

Disease-free survival (DFS) and time to recurrence (TTR) with circulating tumor (ct) DNA—based decision for adjuvant treatment in colon cancer stage II (CIRCULATE): An AIO (KRK-0217)/ABCSG trial.

Gunnar Folprecht, Sebastian Stasik, Jens Christmann, Lukas Weiss, Eray Goekkurt, Lutz Jacobasch, Lena-Christin Conradi, Ulrike Ubbelohde, Ralf Hofheinz, Ruediger Liersch, Matthias Kelm, Jack Chafic Chater Cure, Martin Fuchs, Jorge Riera-Knorrenschild, Joerg Ernst Albert Schubert, Anna Klimova, Daniela Ellen Aust, Andrea Tannapfel, Christian Thiede, Anke C. Reinacher-Schick; Technical University Dresden, Medical Faculty Carl Gustav Carus, NCT/UCC/Medical Department I, Dresden, Germany; Technical University Dresden / Medical Faculty Carl Gustav Carus, Lab. Hematology, Dresden, Germany; COLOPREDICT Platform and Institute of Pathology, Georgius Agricola Stiftung Ruhr, Ruhr-University Bochum, Bochum, Germany; Austrian Breast & Colorectal Cancer Study Group (ABCSG) and IIIrd Medical Department, Paracelsus Medical University, Salzburg, Austria; Hematology-Oncology Practice Hamburg (HOPE), Hamburg, Germany; Onkologische Schwerpunktpraxis, Dresden, Germany; University Medical Center Goettingen, Goettingen, Germany; Mannheim Cancer Center, University of Heidelberg, Mannheim, Germany; Outpatient Clinics for Hematology and Oncology, Münster, Germany; University of Wuerzburg, Surgical Department I, Wuerzburg, Germany; Klinikum Chemnitz, Department of Hematology, Oncology, and Cellular Therapy, Chemnitz, Germany; Staedt. Klinikum Muenchen GmbH, Munich, Germany; Universitätsklinikum Marburg, Klinik für Innere Medizin, Marburg, Germany; Elblandklinikum Riesa, Riesa, Germany; National Center for Tumor Diseases (NCT) Dresden, Dresden, Germany; Institute of Pathology, Faculty of Medicine Carl Gustav Carus, Technical University Dresden, Dresden, Germany; COLOPREDICT Platform and Institute of Pathology, Ruhr-University, Bochum, Germany; COLOPREDICT Platform and Department of Hematology, Oncology and Palliative Care, St. Josef-Hospital, Ruhr-University Bochum, Bochum, Germany

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Informing optimal duration of adjuvant chemotherapy (ACT) in resected stage I-IV colorectal cancer (CRC) based on early circulating tumor DNA (ctDNA) dynamics.

Hiroyuki Yamamoto, Hideaki Bando, Yoshiaki Nakamura, Daisuke Kotani, Saori Mishima, Koji Ando, Daryanz Dargahi, Tony Tin, Charuta C. Palsuledesai, Meenakshi Malhotra, Dina Hafez, Steven Sorscher, Robert William Lentz, Minetta C. Liu, Adham A. Jurdi, Hiroya Taniguchi, Jun Watanabe, Takeshi Kato, Takayuki Yoshino, Eiji Oki, Teine Keijinkai Hospital, Sapporo, Japan; Department for the Promotion of Drug and Diagnostic Development, Division of Drug and Diagnostic Development Promotion, National Cancer Center Hospital East, Kashiwa, Japan; Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan; National Cancer Center Hospital East, Kashiwa, Japan; National Cancer Center East, Kashiwa, Japan; Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; Natera, Inc., Austin, TX; Natera, Inc, San Carlos, CA; Not Currently in Practice, Winston-Salem, NC; Division of Medical Oncology, Department of Medicine, University of Colorado Anschutz School of Medicine, Aurora, CO; Natera, Inc., San Carlos, CA; Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; Department of Surgery, Gastroenterological Center, Yokohama City University Medical Center, Kanagawa, Japan; Department of Gastroenterological Surgery, NHO Osaka National Hospital, Osaka, Japan; Department of Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan; Department of Advanced Medicine and Innovative Technology, Kyushu University Hospital, Fukuoka, Japan

Background: While ACT is recommended by clinical guidelines for patients (pts) with high-risk stage II and stage III CRC, individual benefit varies significantly and appropriate ACT duration is debatable. Here, we evaluated whether on-ACT ctDNA dynamics can inform recurrence risk and benefit from continued ACT beyond 3 months (mo) in resected stage I-IV CRC. **Methods:** This analysis included 1,028 pts from the CIRCULATE-Japan GALAXY observational study who received ACT but no neoadjuvant chemotherapy, with >2 ctDNA results available within 6 mo post-surgery. Patients were divided into long-ACT (>3 mo, N = 651) and short-ACT cohort (< 3 mo, N = 377) cohorts. ctDNA was analyzed using a personalized, tumor-informed Signatera assay at two timepoints: a) pre-ACT (≥ 14 days post-surgery, before ACT), and b) post-3 mo from ACT (short cohort) or 3 mo ± 45 days from ACT (long cohort). Disease-free survival (DFS) was measured from the date of surgery and compared between pts who received long vs short ACT, stratified by ctDNA dynamics. Subanalyses comparing ACT duration were landmarked at the second ctDNA timepoint. **Results:** Of the 1,028 pts (< 1%/17%/75%/7% stages I/II/III/IV), 44% were females; 81% had colon cancer and 19% rectal cancer. Median pt age was 66 (24-89) years. Median follow-up was 30.7 (4.9-55.8) mo. Median ACT duration was 5.7 mo in long-ACT and 2.5 mo in short-ACT cohorts. Pre-ACT sampling was a median of 14 and 20 days before ACT start for long- and short-ACT cohorts, respectively; post-3 mo sampling was a median of 112 days after ACT start for both cohorts. ctDNA dynamics from the pre-ACT to post-3 mo ACT timepoints revealed sustained negativity in 78.7% (N = 809) of pts, ctDNA clearance in 14.7% (N = 151), decreasing but detectable levels in 2.7% (N = 28), rising levels in 2.8% (N = 29), and newly detectable ctDNA on ACT in 1.1% (N = 11). No benefit of short vs long ACT duration was observed among pts with sustained ctDNA negativity (HR 0.71, p = 0.11) or ctDNA clearance (HR 1.06, p = 0.84). Similarly, pts with rising ctDNA experienced no benefit from longer ACT (HR 1.82, p = 0.18). Conversely, within the decreasing but detectable ctDNA subgroup, longer ACT was associated with improved DFS compared with short ACT median DFS 5.9 vs 1.7 mo; HR 3.64, p = 0.012), acknowledging that the analysis was limited by small cohort size and requires further investigation. **Conclusions:** ctDNA dynamics during ACT provide clinically meaningful stratification of recurrence risk and reveal heterogeneity in treatment benefit. Pts with ctDNA clearance or sustained negativity showed durable disease control and may not require longer ACT. Conversely, pts with partial molecular response showed directional benefit from longer ACT. Pts with molecular progression on ACT did not benefit from extended ACT, indicative of chemotherapy refractory disease and the need for alternative treatment regimens. Clinical trial information: R000044197. Research Sponsor: None.

Observation versus maintenance PD-1 inhibitor therapy after clinical complete response in dMMR/MSI-H colorectal cancer managed with non-operative management: A multicentre cohort study.

Xiaohang Gao, Qiaoxuan Wang, Zitong Zhang, Fang He, Yi Ding, Liping Zhang, Duoduo Pei, Shaoqing Niu, Hailan Chen, Rui Sun, Ye Yao, Weiming Han, Yanjun Chen, Hui Chang, Weiwei Xiao, Li-Ren Li, Rong Zhang, Yuan-Hong Gao; Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University, Guangzhou, Guangdong, China; Department of Radiation Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, Guangdong, China; Department of Radiation Oncology, the Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, China; Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong, China; Department of Oncology, Guangdong Provincial Hospital of Integrated Traditional Chinese and Western Medicine, Foshan, Guangdong, China; 1st Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; Department of Radiation Oncology, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong, China; Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University, Guangzhou, China; Department of Colorectal Surgery, Sun Yat-sen University Cancer Center, Guangzhou, China; Department of Endoscopy and Laser, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou, China

