS | | | |
|---|---|---|---|---|---|---|---|---|
| | FOLFOXIRI/bev/ atezo (months) | FOLFOXIRI/ bev (months) | HR 95% CI | P for interaction | FOLFOXIRI/bev/ atezo (months) | FOLFOXIRI/ bev (months) | HR 95% CI | P for interaction |
| **A3** | | | | 0.048 | | | | 0.064 |
| **Pos** | 12.5 | 11.6 | 0.89 (0.53-1.51) | | 27.0 | 31.7 | 0.96 (0.53-1.73) | |
| **Neg** | 15.0 | 10.1 | 0.43 (0.26-0.71) | | NR | 27.3 | 0.44 (0.24-0.81) | |
| **B8** | | | | 0.014 | | | | 0.040 |
| **Pos** | 13.7 | 5.6 | 0.16 (0.05-0.60) | | 35.9 | 16.7 | 0.21 (0.06-0.76) | |
| **Neg** | 13.3 | 11.6 | 0.63 (0.43-0.93) | | 36.1 | 31.4 | 0.70 (0.44-1.11) | |

# Impact of Medicare Advantage (MA) on timely initiation of pembrolizumab among dMMR/MSI-h metastatic colorectal cancer patients.

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**Background:** With MA plans covering over half of Medicare beneficiaries, concerns remain about their ability to manage complex cancer care due to pre-authorization and limited provider network. This study evaluates MA versus Traditional Medicare (TM) regarding timely initiation of Pembrolizumab for dMMR/MSI-H colorectal cancer (CRC), following its 2020 FDA approval. **Methods:** This study utilized nationwide Flatiron Health Electronic Health Record-derived de-identified database. We included patients diagnosed with dMMR/MSI-H CRC from 2020 onward, aged ≥65 years, who had at least one clinic visit within six months of diagnosis and were insured under MA or TM. The primary endpoint was initiation of Pembrolizumab within 30-, 45-, and 90-days post-diagnosis. Multivariable logistic regression with Inverse Probability Weighting, adjusted for SES (defined by Yost score), age, race, ECOG, practice type and diagnosis year, evaluated impact of insurance type on timely treatment initiation. **Results:** Out of 597 dMMR/MSI-H metastatic CRC patients identified since 2020, 219 had at least one clinical visit under MA (N = 86) or TM (N = 133) plans. Predominantly, patients in our cohort were non-Hispanic White (72%), with higher SES (59%), diagnosed with de novo dMMR/MSI-H (59%), and treated in community hospitals (86%). Of 95 patients who commenced pembrolizumab as initial therapy, 62 (65%) had TM and 33 (35%) had MA. The adjusted analysis revealed that MA patients were significantly less likely to start pembrolizumab within 90 days of diagnosis compared to TM patients (OR: 0.58; 95% CI: 0.34-0.97; P: 0.04). There were no statistical differences in starting treatment at 30 (OR: 0.79; 95% CI: 0.39-1.56; P: 0.5) or 45 days (OR: 0.87; 95% CI: 0.48-1.57; P: 0.7). Subgroup analysis indicated substantial delays in pembrolizumab initiation within 90 days among lowest SES (OR: 0.31; 95% CI: 0.13-0.71; P: 0.007; P-interaction: 0.087) and those treated in community hospitals (OR: 0.49; 95% CI: 0.27-0.87; P: 0.016; P-interaction: 0.095). **Conclusions:** Patients with TM were more likely to initiate pembrolizumab earlier than those with MA. This underscores necessity to scrutinize the influence of MA on cancer delivery, especially for patients with lower SES. Research Sponsor: None.

**Baseline characteristics.**

| Variable | TM | MA | P |
|---|---|---|---|
| **Age** | | | 0.4 |
| **>=65** | 66 (50%) | 40 (47%) | |
| **>=75** | 67 (50%) | 45 (52%) | |
| **>=85** | 0 (0%) | 1 (1%) | |
| **Race** | | | 1 |
| **NHW** | 97 (73%) | 62 (72%) | |
| **Non-NHW** | 36 (27%) | 24 (28%) | |
| **ECOG** | | | 0.7 |
| **0/1** | 95 (71%) | 68 (79%) | |
| **2** | 18 (14%) | 8 (9%) | |
| **3/4** | 8 (6%) | 4 (5%) | |
| **Unknown** | 12 (9%) | 6 (7%) | |
| **SES** | | | 0.04 |
| **0/1** | 38 (29%) | 36 (42%) | |
| **3/4/5** | 88 (66%) | 42 (49%) | |
| **Unknown** | 7 (5%) | 8 (9%) | |
| **Diagnosis Year** | | | 0.5 |
| **2020** | 36 (27%) | 22 (26%) | |
| **2021** | 41 (31%) | 34 (40%) | |
| **2022** | 39 (29%) | 18 (21%) | |
| **2023** | 17 (13%) | 12 (14%) | |
| **DeNovo** | | | 0.7 |
| **Yes** | 80 (60%) | 49 (57%) | |
| **No** | 53 (40%) | 37 (43%) | |
| **Practice** | | | 0.4 |
| **Academic** | 16 (12%) | 15 (17%) | |
| **Community** | 117 (88%) | 71 (83%) | |
| **Time to Pembrolizumab Initiation (days)** | | **OR (95CI)** | **P** |
| **30** | 1 | 0.79 (0.39-1.56) | 0.50 |
| **45** | 1 | 0.87 (0.48-1.57) | 0.66 |
| **90** | 1 | 0.58 (0.34-0.97) | 0.04 |

# Outcomes of young-onset colorectal cancer vs late-onset colorectal cancer patients on phase 1 matched and non-matched therapies.

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**Background:** Systemic therapy recommendations for young-onset colorectal cancer (YOCRC), CRC diagnosed at < 50 years old, are similar for late-onset CRC (LOCRC) despite possible differences in biologic behavior. This study aims to compare outcomes among YOCRC and LOCRC patients on Phase 1 matched and non-matched therapies. **Methods:** This was a single-institution retrospective analysis of patients with CRC who received treatment on a Phase 1 clinical trial. Only the first Phase 1 therapy for each patient was included in analysis. Matched therapy was defined as therapy targeting genomic alterations or their signaling pathways. Distributions of progression-free survival (PFS) were estimated by the Kaplan-Meier method. Log-rank test was performed to test the difference in survival between groups. A propensity score matched analysis was created using a multivariate logistic regression model. Covariates in the model included: gender, race, lung metastasis, liver metastasis and tumor sidedness. **Results:** 577 patients were included in analysis (Table 1). 252 patients had YOCRC (43.7%) and 325 had LOCRC (56.3%). 100 YOCRC patients (39.7%) and 90 LOCRC patients (27.7%) received matched therapies. Before propensity score matching YOCRC patients on matched therapy had higher odds of achieving a response compared to LOCRC patients on matched therapy (complete response/partial response) (10.5% vs 3.4%, odds ratio (OR): 3.294 (95% confidence interval (CI)): 0.876, 12.390), p=0.0777). After propensity score matching YOCRC patients on matched therapy had higher odds of achieving a response compared to LOCRC patients on matched therapy (13.3% vs 3.9%, OR was not estimable, p=0.0082). No significant differences in overall response rate were detected between YOCRC and LOCRC patients on non-matched therapy before or after propensity score matching (5.4% vs. 4.1%, OR: 1.362 (95% CI: 0.513, 3.615), p=0.5348; 5.5 vs. 4.3%, OR: 1.167 (CI: 0.392, 3.472), p=0.7815). No significant differences in PFS were detected between patient with YOCRC and those with LOCRC in any of the patient cohorts before or after propensity score matching (all patients: p=0.743, p=0.639; patients receiving matched therapy: p=0.497, p=0.909; patients receiving non-matched therapy: p=0.999, p=0.62). **Conclusions:** YOCRC patients were more likely than LOCRC patients to achieve a response on matched therapy though this did not translate to improved PFS. Nevertheless, matched therapies are associated with increased response rate for YOCRC patients. Research Sponsor: None.

**Patient demographics.**

| Trait | n (%) |
|---|---|
| Age at diagnosis (median, range) | 51 (18-83) |
| White/Caucasian | 425 (74.7%) |
| Black/African American | 67 (11.6%) |
| Asian | 40 (6.9%) |
| Hispanic/Latino | 79 (13.7%) |
| Microsatellite Instability-High Tumor | 5 (0.9%) |
| *KRAS* mutation | 352 (61.0%) |
| *BRAF* V600E mutation | 38 (6.6%) |
| Prior Unique Lines of Therapy (median, range) | 4 (0-11) |

# Amivantamab treatment and intra-tumoral gene expression and immune cell changes in refractory metastatic colorectal cancer (mCRC): Whole transcriptome RNA-sequencing analysis from the OrigAMI-1 study.

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**Background:** Amivantamab (ami) is an FDA- and EMA-approved EGFR-MET bispecific antibody with immune cell–directing activity for *EGFR*-mutated advanced non-small cell lung cancer. Ami monotherapy has shown promising activity in participants (pts) with refractory mCRC, independent of primary tumor sidedness (left- or right-sided). Here, we analyzed gene expression data from the OrigAMI-1 study to identify mechanisms of sensitivity and action in response to ami monotherapy. **Methods:** The phase 1b/2 OrigAMI-1 study (NCT05379595) enrolled pts with mCRC harboring wild-type *KRAS*, *NRAS*, *BRAF*, and *EGFR* ectodomain, without *ERBB2*/*HER2* amplification. Pts with left-sided mCRC without prior anti-EGFR therapy (Cohort A) and with prior anti-EGFR therapy (Cohort B), as well as pts with right-sided mCRC (Cohort C) received intravenous ami monotherapy (1050 mg; ≥80 kg: 1400 mg). Tumor biopsy samples were collected at screening and Cycle 3 Day 1 (C3D1; if feasible). Whole transcriptome RNA-sequencing data of paired baseline and C3D1 tumor samples were generated by Foundation Medicine. Gene expression data were analyzed using standard bioinformatic methods to identify gene signatures associated with ami treatment in baseline tumor samples (n = 76) and paired baseline and C3D1 tumor samples (n = 17). **Results:** High baseline mRNA expression of AREG and EREG ligands was associated with treatment response across all cohorts (n = 76). In Cohort A (n = 16), median progression-free survival was significantly longer for pts with high (n = 8) vs low (n = 8) AREG expression (9.1 mo vs 4.5 mo, respectively; $P< 0.01$). Differential expression analyses after ami treatment showed significant changes in > 800 genes ($P< 0.01$) across all cohorts (n = 17). The EGFR pathway was significantly downregulated after ami treatment ($P< 0.01$). Pathway enrichment analyses identified significant enrichment of cell cycle and natural killer (NK) cell–mediated cytotoxicity pathways. The cell cycle pathway score was significantly downregulated following ami treatment ($P< 0.01$), implying reduced cell proliferation. A significant upregulation of dendritic cell ($P< 0.005$) and T-cell–inflamed signature scores ($P< 0.05$) was observed with ami treatment, potentially implying increased immune cell infiltration of the tumor microenvironment. Ami also increased the cytolytic ($P< 0.05$) and NK cell–mediated cytotoxicity pathway scores ($P< 0.05$), implying an increase in cytotoxic immune cells. Additional biomarker analyses are ongoing and will be presented at the meeting. **Conclusions:** Amivantamab downregulates EGFR and cell cycle pathways and increases cytotoxic immune cell signatures consistent with immune cell infiltration into tumors. Elevated AREG and EREG ligand expression correlated with response in wild-type refractory mCRC. Clinical trial information: NCT05379595. Research Sponsor: Janssen Research & Development, LLC, a Johnson & Johnson company.

# Phase 1 dose escalation results of the WEE1 inhibitor, azenosertib (A), in combination with encorafenib (E) and cetuximab (C) in patients (pts) with previously treated *BRAF V600E* mutant metastatic colorectal cancer (mCRC).

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**Background:** Encorafenib + cetuximab was approved for treating pts with *BRAF V600E* mutant mCRC after prior systemic therapy based on the Phase 3 BEACON study (observed response rate 20%; Kopetz et al. 2019). Azenosertib is a highly selective WEE1 inhibitor that causes mitotic catastrophe and cell death. Combining BRAF targeting treatment (E+C) with orthogonal pathway inhibitors may allow for an additive or synergistic combination effect of A. This study aimed to evaluate safety and tolerability, determine the maximum tolerated dose (MTD), and assess anti-tumor activity in pts with *BRAF* V600E mutant mCRC receiving A+E+C. **Methods:** This phase 1 dose escalation, open-label, multicenter study (NCT05743036) evaluated safety, tolerability, and activity of A administered in combination with E+C in adult pts with *BRAF V600E*-mutant mCRC who received 1-3 prior regimens for metastatic disease. Azenosertib is a CYP3A4 substrate and is predicted to moderately inhibit CYP3A4 while weakly inhibiting CYP2C19. Encorafenib is primarily metabolized by CYP3A4 and CYP2C19, and acts as a CYP3A4 inducer. To allow for exposures to optimize treatment benefits and minimize toxicity, the recommended starting dose of E is 150 mg once a week. The primary endpoint was dose-limiting toxicities (DLTs) in cycle 1. Pts were treated across 5 dose-finding cohorts, receiving A (dose range: 100 mg-400 mg once a day [QD] oral [PO] on a continuous schedule) and E (dose range: 75 mg or 150 mg QD PO), and C (500 mg/m$^2$ intravenous twice a week) until disease progression or unacceptable toxicity. **Results:** As of Nov 25, 2024, 44 pts were enrolled and treated with a median age of 64 years. 52.3% of pts received ≥2 prior lines of therapy, 34 pts were BRAF inhibitor (BRAFi)-naïve. The most frequent treatment-related Grade ≥3 adverse events were asthenia (11.4%) and fatigue (6.8%). DLTs were observed at the dose levels of A300+E150 and A400+E75 and included dose-limiting fatigue, atrial fibrillation, recurring elevated bilirubin (all Grade 3), and Grade 4 neutropenia. The MTD was determined to be A300+E75 and C. Twelve of 34 (35.3%) BRAFi-naïve pts achieved confirmed response per RECIST v1.1 (2 complete response, 10 partial response [PR]) while none of the BRAFi-pretreated pts responded. Seven of 17 (41.2%) BRAFi-naïve pts treated at A300+75 or A300+150 achieved confirmed PR. The median duration of response and the median progression-free survival in the BRAFi-naïve pts were 5.6 and 5.4 months, respectively. **Conclusions:** The combination of A+E+C was well tolerated at the MTD and yielded response rates in BRAFi-naïve mCRC pts which exceeded the historical data from the E+C doublet. Clinical trial information: NCT05743036. Research Sponsor: Zentalis.

# Low-pass whole methylome sequencing–based liquid biopsy for metastatic colorectal cancer monitoring in the VALENTINO trial.

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**Background:** The amount of ctDNA is a proxy for metastatic colorectal cancer (mCRC) disease burden, with potentials for prognostic stratification and treatment monitoring. We investigated two methods based on low-pass whole genome and methylome sequencing (WGS and WMS) for ctDNA detection and quantification in the VALENTINO trial. **Methods:** All patients from the VALENTINO trial - a phase II trial comparing the addition of 5FU to Panitumamb-based maintenance after first line FOLFOX+Panitumamb induction in RAS wild-type mCRC - were eligible. Baseline (BL) and 8-week (8w) plasma samples were collected for low-pass WGS and WMS analysis. Two methods for ctDNA quantification based on DNA methylation (METER) and copy number alterations (ichorCNA) were assayed. Chi-squared, Wilcoxon and Cox regression tests were used. Performances of WMS and variant allele fraction (VAF) of a 14-gene panel were compared. **Results:** A BL liquid biopsy was available for 154 patients, with 142 also having an 8w assessment. METER and ichorCNA detected ctDNA in 112 (72.7%) and 94 (59.7%) BL samples, respectively; all discordant cases were METER+ but ichorCNA-. Detection rate increased in the presence of liver metastases (86.0% vs 42.6% for METER, 75.7% vs 23.4% for ichorCNA; both $p < 0.001$) and decreased with peritoneal metastases (55.6% vs 78.0% for METER, 38.9% vs 66.1% for ichorCNA; $p = 0.011$, $p = 0.006$). Tumor fraction (TF) of both BL METER and ichorCNA correlated with the diameter of measurable lesions (both $p < 0.001$) and CEA ($p < 0.001$ and $p = 0.010$). Both PFS and OS were shorter after baseline ctDNA detection with METER (mPFS: 10.6 vs 18.6 months, HR: 1.65, $p = 0.010$; mOS: 28.7 vs 62.2 months; HR: 2.24, 95%CI: 1.37-3.66; $p = 0.001$) or ichorCNA (mPFS: 10.6 vs 15.0 months, HR: 1.42, 95%CI: 1.00-2.00, $p = 0.047$; mOS: 27.8 vs 48.4 months, HR: 1.35, 95%CI: 1.29-2.95; $p = 0.002$). In the multivariate analysis, METER ctDNA detection was the strongest predictor of both PFS and OS ($p = 0.005$ and $p = 0.001$) while ichorCNA ctDNA detection was significantly associated with OS but not with PFS ($p = 0.002$ and $p = 0.093$). METER ctDNA TF decreased significantly at 8w in patients with CR, PR, or SD (paired Wilcoxon $p = 0.015$, $p < 0.001$, $p < 0.001$) but not PD ($p = 0.560$) as the best radiological response. Patients without METER ctDNA clearance at 8w had a higher risks of progression (HR: 2.70, 95%CI: 1.63-4.49; $p < 0.001$) and death (HR: 3.37, 95%CI: 2.00-5.69; $p < 0.001$). Among 123 patients with both METER and VAF available, concordance was 78.0% and in 10 and 17 patients, respectively, ctDNA was detected only with METER or only with VAF. The mPFS and mOS of discordant cases were longer than METER+ / VAF+ cases and shorter than METER− / VAF− cases. **Conclusions:** CtDNA quantification with low-pass WMS by METER retains a prognostic significance, can be used for disease monitoring during treatment and refines ctDNA detection based on a restricted gene panel assay. Clinical trial information: NCT02476045. Research Sponsor: None.

# Vilastobart (XTX101), a tumor-activated, Fc-enhanced anti–CTLA-4 monoclonal antibody, in combination with atezolizumab in patients with MSS CRC.

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**Background:** Vilastobart (XTX101) is tumor-activated, high affinity, Fc-enhanced aCTLA-4 designed to focus activity toward the tumor and minimize systemic adverse events. Fc-enhancement augments FcγR co-engagement on antigen presenting cells and has been linked with efficacy of aCTLA-4 combinations in patients (pts) with microsatellite stable (MSS) colorectal cancer (CRC) and other tumors [Fakih ASCO GI 2025]. Vilastobart was generally well-tolerated and demonstrated evidence of anti-tumor activity in pts with immunologically "cold" advanced solid tumors, both as a monotherapy and in combination with atezolizumab [Davar SITC 2024]. **Methods:** Phase 2 of the NCT04896697 study evaluated the initial recommended Phase 2 dose of vilastobart 100 mg Q6W in combination with atezolizumab 1200 mg Q3W in pts with MSS CRC who had at least 1 prior chemotherapy regimen in the metastatic setting, excluding pts with prior immune checkpoint inhibitors. Pts with (LM) and without liver metastasis (NLM) were eligible. Tumor biopsies were obtained before and during treatment for translational analyses. **Results:** As of January 13, 2025, 40 pts were dosed in Phase 2. Median age was 55 (25-82) and 70% of pts had 3 or more prior lines of therapy. Of the 24 enrolled NLM pts, 11 were response-evaluable with an available on-treatment scan as of the data cut. In these 11 pts, two confirmed and one unconfirmed partial response (PR) were reported, all accompanied by significant decreases in ctDNA and serum tumor marker CEA and with each pt ongoing on therapy, for a preliminary ORR of 27%. One additional pt (with peritoneal metastasis) had a 24% reduction in target lesions (first scan) and was ongoing on therapy. Of the 16 enrolled LM pts, 7 were response evaluable, with one stable disease and another pt reporting a mixed response with significant serum tumor marker reductions, both ongoing on therapy. Of note, one LM pt in Phase 1C dose escalation treated with vilastobart (150 mg Q6W) combination had a confirmed PR with LM resolution. Six pts (15%) reported G3+ treatment-related adverse events (TRAEs), with two G4 laboratory TRAEs and no G5 TRAEs. Only three pts discontinued therapy for TRAEs. TRAEs occurring in ≥10% (all grade) or ≥5% (G3) of pts are summarized in the Table. **Conclusions:** The combination of vilastobart, a novel tumor-activated, Fc-enhanced a-CTLA-4, and atezolizumab demonstrated initial evidence of anti-tumor activity in late line, metastatic MSS CRC where immune checkpoint blockade has historically been relatively ineffective. Vilastobart was observed to have a differentiated safety profile distinct from systemically active a-CTLA-4, consistent with tumor-selective activation. Clinical trial information: NCT04896697. Research Sponsor: Xilio Therapeutics.

| AE term | All Grade n (%) | Grade 3 n (%) |
|---|---|---|
| **Fatigue** | 12 (30%) | 0 |
| **Diarrhea** | 8 (20%) | 0 |
| **Infusion related reactions** | 5 (13%) | 0 |
| **Pyrexia** | 4 (10%) | 0 |
| **ALT increased** | 4 (10%) | 0 |
| **AST increased** | 4 (10%) | 1 (3%) |
| **Colitis** | 2 (5%) | 2 (5%) |

# mFOLFIRINOX efficacy as rescue regimen for patients with metastatic refractory colorectal cancer: The RE-PLAY trial.

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**Background:** Doublets with Fluoropyrimidines (F), oxaliplatin (Ox), and irinotecan (Ir) are standard chemotherapy agents used to treat metastatic colorectal cancer (mCCR). The role of triplet combination with modified FOLFIRINOX (mFOLFIRINOX) in refractory patients (pts) previously treated with doublets or monotherapy sequential regimens remains unclear. **Methods:** This single-arm, open-label phase II trial employed a Simon two-stage design. Eligible pts had mCCR with documented progression after treatment with doublets or sequential monotherapy regimens containing F, Ox, and Ir. Pts with RAS wild-type tumors were required to be refractory to anti-EGFR therapy. The mFOLFIRINOX regimen consisted of 5-FU (2400 mg/m$^2$, continuous infusion over 46 hours), Ox (85 mg/m$^2$, D1), Ir (150 mg/m$^2$, D1), and leucovorin (200 mg/m$^2$, D1), administered every 14 days. The primary endpoint was the disease control rate (DCR) as assessed by RECIST v1.1. According to the Simon design, the study would be considered positive if 4 or more pts achieve disease control among 25 pts in the second stage. Secondary endpoints included objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** Between October 2021 and October 2024, 25 pts were enrolled. Three pts did not receive treatment due to consent withdrawal (n = 1) or clinical deterioration from disease progression before treatment initiation (n = 2). All pts had proficient mismatch repair (pMMR) tumors; 16 (64%) had KRAS/NRAS mutations, and most tumors were left-sided (n = 20, 80%). At Intention to Treat analyses, 16.6% (n = 4) achieved a partial response, 44% (n = 11) had stable disease, and 28% (n = 7) experienced disease progression as their best radiologic response. The DCR was 60% (n = 15), and the ORR was 16.6% (n = 4). With a median follow-up of 6.8 months, 17 pts experienced disease progression or death. The median PFS was 5.7 months, and the median OS was 9.3 months. No significant differences in DCR, ORR, PFS, or OS were observed based on RAS mutation status or tumor sidedness; among 22 pts who received at least one cycle of mFOLFIRINOX, 68.1% (n = 15) experienced grade 3 or higher adverse events, including one treatment-related death. **Conclusions:** mFOLFIRINOX demonstrated efficacy as a rescue regimen for refractory mCCR previously refractory to doublets or sequential monotherapy regimens containing Ox, Ir, fluoropyrimidines, and anti-EGFR therapy. Clinical trial information: NCT05354817. Research Sponsor: None.

**LBA3555** **Poster Session**

# Safety and efficacy of reduced-port laparoscopic surgery for patients with colon and upper rectal cancer.

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# Analysis of mutational profiles and their correlation with organ-specific metastases in MSS and *BRAF*wt colorectal cancer (mCRC).

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**Background:** In *BRAF*wt/ MSS mCRC, the mechanisms driving distinct metastatic dissemination patterns remain unclear. Understanding them is crucial, as dissemination profiles influence therapeutic strategies, such as immunotherapy for patients (pts) without liver metastasis (mets) or locoregional approaches and liver transplantation for those with liver-limited disease. NGS advances provide genomic data, offering opportunities to identify predictive signatures that link molecular profiles to metastatic patterns. This study investigates mutational profiles to uncover correlations with organ-specific mets in pts treated at our institution. **Methods:** This study included pts with unresectable MSS/*BRAF*wt mCRC treated at Vall d'Hebron Hospital (2010–2020). Pts were grouped into three clinical categories based on metastatic patterns: liver-limited disease (LLD), exclusively extrahepatic disease (EXTRAHEP), and hepatic and extrahepatic disease (BOTH). Molecular analyses were performed using NGS prescreening data available at our institution. Mutations were grouped in two approches: (1) by biological significance using cancer hallmark genes from published datasets (Zhang, *Front Genet* 2020; Sondka, *Nat Rev Cancer* 2018), and (2) by molecular pathways based on the Sanchez-Vega dataset (*Cell* 2018). Statistical analyses were conducted using R version 4.3.2. **Results:** A total of 1,026 pts were included (204 LLD, 297 EXTRAHEP, and 525 BOTH), with molecular analyses performed on 360 samples (35% overall; 31.8%, 39.7%, and 33.7%, in each group, respectively). The median number of genes with pathogenic mutations per sample differed significantly between groups: 2.28 in LLD, 2.44 in EXTRAHEP, and 2.65 in BOTH ($p = 0.01$). BOTH showed significantly greater increase than LLD in mutated genes associated with five of the ten analyzed hallmarks: activation of invasion and mets, resistance to cell death, evasion of growth suppressors, sustaining proliferative signaling, and replicative immortality. Compared to EXTRAHEP, BOTH also had more mutations in invasion and mets activation and proliferative signaling (adjusted p-value $< 0.05$ for all the hallmarks mentioned). For pathway associations, WNT pathway activation was higher in BOTH than EXTRAHEP ($p = 0.004$), driven by more frequent APC mutations in BOTH (82% vs. 69%, adj. $p = 0.049$). **Conclusions:** This study provides evidence that pts with both hepatic and extrahepatic disease exhibit enrichment in five cancer hallmarks and the WNT pathway compared to other metastatic patterns. This suggests the tumor's potential to adapt to diverse microenvironments. Despite the statistical significance, the magnitude of the observed differences in mutated genes is not yet clinically useful. These findings highlight the need for collaborative efforts to develop mutational profiles that predict organotropism and guide therapy. Research Sponsor: None.

# Patterns of immunotherapy use in dMMR/MSI-H metastatic CRC.

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**Background:** Immune checkpoint inhibitors (ICI) are more effective in mismatch repair deficient/microsatellite instability high (dMMR/MSI-H) metastatic colorectal cancers (mCRC) compared to chemotherapy (chemo). However, real-world data and patterns of use are limited. We evaluated real-world ICI use in mCRC after FDA approval in 2017 and approval as first-line (1L) therapy in 2020, and the impact on survival. **Methods:** We used the nationwide Flatiron Health electronic health record (EHR) derived de-identified database to determine patterns of ICI usage in patients diagnosed with dMMR/MSI-H mCRC since 2013. Trends in ICI use were estimated with the Cochran-Armitage test, while real-world time to next treatment (rwTTNT), progression free survival (rwPFS), and overall survival (OS) between ICI vs chemo only groups were estimated with Kaplan Meier curves and log-rank test. Multivariate Cox Proportional-Hazards Models were fitted to adjust for potential cofounding variables (ie sex, performance status (ECOG) and treatment). Hazard ratios, p-values and 95% confidence intervals are presented. Proportional hazards assumptions were tested for violations. **Results:** Of 41,431 patients diagnosed with mCRC since 2013, 1,707 were dMMR/MSI-H and received therapy; thus were included in the analyses. Mean age was 66 years, 925 (54%) were female, and 884 (52%) had de novo mCRC. BRAF and RAS mutations were detected in 604 (35%) and 372 (22%) patients, respectively. Of 1,707 eligible patients, 573 (34%) received 1L ICI and 1,116 (66%) received 1L chemo. Of those who received 1L ICI, 480 (43%) received a single ICI and 56 (5%) received dual ICI. There was a linear increase in the proportion of ICI-based treatments used over time in both the 1L and second line (2L). With a median follow-up of 38.2 months (mo); median OS for patients who received 1L chemo was 25.9 mo vs 51.6 mo with 1L ICI (HR 0.62, $p < 0.0001$, 95% CI 0.52-0.73). Presence of a BRAF mutation was associated with worse OS (median OS 44.4 mo, 95% CI 31.2-61.1) vs. no BRAF mutation (median OS not reached (NR), 95% CI 51.6-NR) in patients receiving 1L ICI ($p = 0.0046$). The presence of a RAS mutation was not significantly associated with OS. Median rwTTNT after 1L ICI was 31.8 mo (95% CI 23.7-50.2), compared to patients whose first ICI was in the 2L (21.9 mo [95% CI 12.9-36.8]) or third line (3L) (9.5 mo [95% CI 5.7-18.0]) ($p = 0.0041$). Median rwPFS for first receipt of ICI in the 1L was 18.1 mo (95% CI 13.2-30.1) compared to first receipt in 2L (8.3 mo [95% CI 6.5-14.5]) or 3L (4.8 mo [95% CI 4.0-13.7]) ($p = 0.0032$). **Conclusions:** There was a linear increase in the proportion of patients with dMMR/MSI-H mCRC treated with ICI, associated with FDA approvals in 2017 and 2020. Male gender and presence of a BRAF mutation in patients receiving 1L ICI and receipt of 1L chemo were inversely associated with OS. Receipt of ICI in earlier treatment lines was associated with increased rwPFS and rwTTNT. Patients with dMMR/MSI-H mCRC benefit from receiving early ICI. Research Sponsor: None.

# Colorectal cancer with gene fusions: Navigating the genomic landscape and treatment selection in a phase I unit.

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**Background:** Gene fusions are rare genomic events in colorectal cancer (CRC) and can co-occur with other potentially actionable alterations. Navigating early-phase trial selection in this scenario can be challenging. Objectives: To evaluate the genomic landscape, treatment selection, and clinical outcomes of patients (pts) with CRC harboring gene fusions enrolled in at least one clinical trial in the Department of Investigational Cancer Therapeutics, The University of Texas, MD Anderson Cancer Center. **Methods:** We used a computerized data extraction tool to review clinical and genomic data of pts with CRC harboring gene fusions between June 2011 and June 2024. The actionability of the genomic alterations was classified by the Precision Oncology Decision Support team. Median overall survival (mOS) was defined as the time from consent to the date of death or last follow up. Kaplan-Meier method was used to estimate survival and the Cox proportional hazards model to evaluate the impact of multiple variables. **Results:** 56 pts were included (28 female; 28 male) with a median age of 50.5 years (range 25-84). Colon was the most frequent tumor location (n=29, 51.8%) followed by rectal (n=15, 26.8%), small bowel (n=8, 14.3%), and appendiceal (n=3, 5.3%). Most cases had adenocarcinoma histology (n=54, 96.4%). The median time from diagnosis to completion of the molecular test identifying the gene fusion was 3 mo (range 0-36) for pts whose tumors were diagnosed in the metastatic setting. A total of 65 fusions were identified (range 1-3 per pt); 48 of them occurring in actionable or potentially actionable genes (78.8%) and 17 in non-actionable genes (26.2%). RAS alterations were present in 27 cases (48.2%) and BRAF alterations in 10 cases (17.9%). 8 patients had alterations in ERBB2 (14.3%) and 32 in genes related to DNA damage repair (DDR; 57.1%). In total, patients were enrolled in 91 trials (range 1-7 per pt). Target therapy (TT) was offered to 33 pts (58.9%) while the remaining were offered non-TT (n=23, 41.1%). Treatment selection was fusion-driven in 10 cases (17.9%; 4 NTRK, 3 FGFR, 1 RET, 1 ROS1, and 1 ALK). Notably, one pt with a ETV6-NTRK fusion was enrolled sequentially in 4 immunotherapy (IO) and TT trials, surviving on-trial for over 3.5 years. 3 patients received TT for KRAS (5.4%), 4 for BRAF (7.1%), 4 for ERBB2 (7.1%), and 8 for DDR alterations (14.3%). The mOS was 10.0 mo (95% CI, 5-NR) for pts receiving non-TT and 11 mo (95% CI, 3-21) for patients receiving TT (p 0.985). Age group (cutoff 50 years), gender, cancer stage at diagnosis, RAS, BRAF and DDR alterations, and treatment type (TT vs. non-TT or IO) were not related to survival in the multivariate level (p=0.9). **Conclusions:** A comprehensive genomic evaluation of pts with CRC harboring gene fusions can expand early-phase treatment possibilities. DDR alterations are more frequent in this group than in unselected CRC cohorts and can represent an additional target for TT. Research Sponsor: None.

# The efficacy of watch and wait strategy or surgery after neoadjuvant immunotherapy for locally advanced colorectal cancer with dMMR/MSI-H guided by ctDNA dynamic monitoring (WINDOW): A single-center, open-label, prospective, phase II study.

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**Background:** Circulating tumor DNA (ctDNA) has shown potential in predicting the efficacy of neoadjuvant treatment for colorectal cancer (CRC). However, evidence is limited for patients with deficient mismatch repair (dMMR) / microsatellite instability-high (MSI-H) CRC, who respond well to immunotherapy. This study explores an optimal ctDNA-guided neoadjuvant immunotherapy (nIT) strategy in locally advanced CRC (LACRC) patients with dMMR/MSI-H. **Methods:** We conducted a single-center, open-label, phase 2 trial named WINDOW involving dMMR/MSI-H LACRC patients. Patients received the anti-PD-1 antibody tislelizumab every three weeks. ctDNA was monitored at baseline, after 2, 4, 5, or even 6 to 8 cycles, and during post-watch-and-wait (W&W) or post-surgery periods using the Signatera platform. Starting from the 4th cycle, patients with two consecutive ctDNA-negative results were eligible for the W&W approach. Those who did not achieve ctDNA-negative or turned positive during follow-up continued immunotherapy. Surgery was performed for patients not meeting W&W criteria by the 8th cycle. The primary endpoint was the complete response (CR) rate, including ctDNA-negative clinical complete response (cCR) and pathological complete response (pCR). The trial is registered at ClinicalTrials.gov (NCT06477991). **Results:** From January 2023 to May 2024, 24 patients with stage II-III dMMR/MSI-H CRC were enrolled, including 18 with colon cancer and 6 with rectal cancer. At baseline, all patients had detectable ctDNA. After nIT, 87.5% (21/24) achieved two consecutive ctDNA-negative results. Among the remaining three, two underwent surgery due to sustained ctDNA-positivity (both TRG3), while one showed continuous ctDNA decrease despite obstruction and achieved pCR. One patient required emergency surgery for perforation (confirmed as pCR), while 20 were managed with the W&W strategy. Of these, 90% (18/20) achieved ctDNA negativity after two cycles, and 95% (19/20) after five cycles of nIT. With a median follow-up of 20.3 months (range: 8.7–25.0 months), none experienced recurrence, resulting in an overall CR rate of 91.7% (22/24). Notably, if ctDNA remained positive after the 5th cycle, the CR rate was only 25% (1/4), while it reached 100% (20/20) if ctDNA became negative. From the perspective of organ preservation, only 45.5% (10/22) of patients avoided surgery based on imaging alone; however, with ctDNA-guided management, 83.3% (20/24) avoided surgery. **Conclusions:** NIT demonstrates high efficacy in dMMR/MSI-H LACRC. The ctDNA-guided W&W strategy significantly improves organ preservation rates. Monitoring ctDNA negativity after the 5th cycle of nIT is a crucial marker of high CR rates, suggesting this cycle may represent the optimal monitoring window during nIT. Clinical trial information: NCT06477991. Research Sponsor: The Joint Special Funds for the Department of Science and Technology of Yunnan Province-Kunming Medical University; 202201AY070001-149.

# Laparoscopic versus open liver resection for colorectal liver metastasis: An individual participant data meta-analysis of randomized controlled trials.

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**Background:** Laparoscopic surgery for colorectal liver metastases (CRLM) is associated with lower physical impact, shorter length of stay and less postoperative morbidity than open surgery. To analyze oncological and procedural outcomes, a European consortium including principal investigators of all 4 completed RCTs on laparoscopic (LLR) vs open (OLR) liver resection performed an individual participant data meta-analysis (IPDMA), including updated survival data. **Methods:** This was an IPDMA with a primary endpoint of postoperative morbidity. Secondary endpoints included overall survival (OS), disease-free survival (DFS) and resection margin status. A generalized linear mixed model was used to compare OLR and LLR , with trial as a fixed-effect. Logistic regression analysis was performed for dichotomous variables and negative binominal regression analysis for continuous variables. Survival analyses were performed using Cox-regression. **Results:** A total of 761 patients with CRLM were randomly allocated to LLR (n = 384) or OLR (n = 377). Preoperative chemotherapy was administered as recommended by the local multidisciplinary team (40% vs 46%). Whilst LLR was associated with significantly less postoperative morbidity overall (19% vs 27%, adjusted OR 0.62 [95%CI 0.44 to 0.88]), this was not observed in the subgroup of patients receiving neoadjuvant chemotherapy (25% vs 24%, adjusted OR 1.06 [95%CI 0.63 to 1.79]), p-value for interaction $< 0.001$). Hospital stay was shorter after LLR (median 4 vs 5 days, adjusted percentage difference: -27 [95%CI -37 to -15]) All cause 90-day mortality was not significantly different (1.9% vs 0.8%, adjusted OR: 3.2 [95%CI 0.65 to 16.00]). At 5-year follow-up OS and DFS were not significantly different (adjusted HR 0.97 [95%CI 0.79 to 1.20] and 1.05 [95%CI 0.86 to 1.27], respectively). In patients who received preoperative chemotherapy, a trend towards fewer R0 resections in LLR compared to OLR was noted (84% vs 90%, adjusted OR 2.00 [95%CI 0.99 to 4.03], p-value for interaction = 0.053). In patients who did not receive preoperative chemotherapy there was no difference in R0 resections (90% vs 86%, adjusted OR 0.76 [95%CI 0.41 to 1.40]). Liver specific recurrence was not different between LLR and OLR (37% vs 37%, adjusted OR 1.02 [95%CI 0.76 to 1.34), neither was time to adjuvant chemotherapy (45 days vs 49 days, adjusted OR 1.12 [95%CI 0.91 to 1.38]) nor median number of adjuvant courses (8 vs 8, adjusted percentage difference 0.07 [95%CI -0.11 to 0.24]). **Conclusions:** This IPDMA of 761 patients in 4 RCTs across Europe confirms that laparoscopic resection for CRLM is superior to open resection with regards to short term outcomes, with no differences observed on long term oncological outcomes. However, in patients who received preoperative chemotherapy, the benefit of the laparoscopic approach is questionable. Research Sponsor: None.

# Prognostic factors of survival and recurrence after liver transplantation for unresectable colorectal liver metastases: Results from the TransMet trial.

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**Background:** Liver transplantation (LT) has recently proved to improve the survival of selected patients with unresectable colorectal liver metastases (uCRLM) compared to chemotherapy (C) alone. However, recurrence rates remain high, stressing the need for a better patient selection. This exploratory study aimed to identify prognostic factors associated with recurrence and death in patients undergoing LT as part of the TransMet trial. **Methods:** Data from 36 patients of the LT+C arm (per protocol population) were analyzed including age, gender, TNM and RAS status of the primary tumor, characteristics of metastases at diagnosis and at LT, chemotherapy regimen, tumor response (RECIST), and timeframe from primary resection to LT. Associations with recurrence and death were explored. Variables with $>$ 5 observations per group and p-values $\leq$ 0.10 in univariable analysis were included in multivariable models. **Results:** Among the 36 transplanted patients, 27 experienced recurrence and 9 died after 50-month follow-up. Recurrence: At univariable analysis two factors were associated to a higher risk: serum CEA levels $>$ 5 ng/ml at time of LT (11/11 vs 11/18, p 0.01) and oxaliplatin-based first line chemotherapy (14/16 vs 13/20, p 0.04). Two other factors showed a trend toward statistical significance: Female sex (14/15 vs 13/21, p 0.10) and $>$ 20 metastases at diagnosis (11/17 vs 16/19, p 0.09). At multivariable analysis, CEA levels at LT $>$ 5 ng/ml (HR: 2.91; 95% CI: 1.0–8.2; p 0.04) emerged as an independent predictor of recurrence. Female sex (HR: 2.2; 95% CI: 0.8–5.3; p 0.08) and oxaliplatin-based first line chemotherapy (HR: 2.0; 95% CI: 0.8–4.8; p 0.13) were also associated with around 2-fold higher risk of recurrence, although not reaching statistical significance. Death: At univariable analysis,two factorswere significantly associated with a higher risk: female sex (7/15 vs 2/21 for male, p 0.03) and $>$ 24 cycles of chemotherapy before LT (8/19 vs 1/15, p 0.05). Two other factors showed a trend toward higher mortality: no response to 1$^{st}$ line chemotherapy (6/14 vs 3/22, p 0.06) and stable disease (vs partial response) before LT (8/22 vs 1/14, p 0.08). At multivariable analysis, female sex emerged as independent predictor of death (HR 5.1; 95% CI: 1.0–25.0; p = 0.04). More than 24 cycles of chemotherapy (HR 7.1; 95% CI: 0.9 – 51.0; p 0.07) and stable disease (vs partial response) at LT, showed an approximately 7-fold increase in the risk of mortality, although not reaching statistical significance. **Conclusions:** Within the limits of a reduced sample size, these results suggest that LT should be envisaged early in the history of potential candidates to LT to reduce the number of cycles of chemotherapy. Both morphological and biological tumor response, initially and at time of LT, are essential. The notable influence of female sex on post-LT outcome needs to be further explored. Clinical trial information: NCT02597348. Research Sponsor: None.

# Impact of inflammatory bowel disease on outcomes of colorectal cancer patients undergoing open resection.

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**Background:** Colorectal cancer(CRC) is, at present, the fourth most common cause of cancer in the United States, with more than 140,000 new cases and 52,000 deaths yearly. Patients with inflammatory bowel disease(IBD) are at increased risk of CRC secondary to the pro-neoplastic effects of chronic mucosal inflammation. Open resection is one of the treatment modalities among CRC patients. Research evaluating the impact of IBD on the short-term outcomes of open resection is limited. **Methods:** The National Inpatient sample was utilized to identify open resection procedures among colorectal cancer patients through International Classification of Diseases, 10th edition (ICD-10) codes. Our study contained patients ages 18 and older. We created two groups of patients consisting of cases with and without a history of IBD. Descriptive statistics were conducted for patient demographics and pre-existing comorbidities. We reported the adjusted odds ratio(aOR) and their 95% confidence intervals for differences in surgical and post-surgical complications. **Results:** This study investigated 318115 open resections among colorectal cancer patients, which involved 3675(1.2%) with IBD. The cases of IBD contained a younger sample with a mean age of 60.95 years, while our non-IBD group had a mean age of 66.95 years($p < 0.01$). In addition, IBD patients expressed a lower mean Charlson Comorbidity Index(CCI) score of 4.21(vs. 4.34, $p < 0.01$). Our IBD group presented with higher aOR of severe sepsis with septic shock (1.224, 95% CI 1.030-1.455, $p = 0.022$), acute kidney injury(AKI)(1.172, 95% CI 1.059-1.297, $p < 0.01$), cardiopulmonary resuscitation (CPR)(2.148, 95% CI 1.437-3.212, $p < 0.01$), and wound infection(1.377, 95% CI 1.139-1.664, $p < 0.01$). On the other hand, IBD was linked with lower odds of bleeding(aOR 0.808, 95% CI 0.686-0.952, $p = 0.011$) but was more likely to undergo blood transfusion(aOR 1.153, 95% CI 1.036-1.284, $p < 0.01$). However, events of acute respiratory failure (aOR 1.024, 95% CI 0.877-1.195, $p = 0.767$), postoperative pneumothorax(aOR 1.286, 95% CI 0.684-2.417, $p = 0.436$), use of mechanical ventilation(aOR 1.181, 95% CI 0.996-1.400, $p = 0.056$), vasopressors (aOR 1.012, 95% CI 0.780-1.315, $p = 0.926$), and all-cause mortality (aOR 1.026, 95% CI 0.808-1.304, $p = 0.831$) did not differ. **Conclusions:** Among CRC patients undergoing open resection, patients with IBD were younger and had higher odds of septic shock, AKI, CPR, wound infection, and blood transfusion. Although we failed to find differences in short-term mortality, it is crucial to conduct long-term studies to evaluate responses and relapses following open resection and post-discharge complications. Research Sponsor: None.

# A multicenter randomized phase II trial assessing the efficacy and safety of mCapOX plus cetuximab and mFOLFOX6 plus cetuximab as first-line treatment for patients with RAS/BRAF wild-type metastatic colorectal cancer: Primary results of the CAPCET study.

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**Background:** This CAPCET randomized phase II trial was designed to assess the efficacy and safety of modified capecitabine and oxaliplatin (mCapOX) plus cetuximab (CET) and modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) plus cetuximab (CET) for the first-line treatment of left-side unresectable RAS/BRAF wild-type (wt) metastatic colorectal cancer (mCRC). **Methods:** CAPCET was an open-label, multicenter, randomized, non-comparative phase II trial. Patients with unresectable RAS/BRAF wt mCRC were randomly assigned (1:1) to receive up to 12 cycles biweekly mCapOX (capecitabine 1000mg/m$^2$ orally twice daily on Day 1-7 and oxaliplatin 85 mg/m$^2$ iv on Day 1) plus CET (500mg/m$^2$ iv on day 1) (arm A) or biweekly mFOLFOX6 (oxaliplatin 85 mg/m$^2$ iv on day 1, leucovorin 400 mg/m$^2$ iv on day 1, fluorouracil 400mg/m$^2$ iv bolus on day 1, then fluorouracil 2400 mg/m$^2$ continuous infusion over 46-48h) plus CET (500mg/m$^2$ iv on day 1)(arm B) followed by maintenance(either capecitabine plus CET or capecitabine alone at the discretion of the investigators) or treatment-free intervals until progression on treatment, toxicity, or death. The primary endpoint was progression-free survival (PFS) rate at 9 months from randomization. **Results:** Between September 2021 and April 2024, 168 patients (84 in arm A and 84 in arm B) were enrolled in 20 China centres. Baseline characteristics were well balanced between arms. After a median follow-up of 21.0 months (IQR,19.5-22.5), the 9 months-PFS rates were 70.9% (95% CI 61.1%-82.3%) in arm A and 66.8% (95% CI 56.7%-78.6%; HR = 1.11, P = 0.558) in arm B, and the primary endpoint was met. The median PFS (arm A/B) was 12.7 months (95% CI 10.8–15.2)/12.0 months (95% CI 9.7–14.1). The overall response rate (ORR) and disease control rate (DCR) in arm A were higher than those in arm B with 69.2% versus 60.3% and 96.2% versus 89.7%, respectively. The 2-year overall survival (OS) rate (arm A/B) was 66.8% (95% CI 54.2%–82.3%)/65.6% (95% CI 52.5%–82.0%), and the median OS not reached. Grade≥3 adverse events (AEs) occurred in 28.8% of safety population set (n = 156), with 7.7% in arm A and 21.2% in arm B. The most commonly Grade≥3 AEs was neutropenia, rash, leukopenia and there were no grade 5 AEs reported. **Conclusions:** The CAPCET study met its first endpoint of 9-month PFS rate in patients with RAS/BRAF wt mCRC. Biweekly mCapOX plus CET had higher ORR and DCR than mFOLFOX6 plus CET, with signally reduced toxicity. Longer follows-up and a multicenter, open-label, randomized, controlled Phase CAPCET- III study (NCT06616259) will be further validate this innovative regimen. Clinical trial information: NCT05022030. Research Sponsor: The Department of Science and Technology of Sichuan Province; The Postdoctor Research Fund of West China Hospital, Sichuan University; The Nation-Sponsored Postdoctor Researcher Program; The Science and Technology Innovation 2030-Major Project (Young Talent Cultivation Program); The 1.3.5 Project for Disciplines of Excellence, West China Hospital, Sichuan University.

# A medically tailored meal (MTM) delivery program to reduce nutritional decline and improve treatment tolerance in patients with colorectal cancer (CRC): A pilot study.

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**Background:** Colorectal cancer (CRC CA) is the 3rd most common CA among US adults. Over 50% of CRC patients (pts) present with advanced disease, necessitating adjuvant or palliative chemotherapy. Nearly 50% CRC pts will be diagnosed with malnutrition (MN) during their CA journey. MN is associated with reduced quality of life, poorer response to chemotherapy, and reduced survival. The provision of medically tailored meals (MTM) improves access to nutritious foods to support pts' caloric/nutrient needs and preferences. Remote delivery of MTMs could serve as an impactful intervention for pts at highest risk of MN and to improve treatment tolerance. **Methods:** Primary outcomes were feasibility (enrollment/adherence/retention) and acceptability of an MTM program in pts undergoing 5-FU based therapy for CRC; secondary included weight maintenance, MN measured by PG-SGA (Patient-Generated Subjective Global Assessment), HEI (Healthy Eating Index) score generated by VioScreen, a validated computerized food frequency tool, QOL measured by FACT-C/FACT-G, and treatment disruption. The MTM program included daily meals delivered weekly and nutritional counseling at 4 timepoints. **Results:** Among 100 eligible CRC pts approached, 48 consented and 52 declined, primarily due to lack of interest in MTMs (35/52, 67%). 40/48 (83%) initiated the MTM program and 32/40 (80%) completed it, including 13 (41%) Stage II/III and 19 (59%) Stage IV patients. 16/48 (33%) consented pts discontinued the study due to non-compliance (n = 4), post-consent refusal (n = 4), dissatisfaction w/meals (n = 7) or death (n = 1). Pts had mean age of 56 yrs (range 32-78), with 51% female, 20% African American, and 15% Hispanic. 34% had < HS diploma, and 56% reported income of <$50,000. Enrollment (44%, goal > 50%, minimum 40%), counseling adherence (52.5%, goal > 66%, minimum 50%) and study retention rate (81%, goal > 70%) measured by end-of-study survey completion all surpassed a priori unfavorable result threshold (lower feasibility limit), but only retention met its target. Acceptability was high: 92% were satisfied with the MTM program and 91% would recommend it. Mean weight was maintained during study (181.2 lbs start, 181.6 lbs end) and mean PG-SGA score declined (7.5 to 5.4, indicating lower risk of MN at the end of the study). Mean HEI scores decreased slightly (63.3 start, 61.6 end, indicating a slight reduction in dietary quality) throughout the program; however, more than half of pts (56%, n = 14) demonstrated an increase in their HEI scores, suggesting improved quality of food consumed. **Conclusions:** Our MTM delivery program was highly acceptable and was associated with weight maintenance and improved PG-SGA scores in CRC pts receiving 5-FU based therapy. Further research of MTM delivery programs should consider retention challenges among pts facing advanced GI cancers.
Research Sponsor: Manna Pilot Funding.

# Relapse patterns, risk factors, re-resectability and survival after curative treatment for metastatic colorectal cancer (mCRC): A RAXO substudy.

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**Background:** In mCRC, metastasectomy and/or local ablative treatment (LAT) cures some. However, over 70% of the patients relapse, with liver, lung and peritoneum being the most common recurrence sites. Data on recurrence patterns and prognostic factors are mainly limited to patients with liver metastases treated before 2008. An update including patients also with multisite metastases treated up-to-date is needed. **Methods:** In this study, 323 patients from the RAXO-study (2012–2018) were analyzed, 312 patients had undergone R0–1 metastasectomy and 11 patients had A0–1 LAT. Three patients with postoperative death were excluded. The remaining 320 patients were prospectively followed for at least five years, with radiological imaging and blood tests every 3–6 months in the first two years and every 6–12 months thereafter. Median time to recurrence (mTTR), and overall survival (mOS) were estimated with Kaplan-Meier from the date of curative surgery/LAT for metastases known at baseline and compared using log-rank. Hazard ratios (HR) were estimated using Cox regression. **Results:** mTTR was 17 months (CI 95% 13–23 months) with 221 patients (69% of all) relapsing during follow-up. Totally 135 recurrences (42% of the patients at risk) occurred during the first year. During the second, third, fourth and fifth year, recurrence occurred in 48 (26%), 27 (20%), 7 (7%) and 1 (1%) patients at risk, respectively. Of patients relapsing during the first year, 65 (60%) were re-resected with numbers for subsequent years being 18 (67%), 3 (43%), 0 (0%) and 1 (33%), respectively. mTTR, mOS, and re-resectability outcomes for the most common recurrence sites are presented in the table. Regional lymph node metastasis (HR 1.4), RAS mutation (1.4), R1 resection (2.3) and treatment with LAT (2.4) were prognostic for recurrence ($p < 0.05$). **Conclusions:** Two-thirds of curatively treated mCRC patients relapse within the first four years. Curative-intent re-resection provides good OS for most sites of recurrence and should be considered when possible. Clinical trial information: NCT01531621.
Research Sponsor: Finska Läkaresällskapet; 2016, 2018, 2019, 2020, 2021, 2022, 2023, 2024, 2025; The Finnish Cancer Foundation; 2019-2020, 2021, 2022-2023, 2025; Relander´s foundation; 2020-2022; The Competitive State Research Financing of the Expert Responsibility Area of Tampere, Helsinki, Turku, Kuopio, Oulu, and Satakunta Hospitals; 2012, 2016, 2017, 2018, 2019, 2020, 2021, 2022, 2023, 2024, 2025; Tampere University Hospital Fund; Tukisäätiö 2019, 2020, 2023, 2024 and OOO-project 2020, 2022; Helsinki University Hospital research fund; 2019, 2020, 2021, 2022, 2023, 2024; Mary and Georg C. Ehrnrooth Foundation; 2023; Liv & Hälsa; 2023; Radiumhemmets fonder; 2022-2023, 2025-2027; Cancerfonden Sweden; 2023-2024; Amgen; Unrestricted grant 2012–2020, 2023, 2024; Eli Lilly and Company; 2012-2017; Merck KGaA; 2012–2020; Roche Oy; 2012–2020; Sanofi; 2012–2017; Servier; 2016–2024.

| | Resected, n (%) | mTTR, months | mOS 1st resection, months | Re-resection, n (%) | mOS re-resected, months | Non-re-resected, n (%) | mOS non-re-resected, months | p |
|---|---|---|---|---|---|---|---|---|
| **R0–1 resected patients** | 320 | 16 | 92 | | | | | |
| **Recurrence at any site** | 221 (100%) | 10 | 61 | 116 (52%) | 79 | 105 (48%) | 44 | < 0.01 |
| **– Lung** | 96 (43%) | 10 | 64 | 45 (20%) | 103 | 51 (23%) | 52 | < 0.01 |
| **– Liver** | 72 (33%) | 8 | 54 | 44 (20%) | 77 | 28 (13%) | 39 | < 0.01 |
| **– Distant lymph nodes** | 37 (17%) | 9 | 56 | 5 (2%) | 58 | 32 (14%) | 48 | 0.31 |
| **– Peritoneum** | 23 (10%) | 10 | 60 | 11 (5%) | 92 | 12 (5%) | 29 | < 0.01 |
| **– Local recurrence** | 21 (10%) | 10 | 58 | 9 (4%) | 58 | 12 (5%) | 56 | 0.31 |
| **– Intrahepatic only** | 56 (25%) | 9 | 56 | 41 (19%) | 77 | 15 (7%) | 38 | < 0.01 |
| **– Intrapulmonary only** | 61 (28%) | 11 | 91 | 41 (19%) | 103 | 20 (9%) | 61 | < 0.01 |

TTR, time to recurrence; m, median; OS, overall survival.

# Single-slide histology-based deep learning model for mismatch repair deficiency prediction in colorectal cancer.

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**Background:** Mismatch repair deficiency (dMMR) is a critical predictive biomarker for determining eligibility and response to immunotherapy in colorectal cancer (CRC). The current gold standards for detecting dMMR include next-generation sequencing (NGS) for microsatellite instability (MSI) detection and immunohistochemistry (IHC) for mismatch repair protein expression. However, discrepancies between these techniques have been observed, potentially impacting clinical decisions and patient outcomes. To address this, we developed a histology-based deep learning (DL) model to predict MMR status, with a specific focus on resolving cases of discordance. **Methods:** Paired hematoxylin and eosin (H&E) slides from 974 CRC tumors were retrospectively collected from the Dana-Farber Cancer Institute, all of which had NGS Oncopanel and IHC MMR reports available. Using NGS-determined MMR status as the training reference, we developed a multi-instance deep learning model to predict MMR status from single H&E slides. Feature extraction employed various pathology foundation models (FMs). The dataset was split into training and tuning sets. A hold-out test set (n = 52, 65% dMMR) was curated including patients treated with immune checkpoint inhibitors or those with NGS-dMMR/IHC-proficient discordance. **Results:** Among the overall cohort, NGS/IHC concordance identified 82 dMMR patients (9%), 881 proficient MMR (pMMR) patients (90%), and 11 cases (1%) with NGS-dMMR/IHC-proficient discordance. In the hold-out test set, the fine-tuned CTransPath FM demonstrated the highest performance, achieving an area under the curve (AUC) of 0.88 (95% CI 0.77–0.98), a positive predictive value of 0.93, and correctly classifying 8 of 11 discordant cases (73%) as dMMR. Comparative FMs, CONCH and UNI, exhibited slightly lower AUCs (0.86 and 0.85, respectively) and lower accuracy in classifying discordant cases (Table). **Conclusions:** Our histology-based DL model shows promise as a complementary tool for IHC in predicting dMMR status in CRC. The single-slide approach offers a rapid, robust and cost-effective method to prioritize IHC-proficient cases for further validation by NGS. Cohort expansion and validation in an external dataset are underway. Research Sponsor: Norwegian Cancer Society.

**Test set (n=52, 65% dMMR).**

| Model | AUC (CI,95%) | Sensitivity | Specificity | PPV | NPV | Accuracy NGS+/IHC- |
|---|---|---|---|---|---|---|
| **CTransPath** | 0.88 (0.77-0.98) | 0.85 | 0.89 | 0.93 | 0.76 | 8/11 |
| **CONCH** | 0.86 (0.76-0.96) | 0.88 | 0.76 | 0.67 | 0.93 | 5/11 |
| **UNI** | 0.85 (0.74-0.96) | 0.78 | 0.82 | 0.70 | 0.87 | 6/11 |

# Time to treatment initiation (TTI) in patients with colorectal cancer and liver metastases.

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**Background:** In colorectal cancer (CRC), the liver represents a common site of metastatic disease, and patients with colorectal liver metastases (CRLM) may sometimes still achieve surgical resection of hepatic metastases. In oncology, delays initiating cancer treatment usually correspond with worse outcomes, yet factors associated with time to treatment initiation (TTI) in patients with CRLM remain unstudied. **Methods:** We utilized the National Cancer Database (NCDB) to identify adults (≥18 years old) with confirmed CRLM diagnosed between 2010-2021. We defined TTI as the number of days between cancer diagnosis and the first non-surgical treatment (radiation, immune, or chemotherapy). We excluded cases in which TTI equaled zero or exceeded 120 days. We compared median TTI across sociodemographic (i.e., age, race, income) and clinical (i.e., primary tumor site, tumor grade, comorbidities [Charlson-Deyo score]) factors reported in the NCDB using a non-parametric Kruskal-Wallis test. **Results:** We included 15,456 patients with CRLM diagnosed between 2010-2021 (55.1% of patients age < 60 years, 44.8% female, 76.3% White, 12.3% Black, 6.3% Hispanic, 3.6% Asian, 0.3% American Indian, 1.2% Other). The median (m) TTI for this cohort was 41 days, with TTI values trending down between subsequent years from 2010 (m = 45) to 2020 (m = 38) until 2021 (m = 41). We found significant differences ($p < 0.0001$) in median TTI across sociodemographic and clinical factors, as detailed in the following sentences. Advanced age (80+) had longer TTI (m = 53), compared with young patients (m = 33). For race/ethnicity, Black patients (m = 47) had the longest TTI, while Asian patients had the shortest (m = 39). Patients earning in the highest income quartile had the shortest TTI (m = 38) compared with those earning in the lowest quartile (m = 44). Patients living in ZIP codes with the highest quartile of high school diploma attainment had the lowest TTI (m = 38) compared with those in the lowest quartile (m = 43). TTI varied significantly by reported geographic location, with the Pacific region having the lowest (m = 37) and the East South Central having the highest TTI (m = 44). Patients with Charlson-Deyo comorbidity scores of 2 had the highest TTI (m = 48) and patients with scores of 0 the lowest (m = 41). Right sided primary tumor locations (m = 46) had longer TTI compared to left sided primary sites (m = 39). Tumor sizes greater than 6 cm (m = 45) received treatment later than tumor sizes less than 2 cm (m = 35). Lower grade tumors had longer TTI (m = 34) compared to high grade tumors (m = 28). **Conclusions:** In our study of patients with CRLM in the NCDB, the median TTI was just under 6 weeks. Our findings suggest that certain patient groups may be at risk of experiencing delays in care. These results could help to motivate and inform future efforts to enhance care delivery and access for patients with CRLM. Research Sponsor: None.

# Immune checkpoint inhibitor (ICI) reuse after failure of first-line ICI in patients with metastatic dMMR/MSI gastrointestinal cancers: The INFLATE study.

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**Background:** Immune checkpoint inhibitors (ICIs) are a standard treatment for gastrointestinal (GI) cancers with mismatch repair deficiency (dMMR) or microsatellite instability (MSI). However, around 50% of patients develop resistance to ICIs, during treatment or after discontinuation. In these patients, the efficacy of reuse an ICI in patients progressing during a previous ICI (rechallenge), or in patients who progressed after discontinuation (reintroduction), remains unknown. The INFLATE study evaluates the efficacy of ICI reuse in patients who progressed on or after discontinuing ICI. **Methods:** This is a multicenter international retrospective study from the IMMUNODIG cohort, including patients from 34 centers in France, the United States, Italy, Belgium and Spain. All patients received ICI for dMMR/MSI GI cancer. We analyzed patients who had progressed following initial ICI (ICI-1) and subsequently received a rechallenge or a reintroduction with ICI (ICI-2), either monotherapy (mono-ICI) or biotherapy (bi-ICI). **Results:** A total of 77 patients were included, receiving bi-ICI (N = 34) or mono-ICI (N = 43) during ICI-2. The majority (76%) had a metastatic colorectal cancer. The reason for discontinuing ICI-1 was disease progression in 53% of cases, end of treatment in 15%, toxicity in 5% and other reasons in 26%. Patients who discontinued ICI-1 due to progression received MONO-ICI-2 in 29% of cases and BI-ICI-2 in 71%, whereas those who stopped for other reasons received MONO-ICI-2 in 86% and BI-ICI-2 in 14% of cases. Efficacy results are shown in Table 1. The ORR and DCR were 26% and 79% with MONO-ICI-2, and 16% and 71% with BI-ICI-2. Among patients who discontinued ICI-1 due to progression, BI-ICI-2 (N = 29) achieved an ORR and DCR of 8% and 65%, with a median PFS of 5.5 months (95%CI 4.07-10.4). These outcomes were 17%, 67%, and 3.7 months (95%CI 2.37-NA), respectively, with MONO-ICI-2 (N = 12). For patients who discontinued ICI-1 for reasons other than progression, BI-ICI-2 (N = 5) achieved an ORR and DCR of 60% and 100%, with a median PFS not reached (95%CI 11.5-NR), while MONO-ICI-2 (N = 31) achieved 29%, 82%, and 14.2 months (95%CI 11.2–NR), respectively. **Conclusions:** This is the first multicenter real-world study evaluating ICI reuse in dMMR/MSI GI cancers. In patients who discontinued ICI for reasons other than progression, reintroduction of ICI therapy upon progression achieves tumor control in 85% of cases. In cases of progression on mono-ICI, Bi-ICI re-challenge achieve tumor control in two-thirds of cases and might be to consider in some patients. Research Sponsor: None.

| | ORR % | DCR % | PFS median (95%CI) | OS median (95%CI) |
|---|---|---|---|---|
| **Overall N=77** | 21 | 76 | 7.65 months (5.5–11.5) | 27.6 months (22.2–55.7) |
| **Discontinued ICI-1 due to Progression N=41** | 11 | 68 | 5.03 months (3.7–8.05) | 26.7 months (21.1–NR) |
| **Discontinued ICI-1 for Other Reasons N=36** | 33 | 85 | 14.22 months (11.24–NR) | 27.6 months (22.2–NR) |

# Comparison of *MET* genomic alterations (GA) identified in colorectal cancer (CRC) vs gastric cancer (GCA).

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**Background:** MET signaling promotes tumor progression and therapeutic resistance across many solid tumors through diverse oncogenic signaling pathways. While MET-targeted therapies are approved in non-small cell lung cancer with novel agents in clinical trials for tumors with *MET* exon 14 splice site mutations, *MET* amplifications, and MET expression, their role in CRC and GCA is still emerging. We aim to understand the co-mutation landscape and genomic context of MET alterations across a large cohort of CRC and GCA cases to identify potential therapeutic targets. **Methods:** FFPE blocks of clinically advanced CRC (50,500 cases) and GCA (9,566 cases) were analyzed by hybrid capture-based comprehensive genomic profiling (CGP) that evaluated all classes of genomic alterations (GA). MSI-high status, tumor mutational burden (TMB), genomic ancestry, mutational signature, and homologous recombination deficiency signature (HRDsig) were assessed for patients with activating *MET* GA. PD-L1 expression was determined by IHC (Dako 22C3 with TPS scoring system). Results were compared using the Fisher exact test with the Benjamini-Hochberg adjustment. **Results:** MET GA (METmut) were more frequently identified in GCA than CRC (4.4% vs 1.0%; $p < .0001$). Median ages were similar in all groups with MET altered CRC and GCA. Median GA per tumor was higher in the METmut cases in both tumor types ($p > .0001$ for both). MSI-high status was less frequent in METmut GCA (1.7% vs 5.5%; $p = .001$) compared with METwt tumors. CRC cases featured higher frequencies of TMB > 10 mutations/Mb in both METmut and METwt groups ($p < .0001$ for all comparisons). Low level PD-L1 expression (1-49% TPS) was higher in CRC than GCA, but similar within tumor type across METmut and METwt tumors. METmut CRC had lower frequencies of GA in *KRAS* (34.7% vs 48.8%; $p < 0.0001$) which was also found in GCA (6.6% vs 16.9%; $p < .0001$). *CDK6* GA were more frequent in GCA than CRC and also were more frequent in METmut cases in both tumor types (19.6% vs 5.2% in GCA and 10.2% vs 0.6%; $p < 0.0001$). *ERBB2* GA were more frequent in both METmut and METwt GCA (13.5% vs 13.8%; NS) than CRC (9.6% vs 5.2%; $p = 0.0004$). *TP53* GA were more frequent in METmut vs METwt CRC (84.1% vs 75.9%; $p < 0.0001$) and GCA (81.8% vs 60.8%; $p < .0001$). BRAF V600E GA were identified in 5.9% METmut CRC and 8.4% METwt CRC ($p = .051$). BRAF V600E GA were uncommon in both METmut and METwt GCA (0.2% vs 0.4%; $p = 1.0$). **Conclusions:** This large-scale analysis reveals distinct genomic profiles of MET-altered tumors in CRC and GCA, characterized by lower prevalence of *KRAS* and MSI-high status, with enrichment for *CDK6*. These molecular differences suggest distinct biologic subsets that could inform patient selection and rational drug combination strategies for novel MET-targeted therapies. Research Sponsor: None.

# The role of gut microbiome composition in the IBD-CRC pathway: A retrospective study of 428 patients.

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**Background:** The progression from inflammatory bowel disease (IBD) to colorectal cancer (CRC) is a significant clinical challenge, driven partly by inflammation and dysbiosis of the gut microbiome. This study aimed to investigate the relationship between gut microbiome composition, systemic inflammation, and CRC risk in patients with IBD. A secondary aim was to evaluate the potential protective effects of microbial diversity and specific bacterial taxa in mitigating CRC progression. **Methods:** This retrospective study analyzed data from 428 patients with a confirmed diagnosis of IBD, of whom 162 (37.9%) were diagnosed with CRC. Stool samples collected within one year of diagnosis were subjected to 16S rRNA gene sequencing to characterize microbial composition and diversity. Alpha and beta diversity indices were calculated to evaluate microbial richness and community dissimilarity, respectively. Specific microbial taxa, including Bacteroides fragilis, Escherichia coli, and Akkermansia muciniphila, were quantified due to their established roles in inflammation and carcinogenesis. Inflammatory biomarkers, including C-reactive protein (CRP), fecal calprotectin, IL-6, and IL-17 were measured from serum and stool samples. Clinical data, including demographics, disease duration, staging, and treatment history, were obtained from electronic medical records. Multivariate regression models were used to determine associations between microbial profiles, inflammatory markers, and CRC risk, adjusted for confounders such as age, sex, BMI, and immunosuppressive therapy. **Results:** Patients with CRC demonstrated reduced gut microbial diversity compared to IBD patients without CRC (Shannon Index: $2.3 \pm 0.4$ vs. $3.1 \pm 0.5$; $p < 0.001$). Dysbiosis in CRC patients was marked by an overrepresentation of pro-inflammatory bacteria (Escherichia coli and Bacteroides fragilis) and a depletion of protective taxa (Akkermansia muciniphila and Faecalibacterium prausnitzii). Pro-inflammatory biomarkers, including CRP ($14.2 \pm 3.6$ mg/L vs. $6.7 \pm 2.1$ mg/L; $p < 0.001$) and fecal calprotectin ($378.5 \pm 85.2$ μg/g vs. $215.3 \pm 64.7$ μg/g; $p < 0.001$), were elevated in patients with CRC. Regression analyses revealed that reduced microbial diversity (OR: 2.87, 95% CI: 1.92–4.28) and the presence of specific pathogenic taxa (Bacteroides fragilis: OR: 3.12, 95% CI: 2.03–4.79) were independently associated with increased CRC risk. Conversely, patients with higher relative abundances of Akkermansia muciniphila exhibited lower levels of inflammation and reduced CRC risk (OR: 0.52, 95% CI: 0.35–0.76), likely due to its role in maintaining mucosal integrity and modulating immune responses. **Conclusions:** This study underscores the critical role of gut microbiome composition in the IBD-CRC pathway, and highlights the need for microbiome-targeted interventions to prevent CRC progression in patients with IBD. Research Sponsor: None.

# Clinicogenomic landscape and outcomes of metastatic colorectal cancer patients with pathogenic *GNAS* variants.

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**Background:** Colorectal cancer (CRC) is a leading cause of cancer-related mortality, with 20-25% of cases presenting with metastatic disease (mCRC). Pathogenic variants in the *GNAS* gene, which encodes the stimulatory alpha subunit of the G protein complex, are found in 1.5% to 4.8% of CRC cases and are more prevalent in mucinous adenocarcinomas. Presence of these mutations have been associated with a lower likelihood of regression following first-line (1L) systemic therapy. However, the specific impact of *GNAS* mutations on treatment (tx) outcomes and overall survival in mCRC patients (pts) remains under investigation. **Methods:** We retrospectively analyzed de-identified data from 5,967 pts with stage IV mCRC treated with 1L oxaliplatin-based chemotherapy in the Tempus Database. Samples were sequenced with the Tempus xT (648-gene panel) or xF DNA assay (105 or 523 genes depending on version) and were divided into *GNAS* wild-type (GNASwt) and *GNAS* mutated (GNASmut) groups. Tumor mutational burden (TMB) and microsatellite instability (MSI) were calculated. Short variant pathogenic/likely pathogenic mutations and copy number alterations were analyzed for patients that underwent xT testing. Real-world (rw) objective response rate (rwORR) was defined as the proportion of pts with a documented complete or partial response within 90 days of tx start. Rw overall survival (rwOS) was defined as the time from 1L start to death from any cause. Hazard ratio (HR) was calculated using a Cox proportional hazards model and p-values were calculated using the Wald test. **Results:** The study included 5,854 *GNAS*wt and 113 *GNAS*mut mCRC pts (prevalence *GNAS*mut = 1.9%). *GNAS*mut pts exhibited higher prevalence of mucinous adenocarcinoma (26% vs. 2.8%) and peritoneal metastases (51% vs. 22%, $p < 0.001$), while liver metastases were more prevalent in the *GNAS*wt group compared to the *GNAS*mut group (77% vs 51%, $p < 0.001$). *KRAS*, *ARID1A*, *MSH2/3/6*, and *ATR* were more frequently altered in the *GNAS*mut group, while *TP53* and *APC* mutations were more frequent in the *GNAS*wt group. Immunophenotype markers such as high TMB and high MSI were also more often observed in the *GNAS*wt pts compared to *GNAS*mut pts ($p < 0.001$). rwORR was significantly lower in *GNAS*mut pts compared to *GNAS*wt (42% vs. 66%, $p = 0.002$). Pts with *GNAS*mut had reduced rwOS compared to pts with *GNAS*wt (HR = 1.31, $p = 0.05$). **Conclusions:** mCRC pts with pathogenic *GNAS* variants exhibit distinct clinicogenomic features and poorer outcomes with first-line oxaliplatin-based chemotherapy compared to *GNAS*wt pts. These findings highlight the need for alternative tx and further research on *GNAS* as a prognostic biomarker in mCRC. Research Sponsor: Tempus AI.