Background: Patients with mismatch repair-deficient (dMMR)/microsatellite instability-high (MSI-H) colorectal cancer (CRC) who achieve a clinical complete response (cCR) after PD-1 inhibitor therapy may undergo non-operative management (NOM) with active surveillance. We aimed to assess the necessity of maintenance immunotherapy after achieving cCR, with a focus on survival outcomes and the burden of immune-related toxicity. **Methods:** A multicentre observational cohort study was conducted at five tertiary hospitals in China between Jan 1, 2018, and March 21, 2025. Patients with dMMR/MSI-H CRC who achieved cCR after PD-1 inhibitor therapy and entered NOM were included. Patients were stratified into an observation group (discontinue PD-1 inhibitor after cCR) and a maintenance group (received ≥ 2 cycles of PD-1 inhibitors after cCR). Disease-free and overall survival were compared between groups using Kaplan-Meier methods with log-rank test, and local regrowth, distant metastasis, and immune-related adverse events were assessed. **Results:** Among 318 patients treated with PD-1 inhibitors, 195 (61.3%) achieved cCR. A total of 129 patients were analysed (observation $n = 66$; maintenance $n = 63$), including 58 with rectal cancer, 61 with colon cancer, and 10 with synchronous dual primary tumours; 14 had distant metastases at diagnosis. Clinical complete response was assessed with endoscopy and pelvic MRI/CT along with digital rectal examination for rectal cancer, and endoscopy with contrast-enhanced CT or PET/CT for colon cancer. Median PD-1 inhibitor exposure to achieve cCR was eight cycles in both groups; 69.8% achieved cCR within eight cycles. Median follow-up was 3.2 years (IQR 2.0–4.0). Local regrowth occurred in two patients in the observation group and none in the maintenance group, and no distant metastases were observed. The 3-year DFS was 96.4% (95% CI 91.6–100.0) in the observation group and 98.4% (95% CI 95.2–100.0) in the maintenance group (log-rank $p = 0.55$). The 3-year OS was 100.0% (95% CI 100.0–100.0) versus 98.4% (95% CI 95.2–100.0) ($p = 0.34$). Any-grade irAEs occurred in 42/66 (63.6%) versus 44/63 (69.8%); grade 3 irAEs were numerically higher with maintenance (7/63 [11.1%] vs 2/66 [3.0%]; $p = 0.091$). **Conclusions:** To our knowledge, this is the largest series of dMMR/MSI-H CRC patients achieving cCR after PD-1 inhibitor therapy and managed with NOM. Maintenance therapy after cCR did not provide a clear survival advantage but was associated with a higher burden of immune-related toxicity, supporting treatment discontinuation with close surveillance. Research Sponsor: None.

BREAKWATER: Progression-free and overall survival analyses of first-line (1L) encorafenib + cetuximab (EC) + FOLFIRI in BRAF V600E-mutant metastatic colorectal cancer (mCRC).

Scott Kopetz, Josep Tabernero, Sara Lonardi, Lin Shen, Harpreet Singh Wasan, Takayuki Yoshino, Eric Van Cutsem, Tae Won Kim, Cathy Eng, Fortunato Ciardiello, Jayesh Desai, Tim Maughan, Rona Yaeger, Tiziana Usari, Xiaoxi Zhang, Elena Beyzarov, Ave Mori, Elizabeth Whalley, Xiaosong Zhang, Elena Elez; Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Vall d'Hebron Hospital Campus and Institute of Oncology (VHIO), University of Vic-Central University of Catalonia, Barcelona, Spain; Veneto Institute of Oncology IOV-IRCCS, Padua, Italy; Beijing Cancer Hospital, Beijing, China; Hammersmith Hospital, Division of Cancer, Imperial College, London, United Kingdom; National Cancer Center Hospital East, Kashiwa, Japan; University Hospitals Gasthuisberg and University of Leuven (KU Leuven), Leuven, Belgium; Oncology Department, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Vanderbilt Ingram Cancer Center, Nashville, TN; University of Campania Luigi Vanvitelli, Naples, Italy; Peter MacCallum Cancer Centre and the University of Melbourne, Melbourne, VIC, Australia; University of Liverpool, Liverpool, United Kingdom; Memorial Sloan Kettering Cancer Center, New York, NY; Pfizer Inc., Milan, Italy; Pfizer Inc., New York, NY; Pfizer, Inc., New York, NY; Pfizer S.R.L., Milan, Italy; Pfizer Inc., Seattle, WA; Pfizer, Inc., South San Francisco, CA; Vall d'Hebron Institute of Oncology, Barcelona, Spain

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SWOG S2107: Randomized phase II trial of encorafenib and cetuximab with or without nivolumab for patients with previously treated MSS, *BRAF*^{V600E} metastatic colorectal cancer (mCRC).

Van K. Morris II, Sarah Colby, Scott Kopetz, Katherine A. Guthrie, William J. Chapin, Rimini Breakstone, Zishuo Ian Hu, Marwan Fakih, Sepideh Gholami, Philip Jordan Gold, E. Gabriela Chiorean, Philip Agop Philip; The University of Texas MD Anderson Cancer Center, Houston, TX; Fred Hutch Cancer Center and SWOG Statistics and Data Management Center, Seattle, WA; Public Health Sciences Division, Fred Hutchinson Cancer Center, Seattle, WA; Penn Medicine Abramson Cancer Center, Philadelphia, PA; Brown University, The Miriam Hospital, Providence, RI; Department of Medical Oncology and Therapeutics Research, City of Hope Comprehensive Cancer Center, Duarte, CA; Northwell Health Cancer Center, New Hyde Park, NY; Swedish Cancer Institute, Seattle, WA; Fred Hutchinson Cancer Center, University of Washington, Seattle, WA; Henry Ford Cancer, Wayne State University School of Medicine, Detroit, MI

Background: *BRAF*^{V600E} mutations are associated with poor survival yet increased immune activation among patients (pts) with microsatellite stable (MSS) mCRC. A prior single-institution trial of the *BRAF* inhibitor encorafenib (E) with the anti-EGFR antibody cetuximab (C) and the anti-PD-1 antibody nivolumab (N) reported an overall response rate (ORR) of 50% and median progression-free survival (PFS) of 7.2 months in pts with MSS, *BRAF*^{V600E} mCRC, promising findings relative to historical controls with E+C. **Methods:** In this phase II SWOG/NCTN study (NCT05308446), pts with previously treated, MSS *BRAF*^{V600E} mCRC were randomized 2:1 to receive E (300 mg PO daily) + C (500 mg/m² IV every 2 weeks) + N (480 mg IV every 4 weeks) vs E+C only. No prior exposure to *BRAF*, EGFR, or immune checkpoint therapies were allowed. The primary endpoint was PFS and targeted a hazard ratio (HR) of 0.57 with a 1-sided $\alpha=0.10$ and 80% power. Randomization was stratified by prior lines of therapy (1 vs 2) and Zubrod PS (0 vs 1). Treatment response was assessed every 8 weeks radiographically (RECIST 1.1). Secondary endpoints were overall survival (OS), ORR, and treatment-related adverse events (TRAE) according to CTCAE v5. Differences in PFS by treatment arm were assessed via stratified log-rank test. **Results:** Of 88 pts enrolled, 85 were eligible and evaluable (57 E+C+N, 28 E+C). Participant characteristics are listed in Table. Median PFS was 5.8 months (95% CI 4.0–7.8) with E+C+N and 6.3 months (95% CI 5.0–11.4; $p=0.64$) with E+C; HR 1.10 (95% CI 0.65–1.86). ORR was 35% for E+C+N and 32% for E+C. OS was similar between E+C+N and E+C: median 13.5 months (95% CI 11.0–18.9) vs. 11.6 months (95% CI 9.2–15.6; $p=0.29$); HR 0.85 (95% CI 0.47–1.52). 31 out of 57 pts (54%) had grade 3–4 TRAEs for E+C+N, vs 10 out of 28 (36%; $p=0.11$) for E+C; Grade 3 TRAEs occurring in >10% pts treated with E+C+N included fatigue (14%) and arthralgia (11%). **Conclusions:** The addition of N to E+C did not improve survival outcomes in this study population of pts with pretreated MSS, *BRAF*^{V600E} mCRC. Ongoing correlative studies seek to identify biomarkers associated with treatment benefit that may be applied to future efforts seeking to personalize treatment approaches for this biologically heterogeneous population. Clinical trial information: NCT05308446. Research Sponsor: NIH/NCI/NCTN; U10CA180888; NIH/NCI/NCTN; U10CA180819; Bristol-Myers Squibb.

Patient demographics.

	E+C+N (N=57)	E+C (N=28)
AGE		
Median	64.3	66.1
SEX (%)		
Male	27 (47)	19 (68)
Females	30 (53)	9 (32)
PRIOR LINES SYSTEMIC THERAPY (%)		
1	40 (70)	18 (64)
2	17 (30)	10 (36)
PERFORMANCE STATUS (%)		
0	32 (56)	16 (57)
1	25 (44)	12 (43)

Phase 3 trial of trastuzumab rezetecan vs standard of care (SOC) for chemotherapy-refractory, HER2-positive, advanced colorectal cancer (CRC).

Jin Li, Ying Yuan, Tianshu Liu, Xiuying Xiao, Yudong Wang, Fengbin Zhang, Zuoxing Niu, Yanhong Deng, Qiu Meng, Hong Zong, Yigui Chen, Xiang Gao, Jun Zhou, Xiaotong Li, Yifan Shen, Ning Dou, Chuanpei Huang; Shanghai GoBroad Cancer Hospital, China Pharmaceutical University, Shanghai, China; The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; Zhongshan Hospital Affiliated to Fudan University, Shanghai, China; Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; The Fourth Hospital of Hebei Medical University, Shijiazhuang, China; Cancer Hospital of Shandong First Medical University, Jinan, China; Department of Medical Oncology, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; West China Hospital, Sichuan University, Chengdu, Sichuan, China; The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; Fujian Provincial Cancer Hospital, Fuzhou, China; Jiangnan University Affiliated Hospital, Wuxi, Jiangsu, China; Shanghai GoBroad Cancer Hospital China Pharmaceutical University, Shanghai, China; Jiangsu Hengrui Pharmaceuticals Co., Ltd., Shanghai, China; Clinical Research & Development, Jiangsu Hengrui Pharmaceuticals Co., Ltd., Shanghai, China

Background: Antibody-drug conjugate (ADC) targeting HER2 represents standard therapy for HER2-positive gastric cancer and breast cancer. This study aimed to assess trastuzumab rezetecan (an HER2-targeted ADC) vs SOC in patients (pts) with chemotherapy-refractory, HER2-positive, RAS and RAF wild-type advanced CRC. **Methods:** In this randomized, open-label, multicenter, phase 3 trial, pts with HER2-positive, RAS and RAF wild-type, advanced CRC who have progressed after standard 2nd-line therapy were randomized 2:1 to receive trastuzumab rezetecan (4.8 mg/kg, d1, iv, q3w) or SOC (TAS-102 [35 mg/m², bid, d1-5 and d8-12], fruquintinib [5 mg, qd, d1-21], or regorafenib [160 mg, qd, d1-21]; po, q4w). Randomization was stratified by HER2 status (IHC 3+ vs IHC 2+/ISH+) and ECOG PS (0 vs 1). Primary endpoint was PFS per RECIST v1.1 by independent review committee (IRC). Key secondary endpoint was OS. **Results:** As of data cutoff (Oct 31, 2025), 130 pts were randomly assigned to trastuzumab rezetecan (N=86) or SOC (N=44). 70.8% of pts had HER2 IHC 3+, and 57.7% had an ECOG PS of 1. Median follow-up was 9.6 mo (95% CI 7.4–10.7). PFS per IRC was significantly increased with trastuzumab rezetecan vs SOC (median 5.5 mo [95% CI 4.8–6.7] vs 2.8 mo [95% CI 2.2–4.2]; HR 0.33 [95% CI 0.21–0.53]; 1-sided p<0.0001). Although median OS were immature, risk of death with trastuzumab rezetecan was reduced by 23% compared with SOC (HR 0.77 [95% CI 0.35–1.73]). PFS per investigator, ORR and DoR were also better with trastuzumab rezetecan vs SOC (Table 1). Grade ≥3 TRAEs occurred in 48.8% with trastuzumab rezetecan and 50.0% with SOC. No patients discontinued treatment due to TRAEs. Treatment-related death was reported in two pts (2.3%) with trastuzumab rezetecan (septic shock and myelosuppression). **Conclusions:** Compared with SOC, trastuzumab rezetecan achieved prolonged PFS and improved ORR in chemotherapy-refractory HER2-positive advanced CRC, with a tolerable safety profile. Clinical trial information: NCT06199973. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Efficacy.				
	Trastuzumab rezetecan (N=86)	SOC (N=44)	Treatment effect (95% CI)	1-sided p value
IRC-assessed PFS, mo	5.5 (4.8-6.7)	2.8 (2.2-4.2)	HR, 0.33 (0.21-0.53)	<0.0001*
Investigator-assessed PFS, mo	5.6 (5.0-6.8)	2.8 (1.5-4.1)	HR, 0.31 (0.20-0.50)	<0.0001*
OS, mo	NR (14.6-NR)	NR (12.5-NR)	HR, 0.77 (0.35-1.73)	0.2651*
IRC-assessed ORR	35 (40.7; 30.2-51.8)	2 (4.5; 0.6-15.5)	RD, 36.2 (24.1-48.2)	<0.0001†
Investigator-assessed ORR	28 (32.6; 22.8-43.5)	2 (4.5; 0.6-15.5)	RD, 28.0 (16.4-39.7)	0.0002†
IRC-assessed DoR, mo	4.4 (3.3-NR)	3.4 (2.7-NR)	-	-
Investigator-assessed DoR, mo	5.8 (4.2-NR)	1.4 (NR-NR)	-	-

Data are median (95% CI), or n (%; 95% CI), unless otherwise stated.

*Stratified log-rank test.

†Stratified Cochran-Mantel-Haenszel test. NR, not reached; RD, rate difference.

Adjuvant hepatic arterial infusion pump chemotherapy with floxuridine for patients with resectable colorectal liver metastases and a low clinical risk score: A randomized controlled trial—The PUMP trial.

Loubna Outmani, Florian Buisman, Wills Floris Filipe, Karen Bolhuis, Leni Van Doorn, Pascal G. Doornebosch, Jan Willem de Groot, Paul D. Gobardhan, Jeroen Hagendoorn, Joost van der Hoeven, Niels F. Kok, J. Sven D. Mieog, Karolina Sikorska, Rutger-Jan Swijnenburg, Maarten Vermaas, Cornelis Verhoef, Marjolein Y.V. Homs, Koert Kuhlmann, Dirk J. Grunhagen, Bas Groot Koerkamp; Erasmus MC, Rotterdam, Netherlands; Netherlands Cancer Institute, Amsterdam, Netherlands; Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands; Surgical Oncology IJsselland Hospital, Capelle Aan Den IJssel, Zuid-Holland, Netherlands; Isala Oncology Center, Zwolle, Overijssel, Netherlands; Department of Surgery, Amphia Hospital, Breda, Noord-Brabant, Netherlands; Department of Surgery, University Medical Center Utrecht, Utrecht, Utrecht, Netherlands; Albert Schweitzer ziekenhuis, Dordrecht, Zuid-Holland, Netherlands; Netherlands Cancer Institute, Amsterdam, Noord Holland, Netherlands; Leiden University Medical Center, Leiden, Zuid-Holland, Netherlands; Department of Biostatistics, Erasmus Medical Center, Amsterdam, Netherlands; Amsterdam UMC, location Vrije Universiteit, Amsterdam, Noord-Holland, Netherlands; Department of Surgery, IJsselland Hospital, Capelle Aan Den IJssel, Zuid-Holland, Netherlands; Department of Surgical Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands; Erasmus MC, Department of Surgical Oncology, Rotterdam, Netherlands; Erasmus MC Cancer Institute, Rotterdam, Netherlands

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Structured exercise program following adjuvant chemotherapy for colon cancer: A cost-utility analysis of the CHALLENGE trial.

Kelvin K. Chan, Ryan W. Chu, Matthew C. Cheung, Kerry S. Courneya, Christopher J. O'Callaghan, Janette L. Vardy, Sharlene Gill, Christine Friedenreich, Rebecca KS Wong, Haryana M. Dhillon, Vicky Coyle, Neil Sun Chua, Derek J. Jonker, Ralph M. Meyer, Shahid Ahmed, John Raymond Zalcberg, Stephen John Clarke, Patti O'Brien, Dongsheng Tu, Christopher M. Booth, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada; University of Toronto, Toronto, ON, Canada; Sunnybrook Health Sciences Centre, Toronto, ON, Canada; Faculty of Kinesiology, Sport, and Recreation, University of Alberta, Edmonton, AB, Canada; Canadian Cancer Trials Group, Queen's University, Kingston, ON, Canada; Sydney Cancer Survivorship Centre, Concord Hospital and Faculty of Medicine and Health, University of Sydney, Concord, Australia; 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; McMaster University, Dundas, ON, Canada; Saskatoon Cancer Centre, Saskatchewan Cancer Agency, University of Saskatchewan, Saskatoon, SK, Canada; Department of Medical Oncology, Alfred Health and School of Public Health, Faculty of Medicine, Monash University, Melbourne, VIC, Australia; University of Sydney, Sydney, Australia; Canadian Cancer Trials Group, Kingston, ON, Canada; Queen's University, Kingston, ON, Canada

Background: The phase III CHALLENGE trial (CCTG CO.21) demonstrated improved disease-free and overall survival with a 3-year structured exercise program (SEP) compared with health education materials (HEM) in participants with stage III or high-risk stage II colon cancer that had undergone surgery and adjuvant chemotherapy. This study evaluated the cost-effectiveness of SEP versus HEM. **Methods:** A pre-specified economic evaluation was conducted using prospectively collected data from all trial participants (n = 889). The base case adopted the Canadian public healthcare payer perspective and included direct healthcare costs (cost categories available in Table 1), a 5-year time horizon, and a 1.5% discount rate. SF-36 trial data were mapped to SF-6D using a validated algorithm to calculate health utilities. Costs (2024 CAD) and effects measured as life-years (LYs) and quality-adjusted life-years (QALYs) were used to estimate an incremental cost-effectiveness ratio (ICER, \$/life year gain (LYG)) and incremental cost-utility ratio (ICUR, \$/QALY). Uncertainty was assessed via bootstrapping (n = 1,000). Notable scenario analyses included a 10-year horizon and a societal perspective capturing indirect costs from wages lost due to missed work, measured using a Work Productivity and Activity Impairment questionnaire. **Results:** In the base case, despite the up-front \$4327 cost of the SEP intervention, the SEP was dominant over HEM (i.e. less costly (-\$179) and more effective (+0.06 LYs; +0.10 QALYs)). The SEP was dominant in 49% of bootstrap samples, while 79% met a \$50,000 per QALY willingness-to-pay threshold. Major cost drivers in both groups were the costs of recurrence or new malignancy and anticancer therapy. Scenario analysis results were consistent with the base case analysis. The SEP remained dominant with a 10-year time horizon yielding greater cost savings (\$-2,528) and more LYG (0.35) than the base case. From a societal perspective, the ICUR was \$3,571/QALY, a highly cost-effective strategy. **Conclusions:** The SEP was less costly and more effective when compared with HEM. These data can inform health systems and payers as they look to implement SEP in routine models of care. Research Sponsor: None.