# Clinicopathologic features of complement activation signatures in colorectal cancer.

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**Background:** Activation of the complement cascade pathway is associated with pro-oncogenic inflammation and immune-suppressing, myeloid-derived M2 macrophages for many solid tumors. Most colorectal cancers (CRC) are microsatellite stable that do not respond to immunotherapy. The role of complement activation (CA) in the "immune cold" CRC phenotype remains poorly detailed. We sought to identify molecular annotations of CRC subpopulations enriched for CA to guide future therapeutic strategies. **Methods:** CRC tumors from 207 patients with stages II-IV CRC at MDACC underwent bulk RNA sequencing. Transcriptomes were analyzed per GSEA "Hallmark Complement" gene set to assign a normalized enrichment score (NES) for CA to each patient and considered "complement high" ("CH"; N = 103) or "complement low" ("CL"; N = 104) if the complement NES score was above or below the median. Associations between CA and clinical and pathologic characteristics - e.g., demographics, mutation status, and Consensus Molecular Subtype (CMS) - were evaluated by chi-squared analysis. Single cell RNA (scRNA) sequencing was performed on a separate cohort of CRC primary tumors (N = 85) and liver metastases (N = 60) to compare CA among different cell types using a Wilcoxon's test. To assess for an association between CA and response to immunotherapy in a previously annotated clinical trial of patients with MSS, $BRAF^{V600E}$ metastatic CRC (NCT04017650), we evaluated pretreatment biopsies by bulk RNA sequencing and compared transcriptomic differences in CA between responders versus non-responders to encorafenib, cetuximab, and nivolumab (E+C+N). **Results:** CH CRC featured a higher prevalence for MSI-H CRC (21.3% vs 4.2%; p = .005), CMS1 (30.1% vs 6.7%; $p < .001$), and CMS4 (26.2% vs 7.7%; $p < .001$) relative to CL CRC. CMS2 was more common among CL CRC (54.8% vs 14.6%, $p < .001$). CH CRC was associated with $BRAF^{V600E}$ mutations (29.7% vs 9.2% for CL, p = .002) but not with *KRAS/NRAS* mutations or $RAS/BRAF^{wild\text{-}type}$ CRC (p = n.s. for both). On scRNA analysis, CA scores were highest in myeloid cells and lowest for B cells ($p < .0001$). Among patients with MSS, $BRAF^{V600E}$ CRC, CH signature was associated with non-response to E+C+N (fold-change 3.0 relative to responders, p = .046). **Conclusions:** Association of CH status with MSI-H CRC is a novel finding that warrants further study in understanding differential patterns of benefit to immune checkpoint blockade. CH CRC, associated uniquely with $BRAF^{V600E}$ CRC, was distributed bimodally across the immune-activated CMS1 and the immune-suppressing CMS4 CRC, similar to known transcriptomic heterogeneity of $BRAF^{V600E}$ CRC. Our data suggest high CA, linked to immune-suppressing myeloid cell subpopulations, as a negative predictive biomarker for response to immunotherapy in MSS $BRAF^{V600E}$ CRC and support broader study of complement-targeting agents to improve treatment for selected patients with CRC. Research Sponsor: None.

# Impact of SARS-CoV-2 mRNA-BNT162b2 vaccination on survival outcomes in metastatic colorectal cancer patients treated with bevacizumab-based therapy.

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**Background:** Colorectal cancer (CRC) is a leading cause of cancer-related mortality worldwide. Bevacizumab, an anti-vascular endothelial growth factor (VEGF) antibody, is widely used in metastatic CRC (mCRC) treatment to inhibit tumor angiogenesis and modulate the immunosuppressive tumor microenvironment. Recent evidence suggests that mRNA-based COVID-19 vaccines, such as SARS-CoV-2 mRNA-BNT162b2, may enhance anti-tumor immune responses. This study aimed to evaluate the impact of SARS-CoV-2 mRNA-BNT162b2 vaccination on progression-free survival (PFS) and overall survival (OS) in mCRC patients treated with bevacizumab-based therapy. **Methods:** This retrospective, single-center study included 92 mCRC patients treated with bevacizumab between June 2021 and October 2024. Patients were divided into vaccinated (n=50) and unvaccinated (n=42) groups. Baseline demographic, clinical, and pathological characteristics were collected. PFS and OS were analyzed using Kaplan-Meier estimates and Cox proportional hazards regression models to identify independent predictors of survival. **Results:** The vaccinated group demonstrated significantly longer median PFS (8.0 months vs. 5.6 months, p=0.010) and OS (39.4 months vs. 17.8 months, p=0.014) compared to the unvaccinated group. Multivariate analysis identified SARS-CoV-2 mRNA-BNT162b2 vaccination as an independent predictor of improved PFS (HR 0.44, p=0.003) and OS (HR 0.39, p=0.018). Vaccinated patients also had a higher proportion of favorable ECOG PS and a lower prevalence of RAS mutations. **Conclusions:** SARS-CoV-2 mRNA-BNT162b2 vaccination was associated with improved PFS and OS in mCRC patients receiving bevacizumab-based therapy, potentially through enhanced anti-tumor immune responses. These findings highlight the potential of mRNA-based vaccines to modulate the tumor microenvironment and improve outcomes in mCRC. Further prospective studies are needed to confirm these results and explore underlying mechanisms. Research Sponsor: None.

# Effect of race/ethnicity on clinical outcomes for metastatic colorectal cancer (mCRC) patients in phase 1 trials: A dual institution experience.

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**Background:** Patients with mCRC who progress on standard of care therapies have limited therapeutic options and are associated with poor prognoses. Phase 1 trials are a valuable resource for these patients, offering novel treatment options. However, the appropriate time of consideration for phase 1 trials remains unclear. We sought to analyze the outcomes in a multi-racial cohort of patients with mCRC enrolled in prospective phase I clinical trials to describe clinical characteristics and gauge efficacy of such trials. **Methods:** We reviewed medical records of patients with mCRC enrolled in phase 1 trials at two institutions from 1999 to 2018 and 2021 to 2024. We collected patient demographics, key clinical characteristics, responses, and deaths. Time on study was calculated as time between first dose of study drug and decision to discontinue study. Overall survival (OS) was calculated as time between the first dose of study drug to date of death or last contact date (censored). Outcomes were analysed by Mantel–Cox test using Prism GraphPad v 10. **Results:** There were 283 enrollments on 66 phase I trials. Median age (range) was: 59 (29-83) years; non-Hispanic whites (NHW, 126; 44.5%), non-Hispanic blacks (NHB, 69; 24.4%), Hispanic (H, 69; 24.4%), Asian (A, 17; 6.0%), and unknown (UNK, 2; 0.7%). Median number of prior therapies was 3 (range 0-11). ECOG performance status was 0, 1, 2, and unknown, among 62 (21.9%), 181 (63.9%), 11 (3.9%), and 29 (10.2%) patients, respectively. Median number of sites of metastases was 3 (range 0-10). Sites of metastases included liver 77.0%, lung 60.1%, lymph nodes 39.9%, peritoneum 24.4%, bone 20.5%, and brain 1.8%. The primary site of cancer for patients on study was colon (84.1%), followed by rectum (11.7%), rectosigmoid (0.7%), and (simply documented as) CRC (3.5%). The median time on study was 1.8 months for all patients, with NHW 1.9 months, NHB 1.8, H 1.7, A 1.6, and UNK 7.4; p = 0.72. The OS was 8.6 months among all patients, and 7.9, 7.8, 8.8, 9.4, and 9.5 months for NHW, NHB, H, A, and UNK, respectively (p = 0.82). Response evaluable patients were n = 236; including complete response (CR, n = 2, 0.8%), partial response (PR, n = 8, 3.4%), stable disease (SD, n = 80, 33.9%), and clinical benefit rate (CBR = CR+PR+SD, n = 90) 38.1%. **Conclusions:** Patients with mCRC enrolled onto phase 1 trials showed CBR of 38.1% and OS of 8.6 months, which is comparable to standard third-line therapies that were available during the time period of this study, thus showing promise for their use in clinical practice. No racial/ethnic variation was observed. There was a non-significant trend towards a lower OS with increase in number of prior lines of therapy. A multivariate model will be presented. Research Sponsor: None.

# Understanding and addressing unmet needs in colorectal cancer: Findings from the Colorectal Cancer Alliance's Patient and Survivor survey.

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**Background:** Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer-related deaths worldwide. Despite advances in survival rates, CRC patients and survivors often face unmet needs, including emotional support, coping strategies, and access to treatment-related information. Beyond physical challenges, patients report emotional distress, disruptions to quality of life (QoL), and difficulty navigating the healthcare system. Even after remission, survivors frequently struggle with lingering psychosocial and physical impacts. **Methods:** The Colorectal Cancer Alliance conducted an IRB-approved cross-sectional survey to assess the needs of CRC patients, survivors, and caregivers. The survey included over 150 questions about demographics, diagnosis experiences, QoL, access to care, and treatment outcomes. Participants (n = 283) were recruited through the Alliance's social media, email campaigns, and online communities to ensure diverse representation. **Results:** The study revealed critical insights into the challenges faced by CRC patients and survivors. The median age group of participants was 46–55. Most respondents (74%) reported difficulty finding someone who could understand and relate to their experience. Furthermore, 41% noted a reduction in support from others after their treatment ended. Many participants faced ongoing challenges, with 54% reporting fatigue and 51% experiencing stress. CRC had a profound impact on several aspects of life: 64% said it negatively affected their career or work life, 58% cited negative effects on their relationship with a spouse or partner, 80% reported a decline in their sex life, and 65% struggled to participate in social activities. Additionally, 51% noted challenges with dating, and 43% indicated that their cancer journey affected their desire to have children. While most patients felt informed before treatment, 46% expressed unmet needs for information on complementary or alternative therapies. These findings highlight the broad and far-reaching effects of CRC on patients and survivors, revealing significant gaps in emotional, psychosocial, and informational support. **Conclusions:** CRC patients and survivors face substantial unmet needs that significantly affect their quality of life and well-being. The Colorectal Cancer Alliance plans to use these insights to develop care programs and targeted support initiatives designed to address these gaps. By tailoring resources to the unique needs of patients and survivors, these efforts aim to improve outcomes and offer hope for a better future for those affected by CRC. Research Sponsor: None.

# Drivers of homologous recombination deficiency (HRD) in metastatic colorectal cancer (mCRC).

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**Background:** HRD is linked to sensitivity to platinum-based chemotherapy and poly (ADP-ribose) polymerase inhibitors across various tumor types. However, the presence of HRD, driver events (such as pathogenic mutations in HR genes or other genomic alterations), and its clinical relevance in mCRC remain underexplored. **Methods:** We performed the VHIO-300 test, an ISO15189 accredited custom NGS panel profiling over 450 genes (including HR-related genes: *ATM, BRCA1, BRCA2, BRIP1, CHEK2 or PALB2*) on 356 Stage IV mCRC patients (corresponding to 247 primary colorectal and 109 to metastatic samples) enrolled in the Vall d'Hebron Institute of Oncology's Molecular Prescreening Program from June 2021 to December 2024. All samples had a tumor cellularity $>$ 40% as per pathologist evaluation. An HR score (sHR) based on genome-wide copy number alterations (CNA) and loss of heterozygosity (LOH) patterns is generated. After cross-validation with Myriad MyChoice, sHR $\geq$ 56 was established based on a cohort of ovarian tumors and used to identify HRD in mCRC tumor samples. **Results:** HRD prevalence was 3.4% in our mCRC cohort (12/356), but, much higher in metastatic lesions, (6.4%, 7/109) than in primary samples (2.03%, 5/247) ($p = 0.05$). In fact, the median sHR between primary (21) vs. metastases (30) in CRC was significantly different ($p < 0.01$). Regarding HR gene status, HR-mutated samples were not significantly within the HRD group ($p = 0.27$) and only 6.5% (2/31) were HRD. Noteworthy, *BRCA2* exhibits a frameshift deletion in a homopolymer stretch, that is a frequent hotspot in microsatellite instable (MSI) tumors, but this event was not found to be associated with HRD. In fact, all HRD tumors (n = 12) were microsatellite stable (MSS). Other frequent alterations in mCRC were studied and *BRAF* mutations were found to be present in 42% of HRD tumors ($p < 0.01$). Inversely, HRD was rare in *KRAS*-mutated samples (0.7%; 1/140) and, in fact, highly correlated with non-HRD status ($p = 0.02$), especially the G12 mutation ($p < 0.01$). Interestingly, CNA profiles also revealed a strong association between the *BCL2L1* loci gain and HRD ($p < 0.01$). Clinically, HRD was not significantly associated with prognostic value nor clinical benefit to oxaliplatin-based combinations. However, the limited sample size and heterogeneous treatment lines restricted robust statistical analysis. **Conclusions:** This study identified a small, yet significant subset of mCRC that displays HRD. sHR and HRD rates were higher in metastatic lesions vs primary tumors, indicating HR scarring could be accumulating over time in some mCRC patients. No clear association between pathogenic HR gene mutations and HRD were found, suggesting the involvement of alternative molecular mechanisms in this process. Frequent co-occurring events, such as *BRAF* mutations or *BCL2L1* gains could be drivers in CRC HRD, and shape, eventually, new therapeutic options for these patients in the metastatic setting. Research Sponsor: None.

# Real-world efficacy of trifluridine/tipiracil and bevacizumab combination according to baseline prognostic factors: The BeTAS study.

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**Background:** The Sunlight Trial demonstrated that trifluridine-tipiracil (FTD/TPI) and bevacizumab (BEV) significantly improved Overall Survival (OS) and Progression-Free Survival (PFS) in patients with pretreated metastatic colorectal cancer (mCRC) after two treatment lines. However, the real-world efficacy and influence of baseline prognostic factors are not fully understood. **Methods:** This retrospective, observational, multicenter study across 18 Spanish hospitals included mCRC patients treated with FTD/TPI+BEV in a real-world setting. Prognostic factors were analyzed, including Tabernero's subgroups, which categorize patients according to time to diagnosis from first metastasis ( $<18$ vs. $>18$ months), number of metastatic sites ( $<3$ vs. $>3$), and liver metastasis (yes vs. no). Patients were grouped into Best (BPC), Good (GPC), and Poor (PPC) prognostic categories. **Results:** 398 patients were treated from July 2019 to December 2024. Median age was 67 years (range 26-92), 65.8% male, and 88.4% had ECOG PS 0-1. 56.3% had RAS mutations. Liver metastases were present in 75.3%, 27.7% had $>3$ metastatic sites, and 28.2% had $<18$ months from diagnosis of first metastasis, resulting in 47.2% of patients categorized as PPC. 67.8% received FTD/TPI+BEV as third-line treatment. ORR was 6.8%, and DCR was 49.9%. With a median follow-up of 14 months, median PFS was 4.9 months (95% CI, 4.1-5.1) and OS was 10.8 months (95% CI, 9.2-12.4). Neutropenia was the most common toxicity, with 33.1% of patients experiencing grade 3-4 neutropenia. OS by ECOG PS 0 vs. 1 vs. 2 was 12.5 vs. 11.1 vs. 5.7 months ($p<0.0001$). PFS by ECOG PS 0 vs. 1 vs. 2 was 5.6 vs. 4.9 vs. 3.5 months ($p=0.102$). OS by BPC vs. GPC vs. PPC was 18.3 vs. 12.8 vs. 7.5 months ($p<0.0001$), and PFS was 7.3 vs. 5.8 vs. 3.7 months ($p<0.0001$). OS in patients with grade 3-4 neutropenia vs. no neutropenia was 17.7 vs. 8.1 months ($p<0.0001$), and PFS was 8.7 vs. 3.9 months ($p<0.0001$). **Conclusions:** Our series confirms the effectiveness of FTD/TPI + BEV in real-world clinical practice, with a median OS of 10.8 months and a median PFS of 4.9 months. The ECOG performance status, Tabernero subgroups, and the occurrence of grade 3-4 neutropenia help identify patients who may obtain the maximum benefit from FTD/TPI + BEV treatment. Interestingly, all subgroups analyzed showed a greater benefit compared to the outcomes previously reported for FTD/TPI monotherapy, highlighting the potential of this combination in clinical practice. Research Sponsor: None.

# Safety and efficacy of ADG126 (an anti-CTLA-4 masking antibody) in combination with pembrolizumab: Updated results of phase 1b/2 study in advanced MSS CRC.

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**Background:** ADG126 is an anti-CTLA-4 IgG1 masked antibody that is preferentially activated in the tumor upon cleavage of masking peptides in the tumor microenvironment. Cleaved ADG126 binds to a unique epitope on CTLA-4, blocks CTLA-4 function, primes T cells and depletes Tregs. ADG126 in combination with pembrolizumab (Pembro) has been evaluated in a Phase 1b/2 clinical trial (NCT05405595) and we have reported outcome in 3L MSS CRC patients (Pts) free of liver metastasis (NLM).[1–4] We update results from additional dose expansion (EXP) in Pts of advanced MSS CRC. **Methods:** This is a Phase 1b/2, open-label, multicenter dose escalation and expansion study. Primary endpoints were safety and tolerability, and early signal of efficacy. Secondary endpoints were PK, ADA, ORR, DCR, DOR, PFS and OS. **Results:** As of Jan.15, 2025, a total of 54 MSS CRC Pts were treated with ADG126/Pembro (200 mg Q3W) in EXP phase across 3 dose levels of ADG126 (Table 1). 18% Pts had ≥ 3 prior therapies and none had prior IO therapy. There was no Grade 4/5 TRAE, and MTD was not reached. Grade 3 TRAEs were dose-dependent: 38% (5/13), 20% (6/30) and 0% (0/11) for 20 mg/kg LD[1], 10 mg/kg Q3W and 10 mg/kg Q6W cohorts, respectively. The discontinuation rate remains low for the EXP cohorts (6%). The ORR, CBR, mPFS and 12-mon OS of MSS CRC Pts without liver and peritoneal metastasis (NLPM) are listed in Table 1. ORR increased as a function of ADG126 dose. Although 10 mg/kg Q6W/Pembro did not yield PR, all 6 EE Pts remain on study (1 on treatment) at 18-mon of follow-up. Correlation between dose level/regimen, ORR, CBR and mPFS between 10 mg/kg Q6W and Q3W cohorts has been observed. mOS is not reached for 10 mg/kg Q3W NLPM after 15.5-mon follow up. Longer term efficacy data from 20 mg/kg LD cohort will be reported. **Conclusions:** Dose-dependent ORR has been observed for ADG126/Pembro IO doublet across multiple dose levels/regimens of ADG126 (10 mg/kg Q6W to 20 mg/kg LD) that is associated with well-tolerated to acceptable safety profile, which is enabled by a relatively large therapeutic window. The overall performance of ADG126/Pembro IO doublet warrants further clinical development including combination with SOCs targeting earlier lines/broader populations, such as MSS CRC with liver metastasis. Clinical trial information: NCT05405595. Research Sponsor: Adagene Inc.

**Key efficacy results from MSS CRC patients.**

| | ADG126 Dose/Pembrolizumab (200 mg, Q3W) | | | |
|---|---|---|---|---|
| | 10 mg/kg Q6W | 10 mg/kg Q3W | 20 mg/kg LD[1] | Total # |
| **Safety Evaluable** | 11 | 30 | 13 | 54 |
| **Efficacy Evaluable (NLPM)** | 10 (6) | 29 (22) | 12 (12) | 51 (40) |
| **MSS CRC NLPM≥≥>=** Objective Response Rate (ORR) | 0 | PR = 23% (5/22)[2] (CI: 8-45) | PR = 33% (4/12)[3] (CI: 10-65) | NA |
| 6-mon CBR% | 33% | 55% (CI: 32-76%) | NM | NA |
| mPFS (mon) | 5.9 | 6.7 (CI: 4.6-9.0) | NM | NA |
| 12-mon OS | 100% | 75.1 (CI: 50-89%) | NM | NA |

[1]20 mg/kg LD: ADG126 20 mg/kg x1 cycle followed by 10 mg/kg Q3W. [2]Including 1 unconfirmed PR. [3]All confirmed. CI: 95% confidence interval (report for n >=12 Pts cohort). NM: data not mature. NA: not applicable.

# Real-world treatment patterns and outcomes with trifluridine/tipiracil monotherapy or in combination with bevacizumab in metastatic colorectal cancer.

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**Background:** Trifluridine/tipiracil (FTD-TPI; Lonsurf) is an oral antineoplastic agent approved for 3rd-line use in combination with or without bevacizumab (BEV) in metastatic colorectal cancer (mCRC). In the Phase III SUNLIGHT trial, the addition of BEV to FTD-TPI was associated with a significant improvement in overall survival (OS) and progression-free survival (PFS) compared to FTD-TPI monotherapy. However, data on the use of FTD-TPI in combination with BEV in the real-world community setting are currently limited. **Methods:** This was a retrospective observational study involving electronic medical records and (where available) chart reviews from mCRC patients treated by the Texas Oncology community practice from Jan 2020 to Oct 2024. Patients had to have received FTD-TPI with or without BEV after progressing on a prior line of therapy with oxaliplatin and irinotecan. Variables included patient characteristics, clinical characteristics, treatment patterns and clinical outcomes. OS and time to next treatment or death (TTNTD) were analyzed using the Kaplan-Meier method. **Results:** In total, 265 patients were included (166 FTD-TPI + BEV; 99 FTD-TPI monotherapy), with the majority receiving FTD-TPI as 3rd-line (83%; n = 220) or 4th-line (14%; n = 38) therapy. The population was 59% male, 66% white, and 35% were ≥65 years of age. The most common previous 1st- and 2nd-line treatment for 3rd-line FTD-TPI patients was chemotherapy + an antiangiogenic (1st-line, 67%; 2nd-line, 74%), which was similar regardless of current BEV use. Median duration of therapy was 2.8 months (range 0.3 to 12.5) with FTD-TPI + BEV and 2.8 months (range 0.1 to 10.4) with monotherapy. Median OS was 11.6 months with FTD-TPI + BEV and 6.2 months with monotherapy (hazard ratio [HR] = 2.1; 95% confidence interval [CI]: 1.5-3.0; $p < 0.001$). At 6 months, OS probability was 0.69 (95% CI: 0.61-0.77) with FTD-TPI + BEV and 0.50 (95% CI: 0.40-0.63) with monotherapy; 12-month OS probability was 0.49 (0.39-0.61) and 0.15 (0.07-0.28), respectively. Median TTNTD was 9.4 months for FTD-TPI + BEV and 5.8 months for FTD-TPI alone (HR = 1.7, 95% CI: 1.2-2.4; $p < 0.001$). The safety/tolerability profile was generally similar irrespective of BEV use, with the most common adverse events being fatigue/asthenia (73%), abdominal discomfort/pain (55%), and nausea (54%). The most notable difference was neutropenia (37% FTD-TPI + BEV, 27% monotherapy). **Conclusions:** In this large real-world community practice setting in the US, FTD-TPI use in mCRC was mostly in the 3rd-line setting and approximately two-thirds of use was in combination with BEV. Patient characteristics were similar to the SUNLIGHT trial, with high rates of previous antiangiogenic use. A statistically significant and clinically relevant OS benefit was seen with the addition of BEV versus monotherapy consistent with the results of the SUNLIGHT trial. Research Sponsor: Taiho Oncology Inc.

# A phase 1 dose-escalation study of GCC19CART: A novel CAR T-cell therapy for metastatic colorectal cancer in the United States.

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**Background:** GCC19CART, the first clinical candidate of the CoupledCAR solid tumor platform, pairs a solid tumor chimeric antigen receptor (CAR) T-cell with CD19-targeting CAR T-cells. The CD19 target enhances proliferation and persistence of the CoupledCAR, overcoming the limitations seen in other solid tumor CAR T-cells. Guanylate cyclase-C (GCC) is an appealing CAR target due to apical-basal polarity of expression in normal colon, which may hamper on-target effects on the mucosa. GCC is present on nearly all colorectal cancers (CRC). GCC19CART showed promise in a prior trial in China, demonstrating expansion, response, and persistence, consistent with the proposed mechanism. The US phase 1 study was initiated for refractory CRC to assess the safety and efficacy of GCC19CART in this population. **Methods:** Eligible patients underwent leukapheresis, lymphodepleting chemotherapy (fludarabine 30mg/$m^2$ and cyclophosphamide 300mg/$m^2$ on day-3), and a single dose of GCC19CART. Safety was the primary endpoint. Efficacy was assessed by RECIST v1.1 based on local review. **Results:** As of January 23, 2025, 9 patients were treated: 4 at dose-level (DL) 1 (1x$10^6$ cells/kg) and 5 at DL2 (2x$10^6$ cells/kg). Cytokine release syndrome occurred in all subjects (grade [G] 1: 6/9 [66.7%] and G2: 3/9 [33.3%]), and diarrhea was reported in 8/9 (G1: 3/9 [33.3%], G2: 3/9 [33.3%], G3: 2/9 [22.2%]). Immune effector cell associated neurotoxicity syndrome occurred in 2/9 subjects (G2: 1/9 [11.1%], G3: 1/9 [11.1%]). A DL2 patient experienced a dose limiting toxicity (G3 diarrhea, G4 enterocolitis, and G5 sepsis) and died 48 days post-infusion. The overall response rate (ORR) in DL1 was 25% (1/4 partial response [PR]) and 80% in DL2 (4/5 with 3 PR and 1 pathological complete response). The PR in DL1 was achieved by month 2, while 3/4 responders in DL2 achieved a PR by month 1, demonstrating dose-dependent tumor-killing activity. Two DL2 patients maintained responses at data cut-off. One patient achieved a complete metabolic response by PET at month 2 and maintained a PR by CT at month 6 with continuous tumor shrinkage (month 1: 38.33%, month 2: 40.77%, month 4: 82.58%, month 6: 75.61%). Another patient maintained a PR at month 6 with progression at month 8. The median progression-free survival (PFS) was 5.0 months in DL1 and 7.8 months in DL2. The median duration of response was 2.2 months in DL1 and 6.9 months in DL2. Compared to the prior trial in China (≥G3 diarrhea: 22.2% vs. 53.3%; ORR: 66.7% vs. 40%, PFS: 7.8 vs 6.0 months in DL2, 5.0 vs 1.9 in DL1. Chen, *JAMA Oncol.*, September 2024), the US study suggests a potential trend towards improved safety and efficacy. **Conclusions:** GCC19CART demonstrated significant clinical activity and durability in refractory CRC. Optimization of diarrhea/colitis management is ongoing. Updated data will be presented. Clinical trial information: NCT05319314. Research Sponsor: None.

# Impact of obesity and lifestyle-associated risk factors on outcomes of early-onset colorectal cancer in patients younger than 50 years old: A propensity-matched analysis.

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**Background:** Early-onset colorectal cancer (CRC) incidence is rising in individuals under 50 years old. This study aims to understand the factors influencing outcomes in this population. We evaluated the impact of obesity and other lifestyle-associated risk factors, such as smoking, alcohol use, and diabetes mellitus, on outcomes in patients with early-onset CRC. **Methods:** A comprehensive retrospective cohort study using the TriNetX database identified adults aged 18–49.9 diagnosed with CRC. Using propensity score matching (PSM), we compared patients with obesity (body mass index [BMI] $\geq$30 kg/m$^2$) and other lifestyle-associated risk factors (smoking, alcohol use, and diabetes mellitus) to those without any risk factor, while accounting for demographics, comorbidities, and treatment. The primary outcome is the 10-year mortality in obese patients as compared to non-obese patients. Secondary outcomes included the 10-year mortality in patients with other lifestyle-associated risk factors. **Results:** A total of 10,220 matched pairs of obese and non-obese patients were included. Before matching, obese CRC patients were older, more likely to be male, Hispanic, or non-Hispanic Black, and had higher rates of colonoscopy, surgery, and comorbidities ($p < 0.001$). After PSM, obese CRC patients had significantly lower odds of 10-year mortality compared to non-obese patients (7.9% vs. 14%; adjusted odds ratio [aOR] = 0.53; 95% confidence interval [CI]: 0.47–0.60). Diabetes, smoking, and alcohol use showed no significant association with 10-year mortality in patients with early-onset CRC (e.g., diabetes: aOR = 0.96; 95% CI: 0.73–1.26). **Conclusions:** Our study suggests that obesity may confer a protective effect on 10-year mortality in patients with early-onset CRC, whereas other lifestyle-associated risk factors showed limited-to-no significant impact. These findings underscore the need for targeted strategies to improve access to CRC screening and treatment, particularly in younger patients with obesity, and they also open up new avenues for research into the potential mechanisms underlying these associations. Prospective studies are warranted to validate these results and explore these potential implications, further enriching our understanding of this complex disease and potentially leading to novel approaches for its management. Research Sponsor: None.

| | Incidence % (N) | | Propensity score matching analysis |
|---|---|---|---|
| **Lifestyle risk factors** | CRC< 50 + risk factor | CRC<50 - risk factor | Adjusted odds ratio (aOR)* [95%CI] |
| **Obesity (BMI ≥ 30)** | 7.9% (406) | 14.0% (714) | 0.53 [0.47 - 0.60] |

Propensity matching analysis assessing the odds of 10-year mortality when comparing patients with early-onset colorectal cancer (< 50 years) with lifestyle-associated risk factors (e.g., obesity (N=5110) compared to equal numbers of patients without lifestyle-associated risk factors.

# Colorectal cancer mortality dynamics: Uncovering critical disparities in U.S. population health (2018–2023).

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**Background:** Colorectal cancer(CRC) remains the third leading cause of cancer-related deaths in the United States, with a disproportionate burden on underserved populations. Despite established screening protocols and preventive measures, fewer than 35% of cases are detected early, significantly impacting survival rates. This study examines mortality patterns across demographic and geographic divides, revealing urgent public health priorities. **Methods:** This retrospective analysis was performed in adults aged 25 and older using the CDC WONDER database (2018-2023) using ICD-10 codes. We stratified mortality data by age, gender, race, geographic region and urbanization level to identify critical disparities and emerging trends. Crude mortality rates (CMRs) and Age-adjusted mortality rates (AAMRs) per 100,000 were calculated by age, gender, region and race, with 95% confidence intervals (CI) for precision. Temporal trends and annual percentage changes (APCs) were analyzed using Joinpoint regression. **Results:** From 2018 to 2023, among 313,744 deaths, mortality increased from 51,891 to 53,497, while the AAMR for CRC consistently declined from 12.92 to 12.44. The highest CMR was in the 85+ group (156.11 per 100,000, 95% CI: 153.05–159.17), followed by 75-84 (74.18, 95% CI: 72.87–75.49), 65-74 (40.27, 95% CI: 39.58–40.96), and 55-64 (23.83, 95% CI: 23.37–24.30). The 45-54 group had a CMR of 11.74 (95% CI: 11.40–12.07), the 35-44 group 3.56 (95% CI: 3.38–3.74), the 25-34 group 0.77 (95% CI: 0.69–0.86), and the 15-24 group had the lowest at 0.09 (95% CI: 0.06–0.12). Males had a higher CMR of 17.23 per 100,000 (AAMR: 15.19, APC: -0.68, p = 0.21) than females, who had 14.42 per 100,000 (AAMR: 10.69, APC: -0.30, p = 0.56). The Midwest had the highest AAMR at 13.33 per 100,000 [APC: -0.78 (95% CI: -2.54 to 1.01, p = 0.31)], followed by the South at 13.54 [APC: 0.05 (95% CI: -0.80 to 0.92, p = 0.91)], the West at 11.90 [APC: 0.09 (95% CI: -0.79 to 0.95, p = 0.82)], and the Northeast at 11.54, with a significant decline in trends [APC: -1.90 (95% CI: -3.24 to -0.58, $p < 0.01$)]. Large central metro areas accounted for 25.3% of deaths (83,341), followed by large fringe metro areas (22.4%), medium metros (19.9%), micropolitan areas (10.0%), small metros (9.4%), and noncore areas (8.2%). Racial disparities showed White individuals with the highest CMR at 17.01 per 100,000 (AAMR: 12.69, APC: -0.78), while Black or African American individuals had a slightly lower CMR at 15.70 per 100,000 but the highest AAMR at 16.18 (APC: -1.63, $p < 0.01$), followed by American Indian or Alaska Native, Asian, Native Hawaiian, and other groups. **Conclusions:** These findings reveal critical gaps in CRC prevention and care, disproportionately affecting young adults, males, and minorities. Public health initiatives must expand screening, improve access to care, and address regional inequities to reduce mortality and promote health equity. Research Sponsor: None.

# Analytic and clinical validation of a negative prediction algorithm for actionable mutations utilizing genomic and epigenomic profiling in cfDNA.

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**Background:** One challenge in cell-free DNA (cfDNA) profiling for genomic tumor profiling is the inability to confidently confirm the absence of actionable genomic mutations. This limitation arises from the challenge of determining whether key driver mutations are truly absent or if tumor levels are below the detection threshold of the assay. Accurate negative variant prediction could enable clinicians to expedite clinical decisions based on cfDNA results without relying on tissue biopsy sequencing when no actionable alterations are found. Here, we report analytic and clinical validation of a novel algorithm to enable negative prediction from liquid biopsy to address this critical clinical need. **Methods:** Using the Guardant Infinity platform, which simultaneously profiles genomic and epigenomic signals in a single sample, we integrated highly sensitive and precise tumor fraction estimates and developed a negative prediction algorithm to allow for confident reporting of samples that do not detect an actionable genomic finding. The algorithm estimates the post-test probability of a cfDNA sample harboring genomic biomarkers with FDA approved therapies relevant to treatment selection, based on population priors, epigenomic tumor fraction (TF), and the analysis of mutant and non-mutant coverage across variants of interest which was assessed for advanced colorectal (CRC) and lung cancer (NSCLC) patients. **Results:** In 3973 CRC and 7654 NSCLC analyzed patients, 41% of CRC and 22.6% of NSCLC were found to have an actionable mutation. Among the remaining samples, 66% of CRC and 56.3% of NSCLC had sufficient tumor fraction to assess the sample as variant negative with $>$ 95% confidence. Reasons why the remaining samples could not be confidently assessed included low tumor shedding (including 15% with nondetectable tumor), low genomic coverage over loci of interest, and mutant allele support below the confident call threshold. An additional cohort of 237 CRC and 316 NSCLC patients with paired tissue and cfDNA results was used to clinically validate the negative prediction algorithm. All samples with sufficient tumor fraction for $>$ 95% confidence and predicted to be negative by the algorithm for genomic biomarkers with FDA-approved therapies were confirmed to be negative in tissue results. **Conclusions:** A plasma-based epigenomics-based approach for confident negative prediction is feasible in CRC and NSCLC, as demonstrated by validation results. Confident negative prediction has the potential to enhance the utility of liquid biopsy and accelerate clinical decision-making in advanced solid tumors with biomarker-guided treatment pathways and should be validated in additional clinical datasets. Research Sponsor: None.

# Cell-free DNA 5-hydroxymethylcytosine profiling for the assessment of colorectal cancer biology and treatment response in blood.