Mean per participant costs, effects, and ICER/ ICUR for the base case analysis.

	SEP (n=445)	HEM (n=444)	Increment
Cost of SEP sessions (including fixed start-up costs) (\$)	4,327	0	4,327
Cost of hospitalization (pre- or without recurrence) (\$)	3,593	3,092	501
Cost of recurrence or new malignancy (physicians, lab tests, drugs, hospitalizations, surgery, emergency room visits, home care)(\$)	12,732	15,772	-3,040
Cost of anticancer therapy (\$)	12,660	14,582	-1,922
Cost of end-of-life care (\$)	54	100	-46
Total cost (\$)	33,367	33,546	-179
Total LYs	4.72	4.66	0.06
Total QALYs	3.84	3.75	0.09
ICER (\$/LYG) and ICUR (\$/QALY)	Dominant*		

*SEP is less costly and more effective than HEM.

Adjuvant aspirin for stage III colorectal cancer after curative resection: Primary analysis of the randomized double-blind placebo-controlled phase III trial (EPISODE-III: JCOG1503C).

Atsuo Takashima, Yasumitsu Hirano, Manabu Shiozawa, Hideki Ueno, Masayuki Ohue, Yusuke Suwa, Hitoshi Ojima, Akio Shiomi, Takeshi Suto, Satoshi Ikeda, Ryo Inada, Yasumasa Takii, Kazuyuki Kawamoto, Naoyuki Toyota, Hiroaki Soda, Junki Mizusawa, Haruhiko Fukuda, Shunsuke Tsukamoto, Yukihide Kanemitsu, Tetsuya Hamaguchi, Colorectal Cancer Study Group in Japan Clinical Oncology Group (JCOG); National Cancer Center Hospital, Chuo-Ku, Tokyo, Japan; Saitama Medical University International Medical, Hidaka, Japan; Department of Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, Japan; Department of Surgery, National Defense Medical College, Saitama, Japan; Osaka International Cancer Institute, Osaka, Japan; Department of Surgery, Gastroenterological Centre, Yokohama City University Medical Center, Yokohama, Japan; Gunma Prefectural Cancer Center, Gunma, Japan; Shizuoka Cancer Center, Shizuoka, Japan; Yamagata Prefectural Central Hospital, Yamagata-Shi, Japan; Hiroshima Prefectural Hospital, Hiroshima, Japan; Kochi Health Sciences Center, Kochi, Japan; Niigata Cancer Center Hospital, Niigata, Japan; Kurashiki Central Hospital, Okayama, Japan; Tochigi Cancer Center, Tochigi, Japan; Chiba Cancer Center, Chiba, Japan; National Cancer Center Hospital, Tokyo, Japan; Saitama Medical University International Medical Center, Saitama, Japan

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

A phase III, randomized, open-label study of tunlametinib plus vemurafenib versus investigator's choice of therapy in patients with previously treated *BRAF*^{V600E}-mutant metastatic colorectal cancer.

Ting Xu, Jian Li, Jufeng Wang, Yanhong Deng, Qiu Meng, Zuoxing Niu, Nanfeng Fan, Xianglin Yuan, Jun Deng, Xuefeng Fang, Yanqiao Zhang, Hongqi Tian, Wenbin Liu, Lin Shen; Department of GI Oncology, Department of Gastrointestinal Oncology, Peking University Cancer Hospital & Institute, Beijing, China; Department of Gastrointestinal Oncology, Peking University Cancer Hospital, Beijing, China; Henan Cancer Hospital, Zhengzhou, China; Department of Medical Oncology, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; West China Hospital, Sichuan University, Chengdu, Sichuan, China; Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China; Fujian Medical University Cancer Hospital, Fuzhou, China; Department of Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; Department of Medical Oncology, The First Affiliated Hospital of Nanchang University, Nanchang, China; Department of Medical Oncology, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; The Affiliated Cancer Hospital of Harbin Medical University, Harbin, China; Shanghai Kechow Pharma, Inc., Shanghai, China; Shanghai Kechow Pharma, Shanghai, China

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

Onvansertib plus standard-of-care chemotherapy plus bevacizumab in first-line RAS-mutated metastatic colorectal cancer (mCRC): Interim results from the phase 2 randomized CRDF-004 trial.

Heinz-Josef Lenz, Hao Xie, Daniel H. Ahn, David L. Bajor, Adel Kardosh, Alisha Heather Bent, Alex Kane, Ramanand Arun Subramanian, Alex Dmitrienko, Roger Sidhu, Joel R. Hecht; University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; Division of Oncology, Mayo Clinic Rochester, Rochester, MN; Division of Hematology and Oncology, Mayo Clinic Arizona, Phoenix, AZ; Department of Oncology, University Hospitals Seidman Cancer Center, Case Western Reserve University, Cleveland, OH; Oregon Health & Science University, Knight Cancer Institute, Portland, OR; The University of Texas MD Anderson Cancer Center, Houston, TX; Cardiff Oncology, Inc., San Diego, CA; Mediana, LLC, San Juan, PR; Cardiff Oncology, San Diego, CA; UCLA Jonsson Comprehensive Cancer Center, Santa Monica, CA

Background: Patients with RAS-mutated mCRC have limited treatment options. Chemotherapy in combination with bevacizumab (Bev) has been the standard first-line treatment for the past two decades, yet the prognosis for these patients remains poor. Onvansertib (Onv), a selective PLK1 inhibitor, has previously demonstrated synergy with chemotherapy in the second line setting. The Phase 2 randomized CRDF-004 trial evaluated onvansertib plus standard-of-care (SoC; FOLFIRI or FOLFOX with Bev) in as first-line RAS-mutated mCRC. **Methods:** Patients with first-line KRAS or NRAS mutant mCRC were randomized to SoC alone or SoC plus onvansertib (20 mg or 30 mg). The primary endpoint was objective response rate (ORR) as determined by a blinded-independent central review (BICR) using RECIST v1.1. Key secondary endpoints included progression-free survival (PFS), duration of response, and safety. PFS was assessed by BICR and investigator assessments combined. Results are presented in the intent-to-treat population (ITT). **Results:** At the data cutoff of 22 Jan 2026, 110 patients were randomized with a median follow up of approximately 10 months. Baseline characteristics were relatively balanced across arms. Onv 30 mg + FOLFIRI + Bev demonstrated numerically higher ORR (n = 13/18, 72.2%, 95% CI: 46.5, 90.3) compared with the FOLFIRI + Bev control arm (n = 8/19, 42.1%, 95% CI: 20.3, 66.5), the FOLFOX + Bev control arm (n = 8/18, 44.4%, 95% CI: 21.5, 69.2) and the combined control arms (SoC: n = 16/37, 43.2%, 95% CI: 27.1–60.5). Onv 30mg + FOLFIRI + Bev demonstrated a p-value of 0.051 for confirmed ORR vs. SoC; and a p-value of 0.045 for the 6-month ORR compared to FOLFIRI + Bev (n = 10/18, 55.6%, 95% CI: 30.8–78.5 vs. n = 4/19, 21.1%, 95% CI: 6.1–45.6, respectively). The median PFS for the control arms was 10.97 months (95% CI: 7.52, NR) for FOLFIRI + Bev, 9.89 months (95% CI: 9.43, NR) for FOLFOX + Bev and 10.97 months (95% CI: 9.43–15.44) for the combined SoC arms. The median PFS in the Onv 30mg+ FOLFIRI + Bev arm was not reached (95% CI: 9.72–NR). The PFS HR of 30mg + Onv + FOLFIRI + Bev vs FOLFIRI + Bev was 0.38 (95% CI: 0.12–1.17) and vs SoC was 0.37 (95% CI: 0.13–1.02, p = 0.048). The clinical benefit from Onv treatment was further evidenced by the 12-month PFS rates, 61.9% (95% CI: 40.1, 95.8) in the Onv 30 mg + FOLFIRI + Bev arm vs. 28.4% (95% CI: 9.3, 86.9) in the FOLFIRI + Bev arm, and 30.1% (95% CI: 13.8–65.7) in the SoC. Onvansertib was well tolerated, with no unexpected toxicities observed; the most common grade ≥ 3 adverse event was neutropenia. PK data support moving forward with the onvansertib 30mg dose with FOLFIRI + Bev. **Conclusions:** Onvansertib plus FOLFIRI and bevacizumab demonstrated improved antitumor activity and manageable safety in first-line RAS-mutated mCRC. These results support further clinical and support planned confirmatory Phase 3 evaluation. Clinical trial information: NCT06106308. Research Sponsor: Cardiff Oncology.

Circulating tumor DNA (ctDNA) clearance as an early indicator of sotorasib + panitumumab efficacy and prognosis in *KRAS* G12C–mutated colorectal cancer (mCRC): Results from phase 3 CodeBreak 300.

Filippo Pietrantonio, Lata Mukundan, Abraham Anderson, Emily Chan, Marko Rehn, Amrita Pati, Lisa Salvatore, Fausto Meriggi, Dominik Paul Modest, Erika Ruiz-Garcia, Chiara Cremolini, Michail Karamouzis, Taito Esaki, Tae Won Kim, Julien Taieb, Yasutoshi Kuboki, Yuliya Katlinskaya; Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Amgen Inc., San Francisco, CA; Amgen Inc., Thousand Oaks, CA; Medical Oncology, Comprehensive Cancer Center, Fondazione Policlinico Universitario, Agostino Gemelli, IRCCS, Roma, Italy; Oncology Department, Fondazione Poliambulanza Istituto Ospedaliero, Brescia, Italy; Department of Hematology and Oncology, Charité – Universitätsmedizin Berlin, Campus Virchow-Klinikum, Berlin, Germany; Superare Centro de Infusión S.A. de C.V., Mexico City, EM, Mexico; Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy; Evgenidio Hospital, National and Kapodistrian University of Athens, Athens, Greece; National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan; Asan Medical Center, University of Ulsan, Seoul, South Korea; Department of Gastroenterology and Digestive Oncology, Hôpital Européen Georges-Pompidou, Paris, France; Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan

Background: Phase 3 CodeBreak 300 (NCT05198934) explored two doses of sotorasib (soto) (240 mg and 960 mg) in combination with panitumumab (pani) 6 mg/kg versus investigator's choice (IC) and demonstrated superior progression-free survival (PFS) with soto 960 mg+pani versus IC in chemorefractory *KRAS* G12C-mutant mCRC. We evaluated whether early ctDNA clearance could serve as non-invasive biomarker of treatment (tx) response using one of the largest cohorts of mCRC patients (pts) treated with a *KRAS*^{G12C} inhibitor plus an EGFR antibody and the only longitudinal ctDNA dataset from a *KRAS*^{G12C} inhibitor trial in mCRC. **Methods:** ctDNA analyzed using the Guardant Infinity assay was quantified using *KRAS* G12C variant allele frequency (VAF) and methylation-based circulating tumor fraction (cTF) metrics. Clearance was defined at $\geq 50\%$, $\geq 80\%$, $\geq 90\%$ and 100% reduction thresholds. Associations with objective response rate (ORR), PFS, and overall survival (OS) were assessed using logistic regression, Fisher-exact tests, Cox proportional hazards models, and Kaplan–Meier methods. **Results:** A total of 142 pts had evaluable baseline and Cycle 2 Day 1 ctDNA results. Early ctDNA clearance was more frequent in the soto arms than in the IC arm. This finding was consistent across ctDNA assessment methods, with high concordance between VAF and cTF. At $\geq 80\%$ threshold, VAF clearance rates (95% CI) were 77.3% (62.2–88.5) and 65.9% (50.1–79.5) in the soto 960 mg and 240 mg arms (each N=44), respectively, compared with 15% (5.7–29.8) in the IC arm (N=40). Complete (100%) VAF clearance (95% CI) was observed in 45.5% (30.4–61.2), 31.8% (18.6–47.6), and 5.0% (0.6–16.9) of pts in the 960 mg, 240 mg, and IC arms, respectively. Reductions in ctDNA were correlated with radiographic tumor shrinkage. Lack of ctDNA clearance was associated with non-response, whereas pts achieving clearance were more likely to respond. Among pts treated with soto 960 mg who achieved $\geq 80\%$ ctDNA clearance, the ORR (95% CI) by VAF was 35.3% (12/34; 19.7–53.5) and 32.3% (10/31; 16.7–51.4) by cTF. Decline in ctDNA was associated with improved PFS and OS independent of tx arm, confirming the role of ctDNA as a prognostic marker. Increasing clearance stringency did not enhance prognostic value. **Conclusions:** Early ctDNA clearance, assessed by *KRAS* G12C VAF or cTF, is prognostic for improved outcomes, supporting its utility as an early response biomarker. Clinical trial information: NCT05198934. Research Sponsor: Amgen Inc.

Survival (months) by VAF clearance ($\geq 80\%$).

Cohort	VAF Clearance	N	mPFS (95% CI)	mOS (95% CI)
IC	N	34	2.0 (1.9–4)	10.3 (6.6–14)
IC	Y	6	8.4 (3.7–NE)	NE
Soto 240	N	15	2.6 (1.8–3.8)	5.1 (3.2–7.5)
Soto 240	Y	29	5.6 (3.8–8.5)	14.0 (8.4–NE)
Soto 960	N	10	1.9 (1.6–3.8)	4.9 (1.6–7)
Soto 960	Y	34	5.8 (5–7.5)	NE (10.8–NE)

m, median; NE, not evaluable; N, no; Y, yes.

Phase III CR-SEQUENCE trial of FOLFOX+panitumumab followed by FOLFIRI+bevacizumab (SEQ1) versus FOLFOX + bevacizumab followed by FOLFIRI + panitumumab (SEQ2) in previously untreated RAS wild-type, left-sided, unresectable metastatic colorectal cancer.

Ramon Salazar, Maria Auxiliadora Gomez, Paula Jimenez-Fonseca, Ferran Losa, Adelaida La Casta, Bartomeu Massuti, Esperanza Torres, Elena Gallardo Martin, Teresa Garcia, Rosario Vidal-Tocino, Yolanda Vidal-Insua, Cristina Gravalos, Ana Fernandez-Montes, Javier Gallego Plazas, Maria Jose Safont, Sandra Merino, Carles Pericay, Antonieta Salud Salvia, Enrique Aranda, Alfredo Carrato; Medical Oncology Department, Institut Català d'Oncologia (ICO), L'Hospitalet De Llobregat, Barcelona, Spain; Medical Oncology Department, Reina Sofía University Hospital. Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC), University Reina Sofía Hospital, Universidad de Córdoba, CIBERONC, Cordoba, Spain; Medical Oncology Department, Hospital Universitario Central de Asturias, ISPA, Oviedo, Spain; Medical Oncology Department, Hospital Sant Joan Despi-Moisés Broggi, Barcelona, Spain; Medical Oncology Department, Hospital Universitario de Donostia, San Sebastián, Spain; Medical Oncology Department, Hospital General de Alicante, Alicante, Spain; Medical Oncology Department, H. Universitario Regional Virgen de la Victoria, Malaga, Spain; Medical Oncology Department, Hospital Álvaro Cunqueiro, Pontevedra, Spain; Medical Oncology Department, Hospital Universitario Santa Lucía, Cartagena, Spain; Medical Oncology Department, Hospital Universitario de Salamanca, IBSAL, Salamanca, Spain; Medical Oncology Department, H. Clínico Universitario de Santiago de Compostela, Santiago de Compostela, Spain; Medical Oncology Department, H. Universitario 12 de Octubre, Instituto de Investigación i+12, Madrid, Spain; Medical Oncology Department, Complejo Hospitalario Universitario de Ourense, Ourense, Spain; Medical Oncology Department, General Universitario de Elche Hospital, Alicante, Spain; Medical Oncology Department, General University Hospital Consortium of Valencia, Valencia University, Valencia, Spain; Medical Oncology Department, Hospital Sant Joan de Reus, Reus, Spain; Medical Oncology Department, H. de Sabadell. Corporación Sanitaria Parc Tauli, Sabadell, Spain; Medical Oncology Department, Hospital Universitario Arnau de Vilanova de Lleida. IRB-Lleida, Lleida, Spain; Medical Oncology Department IMIBIC, Universidad de Córdoba, CIBERONC, Instituto de Salud Carlos III, Hospital Universitario Reina Sofía, Córdoba, Spain; Alcala de Henares University, Madrid, Spain

Background: The optimal sequencing of systemic therapy for patients with RAS wild-type, left-sided metastatic colorectal cancer (mCRC) remains under debate. This study evaluates whether starting with SEQ1 improves the 36-months progression-free survival rate (PFSR) versus SEQ2.

Methods: Adult patients were randomized (1:1) to SEQ1 or SEQ2 and treated until second-line progression or unacceptable toxicity. Key inclusion criteria were untreated left-sided and wild type RAS (per local test) primary mCRC, ECOG-PS<2, measurable disease (RECIST 1.1), and adequate organ function. Primary endpoint was 36-month PFSR in ITT. Secondary endpoints included overall survival (OS), total PFS, objective response rate (ORR), PFS1, PFS2, and safety.