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**Background:** Colorectal cancer is the third most common cancer worldwide, accounting for about 10% of all cancer cases, and is expected to claim more than 50,000 lives in 2025. Approximately 33% of CRC patients will develop metastases throughout their cancer continuum, and their 5-year survival rate is about 15%. The majority of patients with metastatic colorectal cancer (mCRC) cannot be cured. However, a subset of mCRC patients with localized recurrence or isolated metastases in the liver and/or lungs may achieve a cure through surgical intervention. Yet, current methods for identifying patients who are candidates for more favorable responseremain inadequate. Therefore, there is a critical need for predictive biomarkers to accurately identify patients who are likely to experience better outcomes following surgery. 5-hydroxymethylcytosine (5hmC) is an epigenetic modification that is associated with active genes and regulatory regions that are cell type- and disease-specific. Here, we developed a model using cell-free DNA (cfDNA) 5hmC profiles to detect CRC and identified pathways distinguishing mCRC patient outcomes following treatment. **Methods:** Plasma was collected from 294 CRC patients and 588 non-cancer individuals to obtain cfDNA. cfDNA was enriched for 5hmC-containing DNA fragments. Input and 5hmC-enriched cfDNA were subsequently used to generate sequencing libraries to obtain WGS and 5hmC profiles, respectively. Machine learning operating on 5hmC and WGS data was used to develop a CRC detection model which was subsequently tested on an independent set of mCRC (n = 69) and non-cancer samples (n = 70). Differential 5hmC analysis was performed using edgeR and Gene Set Enrichment Analysis (GSEA). **Results:** The performance of the CRC prediction model was evaluated through 10-fold cross-validation producing an auROC curve of 0.86. An independent validation set of mCRC and non-cancer patients displayed an auROC of 0.94. Comparative GSEA using gene body 5hmC levels revealed biological pathways associated with CRC biology such as Myc signaling. cfDNA 5hmC profiling of plasma obtained from mCRC patients before surgery revealed quantitative differences in patients who show recurrence of disease within 2 years post-surgery from the patients who remain recurrence-free for at least 2 years after surgery. These differences between relapsed and non-relapsed groups included 5hmC changes over genes involved in pathways known in mCRC, such as the Wnt/β-catenin signaling ($p < 0.05$). Lastly, quantitative changes in 5hmC profiles measured in pre-surgery plasma samples enabled prediction of disease recurrence in patients within 2 years post-surgery. **Conclusions:** 5hmC analysis of cell free DNA) offers a novel, non-invasive approach for identification of colorectal cancer biology and assessment of treatment response in blood samples. Research Sponsor: ClearNote Health.

# Sintilimab plus bevacizumab, oxaliplatin, and capecitabine as perioperative therapy in microsatellite-stable, resectable colorectal cancer liver metastases: An open-label, single-arm, phase II trial.

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**Background:** Immunotherapy has revolutionized cancer treatment, yet its efficacy in proficient mismatch repair and/or microsatellite stable (pMMR/MSS) colorectal cancer liver metastases (CRLM) remains uncertain. Optimizing neoadjuvant regimens for such patients is crucial. **Methods:** A prospective, open-label, single-arm phase II clinical trial was conducted from June 2021 to January 2023. Patients with resectable pMMR/MSS CRLM were enrolled and received 4 cycles sintilimab combined with bevacizumab, oxaliplatin, and capecitabine preoperatively followed by 4 cycles oxaliplatin, and capecitabine postoperatively. The primary endpoints were safety and feasibility of neoadjuvant therapy and surgery. Secondary endpoints encompassed pathological response rates, objective response rate, progression-free survival (PFS), and overall survival (OS). Biomarker analyses were performed to identify potential predictors related to efficacy and prognosis. The study protocol was registered in ClinicalTrials.gov (NCT04940546). **Results:** Between June 2021 to January 2023, 36 patients were enrolled, and included in the safety analysis. The most common treatment-related adverse events (TRAEs) were fatigue (55.6%), peripheral neuritis (52.8%). Of the 36 patients, 30 received local treatment for liver metastases. 26 of them underwent CRLM surgery resection, and 7 of the 26 experienced surgery - related complications graded from 1-2 such as cholecystitis and pulmonary infection, one patient died from respiratory failure due to a pulmonary infection (immune pneumonia not excluded) a month after liver metastases resection. 34 were analyzed for efficacy. The objective response rate (ORR) was 67.6%, with a disease control rate (DCR) of 88.2%. 26 patients underwent surgery; the pathological complete response rate (pCR) was 11.5%, and the major pathological response rate (MPR) was 38.5%. After a median follow-up of 32.9 months, the median PFS was 14.2 months ( (95% CI: 11.6 - 29.0 months), and the median OS had not yet been reached. Biomarker analysis revealed that *RAS* wild-type (mPFS: 29.0 months (15.0 - NA) vs 11.5 months (9.8 - 15.7), log-rank $P = 0.0087$), *SMAD4* wild-type population (mPFS: 20.2 months (12.3 - NA) vs 6.9 months (5.2 - NA), log-rank $P < 0.0001$) may benifit from immunotherapy combination treatment. The single cell RNA sequencing analysis revealed that higher intrafiltion of FIB_PLAG2A in the TME of CR/PR were associated with favorable prognosis, while higher intrafiltion of MPH_TREM2, FIB_POSTN in the TME of non CR/PR were linked to poor prognosis. **Conclusions:** The neoadjuvant regimen demonstrated acceptable safety and efficacy. *RAS*, *SMAD4* wild-type patients may be a potential beneficiary population. Clinical trial information: NCT04940546. Research Sponsor: Bethune Public Welfare Foundation.

# Safety and efficacy evaluation of neoadjuvant chemoradiotherapy plus thymalfasin and tislelizumab for treating MSS/pMMR locally advanced rectal cancer.

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**Background:** Neoadjuvant chemoradiotherapy is currently the standard strategy for microsatellite stable (MSS) / mismatch repair-proficient (pMMR) locally advanced rectal cancer (LARC) patients. This study aimed to explore the safety and efficacy of combining specific (thymalfasin) and non-specific (tislelizumab) tumor immunotherapy with chemoradiotherapy in MSS/pMMR LARC. **Methods:** This trial is an open, prospective, multi-center, single-arm phase II clinical study assessing the efficacy and safety of neoadjuvant chemoradiotherapy combined with thymosin andtislelizumab in MSS/pMMR LARC. Stage II/III MSS/pMMR LARC patients ($cT_{3-4a}N_0M_0$ and $cT_{1-4a}N_{1-2}M_0$) with the tumor distal location ≤ 10 cm from anal verge at two centers in China were consecutively enrolled. Patients received chemoradiotherapy (50 Gy/25 f, 2 Gy/f, 5 days/week, 5 weeks; plus capecitabine 850-1000 mg/m$^2$, bid, po, 5 days/week, day1-5), thymalfasin (4.8 mg, biw, ih, day 1 and day 4 from week 1-11) and three 21-day cycles tislelizumab (200 mg, iv.gtt, week 2, 5 and 8) as neoadjuvant therapy. Adjuvant therapies after neoadjuvant were nonuniformly specified and decided according to clinical experiences. The primary endpoint is the complete response (CR) rate, defined as the achievement of clinical complete response (cCR) after neoadjuvant therapy or pathological complete response (pCR) after total mesorectal excision (TME). **Results:** From Feb 2024 to Aug 2024, a total number of patients (n = 25) were enrolled and 3 patients were excluded because of T4b and dMMR. Finally, 2 patients were discontinued and 20 completed neoadjuvant therapy. The median age was 67.5 (from 36 to 74) years while the median tumor distal location was6.0 (from 3.5 to 8.5) cm. The CR, PD, and SD rate was 40.0% (8/20), 45.0% (9/20), and 15.0% (3/20) correspondingly, with the ORR rate of 85.0% (17/20). Grade 3 treatment-related adverse events (trAEs) including leukopenia and neutropenia were observed in 1 (5%) patient, while grade 1-2 trAEs were observed in 15(75.0%) patients. As for Dec 31, 2024, the EFS rate was 100% (20/20) with median follow-up time of 18.57 weeks (from 6.86 to 31.86). **Conclusions:** Neoadjuvant chemoradiotherapy plus thymalfasin and tislelizumab show promising anti-tumour activity in MSS/pMMR LARC patients, with manageable toxicities. This study suggests that such combination could be a promising therapeutic strategy for patients with MSS/pMMR LARC. Clinical trial information: NCT06056804. Research Sponsor: Beijing Li Huanying Medical Foundation.

# Neoadjuvant ONO-4578, an EP4 antagonist, in combination with nivolumab after chemoradiation therapy in locally advanced resectable rectal cancer.

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**Background:** Neoadjuvant nivolumab (NIV) after preoperative chemoradiation therapy (CRT) demonstrated promising pathologic complete response (pCR) in patients (pts) with locally advanced resectable rectal cancer (LARC) (Bando, *Clin Cancer Res* 2022). On the other hand, the prostaglandin $E_2$-EP4 signaling is known to induce immunosuppression in tumors. ONO-4578 (4578), an antagonist of EP4, in combination with NIV has shown a manageable safety profile and signs of anti-tumor activity in pts with solid tumors. In this ONO-4578-03 study, we evaluated safety, preliminary efficacy, and biomarkers of 4578 plus NIV after preoperative CRT in pts with LARC. **Methods:** Pts with LARC who received preoperative CRT (50.4 Gy with capecitabine 1,650 mg/m$^2$) were eligible. Pts were divided into two groups for neoadjuvant therapy: 4578 monotherapy lead-in (lead-in) and the combination group. Pts in the lead-in group received 4578 (40 mg, oral, daily) alone for 6 weeks, and then 4578 plus NIV (240 mg, intravenous, every 2 weeks) for 4 weeks, while pts in the combination group received 4578 plus NIV for 10 weeks. Subsequently, pts in both groups received radical resection. The primary endpoint was safety. Secondary endpoint was efficacy, including pCR rate using the AJCC tumor regression grading. Ongoing exploratory endpoints include tissue and blood biomarkers. **Results:** We enrolled 31 pts: 10 and 21 to the lead-in and combination groups, respectively. The median age was 62.0 (range, 39–76) years, 20 pts (64.5%) had a disease stage of III, and all pts were classified as microsatellite stable. The pCR (AJCC grade 0) rates in the lead-in group, the combination group, and overall population were 50.0% (5/10 pts), 23.8% (5/21 pts), and 32.3% (10/31 pts), respectively; the major pathological response (MPR; AJCC grade 0+1) rates were 70.0% (7/10 pts), 71.4% (15/21 pts), and 71.0% (22/31 pts), respectively. Among all pts, any-grade treatment-emergent adverse events (TEAEs) occurred in 23 pts (74.2%). including 3 pts (9.7%) with grade 3 TEAEs (appendicitis, ileus, drug-induced liver injury, hypertension) and 1 pt with serious TEAEs (ileus, drug-induced liver injury). None of the TEAEs led to treatment discontinuation or death. Any-grade treatment-related adverse events (TRAEs) occurred in 11 pts (35.5%), including 1 pt with a serious TRAE (grade 3 drug-induced liver injury). Radical resection was not performed within the protocol-defined window in 1 pt in the lead-in group and in 2 pts in the combination group due to progressive disease, a TRAE (grade 1 hyperthyroidism), or clinical CR, respectively. As of the final analysis, 5 pts experienced recurrence and 1 pts died in the overall population, after the median follow-up of 23.29 (range, 15.9–32.9) months. **Conclusions:** Neoadjuvant 4578 plus NIV after CRT showed a manageable safety profile and promising pCR rates and MPR rates in pts with LARC. Clinical trial information: jRCT2051200096. Research Sponsor: Ono Pharmaceutical Co., Ltd.

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# Single-incision laparoscopic surgery vs conventional laparoscopic surgery for colorectal cancer: Short-term outcomes of a multi-center, randomized, controlled trial.

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**Background:** Single-incision laparoscopic surgery (SILS) is increasingly being embraced in the medical community due to its potential to offer less-invasiveness and quick recovery. This multi-center randomized controlled trial compared the short-term and long-term outcomes of single-incision laparoscopic surgery (SILS) with conventional laparoscopic surgery (CLS) for colorectal cancer, which might be the first of its kind that involved both colon and rectal cancer. Study recruitment has completed, and the follow-up is ongoing. Here we report the short-term outcomes of this trial. **Methods:** The trial was conducted across 11 hospitals in 6 provinces of China. Participants included patients with histologically confirmed colorectal carcinoma that situated above the peritoneal reflection, clinically staged as I-III. Patients were randomly assigned in a 1:1 ratio to SILS or CLS group. Comprehensive perioperative data were meticulously gathered, and follow-up assessments were scheduled postoperatively. The primary endpoint was 3-year disease-free survival (DFS), secondary endpoints included overall survival (OS), oncological efficacy, and postoperative outcomes. **Results:** Between May 2021 and April 2023, a total of 712 patients were randomly assigned to either the Single-incision Laparoscopic Surgery (SILS) group (n = 354) or the Conventional Laparoscopic Surgery (CLS) group (n = 358). The distribution of surgical procedures included 162 (22.8%) right hemicolectomies, 326 (45.8%) left hemicolectomies, and 224 (31.4%) proctectomies. The pathological TNM stages I, II, and III of the mITT population were 10.7%, 36.9%, and 52.4%, respectively. In the SILS group, 92.9% (n = 329) of the cases were completed entirely with a single incision. An additional trocar was used to assist the surgical procedure in 5.6% (n = 20) of the cases, and 0.8% (n = 3) were converted to conventional laparoscopic surgery. Two patients in the SILS group required conversion to open surgery, compared to 10 patients in the CLS group. The incidence of postoperative complications and oncological efficacy were statistically equivalent between the two groups. Moreover, patients in the SILS group reported significantly less postoperative pain (p = 0.02). There were no significant differences in short-term overall survival (OS) and disease-free survival (DFS) between the two arms. **Conclusions:** Single-incision laparoscopic surgery (SILS) for colorectal cancer has demonstrated with feasibility, safety, and efficacy. The less painful postoperative experience was aligned with the principles of Enhanced Recovery After Surgery (ERAS). This surgical approach extended the concept of minimally invasiveness and represents a logical progression towards Natural Orifice Transluminal Endoscopic Surgery (NOTES) or single-incision robotic surgery. Clinical trial information: NCT04527861. Research Sponsor: SHANGHAI HOSPITAL DEVELOPMENT CENTER.

# The association of ctDNA with recurrence in patients with stage II-IV colorectal cancer: The β-CORRECT study.

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**Background:** CRC is a leading cause of cancer-related mortality globally. Detection of molecular residual disease (MRD) is an early indicator of recurrence and may allow for timely intervention. Here, we evaluated an analytically validated tumor-informed ctDNA MRD assay (Oncodetect) in a cohort of patients with CRC. **Methods:** This retrospective study utilized data and specimens from 468 patients with Stage II, III or resectable Stage IV CRC consecutively enrolled from June 1, 2020 through November 30, 2022 in the GALAXY study with available residual samples. Tumor tissue underwent whole-exome sequencing to identify up to 200 tumor-specific variants for designing a personalized MRD test. The test was used to assess ctDNA status in plasma at three timepoints: post-surgical (PS), post-definitive therapy (PDT) and in the surveillance period, which included the PDT and subsequent timepoints. The primary endpoint was the association of ctDNA status during surveillance with disease-free survival (DFS). An analysis of the association between RNA-seq expression and DFS was also planned. **Results:** Analysis included a total of 1648 ctDNA results from 417 patients with ≥1ctDNA result from ≥1 timepoint. Among these patients, 296 (71.0%) had colon and 121 (29.0%) had rectal cancer, 141 (33.8%) had Stage II, 249 (59.7%) Stage III and 27 (6.5%) Stage IV disease, and 255 (61.2%) received adjuvant chemotherapy. Median follow-up was 1.9 years. The median ctDNA level among detections, measured in mean tumor molecules per ml (MTM/ml) was 1.187 (range 0.006-3180.5). During surveillance, ctDNA detection was strongly prognostic for DFS (HR 36.6; CI 21.9 – 61.2; ctDNA status as a time-dependent variable). Similarly, ctDNA detection was strongly associated with DFS at the PS and PDT timepoints (Table). Multivariable analysis showed ctDNA status remained strongly associated with DFS while other clinicopathological factors did not. The median lead time between ctDNA detection and clinical recurrence was 97 days (95% CI: 51-114). RNA-seq analysis is ongoing. **Conclusions:** In a cohort of 468 patients who underwent curative-intent surgery for stage II-IV CRC, a tumor-informed quantitative ctDNA assay using up to 200 variants was strongly prognostic for DFS at all timepoints. The prognostic ability of RNA-seq expression analysis for ctDNA status and outcome in this cohort is currently being determined. Research Sponsor: Exact Sciences; Japan Agency for Medical Research and Development.

**Association of ctDNA status with DFS.**

| | Statistic | Result |
|---|---|---|
| **Surveillance (n= 398)** | HR (95% CI) | 36.6 (21.9 – 61.2), p<0.0001 |
| | Sensitivity (95% CI) | 64.8% (53.2 - 74.9%) |
| | Specificity (95% CI) | 98.8% (96.8 - 99.5%) |
| **PS (n = 241)** | HR (95% CI) | 7.5 (4.3 – 13.1), p<0.0001 |
| | Sensitivity (95% CI) | 44.2% (31.6% - 57.7%) |
| | Specificity (95% CI) | 95.6% (91.6% - 97.8%) |
| **PDT (n = 367)** | HR (95% CI) | 24.0 (13.8 – 41.7), p<0.0001 |
| | Sensitivity (95% CI) | 45.5% (34.0% - 57.4%) |
| | Specificity (95% CI) | 99.0% (97.1% - 99.7%) |

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# Biologic correlates of circulating tumor DNA (ctDNA) shedding in the INTERCEPT colorectal cancer (CRC) study.

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**Background:** ctDNA is a promising tool for early cancer detection and monitoring of minimal residual disease (MRD). The relationship between vesicle trafficking of ctDNA-laden exosomes and shedding of detectable ctDNA in patients is poorly understood and was therefore explored in a large prospective patient cohort. **Methods:** The INTERCEPT program prospectively enrolled patients undergoing curative intent surgery for stage I-IV CRC at MD Anderson Cancer Center. Tumor informed MRD assays (Signatera) were drawn postoperatively and every three months according to reimbursement guidelines. RNA analyses were done from FFPE. Gene set enrichment analyses (GSEA) and Z-Scores comparing ctDNA+ and ctDNA– were analyzed using log2 normalized RNA expression values. **Results:** The cohort included 579 patients with RNA and post-operative ctDNA analyses; median age 56 years, 56% male and 47% stage IV. Of these, 122 (20%) were ctDNA+ in their first draw (32% of stage IV vs. 11% of stage I-III). In GSEA analyses of Hallmark gene sets between ctDNA+ and ctDNA–, an upregulation was seen for 15/50 gene sets among ctDNA+, with p-value $< 0.05$ and false discovery rate $< 0.25$. Two of the top signatures (UV response up and Unfolded protein response) were significant also in analyses stratified by stage. Analysis of the leading-edge genes in these gene set identified several members of the vacuolar ATPase (V-ATPase) family of genes which were highly enriched in ctDNA+. The full V-ATPase gene set substantially differed between ctDNA+ and ctDNA– (mean Z-score 0.48 vs. -0.13, $p < 0.001$), including when stratified by stage (I-III: 0.46 vs. -0.28, $p = 0.002$; IV: 0.49 vs. 0.10, $p = 0.051$). Sixty percent of patients (n = 346) had relapse event data with sufficient follow up. V-ATPases had higher mean Z-scores in those with relapses than those without (0.33 vs. −0.91, $p = 0.012$), also seen in the ctDNA– group (0.30 vs. -0.20, $p = 0.021$). **Conclusions:** V-ATPase genes are differentially expressed in patients with ctDNA+ regardless of tumor stage, a result also mirrored in relapse events. V-ATPases may play a significant role in ctDNA release through regulating intracellular multivesicular bodies to exosome release, thereby providing a potential mechanistic link between tumor biology and ctDNA shedding. This finding may explain the clinical limitations of ctDNA in selected patients and provide personalization of ctDNA testing performance in the future. Research Sponsor: None.

# Phase II study of short-course radiotherapy (SCRT) followed by consolidation chemotherapy with FOLFOXIRI as total neoadjuvant therapy (TNT) for locally advanced rectal cancer (LARC) patients (pts): The ShorTrip study.

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**Background:** TNT is a recognised option for the treatment of LARC. The efficacy of both FOLFIRINOX followed by long-course CTRT and SCRT followed by FOLFOX or CAPOX was demonstrated in two phase III trials. No data are available regarding the feasibility and activity of SCRT followed by the triplet as TNT in LARC. **Methods:** ShorTrip is an Italian, prospective, multicentre, single-arm phase II trial (NCT05253846). Pts ≤70 years with medium-high (5-10 cm from the anal verge) LARC with at least one of the following features: cT4, cN2, involved mesorectal fascia (MRF+) or cT3N+, received SCRT followed by 8 cycles of FOLFOXIRI and surgery. The primary endpoint was the pCR rate. According to the Fleming single stage design, hypothesizing p0 = 0.25 and p1 = 0.40, setting 90% power with an $\alpha$ error of 0.10 (one-sided), the experimental regimen would have been considered promising if at least 21 pCRs were observed out of 63 enrolled pts. After the first 11 pts starting consolidation treatment, a higher than expected occurrence of severe neutropenia after the 1$^{st}$ cycle of FOLFOXIRI (N = 7, 64%) was observed and the protocol was amended to administer one cycle of FOLFOX after SCRT followed by 7 cycles of FOLFOXIRI. **Results:** From January 2022 to February 2024, 64 pts were enrolled in 9 centres with the following characteristics: median age 62 years (IQR 55-66), male 66%, ECOG PS = 0 89%, medium/high rectum 76%/24%, cT2/cT3/cT4 5%/76%/19%, cN0/cN1/cN2 2%/35%/63%, MRF+ 42%, lateral nodes 35%, EMVI+ 41%. The 52 tumors tested for MMR were pMMR. One patient withdrew consent after the 1$^{st}$ cycle of chemotherapy and was not evaluated for pathological response. 21 (33%) and 43 (67%) pts achieved pCR and major pathological response (MPR), respectively. Almost all pCRs (N = 20, 95%) and MPRs (N = 42, 98%) were observed in pts receiving at least 5 cycles of FOLFOXIRI (N = 56). Among 63 resected pts, 62 (98%) and 1 (2%) achieved R0 and R1 resections, respectively. All pts completed SCRT and the only grade 3/4 acute toxicity was diarrhoea in 7 (11%) pts. 49 (77%) pts received 8 cycles of consolidation treatment as planned. Irinotecan was never administered in 5 (8%) pts. Main grade 3/4 toxicity during consolidation are listed in the Table. Early post-surgical complications were reported in 8 (13%) pts. **Conclusions:** SCRT followed by one cycle of FOLFOX and 7 cycles of FOLFOXIRI showed a promising activity and a feasible safety profile and is therefore worth of further studies especially in the NOM scenario. Clinical trial information: NCT05253846. Research Sponsor: GONO Foundation.

| Main G3/4 Adverse Events during consolidation CT | Overall population N=64 n (%) | Pre-amendment N=11 n (%) | Post-amendment N=53 n (%) |
|---|---|---|---|
| Any event | 40 (62) | 9 (82) | 31 (58) |
| Neutropenia | 33 (52) | 8 (72) | 25 (47) |
| Febrile Neutropenia | 3 (5) | 1 (9) | 2 (4) |
| Anaemia | 5 (8) | 1 (9) | 4 (8) |
| Diarrhoea | 6 (9) | 2 (18) | 4 (8) |
| Stomatitis | 5 (8) | 1 (9) | 4 (8) |
| Neurotoxicity | 1 (2) | 1 (9) | - |
| Asthenia | 4 (6) | 2 (18) | 2 (4) |

3593 Poster Session

# Digital spatial profiling: Mapping tumor responses to radiotherapy in rectal cancer.

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**Background:** Variation in response to radiotherapy for the treatment of rectal cancer is likely due to heterogeneity in the tumour microenvironment. However, to date, no reliable predictive biomarkers of response are in clinical use and the mechanisms underlying response are unknown. Tertiary lymphoid structures (TLS), which are ectopic lymphoid aggregates found in the tumour microenvironment, have been linked to response to immunotherapy, but little is known about their role in radiotherapy. Here, we aimed to explore the potential of lymphocytes and tertiary lymphoid structures as predictive biomarkers of response to radiotherapy and profile the tumour immune microenvironment in the context of response to radiotherapy. **Methods:** For this study, we accessed pre-treatment biopsies from 20 rectal cancer patients with known pathological response to long-course chemoradiotherapy (LCCRT). We selected regions of interest based on immunohistological identification of tumour and lymphocytic infiltrate in formalin-fixed paraffin-embedded tissue. We performed targeted proteomic profiling of 87 immuno-oncology proteins using the Nanostring GeoMx Digital Spatial Profiler to quantify protein expression with spatial resolution within regions of interest, including TLSs, in the tumour microenvironment. **Results:** Unsupervised clustering based on normalised protein expression showed a clear separation between the complete responders to LCCRT and all other tumours, and this separation is driven by differences in T cells within TLSs (CD3+). Differentially expressed proteins within CD3+ aggregates include depletion of the natural killer cell marker, CD56 and increased expression of the apoptosis marker, cleaved caspase 9. The distribution of TLS-tumour distance was also significantly different between response groups. **Conclusions:** The study highlights the role of TLSs in modulating the immunogenic landscape of the tumour microenvironment in rectal cancer, likely influencing the response to radiotherapy. Spatially resolved proteomic analyses identifies potential biomarkers for radiotherapy response and underscores the importance of profiling tumour-immune microenvironment complexity when stratifying patients for therapy. Research Sponsor: Health Research Council of New Zealand; Maurice Wilkins Centre for Biomolecular Discovery.

# Clinical and immunopathological evaluation and its comparison with consensus molecular subtypes of colorectal cancer.

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**Background:** This study aims to elucidate the prognostic impact of the immunoscore within the context of consensus molecular subtypes (CMS), tumor budding (TB), and macrophage infiltration in colorectal cancer (CRC), addressing a gap in current research. **Methods:** A retrospective observational study analyzing 255 colorectal cancer cases. Demographic, histopathological, and clinical variables were examined. Molecular classification, immunoscore, and macrophage infiltration were determined via immunohistochemistry. The study adhered to ethical guidelines and received approval from our ethics committee. CMS assessment used automated staining for specific markers, with molecular subtype determined using an online classifier (Ten Hoorn et al.). Immunoscore calculation involved evaluating CD3+ and CD8+ immune cells, classifying patients into low or intermediate-high groups (Jiang et al.). Macrophage assessment focused on CD163+ cells, categorizing them as spindle-cell and round-cell. Statistical analysis employed SPSS, using descriptive statistics, chi-square tests, Kaplan-Meier survival curves, and multivariate analyses. **Results:** In this study of 255 colorectal cancer patients, predominantly with localized disease, 34.9% had stage III disease. Conventional and serrated adenocarcinomas were the main histological subtypes. CMS classification revealed mostly CMS2-3 (69.4%), with relapse occurring across all subtypes. Low immunoscore was common in conventional and serrated histology and CMS2/3, while MSI-H correlated with intermediate-high immunoscore. Tumor budding (TB) was prevalent in relapsed patients, especially in CMS2/3 and CMS4, and associated with serrated histology. Metastatic patterns varied by CMS subtype, with TB $>$ 20 foci linked to hepatic metastases. CD163 macrophage infiltration was associated with CMS1 and CMS2/3, and a high immune score. Over 9.6 years of follow-up, tumor budding was associated with overall and relapse-free survival, while CMS was linked to overall survival. Immunoscore showed no association with survival outcomes. **Conclusions:** This cohort shows heterogeneous disease progression and prognosis, with CMS2/3 exhibiting high tumor budding and relapse rates, especially in serrated histology. Molecular subtypes have distinct metastatic patterns: CMS1 to the peritoneum, CMS2/3 to the liver, and CMS4 to both. Relapsed CMS2/3 cases had low immunoscore, while CD163+ macrophage infiltration correlated with higher immune scores in CMS1 and CMS2/3, highlighting the complex interactions between molecular subtypes, immune responses, and tumor behavior.
Research Sponsor: SEOM (Spanish Society of Medical Oncology); Instituto de Salud Carlos III; ICI20/00044; European Commission H2020; GA: 848098.

# Neoadjuvant chemotherapy and surgery for rectal cancer: Omission of radiation in clinical practice.

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**Background:** PROSPECT proved efficacy of induction chemotherapy and surgery, without radiation, for select stage II and III rectal cancer patients with improvements in bowel function and less diverting ileostomy. This approach also avoids radiation-associated alteration in fertility which is particularly important in the rising early onset population. In this study we review our broader current use of induction chemotherapy without radiation in locally advanced rectal cancer patients. **Methods:** Review of a prospectively maintained IRB approved, institutional database for patients treated with induction chemotherapy and surgery between 2015-2024. Clinicopathologic features are summarized, and disease-free survival (DFS) measured with the Kaplan-Meier method. **Results:** A total of 171 patients, median age 50 years (IQR 43-61), were identified with tumors located ≤5cm (n = 4, 2.3%), 6-10cm (n = 75, 44%), and 11-15cm (n = 92, 54%) from the anal verge. Pre-treatment MRI staging was available for 169/171 patients. 2 (1.2%) and 167 (99%) were MRI stage II and III including 23 with T4 lesions, 15 with extra-TME lymph nodes, and 28 with EMVI. Neoadjuvant chemotherapy regimens included CAPEOX (n = 71, 42%), FOLFOX (n = 98, 57%), and FOLFIRINOX (n = 2, 1.2%). 166 (97%) underwent low anterior resection with (n = 94, 57%) or without (n = 72, 43%) diverting ileostomy, 4 (2.3%) underwent abdominoperineal resection (APR), and 1 (0.6%) underwent a Hartmann procedure. Pathologic responses included: 28 (16%) AJCC TRG 0 (no viable cancer cells); 32 (19%) TRG 1 (small cluster/single cancer cells); 77 (45%) TRG 2 (residual cancer with predominant fibrosis); and 34 (20%) TRG 3 (extensive residual cancer). Tumor deposits were present in 24 (14%) and positive/close margin was noted in 2 (1.2%). With a median follow-up of 24 months, 4 (2.3%) patients developed local recurrence (salvaged with chemotherapy, radiation, and surgery) and 18 (11%) developed distant metastases. 1-year DFS was 92% (CI: 88-97) and 2-year DFS was 87% (CI: 81-93). **Conclusions:** Since PROSPECT, induction chemotherapy and surgery is being offered to higher risk rectal cancer patients, including those with T4 lesions and EMVI, with favorable results. Continued individualized care based on response to chemotherapy and omission of radiation can limit treatment related toxicity while maintaining excellent oncologic outcome. Research Sponsor: P30 CA008748.

# Performance of a targeted enzymatic methylation-based early detection test by different colorectal cancer subgroups.

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**Background:** Colorectal cancer (CRC) is the second most frequently diagnosed cancer in China and early detection could prevent over 90% of CRC-related deaths. Blood-based tests that analyze molecular features of CRC cell-free DNA (cfDNA), such as methylation and fragmentation patterns, hold great promise for early detection. However, the impact of molecular characteristics related to tumor location or mismatch repair (MMR) status on test performance has not been thoroughly investigated. In this study, we developed a blood-based CRC early detection test and analysed its performance across different CRC subgroups. **Methods:** A targeted enzymatic methyl sequencing panel was developed to identify tumor-specific hyper- and hypo-methylation markers and fragmentation profiles. A case-control cohort of 536 participants (268 CRC patients, 268 controls) was enrolled and startified into training and validation sets base on case/control status and cancer stage with 5-fold cross-validation. A gradient-boosted tree model was built by combining probabilities from methylomic and fragmentomic features. The optimal cutoff value for the early detection was determined by Youden's index, High specificity and High sensitivity methods, respectively. **Results:** The overall performance of Youden's index, High specificity and High sensitivity methods was as follows: specificity of 93.7%, 99.3%, 90.3%, and sensitivity of 96.6%, 86.2%, 97.0%, respectively. The area under the curve (AUC) value is 0.989 (95% CI: 0.981-0.996) , which is higher than those in current reports. When employing the High specificity method, the sensitivities were comparable between left and right-sided colon cancer (86.3% vs 85.7%, p = 1.0), and also similar between the dMMR (deficient mismatch repair) and pMMR (proficient mismatch repair) (87.5% vs 85.8%, p = 1.0), indicating that this model is applicable to various CRC subtypes. Additionally the TNM staging, pathological differentiation status, and the expression of Ki67, which are closely related to aggressiveness, were correlated with the sensitivity (Table). **Conclusions:** We have established CRC early detection model based on ctDNA methylation and fragmentation profiles, which shows excellent overall performance. Notably, this newly developed blood-based model shows no significant differences in sensitivity between distinct tumor locations or varying MMR statuses, suggesting its broader applicability across different types of CRC. Research Sponsor: Shanghai Xiaohe Medical Laboratory Co., Ltd.

| Subgroup | Positive/Total no. | Sensitivity | p_value |
|---|---|---|---|
| **Left-sided** | 195/226 | 86.3% | 1 |
| **Right-sided** | 36/42 | 85.7% | |
| **dMMR** | 7/8 | 87.5% | 1 |
| **pMMR** | 200/233 | 85.8% | |
| **Stage I** | 34/50 | 68% | < 0.001 |
| **Stage II** | 92/108 | 85.2% | |
| **Stage III** | 72/76 | 94.7% | |
| **Stage IV** | 33/34 | 100% | |
| **Well differentiated** | 3/3 | 100% | 0.029 |
| **Moderately differentiated** | 160/192 | 83.3% | |
| **Poorly differentiated** | 41/42 | 97.6% | |
| **Ki67_high** | 138/159 | 86.8% | 0.147 |
| **Ki67_low** | 32/42 | 76.2% | |

# ctDNA dynamics and targeted therapies associated with genetic mutations in patients with colorectal cancer.

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**Background:** Colorectal cancer (CRC) is a heterogeneous disease with various genetic mutations that guide targeted therapy decisions, as outlined by NCCN guidelines. Here we evaluated the proportion of CRC patients receiving targeted therapies using Natera's proprietary Real-World Database. **Methods:** Whole-exome sequencing (WES) data of tumor samples from CRC patients undergoing tumor-informed ctDNA testing CRC were analyzed. WES was performed on tumor tissue as part of the assay design workflow for Signatera™ molecular residual disease testing, ordered between June 2019 and July 2024. From the overall cohort of 47,476 CRC cases, we selected those with *BRAF* V600 (prevalence 13.7%) or *KRAS* G12C (prevalence 3.3%) actionable mutations, resulting in 8,473 patients included in the analysis. We utilized commercially available claims data to identify targeted therapy usage among clinical cases in our database. We examined the use of 3 different FDA-approved targeted therapies in patients with CRC. **Results:** Among 8,473 CRC patients with clinically actionable mutations in BRAF or KRAS, the majority had a *BRAF* V600 mutation (78.6%; N = 6,662) followed by *KRAS* G12C (21.4%; N = 1,811). Staging information was available for 93.9% (7,953/8,473) cases, with 15.6% stage IV at first ctDNA testing and 1.5% (123/7953) upstaged to stage IV at subsequent testing. An additional 6.7% (487/7,233) cases were categorized as recurrent/metastatic based on treatment information from claims records. Overall rates of treatment with corresponding targeted therapies were 4.0% (264/6,662) and 3.3% (60/1,811) for *BRAF* and *KRAS*, respectively. Within the subgroup of confirmed recurrent/metastatic cases (N = 1,727), targeted therapy rates were 18.9% (233/1241) for *BRAF* and 10.7% (52/486) for *KRAS*. No therapy overlap and no discordant cases (i.e., BRAF therapy was not given to KRAS mutated cases, and vice versa) were observed. Targeted therapy was typically started after the start of ctDNA testing (*KRAS*: in 96.7%, 58/60 cases, median 422 days after, *BRAF*: in 75.8%, 200/264 cases, median 200 days after). ctDNA clearance rate on therapy (i.e. conversion from ctDNA+ to ctDNA-) was observed to be 37.6% (56/149) which matches objective response rates previously reported for radiological assessment. **Conclusions:** In this analysis, we demonstrate the utility of the commercial claims database to provide insights into different treatment modalities considered for patients with actionable mutations. Understanding patterns of ctDNA dynamics during targeted therapy can potentially act as a surrogate of treatment efficacy and may guide future clinical trials. Research Sponsor: None.