Results: A total of 418 patients were analyzed (SEQ1=210; SEQ2=208); 54.76% and 70.19% of randomized patients received 2L treatment in SEQ1 and SEQ2 arms, respectively. The median follow-up was 62.2 months (95%CI 55.2 – 65.5). SEQ1 yielded a higher 1st-line ORR (80.95% vs 64.25%, $p < 0.01$) and significantly improved median PFS1 (14.09 vs 12.39 months, $p = 0.03$). In second line, SEQ2 (FOLFIRI + panitumumab) resulted in a higher ORR (40.43% vs 27.27%, $p = 0.03$). There was no significant difference in 36-months PFS rate (28.57% vs. 22.36%; $p = 0.224$). Median total PFS and OS were 22.93 vs 21.39 months ($p = 0.2241$) and 36.57 vs 31.74 months ($p = 0.2949$), respectively. Longer follow-up for PFS and OS is ongoing. Curative intent procedures were performed in 22.86% (SEQ1) and 19.23% (SEQ2) of patients, respectively. Rescue surgery improved PFS and OS across both sequences. Common related G3-4 adverse events included neutropenia (42%), rash (15.7%), diarrhea (13%), peripheral neuropathy (12%), and fatigue (12.3%). **Conclusions:** SEQ1 did not improve the 36-month PFSR versus SEQ2. However, starting with SEQ1 yielded superior early efficacy (higher ORR and longer PFS1), which may be clinically relevant in a subset of patients. Molecular profiling and genomic correlation analyses are ongoing to identify biologically defined clusters that may improve selection of sequential treatment strategies. Longer follow-up for clinically relevant secondary endpoints (total PFS and OS) is ongoing. Clinical trial information: 2024-510967-41-00. Research Sponsor: AMGEN.

Baseline characteristic by treatment arm.

Characteristic		SEQ 1 (n=210)	SEQ 2 (n=208)
Age, median (IQR*), years		63 (57-71)	63 (57-71)
	Female	53 (25.2)	58 (27.9)
Sex, n (%)	Male	157 (74.8)	150 (72.1)
ECOG-PS, n (%)	0	112 (53.3)	118 (56.7)
	1	98 (46.7)	90 (43.3)
		2 (1-6)	2 (1-7)
Metastasis per organ, median (range)		40.7 (11.6 – 364.3)	74.5 (11.8 – 643.9)
Baseline CEA, median (IQR), ng/mL		27 (12.9)	24 (11.5)
Prior therapies	Adjuvant chemo	23 (10.9)	18 (8.6)
	Radiation	56 (26.7)	72 (34.6)
	Primary tumor resection		

*IQR: interquartile range.

Development of a computational histology artificial intelligence (CHAI)–powered predictive biomarker for first-line chemotherapy intensification in metastatic colorectal cancer (mCRC) and validation in prospective randomized phase III trials (RCT).

Paolo Ciraci, Viswesh Krishna, Carlotta Antoniotti, Giulia Martinelli, Clara Ugolini, Asit Tarsode, Vrishab Krishna, Haochen Zhang, Waleed Abuzeid, Snehal Sonawane, Lesli Ann Kiedrowski, Trevor Royce, Anirudh Joshi, Ioannis Souglakos, Christopher Lieu, Alan P. Venook, Richard M. Goldberg, Tim Maughan, Chiara Cremolini; 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; Valar Labs, Inc., Palo Alto, CA; University of Pisa, Pisa, Italy; Department of Surgical, Medical, Molecular Pathology and Critical Area, University of Pisa, Pisa, Italy; Wake Forest School of Medicine, Winston-Salem, NC; University of Crete Medical School, Heraklion, Greece; University of Colorado, Anschutz School of Medicine, Aurora, CO; University of California, San Francisco, San Francisco, CA; West Virginia University Cancer Institute and the Mary Babb Randolph Cancer Center, Morgantown, WV; University of Liverpool, Liverpool, United Kingdom

Background: In unresectable mCRC, meta-analysis of RCTs suggests triplet therapy consisting of fluorouracil, oxaliplatin, and irinotecan (FOLFOXIRI) + bevacizumab (bev) may improve survival outcomes over doublet regimens of fluorouracil with irinotecan (FOLFIRI) or oxaliplatin (FOLFOX) + bev, at the expense of increased toxicity. Adoption of triplet therapy remains low. A histology-based biomarker to predict outcomes in mCRC treated with triplet vs doublet regimens could optimize treatment selection. We aimed to use the previously described CHAI platform to develop and validate a histology-based predictive biomarker for doublet vs triplet therapy in mCRC with participant-level data from 3 RCTs. **Methods:** Development used diagnostic H&E-stained whole slide images (WSI) from participants with mCRC treated with first-line (1L) chemotherapy enrolled in the MRC FOCUS RCT. WSIs were analyzed using the CHAI assay and trained towards clinical outcomes as a function of chemotherapy escalation. Weighting of histologic features was optimized for association with progression-free (PFS) & overall survival (OS) to construct a signature that was combined with tumor sidedness to create the mCRCpred biomarker. A cutpoint was selected to optimize treatment effect stratification, assigning each case a binary label. The locked biomarker was evaluated on the independent validation cohort of WSIs from the TRIBE + TRIBE2 RCTs. The association of the biomarker-treatment interaction with PFS & OS was evaluated with multivariable (MVA) Cox models & Likelihood Ratio tests. **Results:** The development cohort included 294 cases from MRC FOCUS. The independent validation cohort (n = 386) comprised cases from TRIBE (n = 159) and TRIBE2 (n = 227). 193 (50%) had 1L triplet+bev and 193 (50%) doublet+bev. Biomarker (+) (indicative of triplet benefit) disease treated with triplet+bev had superior 3-year PFS (17% vs 7%, HR = 0.51 [0.37, 0.70], p < 0.001) and OS (43% vs 22%, HR = 0.51 [0.35, 0.73], p < 0.001) versus doublet+bev. Biomarker (-) cases treated with triplet+bev vs doublet+bev had no significant differences in PFS (5 vs 15%, HR = 1.30 [0.96, 1.74], p = 0.09) or OS (31 vs 40%, HR = 1.35 [0.94, 1.92], p = 0.1). In MVA including cohort, age, ECOG, number of metastatic sites, and timing of metastasis (metachronous/synchronous), the biomarker-treatment interaction was significant (p < 0.001) indicating a predictive association between the biomarker and treatment regimen. **Conclusions:** The CHAI mCRCpred histology-based biomarker predicted differential benefit of chemotherapy escalation (doublet-bev vs triplet-bev) as 1L therapy in mCRC, with independent validation post-hoc in two RCTs (Simons Level of Evidence IB). This biomarker may guide optimal treatment selection for 1L mCRC. Clinical trial information: ISRCTN79877428 (FOCUS); NCT00719797 (TRIBE); NCT02339116 (TRIBE2). Research Sponsor: None.

Phase I study of intraperitoneal fast-manufactured IL-9-secreting CEACAM5-targeted CAR-T cells in advanced colorectal cancer with peritoneal metastases.

Hangyu Zhang, Jie Li, Yang Gao, Yingzi Zhang, Xudong Zhu, Linling Wang, Lulu Liu, Junjie Shen, Xiaomeng Dai, Wenyu Wang, Huihui Wang, Zhou Tong, Yi Zheng, Peng Zhao, Zhi Yang, Weijia Fang, Cheng Qian, Xuanwen Bao; Department of Medical Oncology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; Chongqing Precision Biotech Co., Ltd., Chongqing, China; Chongqing Municipal Key Laboratory of Gene and Cell Therapy, Chongqing, China; The First Affiliated Hospital of Zhejiang University, Hangzhou, China; Department of Medical Oncology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China

Background: Colorectal cancer peritoneal metastasis (CRPM) remains an unmet clinical need with poor prognosis and limited benefit from systemic therapies. Our prior study on intra-peritoneal (I.P.) CEA-targeting CAR-T cells (Nature Cancer) achieved a 25% ORR, yet limited persistence and exhaustion hampered efficacy. Consequently, we developed a novel Th9/Tc9-polarized fast- manufacturing process that exhibited superior T-cell fitness and antitumor function preclinically. We therefore conducted a Phase I study to evaluate the safety and preliminary efficacy of I.P. administration of these optimized CAR-T cells in CRPM population. **Methods:** This open-label, single-arm Phase I study enrolled patients with histologically confirmed, heavily pretreated CEA-positive CRPM. A standard 3+3 dose- escalation design evaluated three dose levels (DLs): DL1 (2.0×10^5 cells/kg), DL2 (3.0×10^5 cells/kg), and DL3 (4.0×10^5 cells/kg), followed by dose expansion. Primary objectives were safety and tolerability; secondary objectives included preliminary antitumor activity, cellular kinetics, and pharmacodynamics. **Results:** Between July 2024 and October 2025, 15 patients were enrolled; 14 were evaluable for efficacy. One dose-limiting toxicity (DLT; Grade 4 pneumonia) occurred at DL2. The most common grade 3 non-hematologic toxicity was diarrhea (53.3%). Cytokine release syndrome (CRS) occurred in all patients and was Grade 1/2 in 93.3%. No treatment-related deaths were reported. Among 14 efficacy-evaluable patients (median 3 prior lines of therapy), ORR was 57.1% and DCR was 100%, with maximum tumor shrinkage reaching 85.6%. Median PFS was 4.7 months (95% CI, 3.7–NE). Peripheral blood CAR- T cells expanded to a mean peak of 1.74×10^4 copies/ μ g, and serum CEA levels decreased in 100% of patients (median reduction: 67.5%). **Conclusions:** Intraperitoneal administration of fast-manufactured Th9/Tc9 like CEA-CAM5-targeted CAR-T cells demonstrated a manageable safety profile and encouraging antitumor activity in heavily pretreated CRPM patients, at approximately one-tenth of conventionally reported CAR-T cell doses. These findings support further development of fitness-enhanced, regionally delivered CAR-T strategies for peritoneal malignancies. Clinical trial information: NCT05396300. Research Sponsor: None.