# Oncologic outcomes of organ preservation in patients with rectal adenocarcinoma treated with total neoadjuvant therapy: A single-center study.

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**Background:** Total neoadjuvant therapy (TNT) reduces the risk of local recurrence and distant metastases in patients (pts) with locally advanced rectal cancer (RC). Selected pts who achieve a complete clinical response (cCR) after TNT who can undergo a strict surveillance protocol may be considered for non operative management (NOM) to preserve rectal function. **Methods:** We conducted an observational, retrospective, single-center study to evaluate watch-and-wait strategy in those achieved organ preservation & survival in pts with locally advanced or resectable metastatic pMMR RC treated with TNT. Pts received either induction chemotherapy followed by chemoradiation (INCT-CRT) or chemoradiation followed by consolidation chemotherapy (CRT-CNCT). INCT and CNCT consisted of 6-8 cycles of FOLFOX or 5 cycles of CAPEOX. CRT consisted of a total dose of 5,040-5,750 CGy to the tumor and lymph nodes along with capecitabine. Pts were assessed for treatment response with digital rectal exam, MRI, flexsig 8 weeks after TNT. Pts who achieved cCR or a near-cCR were offered NOM with WW. Close surveillance with the above-mentioned modalities was repeated every 3 months, CT chest/abdomen or PET scan was performed every 6 months. Data on local recurrence, distant metastases and survival was collected. **Results:** From Dec 2017 to Jan 2024, a total of 109 pts with RC went on WW after TNT in our center. Most pts were males (66%). Median age was 59 (30-88). The proportions of stages I to IV were 2.7%, 19.2%, %, 76.1%, and 3.6% respectively. After a median follow-up of 20.2 months, median time of sustained cCR was 67 weeks, tumor regrowth occurred in 7/109 (6.4%) pts. 3/109 pts developed distant metastases (8.5%). Median time from cCR to local regrowth/metastasis was 42 weeks. Recurrence was detected within the first 2 years in all 7 patients. 3/7 patients are in remission after salvage surgery, 2/7 pts were scheduled for surgery, 1/7 pts died of disease progression and another pt was a poor surgical candidate. 93% (102/109) of our pts are with no evidence of disease. **Conclusions:** Organ preservation for locally advanced rectal cancer is feasible and successful in a large community-based hospital system for selected pts who achieve cCR to TNT. WW is a reasonable and attractive strategy for both patients and oncologists that minimizes post-operative morbidity . Ongoing trials like JANUS aim at increasing cCR rate. Research Sponsor: None.

**Demographic and clinical characteristics of the pt cohort.**

| Variables | All pts (n=109) |
|---|---|
| Age, median (years) | 59.0 (30-88) |
| Gender | |
| Male | 73 (66%) |
| Female | 36 (34%) |
| Ethnicity | |
| Caucasian | 78 (71.5%) |
| Hispanic | 23 (21.1%) |
| Other | 8 (7.3%) |
| Clinical stage at diagnosis | |
| I | 3 (2.7%) |
| II | 21 (19.2%) |
| III | 83 (76.1%) |
| IV | 2 (1.8%) |
| TNT Strategy | |
| NCT-CRT | 45 (41.2%) |
| CRT-CNCT | 64 (58.8%) |
| CT regimen | |
| FOLFOX | 91 (84.4%) |
| CAPEOX | 14 (12.8%) |
| Other | 3 (2.7%) |
| Months of follow-up, median | 20.2 |
| Tumor Grade | |
| 1 | 7 (6.4%) |
| 2 | 53 (48.6%) |
| 3 | 2 (1.8%) |
| Unknown | 47 (43.11%) |

# Neoadjuvant mFOLFOXIRI chemotherapy with or without cadonilimab versus mFOLFOX6 alone in locally advanced colorectal cancer: A randomized phase II study (OPTICAL2).

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**Background:** The current standard treatment for locally advanced rectal cancer is chemoradiotherapy (CRT) followed by total mesorectal excision (TME) . For locally advanced colon cancer, neoadjuvant FOLFOX is also an option. In the era of immunotherapy, several studies have explored the efficacy of CRT combined with immunotherapy treatment. However, no studies have yet investigated the efficacy and safety of chemotherapy combined with immunotherapy in locally advanced colorectal cancer. We aim to explore the efficacy of mFOLFOXIRI with or without cadonilimab (AK104) compared to mFOLFOX6 neoadjuvant chemotherapy in locally advanced colorectal cancer (LACRC). **Methods:** OPTICAL-2 was a randomized, phase II trial in patients with II/III rectal ancer and locally advanced colon cancer (T3 ≥5 mm or T4). Patients were randomly assigned (1:1:1 ) to 3 groups: preoperative mFOLFOXIRI plus AK104 for 6 cycles or mFOLFOXIRI for 6 cycles, or mFOLFOX6 alone for 6 cycles, followed by TME and adjuvant chemotherapy. The primary endpoint was pCR rate in mITT population, and the secondary endpoint was major pathological response (MPR) rate, 3-year disease-free survival, overall survival and safety. **Results:** From July 2023 to August 2024, 123 patients with LACRC were enrolled, with 41 patients in each group, including 22 colon cancer and 101 rectal cancer. As the data cutoff, 121 patients had underwent surgery (41 in mFOLFOXIRI plus AK104, 39 in mFOLFOXIRI group and 41 in mFOLFOX6 group). Preoperative radiotherapy was added after induction treatment in 5 (12.2%), 4 (9.7%) and 3 (7.3%) patients among the 3 groups. In the mITT analysis, the pCR rate was 26.8% vs. 15.4% vs. 9.8% among the 3 groups, respectively. The downstaging (ypStage 0 to 1) was 65.9%, 46.2% and 41.5%, respectively. The MPR rate was 68.3%, 48.7% and 43.9%, respectively. While in the PP analysis (completed 6 cycles of preoperative treatment), the pCR rates were 30.6%, 17.1%, and 10.8%, respectively. The downstaging was 63.8%, 45.7% and 37.8%, respectively. Safety assessments was generally well-tolerated. **Conclusions:** mFOLFOXIRI with AK104 demonstrated a higher pCR rate, downstaging rate and MPR rtae compared with FOLFOX chemotherapy in patients with LACRC. This study suggests that the combination of Intensified chemotherapy and dual immunotherapy may be a promising approach for improving treatment outcomes. Clinical trial information: NCT05571644. Research Sponsor: None.

**Pathologic outcome and surgical parameters.**

| Characteristics | mFOLFOXIRI+AK104 (A) | mFOLFOXIRI (B) | mFOLFOX6 (C) | P1 (A vs. C) |
|---|---|---|---|---|
| **mITT analysis** | n=41 | n=39 | n=41 | |
| **pCR** | 11 (26.83%) | 6 (15.38%) | 4(9.76%) | 0.046 |
| **ypStage 0-I** | 27 (65.9%) | 18 (46.2%) | 17 (41.5%) | 0.026 |
| **MPR** | 28 (68.3%) | 19 (48.7%) | 18 (43.9%) | 0.026 |
| **PP analysis** | n=36 | n=35 | n=37 | |
| **pCR** | 11 (30.6%) | 6 (17.1%) | 4 (10.8%) | 0.036 |
| **ypStage 0-I** | 23 (63.8%) | 16 (45.7%) | 14 (37.8%) | 0.026 |

Footnote: pCR, pathological complete response; MPR, major pathological response.

# Impact of perioperative complications on ctDNA-based MRD detection and prognosis: Insights from the GALAXY study.

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**Background:** The GALAXY study (UMIN000039205) demonstrated the utility of circulating tumor DNA (ctDNA)testing to detect molecular residual disease (MRD) and monitor postoperative recurrence. This analysis evaluates the influence of perioperative complications and the timing of blood sampling on MRD detection rates and predicting clinical outcomes. **Methods:** From the 6,032 patients enrolled in GALAXY, 2,400 were available for this analysis after excluding those enrolled in randomized trials or with insufficient follow-up. A clinically validated, tumor-informed ctDNA assay (Signatera, Natera, Inc.) was utilized to prospectively detect and quantify ctDNA. MRD was assessed within a defined postoperative "MRD window" of 2-10 weeks post-surgery. Perioperative complications were classified as Grade 2 or higher according to the Clavien-Dindo classification. **Results:** Perioperative complications occurred in 302 cases (12.6%), with anastomotic leakage (2.4%), ileus (2.0%), and intra-abdominal abscesses (1.3%) being the most common. Complications were more frequent in males and patients with rectal cancer. Cell-free DNA (cfDNA) concentrations measured at 2–4 weeks post-surgery were significantly higher in cases with complications compared to those without complications (9.2 vs. 6.9 ng/mL; $p < 0.001$). Three-year recurrence-free survival (RFS) was significantly worse in MRD-negative cases with complications (80.7%) compared to those without complications (87.0%; HR 1.63; 95% CI 1.143–2.323; p = 0.007). In MRD-positive cases, 3-year RFS was 15.6% in patients with complications versus 19.9% in those without (HR 1.16; 95% CI 0.831–1.608; p = 0.389). Among patients with complications, ctDNA testing conducted at 2–4 weeks post-surgery versus 4–10 weeks showed marked differences in 3-year RFS based on landmark analysis at 10 weeks. For MRD-negative cases, 3-year RFS was 75.32% versus 90.71% (HR 2.875; 95% CI 1.252–6.605; p = 0.013). In MRD-positive cases, 3-year RFS was 27.7% versus 6.25% (HR 0.46; 95% CI 0.230-0.929; p = 0.030). This trend was similar even when colon and rectal cancer were analyzed separately. In contrast, no timing-related differences were observed in cases without complications. **Conclusions:** Perioperative complications may elevate cfDNA levels, potentially confounding MRD assessment. Our findings suggest delaying ctDNA testing to at least 4 weeks postoperatively in patients experiencing Clavien-Dindo Grade ≥2 complications. These results provide essential guidance for optimizing clinical trial designs involving MRD evaluation through ctDNA analysis. Clinical trial information: UMIN000039205. Research Sponsor: AMED.

# Long-term survival and treatment efficacy in dMMR/MSI-H rectal cancer: A real-world cohort from seven large medical college–affiliated hospitals.

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**Background:** Neoadjuvant immunotherapy provides considerable advantages for patients with dMMR/MSI-H rectal cancer. However, treatment strategies in real-world settings vary depending on tumor characteristics, economic conditions, and the choices made by physicians and patients. **Methods:** We screened more than 10,000 rectal cancer cases from seven large medical college-affiliated hospitals. We used the Kaplan-Meier curve to compare survival and progression, applied Cox regression to analyze impact factors, and examined tumor regression grades with chi-square analysis. **Results:** From March 2010 to April 2024, 502 patients were enrolled and diagnosed with dMMR/MSI-H rectal adenocarcinoma through immunohistochemistry or PCR. 100 patients underwent neoadjuvant immunotherapy, demonstrating a 96.34% 5-year overall survival (95% CI: 86.08-99.08%), and 90.74% 5-year disease-free survival (95% CI: 74.67-96.82%). This indicated a 16.50% enhancement in overall survival ($p = 0.042$) and a 16.87% increase in disease-free survival ($p = 0.002$) compared to conventional chemoradiotherapy (5-year OS: 79.84%, 95% CI: 71.69-85.87%; 5-year DFS: 73.87%, 95% CI: 65.15-80.73%). Neoadjuvant immunotherapy demonstrated significant superiority in tumor regression ($p < 0.0001$), however, the combination with chemotherapy did not enhance the effect ($p = 0.622$), and varying chemotherapeutic agents did not improve tumor regression in conventional chemoradiotherapy either. Additionally, elevated serum CEA levels were associated with an increased risk of both death and disease progression. Patients with advanced age, lower clinical stages, and fewer risk factors were more likely to undergo direct surgical resection. **Conclusions:** Neoadjuvant immunotherapy is advantageous for dMMR/MSI-H rectal cancer patients, as it leads to better tumor regression and enhanced disease control. Research Sponsor: None.

# Phase 1b study to assess the safety of neoadjuvant trifluridine/tipiracil with concurrent radiation in resectable stage II/III rectal cancer: Initial results of the FIERCE study.

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**Background:** Total neoadjuvant therapy (TNT) with chemo-radiation (CRT) followed by doublet chemotherapy for rectal cancer can yield clinical complete response (CR) to allow successful surgery or organ-sparing. Trifluridine exhibited cytotoxic effect of ionizing radiation superior to fluorouracil in colonogenic survival assay (dose modification factor: 2.7). The FIERCE trial (NCT04104139) sought to determine the maximum tolerated dose (MTD) of trifluridine/tipiracil (FTD-TPI) with concurrent CRT during TNT with future goals of improving CR. **Methods:** MRI-staged participants (pts) with stage II (T3-4N0M0) or stage III (TxN+M0) resectable rectal adenocarcinoma, underwent CRT with FTD-TPI for 6 weeks followed by either FOLFOX or CAPOX for 4 months. Cohorts of 3 pts were examined at three dose levels (DLs) until a total of 18 pts were reached per Bayesian Optimal Interval design. FTD-TPI was taken orally BID for five days/week on weeks 1, 3, and 5 at the assigned dose (DL1 = 25mg/m2; DL2 = 30 mg/m2; DL3 = 35 mg/m2) with concurrent pelvic radiation of 25-28 fractions. Dose limiting toxicity (DLT) was defined by sustained hematologic, gastrointestinal, and serious adverse events related to FTD-TPI. Primary endpoint was the proportion of DLT from CRT at MTD. **Results:** Among 22 screened patients (3 ineligible and 1 removed for non-compliance in week 1), 18 pts were evaluable. Median age was 52 years (range 37-73), female sex was 4 (22%), and 16 (89%) were ECOG 0. All pts had proficient mismatch repair. All 18 pts were staged as cT3, with 8 (44%) N0 (stage II), 7 (39%) N1, and 3 (17%) N2. All 18 pts completed CRT in their assigned DL (6 DL1, 3 DL2, 9 DL3) followed by chemotherapy (16 FOLFOX; 2 CAPOX) with the 18th pt scheduled to finish treatment in February 2025. One pt was switched to irinotecan due to intolerable oxaliplatin-related neuropathy. During CRT, grade 3 neutropenia without fevers (4/18, 22%) led to 1/6 DLT in DL1 and 1/9 DLT in DL3, which were mitigated by dose interruptions (2/18 missed last week of FTD-TPI). No grade 4 adverse events were observed during CRT. At data cutoff, 10 (56%) pts entered into watch-and-wait surveillance, 6 (33%) pts had surgery, and 2 (11%) pts await final assessment. **Conclusions:** FTD-TPI at DL3, the MTD of 35 mg/m2 on days 1-5, 15-19, and 29-33, is the recommended phase 2 dose for CRT in TNT for locally-advanced rectal cancer. Short-course filgrastim, or day 29-33 adjustment to DL2, may be needed in last 2 weeks of CRT to prevent dose interruptions. A dose expansion study is being explored as the next step. Clinical trial information: NCT04104139. Research Sponsor: Taiho Oncology; OHSU Knight Cancer Institute.

# Enhancing colorectal cancer precision medicine through multi-omics and clinical data integration with artificial intelligence.

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**Background:** The integration of multi-omics and clinical data in precision medicine research for colorectal cancer (CRC) is a complex task that requires advanced computational tools. Artificial Intelligence agent for High-Optimization and Precision mEdicine (AI-HOPE) has emerged as a transformative platform, streamlining data integration, analysis, and discovery efforts. AI-HOPE is designed to integrate and analyze multi-omics alongside clinical data, facilitating novel insights into CRC pathogenesis, therapeutic responses, and precision medicine applications. **Methods:** AI-HOPE leverages Large Language Models (LLMs) to interpret natural language inputs and convert them into executable pipelines for multi-omics and clinical data analysis. Data from The Cancer Genome Atlas (TCGA) and other publicly available CRC datasets were utilized to demonstrate its capabilities. AI-HOPE supports analyses such as identifying mutation and gene expression patterns, pathway enrichment, survival analysis, and therapeutic outcome predictions. Three case studies were conducted: (1) identifying WNT and TGFβ pathway alterations in early-onset CRC (EO CRC) versus late-onset CRC, (2) evaluating the association between specific multi-omics signatures and progression-free survival in patients treated with FOLFOX chemotherapy, and (3) performing a precision medicine query to identify actionable gene mutations and tailored medications for CRC treatment. **Results:** Overall AI-HOPE answered queries with an accuracy of 0.98 and an F1 score of 0.89 (precision = 0.80). AI-HOPE identified significant alterations in the WNT and TGFβ pathways among EO CRC patients compared to late-onset cases, aligning with findings from published literature. In the second study, the platform revealed that patients with specific transcriptomic signatures (e.g., upregulation of MYC targets) had significantly worse progression-free survival when treated with FOLFOX chemotherapy, further supporting its utility in identifying clinically relevant biomarkers. AI-HOPE was used to query CRC datasets for actionable gene mutations, such as KRAS, BRAF, and MSI-H (microsatellite instability-high), and cross-referenced these findings with drug databases to identify tailored therapies. The analysis highlighted FDA-approved targeted treatments, such as EGFR inhibitors (cetuximab and panitumumab) for KRAS wild-type patients and immune checkpoint inhibitors (pembrolizumab and nivolumab) for MSI-H tumors. AI-HOPE also identified emerging therapeutic options from ongoing clinical trials, showcasing its potential for guiding precision medicine strategies in CRC. **Conclusions:** This study demonstrates the transformative potential of AI-HOPE in advancing CRC precision medicine research by seamlessly integrating multi-omics and clinical data. Research Sponsor: National Cancer Institute; National Cancer Institute; National Cancer Institute.

# Complementary value of a digital pathology biomarker to post-surgery circulating tumor DNA in risk stratification of stage III colon cancer patients receiving adjuvant chemotherapy.

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**Background:** The current standard of care for patients with stage III colon cancer (CC) is resection followed by adjuvant chemotherapy (ACT). About half of patients are cured by surgery and hence overtreated with ACT, whereas ~30% experience recurrence despite ACT. Several studies show that patients with no detectable circulating tumor DNA (ctDNA) after surgery are at a lower risk of recurrence (RR), although false negative ctDNA results remain a concern. Other studies show prognostic value of digital pathology biomarkers on resected CC tissue, like the Combined Analysis of Pathologists and Artificial Intelligence (CAPAI; Kleppe Lancet Oncol 2022). This study aimed to explore the potential added value of CAPAI to post-surgery ctDNA in risk stratification of patients with stage III CC receiving ACT. **Methods:** Patients were selected from the Prospective Dutch ColoRectal Cancer (PLCRC) cohort substudy PROVENC3 (Rubio-Alarcon AACR 2024), based on stage III CC treated with radical resection and adjuvant capecitabine or CAPOX. Post-surgery ctDNA status was determined using Labcorp Plasma Detect. From the resected tumor, a representative H&E slide was digitalized to generate a DoMore-v1-CE-CRC score, which was combined with the pT and pN stage and number of assessed lymph nodes for classification as CAPAI high-, intermediate- or low-risk. Three-year RR and Cox proportional hazard ratios (HR) were reported for ctDNA-based and CAPAI-based risk groups. Time to recurrence was compared between risk groups using the log-rank test. **Results:** Post-surgery ctDNA status and CAPAI risk classification were available for 163 patients. The 20 patients (12%) with detectable ctDNA had a higher recurrence risk (3-year RR 60% [32-77], HR 4.9 [2.5-9.6], $p < 0.001$) than patients with no detectable ctDNA (N = 143, 3-year RR 18% [11-25]). Within the subgroup with no detectable post-surgery ctDNA, 50 patients (35%) were classified as CAPAI high-risk. These CAPAI high-risk patients had a higher recurrence risk (3-year RR 35% [20-48], HR 4.2 [2.0-9.1], $p < 0.001$) than patients classified as CAPAI low/intermediate-risk, who were combined based on their observed similar RR (N = 93, 3-year RR 9% [3-15%]). **Conclusions:** In patients with stage III colon cancer treated with adjuvant CAP(OX), CAPAI risk classification has potential to further stratify RR in the subgroup with no detectable post-surgery ctDNA. These preliminary results suggest that CAPAI high-risk may help identify patients with false negative post-surgery ctDNA results. Over half of all patients had both no detectable ctDNA and were CAPAI low/intermediate-risk. Given their low RR in our preliminary results, future studies on larger patient cohorts should focus on the ability to combine biomarkers to select very low-risk patients and evaluate whether these patients can potentially be spared ACT. Research Sponsor: None.

# A novel active chromatin cell-free DNA (cfDNAac) assay for early detection of colorectal cancer.

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**Background:** Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer-related deaths globally (Xi et al. 2021). In the U.S., it is estimated that 152,810 new cases and 53,010 deaths will occur in 2024, with an increasing incidence among younger adults (ACS, 2024). CRC is a multifactorial disease influenced by both genetic and environmental factors and typically progresses from normal epithelial tissue to adenocarcinoma through a well-established sequence of molecular events. Despite advancements in treatment, early detection remains a key driver of improved survival outcomes. While current screening methods— such as fecal immunochemical testing, fecal DNA testing, and colonoscopy— have reduced CRC mortality and morbidity, low compliance continues to be a significant challenge. In this study, we developed a proof-of-concept machine learning (ML) classifier leveraging active chromatin cell-free DNA ($cfDNA_{ac}$) signals in peripheral blood to differentiate CRC patients from healthy individuals. **Methods:** Plasma samples from treatment-naive colorectal cancer (CRC) patients (stages I–IV, n = 54), advanced adenoma patients (n = 14), and healthy volunteers (n = 40) were processed using Aqtual's proprietary active chromatin capture workflow to enrich regulatory-active chromatin cfDNA. Samples were split into a training set, which included 31 early-stage CRC samples (stage I: n = 13, stage II: n = 13, stage III: n = 5) and 19 healthy samples, and a hold-out set, comprised 37 disease samples (stage I/II: n = 6, stage III: n = 6, stage IV: n = 11, advanced adenoma: n = 14) and 21 healthy samples. A machine learning classifier was trained using 5-fold cross-validation with 5 repeats on the training set, and the performance was assessed on the hold-out set to ensure robustness and generalizability. **Results:** A machine learning classifier trained on genome-wide $cfDNA_{ac}$ signals demonstrated robust performance, achieving a mean AUC of 0.94 (95% CI: 0.92 - 0.96). It exhibited 93% sensitivity (95% CI: 84% -100%) for colorectal cancer detection (Stage I/II: 94%, Stage III: 95%, Stage IV: 91%) and 81% sensitivity (95% CI: 67% - 95%) for advanced adenoma, with a specificity of 90% in the hold-out set. Analysis of the top contributing $cfDNA_{ac}$ signals identified 852 promoter and 2,594 exon features derived from 2,678 unique genes. Gene-set enrichment analysis revealed significant associations with key cancer hallmarks, including KRAS signaling and epithelial-mesenchymal transition (EMT). **Conclusions:** This study highlights the potential of Aqtual's active chromatin capture assay to identify molecular features in plasma that differentiate CRC and advanced adenoma from healthy individuals. The ML classifier based on these signatures shows promise for future development as a non-invasive tool for early colorectal cancer and advanced adenoma detection and monitoring.
Research Sponsor: None.

# Analysis of early onset colorectal cancer: Implications for research and clinical practice.

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**Background:** Young onset colorectal cancer(YOCRC), diagnosed < 50 years old, presents distinct challenges, including life transitions, and psychosocial needs. In Alberta, Canada an Adolescent and Young Adult(AYA) program was introduced at our tertiary cancer centres to address these unique needs through tailored resources and services. This study aimed to explore the YOCRC patients' adjuvant care experiences and describe resource utilization prior to and after the AYA program was established. **Methods:** A retrospective review of YOCRC patients diagnosed with StageIII disease from 2012-2022 and referred to Cancer Care Alberta for adjuvant therapy was performed. This study evaluated the adjuvant care experiences of YOCRC patients, focusing on demographics, tumor characteristics, toxicity, and psychosocial visits. Incidence rates over time was assessed using Joinpoint regression. The Edmonton Symptom Assessment System(ESAS) scores collected during treatment visits were used to characterize symptomatic concerns. Analysis included descriptive statistics and multivariate regression analysis. **Results:** Among 576 patients, the mean age at diagnosis was 42.9 years. There was a positive trend in incidence of diagnoses per year($p < 0.0001$), with an increase in diagnosis of 3.96%(CI 1.30-7.13) per year in patients aged 40-49. Patients with stages IIIB disease were older at time of diagnosis compared to stage IIIC($p = 0.025$). Higher stages had poorer outcomes with stage IIIA, IIIB and IIIC($p < 0.001$), however median survival was not reached for any stages due to a low death rate. Patients reported psychological related symptoms(well-being, sleep problems and tiredness) more commonly than physical symptoms. Psychosocial visits increased after AYA program initiation with annual rates rising from 7.8 visits/year(pre-AYA program implementation) to 24 visits/year(post-AYA implementation). Further, patients who attended psychosocial visits were more likely to be younger($p < 0.001$) and had higher overall mortality($p < 0.001$). Of patients with an ESAS of ≥4, patients who were 40-49 were more likely to attend psychosocial service appointments than those aged 20-39, odds ratio of 3.23(95% CI: 1.28-8.78). There was no difference comparing patients attending psychosocial visits or higher ESAS score with sex or stage. **Conclusions:** Stage III YOCRC patients are increasing in Alberta. An AYA program can improve resource utilization, psychosocial support, and enhance visit frequency for this population with unique needs. Greater prominence of psychological symptoms on ESAS highlight areas that could benefit from focused resources for this population. Research Sponsor: None.

**Demographics of stage III YOCRC patients.**

| Demographics | | n=576 |
|---|---|---|
| **Sex** | | |
| | Male | 320 |
| | Female | 256 |
| **Site** | | |
| | Colon | 291 |
| | Rectum | 245 |
| | Rectosigmoid | 40 |
| **Stage (AJCC 7)** | | |
| | IIIA | 52 |
| | IIIB | 348 |
| | IIIC | 171 |
| | IIINOS | 3 |
| **Incidence** | | |
| | Year | |
| | 2012 | 46 |
| | 2013 | 40 |
| | 2014 | 41 |
| | 2015 | 55 |
| | 2016 | 43 |
| | 2017 | 50 |
| | 2018 | 50 |
| | 2019 | 61 |
| | 2020 | 52 |
| | 2021 | 64 |
| | 2022 | 74 |

# Changes in demographics and patterns of colon cancer in the United States: A comprehensive SEER analysis 2010–2021.

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**Background:** Over the past two decades, colon cancer has remained a leading cause of cancer-related morbidity and mortality in the United States. Changes in population dynamics, environment, and lifestyle have contributed to shifts in age, gender, tumor site, and stage at diagnosis. However, the extent of these changes over time remains underexplored. Understanding these temporal changes is crucial for improving screening strategies, identifying at-risk populations, and optimizing resource allocation. **Methods:** We conducted a cohort study of initial colon cancer diagnoses using the National Cancer Institute, Surveillance Epidemiology and End Results Program (SEER) over the period 2010 through 2021. The SEER data is comprised of 22 different registries across the United States (US), which captures approximately 47.9% of the US population. The exposure was the year of diagnosis, and the outcomes were the distributions of age, sex, site, and stage at initial diagnosis. Temporal trends in proportions were measured using Spearman correlation ($\rho$). The differences between distributions in 2010 vs. 2021 were measured using Fisher's test with the standardized mean difference (SMD) as effect size. 95% confidence intervals (95% CI) for proportions were determined using the normal approximation. **Results:** A total of 670,923 records were included in the study. The distribution of ages at initial diagnosis changed significantly over the study period (SMD = 0.1713, p-value $<$ 0.0001). In 2010, the mode of age group distribution was $\geq$ 85 years, 12.1% (11.8%–12.4%). The proportion aged $\geq$ 85 trended down over the period ($\rho$ = -0.9930, p value $<$ 0.0001) from 12.1% (11.8%–12.4%) to 9.6% (9.3%–9.8%). In 2021 the mode of age group distribution at diagnosis was 65 to 69 years, 13.2% (12.9% - 13.5%). The proportion of males trended up over the period ($\rho$ = +0.9021, p value $<$ 0.0001), increasing from 51.8% (51.4% - 52.2%) to 53.2% (52.8% - 53.6%). The difference in cancer stage was significant (SMD = 0.1818, p value $<$ 0.0001), with localized colon cancer decreasing ($\rho$ = -0.9371, p value $<$ 0.0001) from 38.9% (38.5% - 39.3%) to 33.8% (33.4% - 34.1%) and distant colon cancer increasing ($\rho$ = +0.9301, p value $<$ 0.0001) from 20.1% (19.8% - 20.5%) to 22.9% (22.5% - 23.2%). The difference in location was significant (SMD = 0.1185, p value $<$ 0.0001), with rectum as location trending up ($\rho$ = +0.9330, p value $<$ 0.0001) from 21.7% (21.3% to 22.0%) to 24.6% (24.3% to 25.0%). **Conclusions:** The current findings suggest a significant shift in colon cancer presentation in the United States over the past decade. There is a significant increase in incidence among younger males, a trend towards more distant-stage cancers indicating delay in detection, and a growing prevalence of rectal cancers as the primary site. Changes in screening strategies and reinforcement of community awareness are necessary to improve the mortality rate. Research Sponsor: None.

# Time-weighted ctDNA dynamics for precision monitoring of relapse risk in colon cancer.

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**Background:** Effective monitoring for relapse is a critical component of post-surgical care in colorectal cancer (CRC), particularly for patients who remain at risk of recurrence despite curative-intent treatment. Circulating tumor DNA (ctDNA) is a powerful biomarker for detecting minimal residual disease (MRD) and predicting relapse with high sensitivity and specificity. However, its predictive value varies over time, with negative results closer to surgery being less reliable than results obtained later. Here we introduce a novel time-weighted approach to ctDNA monitoring using a tumor-informed assay (Signatera), assigning greater predictive power to negative results collected further from surgery. **Methods:** A Bayesian logistic regression model using 1,246 Signatera serial measurements was developed to predict recurrence risk across 167 patients with early-stage colon cancer, with time-weighted ctDNA dynamics as the primary predictive feature. Negative ctDNA values were assigned greater predictive power based on their temporal distance from surgery. Secondary covariates included clinical stage and adjuvant treatment status. Time-weighted ctDNA was calculated as the product of the ctDNA level at each timepoint and an inverse time factor ($1/(t+1)$), where $t$ represents the weeks since surgery. The weighted values were aggregated for each patient to compute cumulative and average time-weighted ctDNA levels, which served as inputs to the model. Survival analysis was performed to evaluate recurrence-free survival (RFS), stratified by MRD status. **Results:** Tumor-informed ctDNA levels were measured longitudinally, with a median of 7 timepoints per patient (range, 2-16) collected over a median follow-up of 2.5 years. Stage distribution was 50% stage III (n = 83), 44% stage II (n = 74), and 6% stage I (n = 10). Mismatch repair deficiency was observed in 22 patients (13.2%). Adjuvant chemotherapy was administered in 102 patients (61.1%), and 16 patients (9.6%) experienced recurrence. Survival analysis revealed a significantly worse recurrence-free survival for MRD-positive patients compared to MRD-negative patients (HR = 4.2, 95%CI:2.8–6.4, Log-rank $p < 0.0001$). The Bayesian logistic regression model demonstrated robust predictive performance, with a posterior probability of recurrence $< 5\%$ for patients with three consecutive negative ctDNA results obtained $>$ 6 months after surgery. Conversely, the model assigned a $> 90\%$ probability of recurrence for patients with persistent ctDNA positivity beyond the initial 3-month post-operative window. **Conclusions:** Time-weighted ctDNA dynamics demonstrated promising predictive capability for CRC recurrence. Our findings suggest that incorporating the temporal context of ctDNA measurements and leveraging the increasing reliability of negative results over time could refine risk stratification and improve personalized care strategies for CRC patients. Research Sponsor: None.

# Exploring transcriptomic regulation of the tissue-associated microbiome in oncogenic progression of colorectal cancer.

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**Background:** The association between the tissue microbiome and colorectal cancer (CRC) etiology continues to be explored, and it has been proposed that certain bacteria drive oncogenesis. However, this field is hindered by a lack of mechanistic links. Considering the relationship between bacterial abundance and human gene expression allows us to traverse this functional gap. To date, work in this field has been largely restricted to considering the relationship between bacteria and Consensus Molecular Subtypes (CMS) of CRC. Here, we hypothesise that CRC-associated bacteria correlate with distinct expression profiles that drive CRC progression. **Methods:** Analysis was performed using BioCorteX's knowledge graph and proprietary engines, v20250128_100953. 16S rRNA sequencing and whole RNA data were collated from tissue samples across 3 independent cohorts from CRC patients (n = 59) and healthy volunteers (n = 23). In CRC patients, paired tumour and normal adjacent samples were analysed yielding 108 samples in total. The Pearson correlation between differentially abundant (DA) OTUs and differentially expressed (DE) genes was calculated, and false discovery rates (FDR) were applied. **Results:** 14,460 DE genes (FDR $< 0.05$) were identified between tumour and normal adjacent tissues, 5,097 of which had an absolute log-fold change greater than 1. Seven OTUs were increased in CRC compared to normal adjacent (FDR $< 0.05$) and were present in at least 20% of samples; Fusobacterium nucleatum, Akkermansia muciniphila, and five Streptococcus species. Of the 61,164 OTU-gene pairs analysed, 108 were significant (FRD $< 0.05$) with a Pearson correlation greater than 0.5. The abundance of all five Streptococcus species was correlated with the expression of nine genes including: SPSB4 ($r$= 0.51, p = 1.86x10-8), which has previously been associated with CRC metastasis, and REN ($r$= 0.71, p = 1.21x10-17), which is associated with increased Wnt signaling. Moreover, the expression of LY6G6D, a recently discovered CRC-specific antigen, was positively associated with F. nucleatum abundance ($r$= 0.53, p = 4.94x10-9). **Conclusions:** This study identifies novel interactions between the CRC-associated microbiome and expression profiles. The consistent relationships between five Streptococcus species and specific genes is highly indicative of a functional co-evolution between host transcriptomics and microbiome, and implies relationships have less to do with the specific bacteria and are more related to function. This analysis adds a mechanistic explanation for some of the associations previously identified between the microbiome and CRC. Further analysis is required to identify if the host transcriptome creates a niche for these species or whether the presence of these species is altering the microbiome. This study demonstrates the value of integrated multi-omic analysis in understanding CRC pathogenesis.
Research Sponsor: BioCorteX Inc.

# Postoperative cfDNA levels and ctDNA detection rates in patients with stage II colon cancer screened for CIRCULATE (AIO-KRK-0217, ABCSG).

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**Background:** Postoperative circulating tumor DNA (ctDNA) has emerged as a prognostic biomarker for disease recurrence in patients (pts) with resected colorectal cancer (CRC) and may potentially guide adjuvant treatment decisions. The timing of ctDNA screening is critical, as postop. plasma cell-free DNA (cfDNA) levels may vary due to factors such as tissue disruption from the surgical resection. The CIRCULATE trial (NCT04089631) investigates ctDNA guided adjuvant therapy in stage II CRC pts in > 140 centres in Germany and Austria. **Methods:** To investigate the impact of blood sampling time points on cfDNA concentrations and the ctDNA positivity rates, we analyzed the postop. plasma samples of 1439 pts with stage II CRC screened for CIRCULATE between 2020 and 2024. Blood samples were collected within 5-60 days post tumor resection in stabilizing tubes (Streck or PaxGene). Samples were analyzed for postop. cfDNA concentration and tumor-informed ctDNA in plasma samples by an error-reduced Next-Generation Sequencing (NGS) approach [Stasik S Front Genet. 2022]. **Results:** Plasma cfDNA concentrations (measured by qPCR for beta-globin gene) ranged from 0.02 to 20.32 ng/μL (mean: 0.689 ng/μL; median: 0.360 ng/μL). The highest cfDNA levels were observed within 2 weeks after surgery (mean: 1.079 ng/μL; median: 0.540 ng/μL), with a significant decrease in samples collected > 3 weeks postop. (mean: 0.631 ng/μL; median: 0.355 ng/μL; $p < 0.0001$), suggesting an impact of surgical trauma and subsequent cfDNA release from normal tissue. In ctDNA-neg. pts, cfDNA concentrations stabilized between 0.405 and 0.449 ng/μL during weeks 4-8. In contrast, ctDNA-pos. pts had significantly elevated cfDNA levels at 2 months post-surgery (mean: 0.972 ng/μL; $p = 0.419$), indicating ongoing tumor-specific DNA shedding associated with recurrent disease. Variant allele frequencies (VAFs) in ctDNA-pos samples were negatively correlated with cfDNA concentrations, particularly in early postop. samples (Spearman r = -0.508), suggesting a dilution effect of ctDNA post-surgery. This correlation diminished at later time points, supporting the potential advantage of later sampling to improve ctDNA sensitivity. Despite temporal variations in cfDNA concentrations, ctDNA positivity was consistent across all sampling intervals (i.e. week 1: 4.1%; week 6-8: 5.64%), demonstrating the assay's robust sensitivity. **Conclusions:** We observed a significant variation in cfDNA levels depending on the timing of postop. sampling. Different kinetics, such as cfDNA release from normal tissue and tumor shedding, may influence cfDNA levels and the sensitivity to ctDNA detection. Nonetheless, our assay demonstrates consistent and reliable sensitivity for ctDNA detection across all postop. sampling time points. Clinical trial information: NCT04089631. Research Sponsor: German Federal Ministry for Education and Research (Bundesministerium für Bildung und Forschung) / DLR; 01KG1817.

# Multicentric evaluation of an artificial intelligence model to stratify stage II colon cancer patients from whole slide images.

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**Background:** Stage II colon cancer (IIA T3N0; IIB T4aN0; IIC T4bN0) represents nearly 25% of all colon cancers and includes a wide range of outcomes (5-year overall survival rate (OS) of 58.4% to 87.5%). We aim to test if a deep-learning-based analysis of whole slide histology images (WSI) can predict survival and highlight the most relevant morphologic characteristics underlying prognosis. **Methods:** We identified adult stage II colon cancer cases from the multimodal Cancer Genome Atlas (TCGA) and retrospective consecutive cases diagnosed between 2014-2019 (inclusive) from two independent centers (CHUM, Canada and IHP, France; IRB approved). We tested on these two independent datasets, an artificial intelligence (AI) algorithm trained on TCGA, using a cross-validation and cross-testing (80:20) framework. The model relies on a weakly-supervised attention-based pipeline that extracts survival driven histologic features from H&E WSI and assigns a risk score for each patient. The concordance index (c-index) was used as the primary outcome metric. Further testing of the survival score was performed with a multivariate Cox regression model. The stratification of the cohorts based on the risk scores was evaluated using Kaplan-Meier curves and log-rank test. 95% confidence intervals (CI) are provided. An adjusted two-tailed P value $<0.05$ was considered significant. The specific morphologic characteristics involved in the AI outcomes are under analysis. **Results:** The Discovery TCGA cohort consisted of n=463 colon cancer patients; 5-year OS: 68.7% (CI: 60.0%-75.9%). The external validation cohorts included (1) from CHUM, n=124 patients, 5-year OS: 67.0% (CI: 58.0%-75.0%), and (2) from IHP, n=123 patients, 5-year OS: 55.6% (CI 45.0%-67.0%). Cross-validation and testing yielded a c-index of 0.72 and 0.68 respectively, 0.67 for CHUM and 0.65 for IHP cohorts. After external validation, patients with a 'low-risk' score showed significantly higher 5-year OS than patients with a 'high-risk' score: CHUM: 75.0% (CI: 64.0%-84.0%) vs 53.0% (CI 38.0%-67.0%), $P<0.05$; and IHP 65.0% (CI: 44.0%-80.0%) vs 34% (CI: 21.0%-46.0%), $P<0.01$. Cox regression showed a significant effect of WSI-based survival score on 5-year OS: TCGA cohort HR=8.3 (CI: 3.1-12.8), $P<0.001$; CHUM: 7.6 (CI 2.7-21.8), $p<0.005$; IHP: 5.5 (CI 2.1-16.8), $P<0.005$. **Conclusions:** AI-based risk scoring for stage II colon cancer consistently correlated with 5-year OS across multiple independent cohorts, achieving good performances. These findings highlight the potential of modern computational pathology methods requiring minimal supervision to improve risk stratification of stage II colon cancer and patient care. Research Sponsor: IHP Group (France).

# Development and validation of machine learning risk prediction models for detection of early-onset colorectal cancer: Data from 30 health systems in the United States.

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**Background:** Incidence of early-onset colorectal cancer (EoCRC) in patients without any family history has been increasing in recent years. Our study leveraged advanced Large Language Models (LLM), like GPT-4, to predict EoCRC in a population comprised of multiple health systems across the United States. There is potential to improve patient care by suggesting early screening for patients who are predicted to be at risk by the model. **Methods:** We identified a population of 5532 patients aged between 18 and 44 in the Truveta data, which is a collection of 120+ million patient journeys across 30 U.S. health systems. 1376 (24.87%) were diagnosed of CRC based on their ICD and SNOMED-CT codes. Data was split into training (80%) and testing (20%) sets. For the prediction task, we applied GPT-4o and compared with XGBoost, one of the strongest non-generative machine learning models. We used patient demographics (age, gender, race, ethnicity), conditions, and lab results within the last 2 to 7 months prior to CRC diagnosis for model training. The last month before CRC diagnosis was excluded to avoid highly predictive signals. For XGBoost, the demographics were represented as one-hot feature vectors, indicating their presence or absence. Conditions were encoded by their diagnosis frequency within the time frame, while the actual values of the lab results were used as model features. For the LLM model, all patient information was input as plain text. Both conditions and lab results were represented by the names of ICD and LOINC codes in order to capture the clinical context. A Chain-of-Thought prompting strategy, incorporating detailed instructions and CRC-specific knowledge, was employed to guide the LLM. **Results:** Our test set consisted of 1105 patients in which 279 (25.25%) were diagnosed with CRC. Both XGBoost and GPT-4o achieved comparable results. Despite the uneven distribution of CRC diagnoses in the test samples, the fine-tuned GPT-4o achieved the highest precision (87.43%) and recall (57.35%). This indicates that the model can accurately predict EoCRC in the near future for over half of the patients. **Conclusions:** This study highlights the potential of using LLM to predict EoCRC in younger population. While the GPT-4o base model contains general medical knowledge, supervised fine-tuning with explicit guideline enhances its predictive capabilities. The high precision of the model performance minimizes the burden of unnecessary screening by identifying patients with relatively high risk. As AI technologies continues to advance, with sufficient governance policy in place, predictive models can be valuable tools for clinicians to suggest early screening and mitigate EoCRC for patients. Research Sponsor: Truveta.

| Model | Precision | Recall | F1 score | Accuracy |
|---|---|---|---|---|
| **XGBoost** | 83.77% | 57.35% | 68.09% | 86.43% |
| **GPT-4o (base)** | 68.61% | 54.84% | 60.69% | 82.26% |
| **GPT-4o (fine-tuned)** | 87.43% | 57.35% | 69.26% | 87.15% |

# Use and benefit of adjuvant chemotherapy in early- vs average-onset colorectal cancer.

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**Background:** Despite improved mortality rates in colorectal cancer (CRC), the incidence of early onset-colorectal cancer (EO-CRC) has been rising in the United States. We aimed to explore trends in adjuvant chemotherapy (ACT) administration and evaluate its impact on overall survival (OS) and cancer-specific survival (CSS) in patients with EO-CRC (< 50 years old) and average-onset colorectal cancer (AO-CRC) [> 50 years old]. **Methods:** Adult patients (age >18) with Stage II-low risk (T1-T3 disease and more than 12 lymph nodes examined), stage II-high risk (T4 disease or less than 12 total lymph nodes examined) or stage III CRC diagnosed between 2010-2020 were identified in the Surveillance, Epidemiology, and End Results Program (SEER) Database. Cox proportional hazard models were used to assess the effect of ACT on OS and CSS in patients with EO-CRC and AO-CRC. **Results:** The final dataset included 8,998 patients with EO-CRC and 64,987 patients with AO-CRC (Stage II-low =27,446, Stage II-high =9,060, and Stage III = 37,479). Patients with AO-CRC were less likely to receive ACT compared to patients with EO-CRC across all stages: stage II-low (odds ratio [OR]: 0.27), stage II-high (OR 0.28), and stage III (OR: 0.32). From 2010 to 2020, the use of ACT decreased for EO-CRC (68% to 64%) but increased for AO-CRC (36% to 45%). In patients with AO-CRC, ACT improved OS and CSS in stage II-high (OS Hazard ratio(HR):0.48, 95%CI 0.42-0.54; CSS HR:0.48, 95%CI 0.42-0.54) and stage III (OS HR:0.38, 95%CI 0.37-0.40; CSS HR:0.38, 95%CI 0.37-0.40), but had no benefit in CSS for stage II-low disease (CSS HR: 1.01, 95%CI 0.84-1.22). In patients with EO-CRC, ACT improved OS (HR 0.70, 95% CI 0.56-0.88) and CSS (HR: 0.70, 95% CI 0.56-0.88) in stage III disease. No statistically significant survival benefit was observed for patients with stage II-low (CSS HR:1.11, 95%CI 0.66-1.86) or stage II-high (CSS HR:0.83, 95%CI 0.53-1.31).The 5-year survival probabilities by stage are shown in the table. **Conclusions:** Despite being used more frequently, the benefit of ACT in EO-CRC seems to be of less magnitude than in AO-CRC. These differences might be partially explained by the better survival outcomes of EO-CRC even without ACT. Though recommended by most clinical guidelines, ACT does not improve survival outcomes in patients with stage II high-risk EO-CRC. These findings highlight the need to improve risk stratification in early stage EO-CRC to better identify patients who may benefit from ACT. Research Sponsor: None.

**5-Year survival probabilities by stage (II-Low, II-High, III).**

| Variable | OS II-Low | OS II-High | OS III | CSS II-Low | CSS II-High | CSS III |
|---|---|---|---|---|---|---|
| **AO; Chemo** | 84.77% | 72.51% | 69.66% | 88.86% | 76.96% | 75.08% |
| **AO; No Chemo** | 74.11% | 53.47% | 41.54% | 89.63% | 70.93% | 56.55% |
| **EO; Chemo** | 93.53% | 84.34% | 78.72% | 94.54% | 86.34% | 80.18% |
| **EO; No Chemo** | 93.68% | 80.19% | 71.77% | 95.32% | 84.28% | 75.84% |

# Detection of early-stage colorectal cancer using multiplexed extracellular vesicle proteomic biomarkers.

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**Background:** Colorectal cancer (CRC) is very common worldwide, and detection of early-stage cancer is critical for improved survival rates. Advanced adenoma (AA) and early-stage CRC present challenges due to their small size and very low plasma expression of tumor-specific biomarkers. Genomics-based diagnostics struggle to detect these lesions, making it imperative to develop more sensitive approaches. Extracellular vesicles (EVs) are emerging as a promising solution for early-stage CRC detection. EVs are produced by tumor, tumor microenvironment and host cells, thus, unbiased analysis of all plasma EVs offers an expanded set of cancer specific biomarkers, and may aid in detection of small early-stage tumors. **Methods:** EVs were purified from patient plasma using size exclusion chromatography and a proprietary buffer system that enhances EV and corona recovery. TrueDiscovery Data-independent acquisition mass spectrometry (MS) analysis was conducted on EVs purified from 24 advanced adenoma (AA)/stage 0 dysplasia, 25 Stage 1 CRC and 75 normal patient plasma samples. An in-house Machine Learning (ML) pipeline was developed to identify differentially expressed proteins and to define protein multiplexes with extremely high Sens/Spec ($> 0.99$). **Results:** Around 2,500 QC'd proteins were ID'd per sample and ML identified 336 (AA/Stage 0) and 493 (Stage 1) differentially expressed proteins (DEP: absolute Log2FC$>0.5$; q-value $<0.001$; AUC$>0.5$). The DEPs from AA/Stage 0 and Stage 1 were trained and tested using ML and SMV to identified dozens of MS based multiplexes for each stage with near perfect diagnostic accuracy (~98-100%). These biomarkers were enriched with metabolic, immune and inflammatory proteins in line with our unbiased approach. MS protein multiplexes were then translated to ELISAs to build simple, high throughput assays. ELISA analysis of multiple biomarkers was performed in the training cohort, ML/SMV was used to define multiplex ELISA-based classifiers for Stage 1 CRC (Sen=0.95/Spec=0.96). This Stage 1 CRC training assay was locked and tested on a blinded cohort of Stage 1 CRC (30 control, 30 cancer). In this blinded cohort, we targeted maximal specificity yielding Sen=0.80, Spec=0.97 and AUC=0.95. These data represent significantly higher Sen/Spec than current genomic based liquid biopsy assays. Training and validation of AA and Stage 0 ELISAs is underway and will be presented. **Conclusions:** Blinded validation of EV proteomic biomarkers yielded extremely high Sen/Spec early-stage CRC. The unbiased EV analysis underscores the need to assess cancer specific biomarkers from TME and host response and highlights the value and opportunity of expanding liquid biopsy analysis beyond tumor specific genomics. Taken together this platform provides an exceptional opportunity to increase early-stage cancer detection which should result in better patient outcomes. Research Sponsor: None.

# An early colorectal cancer screening programme based on bisulfite-free sequencing of methylated circulating tumor DNA.

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**Background:** Colorectal cancer (CRC) screening tests based on colonoscopy and fecal DNA testing are limited due to their invasive nature and low compliance rates. Herein, we develop a non-invasive early screening test for CRC based on ColoSeer assay, which combines methylated DNA immunoprecipitation and bisulfite-free sequencing to analyze methylation patterns of circulating tumor DNA (ctDNA). **Methods:** Tumor and ctDNA methylation patterns in 1,336 subjects (430 healthy controls, 202 colorectal precursor lesions (CPLs), 704 CRCs) undergoing colonoscopy were evaluated using the ColoSeer assay. **Results:** In the discovery phase, we identified a set of 46 differential methylation markers to screen for CPLs or CRCs from healthy controls. The overall detection sensitivity of ColoSeer was 85.6% for CPL and 97.5% for TMN stage (0-II) CRC, with 92.8% specificity. **Conclusions:** The ColoSeer assay demonstrated a high degree of accuracy for predicting subjects with CPL or early-stage malignant tumors and has potential as a first-tier health screen for early detection of CRC. Research Sponsor: None.

# The impact of dietary patterns on inflammation and colon cancer risk: A retrospective study of 796 patients.

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**Background:** Colon cancer significantly contributes to global cancer rates, with rising incidence linked to dietary and lifestyle changes. Diets high in ultra-processed foods promote systemic inflammation, while anti-inflammatory diets may reduce inflammation and cancer risk. This study investigates the relationship between dietary patterns, inflammatory biomarkers, and colon cancer risk. **Methods:** This retrospective study analyzed data from 796 patients with histologically confirmed colon cancer (2015–2023). Dietary habits were assessed using validated food frequency questionnaires (FFQs), categorizing participants by adherence to ultra-processed or anti-inflammatory diets using the Dietary Inflammatory Index (DII). Systemic inflammation was evaluated via biomarkers: C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-$\alpha$), and white blood cell (WBC) count. Clinical data, including age, sex, BMI, smoking, physical activity, co-morbidities like metabolic syndrome and obesity, were extracted from medical records. Multivariate logistic regression was used to assess associations between dietary patterns, inflammation, and colon cancer risk. Subgroup analyses stratified by metabolic conditions and cancer stage identified potential interactions. The study adhered to STROBE guidelines. **Results:** Patients consuming diets high in ultra-processed foods (top DII quartile) had elevated inflammatory biomarkers (CRP: 14.8 $\pm$ 3.2 mg/L; IL-6: 8.6 $\pm$ 2.4 pg/mL; TNF-$\alpha$: 7.2 $\pm$ 1.9 pg/mL) compared to those on anti-inflammatory diets (CRP: 4.3 $\pm$ 1.1 mg/L; IL-6: 2.9 $\pm$ 0.8 pg/mL; TNF-$\alpha$: 2.3 $\pm$ 0.7 pg/mL; $p < 0.001$). Dietary patterns strongly correlated with colon cancer risk. Ultra-processed food consumers had an adjusted odds ratio (aOR) of 2.47 (95% CI: 2.01–3.03) for colon cancer, while anti-inflammatory diets had a protective effect (aOR: 0.62, 95% CI: 0.51–0.76). Subgroup analysis showed anti-inflammatory diets' protective effects were more pronounced in patients with metabolic syndrome or obesity, reducing cancer risk by 45% ($p < 0.001$). Early-stage colon cancer patients (Stage I–II) adhering to anti-inflammatory diets exhibited lower inflammation, suggesting potential benefits for disease progression and prognosis. Further analysis highlighted omega-3 fatty acids and polyphenols in anti-inflammatory diets as key in reducing inflammation by downregulating NF-$\kappa$B signaling and pro-inflammatory cytokine production. **Conclusions:** Diets high in ultra-processed foods elevate inflammation and colon cancer risk, while anti-inflammatory diets provide protective benefits, especially in individuals with metabolic conditions. These findings emphasize the need for dietary interventions promoting anti-inflammatory patterns in cancer prevention and management. Further research should validate these results and explore underlying mechanisms. Research Sponsor: None.

# Risk of pre-cancerous advanced adenomas of the colon in long distance runners.

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**Background:** Exercise induced gastrointestinal injury is believed to be associated with reduced blood flow to the intestines during long distance running. To our knowledge, there has not been evidence linking this type of exercise- induced bowel ischemia to carcinogenesis. After observing multiple "ultramarathoners" present to our cancer center with advanced colorectal cancer, we initiated a prospective IRB-approved study to evaluate the risk of advanced adenomas (AA) in long distance runners between the ages of 35-50. **Methods:** NCT 05419531 was a prospective study of subjects aged 35-50 years who had completed at least two registered ultramarathons (50 km or longer) or five registered marathons (26.2 miles). Subjects were excluded if they were known or suspected to have inflammatory bowel disease, familial adenomatous polyposis (FAP), or Lynch Syndrome. Prior to colonoscopy, each subject completed a questionnaire regarding dietary habits, bowel habits, and long-distance running history, with results to be reported in the future. All polyps discovered during colonoscopy were reviewed by a panel of gastroenterologists, pathologists, and oncologists to determine if they met the criteria for advanced adenomas, defined as lesions >10 mm, >25% tubulovillous features, or high-grade dysplasia. **Results:** Between October 2022 and December 2024, 102 subjects were screened, and 100 underwent colonoscopy as part of the study. The median age was 42.5 years; 55 of the participants were female and 45 were male. The historical benchmark used for expected AAs in average-risk individuals aged 40-49 years was 1.2%. Among the 100 subjects in this study, 15% (95% exact confidence interval: 7.9%- 22.4%) had confirmed AAs. 39 out of 100 subjects had at least one adenoma. Three additional subjects had three or more adenomas but did not meet our predefined criteria for AA and were not included among the 15 patients with AA. **Conclusions:** NCT 05419531 achieved its predefined endpoint for advanced adenomas, suggesting that "intensive" long distance running is a risk factor for advanced adenomas of the colon. Consideration of refined screening strategies for this population is warranted. Future pathological and epidemiological evaluations should explore causation and ancillary risk factors in this unique population. Clinical trial information: NCT05419531. Research Sponsor: Inova Schar Cancer Institute.

**Subjects with advanced adenoma.**

| Participant ID | 3 | 9 | 15 | 16 | 37 | 53 | 55 | 67 | 69 | 71 | 77 | 87 | 91 | 98 | 100 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Gender | F | M | M | F | F | M | F | F | F | F | F | M | M | F | M |
| Age | 44 | 45 | 48 | 41 | 45 | 49 | 40 | 40 | 45 | 39 | 42 | 50 | 42 | 44 | 41 |
| Endurance Eligibility (U – Ultramarathons; M – Marathons) | 4 - 6 U | 4 - 6 U | > 15 U | 4 - 6 U | > 15 U | 7 - 15 U | 6 M | 5 M | 7 - 15 U | 1 U / 7-8 M | > 15 U | > 15 U | 10 M | > 15 U | 5 M |
| # of Polyps | 3 on primary; 2 on secondary | 5 | 2 | 3 | 1 | 1 | 3 | 2 | 7 | 1 | 2 | 4 | 2 | 6 | 3 |
| Size of largest polyp (Colonoscopy/ Pathology) (mm) | 25 / 15 | 12 / 15 | 10 / 13 | 10 / 10 | 3 / 3 | 20 / 9 | 5-6 / 5 | 12/ 11 | 12 / 12 | 5 / 5 | 5 / 5 | 15-20 / 12 | 6 / 7 | 10 / 7 | 10 / 19 |
| >25% Tubulovillous Features (Y/N) | N | N | N | N | Y | N | Y | N | N | Y | Y | N | N | Y | N |
| High-grade Dysplasia (Y/N) | N | N | N | N | N | N | N | N | N | N | N | N | Y | N | N |

# Reassessing colorectal cancer recurrence in solid organ transplant recipients: Implications for revised management guidelines.

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**Background:** Patients with solid organ transplants (SOT) are at an increased risk of developing secondary malignancies, including colorectal cancer (CRC). However, the influence of SOT and associated immunosuppression on recurrence risk following definitive treatment is poorly understood. This study characterizes the recurrence risk of CRC in a cohort of patients that developed CRC after SOT. **Methods:** Patients treated within the Johns Hopkins and University of Wisconsin medical systems meeting study criteria were identified using SlicerDicer Epic reports. Manual chart review was performed to determine treatment course, patient/disease characteristics, and whether or not their disease recurred. **Results:** Fifty-two patients with CRC following SOT were identified, including those who had liver (n = 12), kidney (n = 26), combined liver and kidney (n = 5), combined pancreas and kidney (n=4), lung (n = 4), and heart (n = 1) transplants. Among these patients, 30 were male and 22 were female. Ten patients had recurrent CRC after curative intent treatment. Recurrence rates were as follows: 1 of 10 (10.00%) patients with stage I CRC, 5 of 12 (41.67%) patients with stage II CRC, and 4 of 18 (22.22%) patients with stage III CRC. The overall CRC recurrence rate in the cohort was 32.26%. **Conclusions:** In summary, a multi-institution retrospective cohort study of patients with CRC diagnosis following SOT demonstrated higher than traditionally expected recurrence rates in patients with stage I and II disease when compared to patients diagnosed with CRC without history of SOT. Further multi-institutional studies are warranted to validate this finding. If confirmed, this would suggest transplant status may alter adjuvant treatment decisions and warrant future prospective studies in this patient population. Research Sponsor: None.

**Study cohort variables stratified by CRC staging.**

| Stage at Diagnosis | Avg. Age at Time of Diagnosis | Sex | Race | Transplant Type | Avg. Time from Transplant to CRC Diagnosis (months) | Recurrence Rate | Avg. Time to CRC Recurrence (months) | Avg. Overall Survival (months) |
|---|---|---|---|---|---|---|---|---|
| **Stage 0** | 72.00 | 1 Female | 1 Caucasian | 1 Liver | 34.73 | 0.00% | N/A | 4.70 |
| **Stage I** | 57.50 | 6 Male, 4 Female | 3 African American, 6 Caucasian, 1 Pacific Islander | 5 Kidney, 2 Liver, 2 Pancreas/ Kidney, 1 Lung | 159.73 | 10.00% | 51.78 | 54.42 |
| **Stage II** | 56.33 | 7 Male, 5 Female | 3 African American, 9 Caucasian | 7 Kidney, 1 Liver, 2 Liver/ Kidney, 2 Pancreas/ Kidney | 172.35 | 41.67% | 29.87 | 61.34 |
| **Stage III** | 62.39 | 12 Male, 6 Female | 3 African American, 14 Caucasian, 1 Asian | 9 Kidney, 4 Liver, 3 Liver/ Kidney, 1 Lung, 1 Heart | 148.76 | 22.22% | 18.03 | 52.15 |
| **Stage IV** | 52.18 | 5 Male, 6 Female | 2 African American, 9 Caucasian | 5 Kidney, 4 Liver, 2 Lung | 148.83 | N/A | N/A | 18.70 |
| **All Stages** | 58.08 | 30 Male, 22 Female | 11 African American, 39 Caucasian, 1 Asian, 1 Pacific Islander | 26 Kidney, 12 Liver, 5 Liver/ Kidney, 4 Pancreas/ Kidney, 4 Lung, 1 Heart | 154.14 | 32.26% | 27.33 | 46.72 |

# Impact of COVID-19 on the stage at diagnosis and mortality of colorectal cancer.

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**Background:** When the COVID-19 pandemic started in 2020 in the US, the Centers for Medicare and Medicaid Services (CMS) recommended delaying all non-urgent procedures, including screening colonoscopies to prevent virus spread. An analysis of the CMS claims data showed a decrease in all screening modalities for colorectal cancer (CRC) including colonoscopy, fecal occult blood test, and blood-based gene analysis in 2020 compared to 2013-2019. We investigated the impact of COVID-19 on stage at diagnosis and mortality of CRC across racial groups. **Methods:** We utilized the Surveillance, Epidemiology, and End Results (SEER) database to obtain the age-adjusted incidence of localized, regional, and distant CRC at the time of diagnosis from 2013 to 2021. The year-over-year (YOY) change in the proportion of advanced (regional + distant) CRC was calculated. YOY changes in age-adjusted CRC mortality rates from 2014 to 2021 were also calculated. **Results:** From 2014 to 2019, the average YOY change in the proportion of advanced CRC across all races was 1.0% whereas in 2020, the rate was 3.9%. The increase in proportion of advanced CRC in 2020 was greatest in non-Hispanic Asian/Pacific Islanders (NHAPI), followed by Hispanics, non-Hispanic Whites (NHW), non-Hispanic American Indian/Alaskan Natives (NHAIAN), and non-Hispanic Blacks (NHB; 7.9%, 4.7%, 3.6%, 3.3%, and 3.3%, respectively). From 2014 to 2019, the average YOY change in CRC mortality across all races was -0.7% while in 2020, it increased by 5.4%. In 2020, the YOY change in mortality was greatest in NHAIAN, followed by Hispanics, NHB, NHW, and NHAPI (25.3%, 16.5%, 15.1%, 3.2%, and 1.2%, respectively). **Conclusions:** The proportion of advanced CRC increased in 2020 likely due to decreased screening most significantly in NHAPI. Also, mortality increased in 2020 possibly due to delay in access to care during COVID-19. Further studies are needed to evaluate the long-term effect of COVID-19 on the screening and mortality of CRC. Research Sponsor: None.

**Proportion of advanced colorectal cancer and mortality rates of colorectal cancer from 2013 to 2021 by race.**

| Proportion of advanced colorectal cancer (%) | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 |
|---|---|---|---|---|---|---|---|---|---|
| **Total** | 59.9 | 59.7 | 59.8 | 63.1 | 63.8 | 62.6 | 63.3 | 65.8 | 64.6 |
| **Non-Hispanic White** | 59.9 | 59.6 | 59.6 | 62.2 | 63.3 | 62.3 | 62.9 | 65.1 | 64.4 |
| **Non-Hispanic Black** | 60.7 | 60.8 | 61.2 | 64.6 | 65.1 | 64.1 | 65.2 | 67.3 | 64.8 |
| **Non-Hispanic American Indian/Alaska native** | 60.9 | 62.6 | 59.0 | 64.2 | 64.5 | 65.0 | 66.3 | 68.5 | 65.3 |
| **Non-Hispanic Asian/Pacific** | 59.0 | 59.2 | 59.1 | 64.8 | 66.4 | 61.6 | 63.2 | 68.1 | 64.1 |
| **Hispanic** | 61.6 | 61.2 | 61.0 | 65.3 | 64.8 | 64.2 | 65.0 | 68.1 | 66.7 |
| **Mortality (per 100,000)** | | | | | | | | | |
| **Total** | 24.9 | 24.6 | 24.7 | 24.3 | 24.6 | 24.5 | 24.0 | 25.3 | 25.0 |
| **Non-Hispanic White** | 25.5 | 25.5 | 25.6 | 25.1 | 25.6 | 25.6 | 25.1 | 25.9 | 26.2 |
| **Non-Hispanic Black** | 33.3 | 31.5 | 32.7 | 31.7 | 31.8 | 31.0 | 30.4 | 35.0 | 32.0 |
| **Non-Hispanic American Indian/Alaska native** | 31.3 | 23.0 | 23.1 | 29.6 | 28.7 | 31.7 | 24.9 | 31.2 | 31.7 |
| **Non-Hispanic Asian/Pacific** | 16.9 | 17.1 | 17.1 | 16.9 | 17.3 | 16.3 | 16.6 | 16.8 | 17.0 |
| **Hispanic** | 19.9 | 19.1 | 19.1 | 20.3 | 18.9 | 20.0 | 18.8 | 21.9 | 20.9 |

# Leveraging EHRs and a phenome-wide association study to identify pre-diagnostic clinical markers in early-onset colorectal cancer.

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**Background:** The incidence of colorectal cancer (CRC) has undergone a significant demographic shift, with diagnosis in individuals under 55 years escalating from 11% in 1995 to 20% in 2019 (Siegal et al., 2019). Traditional risk factors, such as obesity, diabetes, and colon microbiome changes, fail to fully explain this emerging clinical phenomenon, necessitating new approaches to identify pre-diagnostic markers in younger patients. Our study leverages electronic health records (EHR) and employs a Phenome-Wide Association Study (PheWAS) to characterize age-specific manifestations prior to diagnosis. **Methods:** A PheWAS was conducted with a cohort of 2,799 CRC patients from Northwestern Medicine (NM, 2012 – 2022). ICD-9/10 codes were categorized into 527 phenotypes using the PheCode framework. Logistic regression models were employed to examine associations between age groups ( $<$ 55 vs. $\geq$55 years) and each phenotype during the 6 months preceding diagnosis. A control cohort of 294,590 non-cancer NM patients adjusted for age-related and baseline disease patterns. **Results:** Our approach revealed significant associations with age in 9 of 527 analyzed phenotypes, identifying well-documented CRC features and less recognized clinical markers. Younger patient cohorts exhibited elevated probabilities of critical clinical indicators, including lower gastrointestinal hemorrhage (22% [95% CI: 19-25%] vs. 11% [95% CI: 10-13%]; $p = 1.0 \times 10^{-11}$), hepatic dysfunction (6% [95% CI: 4-8%] vs. 4% [95% CI: 3-4%]; $p = 2.7 \times 10^{-6}$), and diverticular disease (4% [95% CI: 3-6%] vs. 3% [95% CI: 2-3%]; $p = 2.4 \times 10^{-11}$) compared to older patients. Furthermore, an analysis of 1,866 NM pathology reports revealed single-institution trends consistent with global CRC literature. Notably, younger patients showed higher prevalence of hereditary CRC (28% vs. 24%; $\chi^2$ $p = 6.3 \times 10^{-8}$), greater left-sided tumor localization (51% vs. 45%; $\chi^2$ $p = 0$), and increased proximal tumors (58% vs. 53%; $\chi^2$ $p = 0$), corroborating studies that show a rise in proximal tumor incidence in patients under 50 and a decline in those aged 50–79. **Conclusions:** Our PheWAS study uncovered clinicopathological distinctions, revealing statistically significant variations in pre-diagnostic clinical markers that suggest a more aggressive and complex disease progression mechanism in early-onset CRC. The increased probabilities of clinical indicators—such as gastrointestinal hemorrhage, hepatic dysfunction, and diverticular disease—underscore the need for tailored diagnostic and screening strategies for younger populations. These results also highlight the value of utilizing phenotype-based methodologies to identify nuanced clinical features that may enable earlier detection and improve outcomes for younger CRC patients. Towards this goal, ongoing research aims to further delineate CRC clinical profiles between age groups. Research Sponsor: Northwestern University Office of Undergraduate Research.

# Colorectal cancer screening and detection following USPSTF recommendations for ages 45-49: Insights from a large EHR cohort.

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**Background:** Rising colorectal cancer (CRC) incidence in relatively younger adults prompted the US Preventative Services Task Force (USPSTF) to recommend screening in average-risk adults aged 45-49 in May 2021. While screening has increased for ages 45-49, differences in polyp and CRC detection by age group are unclear. **Methods:** Using a subset of Truveta Data, we identified patients aged 40-64, with no prior history of CRC, who underwent CRC screening procedures (colonoscopy or sigmoidoscopy) between 2018 and 2024, and for whom an associated report was available. Truveta Data contains de-identified electronic health record (EHR) data from a collective of US health care systems. Screening outcomes were extracted from pathology reports using natural language processing, including findings of polyps (tubular adenoma/adenomatous polyp, hyperplastic polyp, tubulovillous adenoma, sessile serrated adenoma, traditional sessile adenoma, juvenile polyp, and inflammatory polyp), adenocarcinoma, and benign/normal colonic mucosa. For patients with multiple screenings, the first was used. Family history of CRC and related syndromes (e.g., Lynch, Peutz-Jeghers) were similarly extracted from notes. Patient characteristics and screening outcomes were described by 5-year age band, before and after May 2021 USPSTF recommendations. **Results:** Of85,062 patients aged 40-64 who underwent CRC screening, 46,168 had first screening records in May 2021 or earlier ('pre period') and 38,894 after ('post period'). In the pre period, 4,270 (9%) patients were aged 45-49, compared to 7,403 (19%) in the post period. Sex balance improved for the 45-49 age group (56% were female pre vs. 50% post; $p < 0.05$), compared to younger and older age groups (40-44: 57% vs. 57%, 50-54: 48% vs. 48%, 55-59: 51% vs.49%, 60-64: 50% vs. 49%; $<$ 0.05 for 55-59 only). Adenomatous polyp findings increased for all age groups, but to the greatest degree for the 45-49 group (45-49: 45.7% pre vs. 53.4% post; $p < 0.01$) compared to other groups (40-44: 33.1% vs. 35.9%, 50-54: 58.3% vs. 59.9%, 55-59: 60.4% vs. 62.5%, 60-64: 63.2% vs. 64.5%; all $p < 0.05$). In contrast, adenocarcinoma findings occurred less frequently for ages 45-49 (2.1% pre vs. 1.0% post, $p < 0.01$), while remaining stable in both younger and older groups (40-44: 1.6% vs. 1.4%, 50-54: 1.2% vs. 1.1%, 55-59: 1.4% vs. 1.6%, 60-64: 1.3% vs. 1.3%; all $p > 0.05$). **Conclusions:** Following 2021 USPSTF CRC screening recommendations for average-risk adults aged 45-49, sex balance in screening increased, findings of adenomatous polyps increased, and findings of adenocarcinoma declined in this group. These results may reflect expected decreases in adenocarcinoma detection with expansion of screening to average-risk adults, or suggest that recommendations contributed to earlier detection of pre-cancerous polyps, before progression to adenocarcinoma. Additional studies are needed to explore complex causal relationships. Research Sponsor: None.

# Sex differences in chemotherapy completion and adverse events among patients with colon cancer (CALGB/SWOG 80702) (Alliance).

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**Background:** Increasing chemotherapy completion and reducing chemotherapy adverse events (AE) are critical to improve survival after colon cancer diagnosis. Sex, as a biological variable, may impact chemotherapy treatment differently, and thus further investigation is needed to examine sex differences in chemotherapy completion and adverse events among patients with colon cancer. **Methods:** Among an NCI-sponsored trial conducted among patients with stage III colon cancer (CALGB/SWOG 80702), all patients received standard adjuvant chemotherapy FOLFOX (fluorouracil, leucovorin, and oxaliplatin). To signal chemotherapy completion, we utilized relative dose intensity (RDI) calculated as the ratio of the delivered dose intensity to planned dose intensity; and reduced RDI (RDI $<85\%$) was considered as a clinically significant deviation from standard FOLFOX. From clinicians' records of NCI's Common Terminology Criteria for Adverse Events (CTCAE), we primarily focused on clinically significant AE such as neutrophils decrease, nausea, platelets decrease, hypertension, peripheral neuropathy, diarrhea, fatigue, gastritis, creatinine increase, gastric ulcer, myocardial ischemia, and cerebral ischemia; and severe AE was defined as the occurrence of any above AE with CTCAE grade $\geq 3$. Using multivariable logistic regression that adjusted for body surface area (BSA) and other clinicopathological confounders, we estimated adjusted odds ratios (OR) for the associations of sex with reduced RDI and severe AE. **Results:** Of 2201 patients, mean (standard deviation [SD]) age was 60.9 (10.9) years, 1019 (46.3%) were female, 1750 (79.5%) were White, 172 (7.8%) were Hispanic, 964 (43.8%) experienced reduced RDI, and 1156 (52.5%) had severe adverse events. Compared to males, females were at significantly higher risks of experiencing reduced RDI (OR [95% CI]: 1.57 [1.27-1.93], $P<0.001$) and severe AE (OR [95% CI]: 1.73 [1.41-2.12], $P<0.001$). **Conclusions:** Our findings suggested females are more likely than men to experience reduced RDI and severe AE during colon cancer chemotherapy. Clinical Impact: In the era of precision medicine, sex (as a biological variable) should be considered in optimizing colon cancer chemotherapy to improve completion and reduce toxicities. Clinical trial information: NCT01150045. Research Sponsor: National Cancer Institute; U10CA180821; National Cancer Institute; U10CA180882; National Cancer Institute; U24CA196171; National Cancer Institute; U10CA180863; Canadian Cancer Society; CCS707213; National Cancer Institute; UG1CA233234; National Cancer Institute; U10CA180820; National Cancer Institute; U10CA180868; National Cancer Institute; U10CA180888; Pfizer; https://acknowledgments.alliancefound.org; Health and Environmental Sciences Institute.