Variable	DL1 (n=3)	DL2 (n=5)	DL3 (n=6)	Total (n=14)
PR, n (%)	1 (33.3)	4 (80.0)	3 (50.0)	8 (57.1)
SD, n (%)	2 (66.7)	1 (20.0)	3 (50.0)	6 (42.9)
ORR, n (%)	1 (33.3)	4 (80.0)	3 (50.0)	8 (57.1)
DCR, n (%)	3 (100.0)	5 (100.0)	6 (100.0)	14 (100.0)
Median PFS, months	5.6 [3.8–NE]	3.4 [3.2–NE]	NA	4.7 [3.4–NE]

Real-world outcomes and circulating tumor DNA (ctDNA) dynamics in patients (pts) with microsatellite instability–high (MSI-H) metastatic colorectal cancer (CRC) treated with immune checkpoint inhibitors (ICI).

Hannah Ruth Robinson, Nicholas James Hornstein, Patrick M. Boland, Daniel H. Ahn, Vasily N. Aushev, Antony Tin, Darryl Nousome, J. Bryce Ortiz, Shruti Sharma, Robert William Lentz, Adham A. Jurdi, Minetta C. Liu, Joel R. Hecht, Kristen Keon Ciombor, Christopher Lieu; Division of Medical Oncology, Department of Medicine, University of Colorado Anschutz School of Medicine, Aurora, CO; Northwell Health Cancer Center, New York, NY; Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; Division of Hematology and Oncology, Mayo Clinic Arizona, Phoenix, AZ; Natera, Inc., Austin, TX; UCLA Jonsson Comprehensive Cancer Center, Santa Monica, CA; Vanderbilt University Medical Center, Vanderbilt University, Nashville, TN; University of Colorado, Anschutz School of Medicine, Aurora, CO

Background: ICIs produce durable benefit in MSI-H CRC, yet optimal treatment duration and monitoring strategies remain unclear. ctDNA enables minimally invasive assessment of molecular response during and after ICI. We evaluated real-world treatment patterns, outcomes, and longitudinal ctDNA dynamics in pts with MSI-H CRC treated with ICI. **Methods:** Pts with MSI-H mCRC treated with first-line ICI were identified from Natera's Real-World Database with linked longitudinal ctDNA results (Signatera, Natera, Inc.) and commercial claims data (Forian's Hybrid data ecosystem, CHRONOS). Overall survival (OS) was estimated using available mortality data (Veritas Data Research, Fact of Death Mortality Data Index). ctDNA status was assessed pre-ICI when available and longitudinally following ICI initiation. Outcomes included OS and time to next trmt (TTNT); ctDNA dynamics following ICI discontinuation were descriptively evaluated. **Results:** Among 559 pts treated with first line ICI (pembrolizumab [70.1%], ipilimumab+nivolumab [15.7%], and nivolumab [11.8%]), the median duration of ICI was 266 days. Baseline (pre-ICI) ctDNA results were available for 180 pts, including 38% who were treated with chemotherapy, and most pts (71.7%, 129/180) were ctDNA-positive (ctDNA(+)) prior to ICI initiation. Of these, 89.9% (116/129) had ctDNA-timepoints after the start of ICI, and 81.0% (94/116) achieved anytime ctDNA clearance (from ctDNA(+) to negative), while 19.0% (22/116) remained ctDNA(+). ctDNA(+) at anytime after the start of ICI (HR: 8.0, $p < 0.0001$) or on first result after the start of ICI (HR: 3.4, $p < 0.0001$) was associated with inferior OS compared ctDNA-negativity (ctDNA(-)) at these time points. Among pts whose first post-ICI test was ctDNA(+), 32% switched treatments, with a median TTNT of 302 days, compared to only 6.6% of pts (median TTNT 683 days) whose first post-ICI test was ctDNA(-). First post-ICI ctDNA status was associated with longer ICI duration (median 192 days for ctDNA(+) vs 303 days for ctDNA(-)), and ctDNA(+) was predictive of inferior OS (HR: 4.9; $p < 0.001$). ctDNA after the end of ICI was available for 392 patients; it was persistently negative in 77.2% (303/392), persistently positive in 12.8% (50/392), cleared after the end of ICI (positive to persistently negative) in 4.1%, and the remaining 5.9% had variable patterns (e.g. positive to negative to positive). **Conclusions:** In this large real-world cohort of MSI-H mCRC treated with ICI, longitudinal ctDNA dynamics strongly correlated with treatment durability, time to subsequent therapy, and OS. These findings support further evaluation of ctDNA to inform treatment duration and surveillance strategies in MSI-H mCRC. Research Sponsor: None.

Role of microbiota in response to treatment in anal squamous cell carcinoma.

Jaime Feliú, Andrea Garcia-Leal, Fernando Becerril-Gomez, Angelo Gámez-Pozo, Isabel Busquier Hernandez, Fernando Arias, Fernando López-Campos, Ana Fernandez Fernandez Montes, Ana Ruiz-Casado, Concepción Velázquez, Celia Martín, Elena Asensio Martinez, Hernández-Yagüe Javier, Aline Rodrigues Francoso, Antje Dittmann, Juan Angel Fresno-Vara, Joan Maurel, Ismael Ghanem Canete, Lucía Trilla-Fuertes; Hospital Universitario La Paz, Madrid, Spain; Medical Oncology Service, Hospital Universitario La Paz, Madrid, Spain; Molecular Oncology Lab, INGEMM, University Hospital La Paz - IdiPAZ, Madrid, Spain; Medical Oncology Service, Hospital Provincial de Castellón, Castellon, Spain; Complejo Hospitalario De Navarra, Pamplona, Spain; Hospital Universitario Ramón y Cajal, Madrid, Spain; Department of Medical Oncology, Complejo Hospitalario Universitario de Ourense, Ourense, Spain; Medical Oncology Department, HU Puerta de Hierro Majadahonda, IDIPHISA, Madrid, Spain; Medical Oncology Service, Hospital Miguel Servet, Zaragoza, Spain; Medical Oncology Service, Hospital Regional Universitario De Málaga, Málaga, Spain; Hospital de Elche, Alicante, Spain; Institut Català Oncologia, Girona, Spain; University Hospital of Salamanca, Institute of Biomedical Research of Salamanca (IBSAL), Salamanca, Spain; Functional Genomics Center Zurich, Zurich, Switzerland; Molecular Oncology Lab, University Hospital La Paz-IdiPAZ, Biomedical Research Networking Center on Oncology-CIBERONC, ISCIII, Madrid, Spain; Hospital Clínic Barcelona, Barcelona, Spain; Department of Medical Oncology, Hospital Universitario La Paz, Madrid, Spain

Background: Anal squamous cell carcinoma (ASCC) is a rare tumor whose management and treatment have not changed since the 1970s, consisting of classical chemotherapy combined with radiotherapy. Microbiota has been recently included as a hallmark of cancer, playing a relevant role in oncogenesis and tumor progression. Therefore, the aim of this study is the characterization of tumor microbiota in ASCC. **Methods:** Paraffin samples from seventy-six ASCC patients were analyzed. First, DNA was extracted, followed by 16S rDNA sequencing to identify microbiota. Then, a bacterial reference proteome was built, including the bacteria genera identified by 16S, and proteins from human and microbiota were identified and quantified by mass-spectrometry proteomics. **Results:** Seventy-six ASCC patients were included in this study: 46 (60%) female; median age 61 years; 62 (81%) HPV-positive; 1 (1%) stage I, 30 (40%) stage II, 43 (57%) stage III, 1 (1%) stage IV, and 1 (1%) unknown stage. Of these, sixty-nine (stages II-III, treated with chemoradiotherapy) were considered for survival analyses. One thousand and fifty-seven bacteria genera were identified by 16S sequencing, with *Cutibacterium*, *Bacteroides*, and *Fusobacterium* being the most abundant. Using proteomics and after applying quality criteria, 1735 proteins were identified and quantified. Of them, 1727 were human proteins and eight were bacterial proteins. Two oncomicrobiota protein profiles were identified in ASCC, ASCC-OMP1 (36 [47%] pts) and ASCC-OMP2 (40 [53%] pts). ASCC-OMP1 presented a higher expression of proteins from *Sutterella* and *Staphylococcus* whereas ASCC-OMP2 showed higher expression of proteins from *Dialister*, *Campylobacter A*, and *Dysosmobacter*. In addition, the two microbiota profiles showed differences in human proteins related to immune response, adhesion, extracellular matrix, translation, and metabolism. Interestingly, significant differences in disease-free survival (DFS) ($p=0.02$, HR= 2.73, DFS at 5 years: ASCC-OMP1 78.43%, ASCC-OMP2 52.33%) were shown between ASCC-OMP1 and ASCC-OMP2. Overall survival (OS) is not significant between the two groups but a trend can be observed ($p=0.06$, HR=2.55, OS at 5 years: ASCC-OMP1 79.28%, ASCC-OMP2 62.92%). In a multivariate analysis including the classical clinical prognostic factors, the prognostic value in disease-free survival of the oncomicrobiota profiles remains. **Conclusions:** Two different oncomicrobiota protein profiles with implications in disease-free survival exist in anal squamous cell carcinoma. Research Sponsor: None.