# Comprehensive analysis of outcomes of patients with colorectal cancer in a racially diverse cohort.

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**Background:** Disparate outcomes have been reported among patients with colorectal cancer (CRC) as those with Medicare or Medicaid insurance and those of Native Hawaiian ancestry experience inferior survival. However, many CRC studies addressing Native Hawaiians and other Pacific Islanders and insurance status have not adjusted for a comprehensive range of confounding variables. In this study, we perform a comprehensive analysis of CRC outcomes adjusted for clinicopathological and socioeconomic factors. **Methods:** Data were abstracted for patients diagnosed with colorectal cancer between 2000 and 2022 in Hawaii. Overall survival of Asians, Whites, and Native Hawaiian or Other Pacific Islanders (NHOPI) was assessed using Cox proportional hazards regression models adjusting for clinical, pathological, and sociodemographic factors. **Results:** A total of 3275 patients were included in the final analysis. NHOPI were more likely to be younger ($p<0.001$), had a higher proportion of stable microsatellite status tumors($p=0.049$) and were more likely to have Medicaid insurance or be uninsured($p<0.001$) compared to Whites and Asians. NHOPI patients more often had high grade cancers compared to White and Asian groups. Medicaid or no insurance was associated with significantly higher mortality compared to private insurance in both univariate(HR: 1.373, 95% CI: 1.202–1.568, $p < 0.001$) and multivariate analysis(HR: 1.505, 95% CI: 1.309–1.729, $p < 0.001$). However, while Medicare showed higher mortality in univariate analysis(HR: 1.409, 95% CI: 1.245–1.594, $p < 0.001$), this association normalized after adjustment(HR: 1.088, 95% CI: 0.958–1.237, $p = 0.195$) (Table). NHOPI had significantly higher mortality compared to Whites after adjustment for variables(HR: 1.293, 95% CI: 1.107–1.510, $p = 0.001$). Interestingly, rectal tumors demonstrated higher mortality compared to right-sided tumors(HR: 1.318, 95% CI: 1.156–1.503, $p < 0.001$), while left-sided tumors showed no significant difference (Table). **Conclusions:** This study of a racially diverse population that NHOPI patients with CRC had significantly worse mortality compared to Whites after adjusting for clinicopathological and socioeconomic variables. We did not identify a significant association between Medicare insurance and increased mortality. Having Medicaid or being uninsured was significantly associated with worse survival outcomes, emphasizing the critical impact of healthcare access on survival. Research Sponsor: None.

**Univariate and multivariate analysis.**

| | Univariate analysis Hazard ratio (95% CI), p-value | Multivariate analysis Hazard ratio (95% CI), p-value |
|---|---|---|
| **Private insurance** | | |
| **Medicaid and Uninsured** | 1.373 (1.202 - 1.568), <0.001 | 1.505 (1.309 - 1.729), <0.001 |
| **Medicare** | 1.409 (1.245 - 1.594), <0.001 | 1.088 (0.958 - 1.237), 0.195 |
| **White** | | |
| **Asian** | 0.947 (0.844 - 1.063), 0.354 | 0.908 (0.808 - 1.02), 0.103 |
| **NHOPI** | 1.143 (0.982 - 1.33), 0.084 | 1.293 (1.107-1.51), 0.001 |
| **Age at diagnosis** | 1.032 (1.028 - 1.036), <0.001 | 1.044 (1.039 - 1.048), <0.001 |
| **Grade 1&2** | | |
| **Grade 3&4** | 1.786 (1.586 - 2.012), <0.001 | 1.485 (1.313 - 1.681), <0.001 |
| **Stage 1** | | |
| **Stage 2** | 1.466 (1.249 - 1.722), <0.001 | 1.401 (1.192 - 1.647), <0.001 |
| **Stage 3** | 1.644 (1.41 - 1.918), <0.001 | 1.64 (1.403 - 1.916), <0.001 |
| **Stage 4** | 6.943 (5.898 - 8.173), <0.001 | 7.681 (6.495 - 9.082), <0.001 |
| **Unknown Stage** | 3.063 (2.525 - 3.714), <0.001 | 2.99 (2.455 - 3.641), <0.001 |
| **Female** | 0.853 (0.775 - 0.939), 0.001 | 0.844 (0.765 - 0.931), <0.001 |
| **MSI Stable** | | |
| **MSI Unstable** | 1.146 (0.808 - 1.626), 0.444 | 1.015 (0.71 - 1.449), 0.936 |
| **Unknown MSI** | 1.197 (1.055 - 1.357), 0.005 | 1.142 (1.003 - 1.3), 0.044 |
| **Right sided** | | |
| **Left sided** | 0.899 (0.802 - 1.007), 0.066 | 1.081 (0.961 - 1.216), 0.197 |
| **Rectal** | 1.016 (0.9 - 1.147), 0.797 | 1.318 (1.156 - 1.503), <0.001 |
| **Time to treatment <31 days** | | |
| **Time to treatment >31 days** | 0.674 (0.593 - 0.766), <0.001 | 1.064 (0.957 - 1.183), 0.09 |

# Dietary risk factors associated with colorectal polyp risk and potential for progression to malignancy.

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**Background:** Colorectal polyp development and progression to cancer are associated with diet and microbial dysbiosis. Red and processed meat intakes have been associated with colorectal polyps, but evidence on probiotic and prebiotic usage is inconclusive. This study examines the association of dietary factors with colorectal adenomas (ADs) and sessile serrated polyps (SSPs) of low and high potential of progression to cancer. **Methods:** In the Colorectal Molecular Atlas Project, 1082 participants underwent a colonoscopy, and completed a questionnaire. Individuals were classified as polyp-free controls, and polyp cases with high potential for progression to cancer ($\geq$ 1 cm, villous component, high-grade dysplasia, or multiple AD and/or SSPs) or low potential (all other AD or SSP cases). Frequency of dietary intake derived from questionnaire responses was divided into quartiles (total meat, total red meat, total processed meat, chicken, and fish) or no intake/tertiles (total probiotic food: yogurt, kefir, sauerkraut, kimchi, fermented cabbage, kombucha, other fermented beverages). Multinomial logistic regression models were used to derive odds ratios and 95%CI after adjusting for confounders. **Results:** Highest intake of total meat was associated with increased risk of high progression potential polyps (OR 1.63, 95%CI 1.03-2.60) and sessile serrated lesions (OR 1.60, 95%CI 1.03-2.50) in comparison to lowest intake. Highest intake of red meat was associated with increased risk of high progression potential polyps (OR 1.80, 95%CI 1.16-2.80) and SSPs (OR 1.68, 95%CI 1.10-2.56) in comparison to lowest intake. The second quartile of fish intake was significantly associated with a reduced risk of polyps with low progression potential (OR 0.63, 95%CI 0.44-0.99) and ADs (OR 0.63, 95%CI 0.42-0.96) compared to lowest intake; however, the third and fourth quartiles were not significantly associated with risk. Chicken, processed meat, probiotic food, probiotic supplement, and prebiotic supplement intake were not associated with risk. **Conclusions:** Dietary risk factors may vary by type of polyp, thus, dietary recommendations should reflect these differences. Increased total and red meat intake may increase risk of polyps with high progression potential and sessile serrated lesions, and fish intake may reduce risk for polyps with low progression potential and adenomas. Probiotics and prebiotics may not be an effective risk reduction strategy. Research Sponsor: None.

# Characterizing clinical outcomes and DNA co-alterations of ERBB2-amplified colorectal cancer.

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**Background:** A subset of colorectal cancer (CRC) features amplification (amp) of the ERBB2 gene. The prognostic role and treatment in these patients are poorly understood. This study aims to characterize the clinical outcomes and molecular profiles of ERBB2-amp CRC. **Methods:** This is a retrospective analysis of clinical outcomes data and next-generation sequencing at MD Anderson from 2006-2025 in patients with ERBB2-amp CRC including all classes of genomic alterations (GA) in other genes. Progression-free survival (PFS) and overall survival (OS) were assessed by Kaplan-Meier, log-rank, and cox regression. Chi square goodness of fit was assessed for the proportion of left versus right sided CRC. **Results:** 100 pts with ERBB2-amp CRC were identified. Patients (Table) who received ERBB2-directed therapy (n = 36) did not have significantly longer OS compared to those who received other systemic therapy (n = 57) (53.8 vs. 45.5 m, p = 0.35). Patients who underwent surgery (n = 64) (56.8 vs. 23.2 m, p = 0.01) or non-surgical localized therapy (n = 45) had longer OS (64.4 vs 45.5 m, p = 0.01). ERBB2-amp was more associated with left sided CRC (n = 80) than right-sided CRC (n = 19) ($X^2$= 39.34, df = 1, $p < 0.0001$) but there was no significant OS difference (53.8 vs. 45.5 m, p = 0.76). Median PFS (mPFS) for all 1st (n = 93), 2nd (n = 80), and 3rd line (n = 61) systemic therapy was 8.0, 5.1, and 4.9 m, respectively. mPFS for all ERBB-2 directed therapy (n = 59) was 3.5 m. The most common concurrent co-GA were TP53 (90%) and APC (64%) and most common co-amp were CDK12 (31%) and EGFR (23%). Concurrent APC mutation was associated with improved OS (53.8 vs. 26.2 m, p = 0.003). No other co-GA or co-amp, including KRAS, showed significant survival outcome associations. TP53 co-GA was present in 90% of both left and right-sided ERBB-2 CRC and KRAS co-GA in 15% and 32%, respectively. **Conclusions:** There was no difference in OS in ERBB2 amp CRC in patients who received ERBB2 directed therapy, however patients had improved OS with surgery or localized therapy options and should be offered to eligible patients if possible. Co-GA with APC mutation correlated with improvement in survival outcomes. Research Sponsor: None.

**Baseline data, initial staging, treatments, and mutational profile for ERBB2 co-amp CRC.**

| Age at Diagnosis (median) | 55 years |
|---|---|
| **Gender – no.** | M (56), F (44) |
| **Stage at Initial Diagnosis – no.** | I (6), II (6), III (18), IV (69) |
| **Location of Primary Tumor – no.** | R-sided (19), L-sided (80), Cecum (7), Ascending (8), Transverse (5), Descending (7), Sigmoid/Rectum (73) |
| **Surgery – no.** | Primary tumor (55), Liver metastectomy (24), Lung metastectomy (8) |
| **Localized Therapy – no.** | RT (36), Ablation (6), Y90 (4), Cryotherapy (1) |
| **ERBB2 Directed Therapy (excluded if n=1) – no.** | Trastuzumab (TRA) + Pertuzumab (20), ERBB2-directed trial drug (14), Trastuzumab deruxtecan (8), TRA (7), TRA + Tucatinib (4) |
| **Mutational Profile** | Co-GA: TP53 (90%), APC (64%), SMAD4 (18%), KRAS (18%)<br>Co-amp: CDK12 (31%), EGFR (23%), MYC (19%), BRAF (13%) |

# Effects of marital status on survival in patients with colorectal cancer.

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**Background:** Demographic factors such as marital status have been shown to have differential effects on cancer outcomes. It has been shown that married patients have higher 5-year survival rates compared with unmarried patients with colorectal cancer (CRC). However, most of these studies looked at patients diagnosed prior to 2015. This study compares the survival trends between 2000–2010 and 2011–2021 and analyzes marital status associations with stage at diagnosis. **Methods:** Patients with CRC diagnosed between 2000 and 2021 were identified in the SEER database and stratified by marital status (single, separated/divorced/widowed (SDW), and married). 5-year survival rates with 95% confidence intervals were calculated for each marital status group across three periods: 2000–2010, 2011–2021, and 2000–2021. Kaplan-Meier survival analysis was used to compare survival outcomes across these variables. Disease severity was classified into three stages: localized, regional, and distant. The distribution of patients across disease stages is reported as the proportion of individuals within each marital status group at each cancer stage. **Results:** Overall survival was statistically different amongst patients with different marital statuses ($p < 0.01$). Our results show that the highest 5-year overall survival rate is seen in married individuals at 62.1% (61.9% - 62.2%), followed by single individuals at 53.0% (52.6% - 53.3%), and SDW individuals at 44.6% (44.3% - 44.8%). Overall survival improved over time across all marital groups when comparing the 2000–2010 and 2011–2021 periods. For married individuals, 5-year overall survival rate increased from 61.2% (61.0%–61.4%) to 63.1% (62.9%–63.4%). Similarly, survival improved for single individuals (51.1% [50.6%–51.6%] to 54.5% [54.0%–54.9%]) and for SDW individuals (43.8% [43.5%–44.1%] to 45.7% [45.3%–46.1%]). Our results show that married individuals were most commonly diagnosed with localized cancer compared with single and SDW individuals (41.8% vs 36.5% vs 39.0%, $p < 0.01$), SDW individuals with regional cancer compared with single and married individuals (38.3% vs 37.06% vs 37.5%, $p < 0.01$) and single individuals with distant disease compared with married and SDW individuals (26.4% vs 20.69% vs 22.69%, $p < 0.01$). **Conclusions:** Marital status significantly impacts CRC survival, with married individuals having higher survival rates than single or SDW patients. This suggests that social support may contribute to improved outcomes, although it is important to note that the higher survival rates may be associated with earlier diagnosis in married individuals. These findings highlight the potential need for additional support services for single and SDW individuals, underscoring the importance of considering marital status when addressing demographic disparities in cancer care. Research Sponsor: None.

# Clinicopathological features of colorectal cancer in adolescents and young adults (AYA) at a tertiary referral centre in Nigeria.

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**Background:** Colorectal cancer (CRC) is traditionally considered a disease of older adults; however, its incidence among AYA has been rising globally. In sub-Saharan Africa, including Nigeria, there is limited data on the clinicopathological characteristics of CRC in this age group. Understanding the patterns of CRC in AYA in Nigeria is crucial for developing targeted screening, early detection, and treatment strategies in this population. This study aims to investigate the clinicopathological features of CRC in AYA at a tertiary referral centre in Nigeria. **Methods:** A retrospective review of the ARGO-OAUTHC database was conducted to identify adolescents and young adults (age less than 40) diagnosed with colorectal cancer between 2013 and 2024. We compared AYA patients with middle-aged adults (ages 40-65) to assess differences in clinical presentation and histopathological features. Only patients with complete histopathology were included in the analysis while patients older than 65 years were excluded. Descriptive statistics were used to summarize the data, and statistical tests were performed to assess significant differences between the two groups. **Results:** 866 patients diagnosed with CRC were identified. Of these, 150 (18%) were AYA, with a median age of 33 years, and 448 (54%) were middle-aged adults (ages 40-65). The presenting symptoms were similar between the AYA and middle-aged groups, however, AYA patients were less likely to be diagnosed by colonoscopy (14.9% vs 29.4%, p = 0.002). Additionally, more AYA patients presented with symptoms that did not limit their daily activities , leading to a delay in seeking medical attention (9.3% vs 2.8%, p = 0.016). AYA patients were less likely to present with early-stage disease (Stages I and II) compared to middle-aged patients, (13.1% vs 20.9%, p = 0.045). Histopathological features were similar between the two groups overall, though mucin production was more prevalent in AYA patients (64.1% vs 45.2%, p = 0.044). Lung metastasis was less common in AYA patients (8.3% vs 23.5%, p = 0.011), the pattern of metastasis to other organs was however similar between the two groups. **Conclusions:** AYA patients in Nigeria tend to present at more advanced stages, partly due to the non-restrictive nature of their symptoms. They were less likely to be diagnosed via colonoscopy and were more likely to exhibit mucin production in their tumors. These findings underscore the need for increased awareness and early screening efforts for colorectal cancer in AYA populations to facilitate earlier diagnosis. Research Sponsor: African Research Group for Oncology.

# Adherence to repeat screening for colorectal cancer using the multi-target stool DNA test: Real-world analysis of patients from federally qualified health centers.

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**Background:** Initial and repeat colorectal cancer (CRC) screening rates are suboptimal and fall short of national goals in adults from historically disadvantaged backgrounds. This real-world study examined adherence to repeat mt-sDNA screening among patients from federally qualified health centers (FQHCs) across the US and among different payer types. **Methods:** Laboratory data from Exact Sciences Laboratories LLC were utilized for the period between January 1, 2023, and December 31, 2023, for those who had previously completed a mt-sDNA test. Study outcomes included adherence rate to mt-sDNA repeat screening and time to test return. The mt-sDNA screening adherence rate was defined as the percentage of patients who completed and returned the test kit and received a valid test result within 180 days of the initial shipment date. Time to test return was defined as the number of days from the date the test kit was shipped to the patient to the date ESL received the test kit with a specimen. **Results:** The study sample consisted of 19,536 eligible patients, including 9,592 (49.1%) aged 45-64 years, 8,689 (44.5%) aged 65-75 years and 1,225 (6.4%) aged 76-85 years. Overall, the mt-sDNA repeat screening adherence rate was 79.7% and the mean time to return the kit was 21.1±20.8 days. A total of 2,375 (15.3%) individuals tested positive for CRC. Screening adherence for patients with Medicare was 84.7%, Medicare Advantage was 80%, commercial insurance was 78.2%, managed care organization was 74.6% and Medicaid was 65.9% ($p < 0.001$). Compared with patients covered by commercial insurance, those covered by Medicaid had 42% lower odds of adhering to mt-sDNA screening (OR: 0.582, 95% CI]: 0.461-0.733, $p < 0.001$). Patients with 2 or more prior successful tests had a numerically shorter mean time to test return compared to those with only 1 prior successful test, both overall and within each payer type. **Conclusions:** Findings from this real-world study suggest that patients receiving care from FQHCs had relatively high repeat mt-sDNA screening rates. While repeat screening adherence was generally high across patient demographic categories, there were significant differences by type of insurance coverage and number of prior successful mt-sDNA screenings.
Research Sponsor: None.

# Quality-adjusted time without symptoms of disease or toxicity (Q-TWiST) analysis of pembrolizumab (pembro) versus chemotherapy (chemo) in microsatellite instability–high (MSI-H)/mismatch repair–deficient (dMMR) metastatic colorectal cancer (mCRC) in the KEYNOTE-177 trial.

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**Background:** In KEYNOTE-177 (NCT02563002),first-line pembro provided significantly longer progression-free survival and a trend toward improvement in overall survival (OS) compared with chemo in participants (pts) with MSI-H/dMMR mCRC after > 5 years of median follow-up. The objective of this analysis was to assess Q-TWiST for pts treated in KEYNOTE-177. **Methods:** Q-TWiST combines efficacy, safety, and quality of life in a single measure. The analysis categorized survival time into 3 health states: time with grade ≥3adverse events before disease progression or death (toxicity [TOX]), time without symptoms or toxicity before disease progression (TWiST), and time from disease progression to death (relapse [REL]). In all randomly assigned pts, the restricted mean survival time (RMST) in each state was first weighted by a quality-of-life utility value, measured as treatment-specific EQ-5D-3L scores for each health state using the US value set, and then summed to calculate the Q-TWiST value. Relative gains (defined as the Q-TWiST differences between pembro and chemo divided by the RMST of chemo) of ≥15% were defined as "clearly clinically important." Treatment difference 95% CIs were generated using the nonparametric bootstrapping method. The data cutoff date was July 17, 2023. **Results:** At a maximum follow-up of 84 months, pts in the pembro arm had a 13.8-mo (95% CI, 4.8-21.7) longer RMST in TWiST (24.3 vs 10.5 mo), a 4.8-mo (95% CI, −0.5 to 10.2) longer RMST in TOX (10.7 vs 5.9 mo), and an 11.1-mo (95% CI, −21.2 to −0.8) shorter RMST in REL (18.1 vs 29.3 mo) compared with chemo. As a proportion of overall preprogression time, pts in the pembro arm spent less time in TOX than the chemo arm (31% vs 36%). For the analysis of restricted mean Q-TWiST based on treatment-specific utility weights, the difference between pembro and chemo favored pembro by 9.1 mo (95% CI, 2.3-15.5), a 20.0% (95% CI, 4.8-36.8) relative Q-TWiST gain. When TOX definition included grade ≥2 adverse events, the relative Q-TWiST gain was 19.7% (95% CI, 4.7-36.5). When OS was adjusted for crossover to anti–PD-(L)1 therapy as second-line treatment, relative Q-TWiST gain was 39.7% (95% CI, 20.1-63.7). **Conclusions:** Pembro provided clearly clinically important improvement in quality-adjusted survival time based on Q-TWiST analyses compared with chemo as first-line treatment in pts with MSI-H/dMMR mCRC. The magnitude of results related to established thresholds for clinically important Q-TWiST gain suggests that results from this analysis provide additional evidence for the use of pembro in this population. Clinical trial information: NCT02563002. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

# Association between fine particulate matter exposure and colorectal cancer mortality by age at diagnosis: Insights from county-level analysis in the United States.

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**Background:** Colorectal cancer (CRC) remains a leading cause of cancer mortality in the U.S., with environmental factors like air pollution potentially contributing to mortality. This study examines the association between fine particulate matter (PM2.5) exposure and CRC mortality rates, stratified by average-onset (aoCRC [≥50 years at diagnosis]) and early-onset (eoCRC [ < 50 years at diagnosis]) cases. **Methods:** Age-adjusted county CRC mortality data (1999–2020, n = 2981 counties) were obtained from CDC Underlying Cause of Death (ICD-10: C18-C19 [excluding C18.1], C20), while 1999-2019 PM2.5 estimates (ug/m3), derived from Atmospheric Composition Analysis Group data, were mapped to U.S. county boundaries using R v.4.3.2. Covariates were derived from Census American Community Survey (ACS) 5-year estimates, CDC data, and County Health Rankings (CHR) data and included county-level area deprivation index (ACS), non-Hispanic Black % (ACS), Hispanic % (ACS), obesity prevalence (CDC), smoking prevalence (CHR), binge alcohol consumption (CHR), and uninsured % (ACS). Negative binomial count models were fit to explore associations between PM2.5 and CRC mortality rates, adjusted for covariates. Deviance $R^2$ was computed to examine model fits. **Results:** We found that for every 1% increase in PM2.5 exposure, aoCRC mortality increased by 0.98% ($p < 0.001$) and eoCRC mortality increased by 0.24% ($p = 0.435$), after adjustment for covariates. Deviance $R^2$ values indicated that PM2.5 and covariates explained 32.0% and 37.0% of the deviance in aoCRC and eoCRC mortality, respectively. **Conclusions:** PM2.5 exposure was a significant predictor of CRC mortality, but only for aoCRC cases. Air pollution and other covariates accounted for roughly one-third of the county-level deviance, suggesting the influence of additional factors. Systemic and individual-level interventions to reduce air pollution exposure may mitigate CRC mortality disparities in older populations. Further studies are needed to explore other potential contributors to CRC mortality. Research Sponsor: None.

**TPS3633** **Poster Session**

# A phase II study of pembrolizumab, carboplatin, paclitaxel, and radiation for the treatment of early-stage anal cancer: Big Ten Cancer Research Consortium GI22-588.

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**Background:** Anal squamous cell carcinoma (SCC) is an evolving public health challenge, with increasing incidence and mortality rates, particularly in older women with long-standing HPV infections. Standard-of-care treatment for early-stage anal SCC—5-fluorouracil (5FU) and mitomycin-C (MMC) with radiation—achieves high cure rates but poses significant toxicity risks, with grade 3-5 adverse events occurring in up to 70% of patients. Recent clinical trials, such as DECREASE and ACT4, have explored radiation de-escalation strategies, but limited progress has been made in expanding systemic treatment options for locally advanced disease. Building on pilot data demonstrating favorable clinical complete responses (cCR) with carboplatin and paclitaxel combined with radiation in patients ineligible for SOC regimens, this phase II trial evaluates the addition of pembrolizumab to this combination to enhance efficacy while reducing toxicity. **Methods:** This is a single-arm, phase II trial evaluating concurrent chemoradiation with weekly carboplatin (AUC 2), paclitaxel (50 mg/m$^2$), and pembrolizumab (200 mg every three weeks during chemoradiation and 400 mg every six weeks during maintenance) for early-stage anal SCC in patients ineligible for 5FU and MMC. The chemoradiation phase consists of up to six weeks of therapy with 50.4 Gy delivered over 28 fractions. Maintenance pembrolizumab is administered for up to eight cycles. The primary endpoint is the cCR rate at six months post-chemoradiation. Secondary endpoints include safety, tolerability, tumor downstaging, and disease-free survival. Exploratory objectives include the evaluation of genomic alterations and biomarkers such as versican and keratin 17 as predictors of therapeutic response. Major eligibility criteria include histologically confirmed stage I-IIIA anal SCC, measurable disease per RECIST v1.1, and treatment-naïve status. Key exclusions include active autoimmune disease requiring immunosuppression within two years and prior checkpoint inhibitor therapy. The target enrollment is 23 patients, with an accrual period of 12 months and an anticipated study duration of two years. The study is currently enrolling participants through the Big Ten Cancer Research Consortium. Clinical trial information: NCT06493019. Research Sponsor: Merck.

TPS3634 Poster Session

# Alliance A022101/NRG-GI009: A pragmatic randomized phase III trial evaluating total ablative therapy for patients with limited metastatic colorectal cancer—Evaluating radiation, ablation, and surgery (ERASur).

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**Background:** For patients with oligometastatic colorectal cancer (CRC), aggressive local therapy of isolated metastases, particularly in the liver, has been associated with long-term progression-free and overall survival (OS) primarily based on retrospective evidence. However, in patients with limited metastatic CRC that is deemed inoperable or those with additional disease outside of the liver or lungs, the role of local ablative therapies, including microwave ablation (MWA) and stereotactic body radiation therapy (SBRT), to render patients disease free is less clear. Despite the long history of treating oligometastatic CRC with local therapy, which is largely provider biased, questions remain regarding the benefit of extending the paradigm of metastatic directed therapy to patients with more extensive disease. This trial seeks to use a pragmatic multimodality approach that mirrors the current clinical dilemma. This study is designed to evaluate the safety and efficacy of adding total ablative therapy (TAT) of all sites of disease to standard of care systemic treatment in those with limited metastatic CRC. **Methods:** A022101/NRG-GI009 is a National Clinical Trials Network randomized phase III study planned to enroll 364 patients with newly diagnosed metastatic CRC (BRAF wild-type, microsatellite stable) without peritoneal metastasis or liver-only disease on baseline imaging. Patients receive first-line systemic therapy for 12-39 weeks. Patients with ≤4 sites of metastatic disease following initial systemic therapy that are amenable to any combination of surgical resection, MWA, and/or SBRT are then randomized 1:1, stratified by number of metastatic organ sites (1-2 vs. 3-4), timing of metastatic disease diagnosis (de novo vs. secondary), and presence of metastatic disease outside the liver/lungs in at least 1 site. Patients in Arm 1 will receive TAT consisting of treatment of all metastatic sites with SBRT, MWA, and/or surgical resection followed by standard of care systemic therapy. Patients in Arm 2 will continue with standard of care systemic therapy alone. The primary endpoint is OS. Secondary endpoints include event-free survival, treatment-related toxicities, and local recurrence with exploratory biomarker analyses. The study needs 346 evaluable patients combined in the 2 arms to demonstrate an improvement in OS with a hazard ratio of 0.7 to provide 80% power with a one-sided alpha of 5%. The trial utilizes a group sequential design with two interim analyses (25% and 50% of events) for futility. The trial activated in January 2023 and recruitment is ongoing. Support: U10CA180821, U10CA180882; https://acknowledgments.alliancefound.org. U10CA180820 (ECOG-ACRIN); U10CA180868 (NRG); U10CA180888 (SWOG); Clinical trial information: NCT05673148. Research Sponsor: U.S. National Institutes of Health.

TPS3635 Poster Session

# Telisotuzumab adizutecan (ABBV-400; Temab-A) monotherapy vs trifluridine/tipiracil plus bevacizumab in patients with refractory metastatic colorectal cancer with increased c-Met protein expression: An open-label, randomized, phase 3 trial.

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**Background:** c-Met protein expression is increased in several solid tumors, including colorectal cancer (CRC). Temab-A is a c-Met–directed antibody-drug conjugate consisting of the antibody telisotuzumab conjugated to a potent topoisomerase 1 inhibitor payload. Preliminary data from the ongoing first-in-human study of Temab-A (NCT05029882) indicate a tolerable safety profile and promising antitumor activity in patients with third-line or later metastatic (m)CRC (Sharma et al. *JCO* 2023;41:3015). Herein, we describe a phase 3 study comparing Temab-A monotherapy with the standard of care (trifluridine/tipiracil plus bevacizumab) in patients with refractory mCRC with c-Met expression of 3+ in ≥10% of tumor cells by immunohistochemistry (IHC). **Methods:** This is an open-label, randomized, controlled, global phase 3 study(NCT06614192). Patient eligibility includes age ≥18 years, confirmed c-Met expression of 3+ in ≥10% of tumor cells, metastatic adenocarcinoma of the colon/rectum, measurable disease per RECIST v1.1, ECOG performance status 0–1, prior treatment with a fluoropyrimidine (eg, 5-FU or capecitabine), oxaliplatin, irinotecan, and an anti-VEGF antibody (unless locally not approved) or an anti-EGFR antibody if indicated, and appropriate targeted therapy or immunotherapy if targetable mutations present (eg, *BRAF* V600E or *HER2*) or MSI-H/dMMR. Prior treatment with regorafenib and/or fruquintinib is permitted, but no prior treatment with trifluridine/tipiracil Study-specific c-Met protein expression IHC cutoff is defined as 3+ intensity in ≥10% of tumor cells. The study consists of 2 stages. In stage 1, at least 60 patients will be randomized 1:1 to receive 2 different doses of intravenous (IV) Temab-A. In stage 2, 400 patients will be randomly assigned 1:1 to receive either the optimized dose of IV Temab-A or oral trifluridine/tipiracil plus IV bevacizumab. In stage 1, primary objectives are to determine the recommended phase 3 dose and to evaluate the efficacy, as measured by objective response (OR), and safety of Temab-A; secondary objectives are to assess progression-free survival (PFS), overall survival (OS), duration of response (DOR), disease control rate (DCR), and pharmacokinetics. In stage 2, the primary objectives are to demonstrate the superiority of Temab-A over trifluridine/tipiracil plus bevacizumab in terms of OR and OS; secondary objectives are to evaluate PFS, DOR, DCR, and safety of Temab-A treatment, and its impact on patient-reported outcomes. Response will be assessed by blinded independent central review per RECIST v1.1. Safety evaluations include adverse event monitoring, vital sign measurements, ECG variables, and clinical laboratory testing. Enrollment began in December 2024. Clinical trial information: NCT06614192. Research Sponsor: AbbVie Inc.; n/a.

**TPS3636** **Poster Session**

# OrigAMI-2: A randomized, phase 3 study of amivantamab vs cetuximab, both in combination with FOLFOX or FOLFIRI, as first-line treatment in left-sided *RAS/BRAF* wild-type metastatic colorectal cancer.

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**Background:** Approximately 50% of patients diagnosed with metastatic colorectal cancer (mCRC) are wild-type for *KRAS*, *NRAS*, and *BRAF* (*RAS/BRAF* WT). Standard initial therapy for left-sided *RAS/BRAF* WT mCRC is doublet chemotherapy (FOLFOX or FOLFIRI) combined with anti-EGFR therapy. However, resistance is nearly inevitable. *MET* alterations are known resistance mechanisms to EGFR inhibition, with *MET* amplification occurring in 5%-23% of EGFR-resistant mCRC. Amivantamab is an EGFR-MET bispecific antibody with immune cell-directing activity that is approved by the FDA for 4 indications in *EGFR*-mutated advanced non-small cell lung cancer. In the phase 1b/2 OrigAMI-1 study (NCT05379595), the combination of amivantamab plus FOLFOX or FOLFIRI demonstrated rapid and durable antitumor activity, regardless of tumor sidedness, in participants with *RAS/BRAF* WT mCRC (Pietrantonio ESMO 2024). The objective of this phase 3 randomized study is to assess the efficacy of amivantamab, as compared with cetuximab, both in combination with FOLFOX or FOLFIRI, as first-line therapy for participants with left-sided *RAS/BRAF* WT unresectable or metastatic CRC. **Methods:** The multicenter, global OrigAMI-2 study (NCT06662786) is planned to open in 216 sites in 21 countries. Eligible participants will be WT for *KRAS*, *NRAS*, and *BRAF* by local testing, have left-sided unresectable or metastatic colorectal cancer, and be treatment-naïve for advanced disease. Left-sided disease will be defined as a primary tumor arising from the splenic flexure, descending colon, sigmoid colon, rectosigmoid, or rectum. Key exclusion criteria include known dMMR/MSI-H status, HER2-positive or amplified tumor, and prior exposure to EGFR or MET targeting agents. Approximately 1000 participants will be randomly assigned 1:1 to receive subcutaneous amivantamab (co-formulated with recombinant human hyaluronidase [rHuPH20]) or intravenous cetuximab, both combined with FOLFOX or FOLFIRI (investigator's choice). Randomization will be stratified by chemotherapy choice (FOLFOX or FOLFIRI), limited disease (yes or no), and prior adjuvant therapy (yes or no). The primary endpoint will be progression-free survival by blinded independent central review. Secondary endpoints include overall survival, objective response rate, duration of response, and patient-reported outcomes. Safety assessments will include monitoring adverse events and laboratory abnormalities. Clinical trial information: NCT06662786. Research Sponsor: Janssen Research & Development, LLC, a Johnson & Johnson Company.

TPS3637 Poster Session

# An observational/translational study to conduct real-world evidence and develop biomarkers of fruquintinib for patients with metastatic colorectal cancer (mCRC): FruBLOOM trial (JACCRO CC-19).

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**Background:** The FRESCO-1/2 trials demonstrated a survival benefit of fruquintinib (FRU) in mCRC after 3rd-line therapy. FRU can be considered as one of the standard treatments for mCRC. The FRESCO-2 trial was conducted in patients (pts) treated with FTD/TPI and/or regorafenib (Rego) and did not include pts who were not using either agent. Although FTD/TPI + bevacizumab (Bev) is currently one of 3rd-line standard treatments for mCRC, there are few data regarding the efficacy and safety of FRU in pts after FTD/TPI + Bev. Therefore, this study will accumulate real-world-data of FRU in clinical practice and evaluate the efficacy and safety of FRU after FTD/TPI + Bev. Also, we will evaluate clinical outcomes of FRU as 3rd- or later-line treatment after both FTD/TPI + Bev and Rego. The predictive biomarkers of FRU in the later-line setting hold significant clinical promise, for choosing personalized treatment plans (e.g., FRU vs. FTD/TPI + Bev / Rego) and enhancing the prognosis of mCRC pts. Therefore, this translational study approaches developing biomarkers for predicting FRU efficacy by analyzing pre-treatment blood samples. Furthermore, we will explore treatment resistance mechanisms using post-treatment blood samples. **Methods:** This is a multicenter observational/translational study to prospectively evaluate the efficacy and safety of FRU as a 3rd- or later-line treatment, mainly after FTD/TPI + Bev in mCRC pts in clinical practice. We will enroll 200 pts receiving FRU after FTD/TPI + Bev to the cohort A, and 100 pts receiving FRU as 3rd-line or after both FTD/TPI + Bev and Rego to the cohort B. Eligibility criteria are (1) pts with CRC confirmed as adenocarcinoma, (2) pts planning to receive FRU monotherapy as 3rd- or later-line treatment, (3) prior treatments with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, an anti-EGFR therapy (if *RAS*/*BRAF* wild-type), BRAF therapy (if *BRAF* mutant), and immune checkpoint inhibitor (if MSI-high), (4) pts with ECOG Performance Status of 0-2, (5) pts must be at least 18 years of age at the time of consent, and (5) pts have measurable or evaluable lesions in RECIST v1.1. The primary endpoint is overall survival in pts of the cohort A. The secondary endpoints are clinical outcomes including response rate, progression-free survival, duration of response, and safety in pts of the cohort A and B. In the biomarker study, blood samples will be prospectively collected before and after treatment, for translational research including genomic alteration analysis in circulating tumor-DNA by DNA exome sequencing, gene expression measurement in cfRNA by tumor-educated blood platelets (TEP)-Seq RNA analysis, and plasma proteins analysis by multiplex immunoassay panels. Enrollment opens in February 2025 (UMIN000056813). Clinical trial information: UMIN000056813. Research Sponsor: Takeda.

TPS3638 Poster Session

# OrigAMI-3: A randomized, phase 3 study of amivantamab plus FOLFIRI vs cetuximab or bevacizumab plus FOLFIRI in participants with recurrent, unresectable, or metastatic *RAS/BRAF* wild-type colorectal cancer.

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**Background:** Among patients with metastatic colorectal cancer (mCRC), approximately 50% are wild-type for *KRAS*, *NRAS*, and *BRAF* (*RAS/BRAF* WT) without actionable genomic alterations. Standard first-line therapy for *RAS/BRAF* WT mCRC is 5-FU-based doublet chemotherapy (FOLFOX or FOLFIRI) plus anti-EGFR or anti-VEGF therapy. The choice of second-line treatment is dependent on first-line treatment (eg, oxaliplatin-based chemotherapy in the first-line necessitates irinotecan-based in the second-line, and vice versa). Known resistance mechanisms to anti-EGFR therapy are *MET* alterations, with *MET* amplification occurring in 5%-23% of EGFR-resistant mCRC and increasing in prevalence over subsequent lines of therapy. Amivantamab is an EGFR-MET bispecific antibody with immune cell-directing activity and is FDA-approved for 4 indications in *EGFR*-mutated advanced non-small cell lung cancer. In the phase 1b/2 OrigAMI-1 study (NCT05379595), amivantamab plus FOLFIRI demonstrated promising antitumor activity, independent of line of therapy, in participants (pts) with *RAS*/*BRAF* WT mCRC without prior anti-EGFR exposure (Pietrantonio ESMO 2024). The objective of this phase 3 randomized study is to assess the efficacy of amivantamab plus FOLFIRI vs cetuximab or bevacizumab plus FOLFIRI, as second-line therapy for pts with recurrent *RAS*/*BRAF* WT mCRC. **Methods:** The global OrigAMI-3 study (NCT06750094) is planned to open in 230 sites in 25 countries. Eligible pts will be WT for *KRAS*, *NRAS*, and *BRAF*, have recurrent unresectable or mCRC, and must have had disease progression on one prior line of systemic therapy for metastatic disease (prior regimen must be fluoropyrimidine-based and oxaliplatin-based therapy). Pts with treated, stable, and asymptomatic brain metastases are allowed. Key exclusion criteria include known dMMR/MSI-H status without prior immunotherapy, HER2-positive or amplified tumor, and prior exposure to irinotecan or agents targeting EGFR or MET. Approximately 700 pts will be randomly assigned 1:1 to receive subcutaneous amivantamab (co-formulated with recombinant human hyaluronidase [rHuPH20]) plus FOLFIRI vs intravenous cetuximab or bevacizumab (investigator's choice, per local guidelines) plus FOLFIRI. Randomization will be stratified by choice of cetuximab or bevacizumab, primary tumor location (left vs right-sided), duration of first-line therapy ($< 6$ months or $\geq 6$ months), and prior anti-VEGF therapy (yes or no). The dual primary endpoints will be progression-free survival by blinded independent central review and overall survival. Secondary endpoints include objective response rate, duration of response, and patient-reported outcomes. Safety assessments will include monitoring adverse events and laboratory abnormalities. Clinical trial information: NCT06750094. Research Sponsor: Janssen Research & Development, LLC, a Johnson & Johnson company.

**TPS3639** **Poster Session**

# Stereotactic body radiotherapy combined with PD-1 antibody in unresectable colorectal liver metastases: A prospective, multicenter, single-arm, phase II study (SPARKLE-L).

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**Background:** Colorectal cancer liver metastasis (CRLM) significantly decreases colorectal cancer (CRC) patient prognosis, affecting 30-50% of CRC patients at diagnosis or thereafter. Notably, up to 70%-90% CRLM are diagnosed as unresectable. Standard treatments include systemic chemotargeted-therapies (CT). However, only 10-30% CRLM can be converse to resectable state by CT, with an objective response rate (ORR) of just 15%-20% and a median overall survival (OS) of approximately 20-30 months. Improving prognosis of CRLM patients remains challenging. Stereotactic body radiation therapy (SBRT) combined with immunotherapy might offer promising alternatives. SBRT provides high-dose tumor control while protecting surrounding tissues better than conventional radiotherapy. It also facilitates the release of tumor-associated antigens, reshaping the immune microenvironment and inducing stronger immune responses. The combination of SBRT and PD-1 antibodies might synergistically enhance the anti-tumor efficacy. Despite SBRT's demonstrated efficacy in unresectable CRLM with few adverse reactions, no prospective studies have explored its combination with PD-1 antibodies. **Methods:** This is a multicenter, open-label, single-arm, phase II trial conducted in China. Patients will receive SBRT at 8-12 Gy per fraction over 5 fractions, combined with 5-FU-based CT and PD-1 antibody therapy before and after SBRT. Eight weeks ($\pm$2 weeks) post SBRT, imaging assessments or multi-point liver biopsies will be performed. Multidisciplinary teams (MDT) will determine subsequent plans: cCR/pCR patients will undergo maintenance CT or enter a watch-and-wait phase; non-cCR/pCR patients will continue maintenance CT or exit the study. This is the first study exploring whether SBRT combined with PD-1 monoclonal antibody can improve ORR, OS, quality of life (QOL) and potentially achieve no evidence of disease (NED) status for unresectable CRLM. Key inclusion criteria: pMMR/MSS CRC, MDT-assessed unresectability due to main portal vein invasion, multiple hepatic vein invasion or lack of R0 resection/ablation feasibility. Main exclusion criteria encompass active hepatitis, cirrhosis, Child-Pugh B/C, checkpoint inhibitor therapies history and ECOG performance status $\geq$2. Twenty-four patients are planned for enrollment, with two already enrolled as of January 25, 2025. The study is registered with ClinicalTrials.gov (NCT06794086) and is ongoing. Clinical trial information: NCT06794086. Research Sponsor: None.

TPS3640 Poster Session

# Neoadjuvant cetuximab plus tislelizumab combined with chemotherapy in pMMR RAS/BRAF wild-type (wt) locally advanced rectal cancer (LARC): A prospective, multicenter, phase II study.

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**Background:** For patients (pts) with locally advanced rectal cancer (LARC), chemoradiotherapy followed by total mesorectal excisionis is recommended as standard therapy according to the NCCN guidelines. However, there is no stratification strategy for neoadjuvant therapy based on molecular alterations, and radiotherapy is insufficient with pathologic complete response (pCR) rates at 11%-15%. There is an urgent need for new therapeutical options to improve the pCR rate in these pts. Adding anti-EGFR therapy to neoadjuvant chemotherapy may improve progression-free survival for RAS/BRAF WT LARC pts. Furthermore, previous studies demonstrated that combining anti-EGFR with immune checkpoint inhibitors could further improve pCR rate. Cetuximab, an anti-EGFR monoclonal antibody, has gained FDA approval for RAS WT metastatic colorectal cancer. Tislelizumab, an anti-PD-1 monoclonal antibody, is effective in blocking PD-1/PD-L1 interaction in preclinical experiments. This study introduces an innovative approach, combining Cetuximab, Tislelizumab and chemotherapy, as a total neoadjuvant therapy for pMMR RAS/BRAF wt LARC pts. **Methods:** This prospective, multi-center, phase II study investigated the efficacy and safety of neoadjuvant treatment with FOLFOX chemotherapy plus Cetuximab and Tislelizumab for MSS-RAS/BRAF WT LARC. Eligible participants were 18 years or older, with an ECOG PS of 0–2, primary, and a biopsy-proven tumors meeting all the following criteria: clinical tumour stage cT3-4 N0M0 or cT1-4N+M0, tumor distance from the anus≦10 cm, no distant metastasis. Pts initially received a cycle chemotherapy of FOLFOX pending genetic results. Eligible pts with MSS-RAS/BRAF WT LARC then underwent 5 preoperative neoadjuvant cycles of mFolfOx6 (oxaliplatin 85 mg/m$^2$, D1; leucovorin 200 mg/m$^2$,D1; 5-FU bolus 400 mg/m2 D1 then 2.4 g/m$^2$,D2-3) + Cetuximab (500mg/m2, D1, q2w) + Tislelizumab (200mg, D1, q2w). Subsequently, pts underwent TME about 4 weeks after the last cycle. Imaging evaluation will be conducted 6 weeks after the initiation of treatment, pts with regressed tumors will receive a standard chemoradiotherapy. The primary endpoint was pCR rate. Secondary endpoints included the Neoadjuvant Rectal Score, Objective Response Rate, R0 resection rate, Major Pathological Response rate, Anal Sparing rate, 3-year Disease-Free Survival, 3-year Local Recurrence Rate, 3-year Overall Survival. Based on a review of the literature, the estimated pCR rate for standard preoperative neoadjuvant chemoradiotherapy is approximately 15%. The expected pCR rate for the MSS-RASwt/BRAFwt group is around 30%, with a one-sided significance level ( $\alpha$ ) of 0.05 and a power (1-$\beta$) of 0.8, using the Simon two-stage method, the sample size is calculated to be 25 cases. The study started in middle 2022 and is recruiting. Clinical trial information: ChiCTR2200062002. Research Sponsor: None.

TPS3641 Poster Session

# Node-sparing modified short-course radiotherapy combined with CAPOX and tislelizumab versus conventional short-course preoperative chemoradiotherapy for proficient mismatch repair or microsatellite stable locally advanced rectal cancer (mRCAT-III): A multicenter, randomized, open-label, phase 3 trial.

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**Background:** Total neoadjuvant chemoradiotherapy is the standard of care for locally advanced rectal cancer (LARC) to control local recurrence and achieve organ preservation. However, for proficient mismatch repair (pMMR) or microsatellite stable (MSS) LARC, which accounts for nearly 90% of rectal cancers, conventional chemoradiotherapy has limited efficacy and is associated with significant side effects. Recent studies have shown that combining radiotherapy with immunochemotherapy can improve pathological complete response (pCR) rates, but the inclusion of tumor-draining lymph nodes (TDLNs) in the conventional irradiation field may impair T-cell immunity and reduce response to immunotherapy. Our previous phase II trial demonstrated that node-sparing modified short-course radiotherapy combined with chemotherapy and PD-1 blockade could achieve a high pCR rate of 78.8% in pMMR LARC[1]. Building on these findings, we initiated this phase III trial to compare this novel treatment regime with conventional short-course chemoradiotherapy in improving pCR rates. **Methods:** This is a phase III, open-label, multicenter, randomized trial conducted across 17 hospitals in China. A total of 170 eligible MSS/pMMR middle or low rectal cancer patients (cT3-4N0/+M0) will be recruited and randomly assigned (5:5:1) to three groups: control group (conventional short-course chemoradiotherapy), experimental group (node-sparing modified short-course chemoradiotherapy plus PD-1 blockade), and exploratory group (conventional short-course chemoradiotherapy plus PD-1 blockade). The innovative node-sparing modified short-course radiotherapy targets only the primary tumor bed, excluding TDLNs. Following randomization, patients will receive short-course radiotherapy (conventional or node-sparing) followed by four cycles of CAPOX ± tislelizumab: tislelizumab 200 mg IV on day 1, oxaliplatin 130 mg/m$^2$ IV on day 1, and capecitabine 1000 mg/m$^2$ orally on days 1-14, and Total mesorectal excision (TME) will be performed at weeks 14-15. The primary endpoint is pCR rate, while secondary endpoints include organ preservation rate, disease-free survival, overall survival, adverse effects, and quality of life. As of January 2025, 46 of the planned 170 patients have been enrolled. The Data Monitoring Committee (DMC) reviewed the trial in December 2024 and recommended continuing as planned. Reference: Annals of Oncology (2024) 24 (suppl_1): 1-20. 10.1016/iotech/iotech100744. Clinical trial information: NCT06507371. Research Sponsor: Sir Run Run Shaw Hospital Clinical Research Cultivation Program.

**TPS3642** **Poster Session**

# A phase II study of encorafenib and cetuximab (EC) beyond progression in combination with FOLFIRI in *BRAF* V600E-mutated metastatic colorectal cancer (mCRC).

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**Background:** *BRAF* V600E mutation occurs in approximately 10% of metastatic colorectal cancers (mCRC) and confers poor prognosis. While the combination of encorafenib and cetuximab (EC) has demonstrated improved outcomes in previously treated *BRAF* V600E-mutated mCRC patients (pts), the duration of response remains suboptimal with median progression-free survival (mPFS) of 4.3 months (m). Approximately half of pts (45%) receive subsequent treatment after EC progression, predominantly with chemotherapy (ChT). Data from the safety lead-in (SLI) of the BREAKWATER trial, assessing EC in combination with ChT doublet in the first-line setting, demonstrated manageable safety profile and promising early efficacy signals for EC in combination with FOLFIRI, despite pharmacokinetic interaction. **Methods:** ECLYPse (NCT06640166; EU CT Number 2023-508615-24-00) is a multicenter, single-arm, phase II study evaluating EC continuation beyond progression in combination with FOLFIRI in pts with *BRAF* V600E-mutated mCRC who progressed on second-line EC. Key eligibility criteria include: histologically confirmed colorectal adenocarcinoma, *BRAF* V600E mutation, documented disease progression on EC in second-line setting, benefit to previous treatment with EC (best response: complete response, partial response or stable disease lasting for at least 3 months), measurable disease according to RECIST 1.1 criteria, ECOG PS $\leq$1, and availability of archival tumor tissue. Patients receive encorafenib 300 mg daily, cetuximab 500mg/m2 iv every 2 weeks, and standard FOLFIRI regimen. The primary endpoint is 6-month PFS rate. Secondary endpoints include PFS, overall survival, duration of response, objective response rate, disease control rate, and safety. Translational analyses include comprehensive genomic profiling on archival tissue and serial ctDNA analysis. Tumor assessment with contrast-enhanced CT scan of thorax, abdomen and pelvis is performed every 8 weeks. Using a single-stage design with one-sided $\alpha$ = 0.05 and 80% power, 25 patients will be enrolled to detect an improvement in 6-month PFS rate from 10% (null hypothesis) to 30% (alternative hypothesis). If at least 7 pts will be alive and not progressing at 6 months, the treatment will be considered sufficiently active to warrant further investigation. The study is currently enrolling at multiple sites in Italy. Clinical trial information: NCT06640166. Research Sponsor: Pierre Fabre.

TPS3643 Poster Session

# Combining low-dose regorafenib with pembrolizumab as a front-line therapy for patients with MSI-H colorectal cancer: REGPEM-CRC-01.

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**Background:** Currently, pembrolizumab is one of the front-line therapies for patients with MSI-H CRC. However, approximately 40% of patients who received pembrolizumab experienced disease progression early in the course of disease (KEYNOTE 177). Therefore, there is still an unmet need to enhance the efficacy of checkpoint inhibitors in MSI-H CRC. MSI-H CRC has a higher level of expression of VEGF in blood compared to patients compared to its MSS counterpart (Hansen et al. Colorectal Dis. 2011). Consistently, exploratory analysis of CALBG-80405 and PARADIGM trial showed that patients with MSI-H CRC were more likely to benefit from anti-VEGF therapy than anti-EGFR therapy regardless of the side of the tumor. NSABP C-08 also suggested that anti-VEGF therapy may have biological activity even in as adjuvant therapy for patients with MSI-H colon cancer. Regorafenib is a potent VEGF and multikinase inhibitor involved in pathologic processes such as oncogenesis, tumor angiogenesis, metastasis and tumor immunity, with preclinical evidence showing its immune modulatory effect in the tumor microenvironment. In this trial, we hypothesize that adding low-dose regorafenib to pembrolizumab may induce synergistic activity beyond their independent clinical efficacy and create deep and durable responses for patients with MSI-H CRC. **Methods:** In the lead arm of this prospective randomized study, 22 patients will be enrolled through Hoosier Cancer Research Network (HCRN-GI23-643). In this first line clinical trial, patients will receive regorafenib 60 mg daily in combination with pembrolizumab 200mg IV in cycle 1, followed by regorafenib 90mg in subsequent cycles to optimize the treatment tolerance and compliance. The primary outcome that will be measured is ORR, defined as the percentage of partial or complete response to the treatment within 12 months. ORR will be measured using RECIST 1.1. criteria. A formal one-sided hypothesis test will be conducted for futility, assuming that we will reject the null hypothesis of a target ORR only if we have strong evidence. In this study, we assume a null hypothesis that ORR is 0.60, which would reflect significant clinical improvement over the current standard of ORR = 0.43 from KEYNOTE 177. The alternative hypothesis is that ORR is less than 0.60. For the lead-in phase of the study, the emphasis is on controlling Type I error to be small, to be 0.05 or lower. An exact binomial test will be conducted, based on the number of ORRs in the 22 patients. The study is currently accruing through Hoosier Cancer Research Network was activated in July 2024. Clinical trial information: NCT06006923. Research Sponsor: None.

**TPS3644** **Poster Session**

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

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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) represents a highly specific and sensitive approach (especially with serial monitoring) for identifying minimal/molecular residual disease (MRD) post-surgery 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 be spared the toxicities associated with 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 CC 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 IIB, IIC, and III CC will be enrolled. Based on the post-operative ctDNA status using personalized and tumor-informed assay (Signatera™, bespoke 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 *v* serial ctDNA monitoring. Patients who are ctDNA+ post-operatively, or with serial monitoring (Cohort B), will be randomized to FP+Ox *v* more intensive AC with addition of irinotecan (I) for 6 mos. One cycle of chemotherapy is allowed while awaiting ctDNA testing results for cohort assignment. The primary endpoints for Cohort A are time to ctDNA+ status (phase II) and disease-free survival (DFS) (phase III) in the immediate *v* delayed AC arms. The primary endpoint for Cohort B is DFS in the FP+Ox *v* FP+Ox+I arms for both phase II and phase III portions of the trial. Secondary endpoints include prevalence of detectable ctDNA post-operatively, time-to-event outcomes (overall survival and time to recurrence) by ctDNA status, and the assessment of compliance to adjuvant therapy. Biospecimens including archival tumor tissue, as well as post-operative plus serial matched/normal blood samples, will be collected for exploratory correlative research. Active enrollment across the NCTN started in June 2022 with CCTG sites joining in August 2023. Current accrual (as of 1-27-2025): 647/1,912. NCT: 05174169. Support: U10 CA180868, -180822; -180888; UG1 CA189867; Natera, Inc. Clinical trial information: NCT05174169. Research Sponsor: National Cancer Institute; U10CA180868; National Cancer Institute; U10 CA180822; National Cancer Institute; UG1CA189867; Natera, Inc.

TPS3645 Poster Session

# Platform study of circulating tumor DNA–directed adjuvant chemotherapy in colon cancer (CLAUDIA Colon Cancer, KCSG CO22-12).

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**Background:** Tumor-informed circulating tumor DNA (ctDNA) analysis allows for the sensitive detection of minimal residual disease (MRD) and has the potential to enhance patient stratification for adjuvant chemotherapy (AC). In patients with stage II-III colon cancer, we demonstrated that postoperative MRD is associated with poor disease-free survival (DFS) despite oxaliplatin-based AC. We hypothesize that intensifying AC in colon cancer patients with postoperative MRD may improve survival outcomes. **Methods:** This multi-center platform trial (NCT05534087) consists of a prospective observational study (Part 1) and an interventional randomized trial (Part 2). In Part 1, approximately 1,200 patients with colon cancer will be screened for MRD at 3–6 weeks postoperatively using atumor-informed hybrid-capture-based ctDNA MRD assay (CancerDETECT) which tracks ~100 patient-specific somatic variants identified through tumor whole-exome sequencing. Key eligibility criteria include: age ≥19 years, ≤6 weeks post-curative resection, pathological diagnosis of colon cancer, stage III or stage II with high-risk features requiring AC with FOLFOX/CAPOX, and no macroscopic residual disease. All patients in Part 1 will complete 3 months of standard adjuvant FOLFOX/CAPOX while awaiting MRD results. After 3 months of AC, MRD-negative patients are managed at the investigator's discretion. Patients with MRD positivity will be screened for Part 2 clinical trial following the completion of initial 3 months of standard AC titled "*Randomized Controlled Phase III Trial of Treatment Intensification in Stage II–III Colon Cancer Patients with Positive MRD after Curative Resection*." Part 2 investigates the superiority of an experimental arm (modified FOLFIRINOX for 3 months) compared to a control arm (FOLFOX/CAPOX for 3 months). The primary endpoint is the 3-year DFS rate, while secondary endpoints include the 5-year overall survival rate, treatment-related adverse events, treatment adherence, and patient-reported outcomes. A total of 236 patients will be enrolled, assuming a hazard ratio of 0.64, 80% power, a two-sided alpha of 0.05, and a 10% dropout rate. As of November 2024, 630 patients have been screened in Part 1, and 99 patients have been enrolled in Part 2. Both studies are ongoing, and an interim analysis is planned after ≥ 48 events. Clinical trial information: NCT05534087. Research Sponsor: National R&D Program for Cancer Control through the National Cancer Center (NCC) funded by the Ministry of Health & Welfare, Republic of Korea (HA22C0062).

**TPS3646** **Poster Session**

# mFOLFOX6 + bevacizumab + PD-1 monoclonal antibody vs. mFOLFOX6 in locally advanced pMMR/MSS CRC: A multicenter, randomized controlled phase III study (BASKETIII).

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**Background:** Immunotherapy has shown promising therapeutic effects in mismatch repair-deficient or microsatellite instability-high (dMMR/MSI-H) colorectal cancer (CRC). However, for patients with mismatch repair-proficient or microsatellite stable (pMMR/MSS) CRC, the efficacy of single-agent PD-1 monoclonal antibody remains limited. Previous studies reported that combining anti-angiogenic drugs with PD-1 monoclonal antibody might improve the efficacy of immunotherapy. Our BASKETII study (NCT04895137) demonstrated that the neoadjuvant therapy regimen of mFOLFOX6 combined with Bevacizumab and sintilimab significantly enhanced the immunotherapy sensitivity of pMMR/MSS locally advanced CRC (LACRC), resulting in improved pathological complete response (pCR) rates and higher R0 resection rates. **Methods:** BASKETIII is a multicenter, randomized controlled, phase III study with a parallel design conducted in China. This trial aims to evaluate whether the neoadjuvant therapy regimen of mFOLFOX6 combined with Bevacizumab and sintilimab can further improve survival outcomes, and maintain the higher pCR rate and acceptable safety profile compared to mFOLFOX6 in pMMR/MSS LACRC patients. Eligible participants will be randomly assigned in a 1:1 ratio to either the experimental group or the control group. Participants in the experimental group will receive the neoadjuvant therapy regimen of mFOLFOX6 + Bevacizumab + sintilimab. The first five doses will follow the mFOLFOX6 combined with Bevacizumab and sintilimab regimen, and the sixth dose will receive only mFOLFOX6 and sintilimab but without Bevacizumab, in order to avoid delay of surgery. Participants in the control group will receive the neoadjuvant therapy regimen of mFOLFOX6 alone. Participants in both groups will undergo radical surgical treatment after neoadjuvant therapies. Participants who achieve pCR based on postoperative pathology will be regularly followed up. Participants who do not achieve pCR will receive adjuvant therapy with a maxim of six doses and will be regular followed up after the final dose of adjuvant therapy. The primary outcome of this study is to evaluate the 3-year disease-free survival (DFS). The key inclusion criteria include histologically confirmed adenocarcinoma of the colon or upper rectum; tumor biopsy immunohistochemical identified pMMR or MSS identified through next-generation sequencing or polymerase chain reaction; Clinical staging of cT4NxM0. The main exclusion criteria include evidence of distant metastasis beyond the pelvic region; history of pelvic or abdominal radiotherapy; multiple CRC or multiple primary tumors; history of immunotherapy and other malignancies within the past 5 years. A total of 122 patients are planned to be enrolled in this study. This study is registered with ClinicalTrials.gov (NCT06791512) and is recruiting. Clinical trial information: NCT06791512. Research Sponsor: National Natural Science Foundation of China.

TPS3647 Poster Session

# A precision medicine trial leveraging tissue and blood-based tumor genomics to optimize treatment in resected stage III and high-risk stage II colon cancer (CC) patients (pts): The SAGITTARIUS trial.

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**Background:** Circulating tumor DNA (ctDNA) testing has emerged as a transformative tool for detecting molecular residual disease (MRD). Multiple prospective trials have demonstrated the potential of ctDNA in guiding treatment decisions for stage II-III CC pts. Numerous ongoing randomized clinical trials (RCTs) are adjusting adjuvant chemotherapy (ACT) intensity based on MRD status. However, data from ctDNA-guided trials, including PEGASUS (NCT04259944), reveal that intensified ACT is curative in only a small proportion of MRD cases. To address this limitation, the SAGITTARIUS RCT was designed to evaluate whether combining ctDNA detection with targeted agents selected on the basis of tissue-based comprehensive genomic profiling (CGP) can optimize treatment in high risk (i.e. MRD+) pts while sparing low risk (i.e. MRD−) from unnecessary toxicity. **Methods:** SAGITTARIUS is a Phase III RCT evaluating ctDNA and tissue-guided personalized post-surgical management in resected stage III and high-risk stage II CC pts. Tumor-informed, personalized ctDNA test (Signatera, Natera, Inc.) and CGP (TruSight™ Oncology Comprehensive EU, Illumina, Inc.) are used to determine MRD status and tumor genomic landscape, respectively, including genetic mutation (mut) and amplification (ampl), tumor mutational burden (TMB) and microsatellite instability (MSI) status. Pts are stratified based on post-surgery (3-5 weeks) ctDNA status into two embedded RCTs:Trial-1) ctDNA-positive (ctDNA+) ptsare further stratified based on MSI and RAS/RAF status and randomized 1:1 to standard 6-month ACT (CAPOX/FOLFOX) or personalized treatment (PT) guided by CGP biomarkers with reassessment of ctDNA status to guiding subsequent therapies (chemotherapy regimens in ctDNA+ or maintenance and follow-up in seroconverted; Trial-2) ctDNA-negative (ctDNA−) ptsare randomized 1:1 to a physician-choice strategy or observation with ctDNA reassessed at 2 and 4 months and, in cases of positivity, cross over to Trial-1. PT include 3-month CAPOX followed by FOLFIRI or TEMIRI based on MGMT status (RAS/RAFmut), Ipilimumab + nivolumab (MSI and TMB-high POLEmut), pertuzumab + trastuzumab (HER2-ampl), FOLFOX + panitumumab (RAS/RAF/HER2 wild-type). The primary endpoint (EP) is 2-year recurrence-free survival (RFS) in ctDNA+ pts. Secondary EPs include 2-year RFS in ctDNA− pts, 3- and 5-year overall survival, and ctDNA conversion rate. Quality of life and health costs data are collected for cost effectiveness analysis. Biospecimens, including archival tumor tissue, serial blood samples, and buccal swabs, are collected for exploratory analyses. To detect a hazard ratio of 0.6325 for ctDNA-guided PT vs standard ACT, 200 ctDNA+ pts will be randomized in Trial-1. Recruitment began in October 2024 across 26 institutions in Italy, Spain, and Germany. Clinical trial information: NCT06490536. Research Sponsor: European Union; 101104657.

**TPS3648** **Poster Session**

# Phase II study of epacadostat (INCB024360) added to preoperative chemoradiation in patients with locally advanced rectal cancer.

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**Background:** Indoleamine 2,3-dioxygenase 1 (IDO1) metabolizes tryptophan along the kynurenine pathway and is recognized as a potent suppressor of tumor reactive immunity. Epacadostat is an orally active, potent and selective inhibitor of IDO1. In preclinical studies, IDO1 was found to promote resistance to radiation in rectal cancer, irrespective of microsatellite instability (MSI) status. IDO1 inhibition with epacadostat improved tumor radiosensitivity by relieving immune suppression and augmenting radiation-induced apoptosis while protecting the normal intestine from radiation damage. In a phase 1 trial, 17 patients were enrolled from 4/2019 to 8/2023. Epacadostat in combination with short-course radiation therapy (SCRT) and CAPOX was well-tolerated and the recommended phase 2 dose (RP2D) of epacadostat was determined to be 400 mg BID. An NCI supported Phase 2 trial is ongoing to further evaluate the promising disease responses reported in the dose escalation phase. **Methods:** This phase 2 multicenter, open-label trial includes treatment and biomarker cohorts. In the treatment cohort, epacadostat at 400 mg BID will be administered concurrently with SCRT followed by epacadostat monotherapy until 1 day prior to neoadjuvant chemotherapy, followed by standard-of-care (SOC) neoadjuvant chemotherapy and, ultimately, surgical resection or non-operative management (NOM). Biomarker cohort enrollment will commence at completion of treatment cohort accrual. Enrolled patients will be treated with SOC SCRT followed by SOC neoadjuvant chemotherapy and surgical resection or NOM. Eligible patients must be a treatment-naïve, newly diagnosed, pathologically confirmed, locally advanced rectal cancer (defined by 8$^{th}$ edition AJCC stage 2 or 3, or stage 1 not eligible for sphincter-sparing surgery) with plans to proceed with neoadjuvant SCRT and chemotherapy. The primary endpoint is the neoadjuvant rectal (NAR) score. Secondary endpoints are pathologic complete response (pCR) rate, complete clinical response (cCR) rate and progression-free survival (PFS). Exploratory endpoints are pharmacodynamics, PDX and organoid generation, identification of molecular predictors of response and resistance, correlation of radiographic and pathologic response and effect of treatment on patient quality of life. We aim to enroll 27 patients in the treatment cohort and 10 in the biomarker cohort. Clinical Trial Registration: NCT03516708. Research Sponsor: NIH (grant number 1R01CA278197-01A1); Incyte (drug only).

TPS3649 Poster Session

# AZUR-4, a phase 2, open label, randomized study of neoadjuvant dostarlimab plus capecitabine plus oxaliplatin (CAPEOX) versus CAPEOX alone in previously untreated T4N0 or stage III mismatch repair proficient/microsatellite stable resectable colon cancer.

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**Background:** Colon cancer is the third most common cancer globally, with a standard of care in the nonmetastatic setting that includes surgery followed by adjuvant chemotherapy. Results of recent clinical trials suggest that neoadjuvant therapy may be beneficial in locally advanced colon cancer. Neoadjuvant immunotherapy has shown impressive responses in mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) disease with pathological complete responses of up to 67% and 3-year disease-free survival of 100% reported in the NICHE 2 trial. However, most colon cancer (85%–90%) is mismatch repair proficient (MMRp)/microsatellite stable (MSS), which has been shown to have poor response to conventional immunotherapy. Dostarlimab, a programmed cell death protein-1 (PD-1) inhibitor, has a high affinity for binding to PD-1, blocking the interaction between PD-1 and its ligands (PD-L1 and PD-L2). Dostarlimab monotherapy has been approved in the US for the treatment of adults with dMMR advanced/recurrent solid tumors. The AZUR-4 trial (NCT06567782) evaluates dostarlimab + CAPEOX versus CAPEOX alone as neoadjuvant treatment to identify early signals of efficacy in resectable MMRp/MSS colon cancer. The study will assess the relationship between conventional and advanced blood- and tumor-based immune response to better understand the contribution of dostarlimab to pathological response. **Methods:** AZUR-4 is a multicenter, randomized, open-label phase 2 study in MMRp/MSS resectable colon cancer. Approximately 120 patients will be enrolled and randomized 3:1 to the dostarlimab + CAPEOX and CAPEOX arms, respectively, in which they will receive 4 cycles of Q3W neoadjuvant therapy. Key eligibility criteria include age ≥18 years, confirmed resectable MMRp/MSS colon adenocarcinoma with no prior treatment, clinically staged as T4N0 or stage III, Eastern Cooperative Oncology Group performance status of 0 or 1, and required tissue biopsies providing fresh tumor tissue either at prescreening or screening. Primary endpoints are major pathologic response rate (mPR) assessed at ≤10% residual viable tumor (RVT) and treatment-emergent adverse events (AEs), serious AEs, immune-mediated AEs, and AEs leading to death or discontinuation of study drug. Secondary endpoints include primary tumor resection not being excluded by either disease progression or treatment-related toxicities, and pathological response categories that include complete pathological response (cPR) and partial pathologic response (pPR). Exploratory endpoints include overall survival, event-free survival, effects on circulating tumor DNA dynamics, and pathological response rate in biomarker subsets. Clinical trial information: NCT06567782. Research Sponsor: GSK.

TPS3650 Poster Session

# Trials in progress: Alliance A022104/NRG-GI010—A randomized phase II/III trial testing the efficacy of triplet versus doublet chemotherapy regarding clinical complete response and disease-free survival in patients with locally advanced rectal cancer (LARC; the Janus Rectal Cancer trial).

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**Background:** A total neoadjuvant therapy (TNT) approach improves compliance with chemotherapy and increases rates of tumor response compared to neoadjuvant chemoradiation (CRT) alone in those with locally advanced rectal cancer. Recent data indicate that optimal sequencing of TNT involves consolidation (rather than induction) chemotherapy to improve complete response rates. The use of FOLFIRINOX has shown to improve response and outcomes compared to CRT and surgery alone. Data have also shown that patients with clinical complete response (cCR) after TNT may be managed with a watch and wait approach (WW) instead of preemptive total mesorectal resection (TME). However, the optimal consolidation chemotherapy regimen to improve cCR rates has not been established, and a randomized clinical trial has not robustly evaluated cCR as a primary endpoint. We designed this NCI-sponsored study of chemotherapy intensification to address this and to increase cCR rates, provide opportunity for organ preservation, and survival outcomes. **Methods:** In this multigroup randomized, seamless phase II/III trial (1:1), up to 760 patients with LARC, T4N0, any T with node positive disease (any T, N+) or T3N0 requiring abdominoperineal resection or coloanal anastomosis and distal margin within 12 cm of anal verge will be enrolled. Stratification factors include tumor stage (T4 vs T1-3), nodal stage (N+ vs N0) and distance from anal verge (0–4; 4–8; 8–12 cm). Patients will be randomized to receive neoadjuvant long-course chemoradiation (LCRT) followed by consolidation doublet (mFOLFOX6 or CAPOX (control arm)) or triplet chemotherapy (FOLFIRINOX (experimental arm)) for 3–4 months. LCRT in both arms involve 4500 cGy in 25 fractions over 5 weeks +900 cGy boost in 5 fractions with a fluoropyrimidine. Patients will undergo assessment 8–12 ($\pm$4) weeks post-TNT completion. The primary endpoint for the phase II portion will compare cCR between treatment arms. A total number of 312 patients (156 per arm) will provide statistical power of 90.5% to detect a 17% increase in cCR rate, at a one-sided alpha = 0.048. The primary endpoint for the phase III portion will compare disease-free survival (DFS) between arms. A total of 285 DFS events will provide 85% power to detect an effect size of hazard ratio 0.70 at a one-sided alpha of 0.025, requiring enrollment of 760 patients (380 per arm). Secondary objectives include overall survival, organ preservation time, time to distant metastasis, and adverse event rates. This study has accrued 587 patients as of January 2025, and is investigating exploratory correlatives (e.g., ctDNA). Support: U10CA180821, U10CA180882, U24 CA196171. https://acknowledgments.alliancefound.org. Clinicaltrials.gov ID: NCT05610163. Clinical trial information: NCT05610163. Research Sponsor: National Cancer Institute; U10CA180821; National Cancer Institute; U10CA180882; U.S. National Institutes of Health; U24CA196171; ECOG-ACRIN MEDICAL RESEARCH FOUNDATION; U10CA180820; National Cancer Institute; U10CA18086; National Cancer Institute; U10CA180888.