TROP2 as an actionable biomarker for anal cancer.

Mir Lim, Nejla Ozirmak Lermi, Alejandra G. Serrano, Alexey Sorokin, Preeti Kanikarla Marie, Xinyue Chen, Wei Lu, James Yu, Jarett L. Feldman, Victoria Higbie, Songwit Payapwattanawong, Mei Jiang, Ken Chen, Jesse Joshua Smith, Luisa Maren Solis, Van K. Morris II; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of GI Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Bioinformatics and Computational Biology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Chemoimmunotherapy is standard frontline therapy for metastatic anal cancer, with no effective treatment options afterward. Mutation profiling has not yielded matched targeted therapies against anal cancer. Trophoblast cell-surface antigen 2 (TROP2) is over-expressed in other solid tumors, and TROP2 antibody-drug conjugates (ADCs) have demonstrated efficacy in breast and lung cancers. Given the therapeutic availability against TROP2, we evaluated expression of TROP2 in anal cancer as an actionable therapeutic target. **Methods:** Metastatic anal cancer tumors from 33 patients at MD Anderson were sequenced by bulk RNA sequencing (“Tumor Portrait” assay, Boston Gene) to quantify *TACSTD2* (TROP2) gene expression. *TACSTD2* expression was compared across all solid tumors and classified according to ranked expression percentile: high (>83rd percentile), medium (17–83rd percentile), or low (<17th percentile). Gene expression (Nanostring) for >18,000 genes was measured using whole-genome digital spatial profiling (DSP) on a separate cohort of 40 chemoradiotherapy-refractory localized anal cancers collected at salvage surgery. *TACSTD2* gene expression on tumor cells vs TME cells was compared with a t-test (SPSS). TROP2 protein expression (Invitrogen) was quantified by H-score using immunohistochemistry (IHC) and correlated with *TACSTD2* expression via Spearman’s correlation. Three patient-derived xenograft (PDX) models of anal cancer (C1411, C1436, O0026) were treated with normal saline (untreated control, UTC) or the TROP2 ADC sacituzumab govitecan (sac-gov; 10 mg/kg IP twice weekly). Tumor growth inhibition (TGI) was defined as 1 – (mean tumor volumes of sac-gov/UTC) at 21 days. **Results:** Median *TACSTD2* (TROP2) gene expression for patients with metastatic anal cancer was ranked at the 75th percentile (IQR 63–85) relative to all solid tumors: 13/33 (39%) with high, 20/33 (61%) with medium, and none with low *TACSTD2* expression. For localized anal cancers, *TACSTD2* gene expression using DSP was significantly higher on tumor segments vs TME segments (log fold change 3.49, adjusted $p < 0.0001$). 30/39 (77%) anal cancers had high TROP2 expression by IHC, defined by H-score >200. Correlation between *TACSTD2* gene expression and TROP2 protein expression by IHC was observed ($r = 0.43$, $p < 0.001$). In PDX models, TGI with sac-gov relative to UTC was observed in both models with high TROP2 expression (C1411: TGI 54%, $p < 0.001$; C1436: TGI 52%, $p < 0.001$) but not in a model with no TROP2 expression (O0026: TGI 12%, $p = \text{n.s.}$). **Conclusions:** TROP2 expression is high for localized and metastatic anal cancer. *TACSTD2* gene expression correlates with matched TROP2 protein expression for anal cancer. Anti-tumor efficacy of TROP2 ADCs in vivo supports a forthcoming trial of sacituzumab tirumotecan for patients with treatment-refractory metastatic anal cancer, with the ultimate goal of establishing TROP2 as a predictive biomarker for treatment benefit in this rare cancer. Research Sponsor: None.

H&E-based MSI/MMR testing with artificial intelligence in colorectal cancer: A blinded evaluation across diverse clinicopathological subgroups.

Pahini Pandya, Cher Bass, Foivos Ntelemis, Julian Schmidt, Debapriya Mehrotra, Naren Kumar, Vishali Sharma, Nicholas Bennett, Mitchell Hyde, Grace Rogerson, Elizabeth Walsh, Nicolas M. Orsi, Jakob Nikolas Kather, Salim Arslan; Panakeia Technologies, Cambridge, United Kingdom; University of Leeds, Leeds, United Kingdom; Else Kröner Fresenius Center For Digital Health, Faculty of Medicine, Dresden, Germany

Background: Mismatch repair (MMR) deficiency and microsatellite instability (MSI) testing is integral to colorectal cancer management. Despite guideline recommendations, routine testing remains limited by cost, turnaround time, and pathology resources. PANProfiler Colorectal (PPC) is an artificial intelligence (AI) system that infers MSI/MMR status directly from H&E-stained whole slide images (WSIs), offering a rapid, resource-efficient alternative. This study reports blinded validation of PPC, specifically evaluating performance across clinically relevant subgroups. **Methods:** A total of 2,636 WSIs from St. James’s University Hospital (Leeds, UK) were retrospectively analyzed, with the dataset representing a broad range of clinicopathological characteristics including age (< 50 to > 75 years), gender, tumor stage, differentiation, and histological subtypes. PPC returned proficient MMR (*pMMR*), deficient MMR (*dMMR*) or *indeterminate* (no definitive result), with results evaluated for agreement against immunohistochemistry. **Results:** PPC generated definitive results for 2,109 WSIs, achieving a test replacement rate (TRR) of 80%. Overall positive percent agreement (PPA) was 97.9% and negative percent agreement (NPA) 93.8% (Table). Performance was consistent across all age groups and genders. PPA and NPA were mostly robust in all cancer stages, with PPA exceeding 99% in Stage II disease, where MMR status primarily informs adjuvant therapy decisions. In Stage III/IV disease, PPA reduced to 82.6%, which may reflect greater histological heterogeneity in advanced tumors. In mucinous and poorly differentiated tumors, PPA remained high (98.7–100%), supporting reliable detection of *dMMR* samples, while NPA ranged from 75.4–80%, indicating more conservative classification of *pMMR* tumors that would require lab tests. **Conclusions:** PPC demonstrated a high overall performance, providing definitive results for the majority of cases. PPA and NPA were consistent in key clinical groups, including younger patients and early stage disease. In more challenging cases like mucinous and poorly differentiated tumors, PPA remained robust despite reductions in NPA, supporting safe guidance of subsequent testing. These findings suggest PPC could streamline MSI/MMR workflows, reducing reliance on conventional testing while maintaining diagnostic safety across diverse clinicopathological profiles. Research Sponsor: None.

Performance across diverse subgroups.														
	Overall	Age <50	Age 50-65	Age 65-75	Age >75	Male	Female	Stage I	Stage II	Stage III/IV	Well Diff.	Moderately Diff.	Poorly Diff.	Adenocarcinoma
Definitive (n)	2109	155	159	698	703	1165	944	395	1015	694	245	1655	187	1879
PPA (%)	97.9	100	100	92.1	100	95.5	99.4	97.8	99.5	82.6	100	96	100	99.5
NPA (%)	93.8	91.7	98	91.3	94.1	95.5	91.5	95.1	91.8	95.5	92.5	95.6	80	95.3
TRR (%)	80	74.5	76.4	81.2	82.2	81.1	78.7	74.5	81	81.8	76.1	80.8	80.3	82.4
Mucinous	210													75.4
														63.6

Large language model–assisted decision-making in multidisciplinary tumor boards for colorectal cancer.

Aydan Farzaliyeva, Arzu Oguz, Ozden Altundag, Zafer Akcali; Department of Medical Oncology, Baskent University, Ankara, Turkey

Background: Evolving colorectal cancer management and rising incidence have increased the workload of multidisciplinary tumor boards (MTBs), placing growing time demands on health-care professionals. This study evaluates large language models (LLMs) as decision-support tools by comparing AI-generated recommendations with MTB decisions. **Methods:** This retrospective study used two large language models, Gemini 2.5 (general-purpose) and MedGemma 27B (medical-domain specific), to generate treatment recommendations for patients discussed at MTB. MedGemma 27B was evaluated at two temperature settings (T = 0.0 and T = 1.0). MTB decisions served as the reference standard. Agreement was quantified using Cohen’s kappa, and classification performance was assessed with accuracy, F1 score, and recall. Recommendations were independently reviewed by two MTB members for clinical concordance and safety. **Results:** A total of 300 colorectal cancer cases were included. Gemini 2.5 demonstrated high agreement with MTB decisions (Cohen’s kappa = 0.792, p < 0.001), with 81.7% full concordance, significantly outperforming MedGemma 27B at both temperature settings (57.0% at T = 0.0 and 62.3% at T = 1.0, p < 0.001 for both). MedGemma 27B showed moderate agreement (k = 0.566 at T = 0.0, k = 0.610 at T = 1.0, p < 0.001), with a modest improvement in concordance at T = 1.0 (p = 0.038). In safety, Gemini 2.5 had the highest rate of clinically safe recommendations (83.7%), outperforming MedGemma at both temperature settings (p < 0.001), with no significant safety difference between MedGemma’s temperature settings (p = 0.567). Subgroup analyses showed that Gemini 2.5 had higher discordance in stage IV (p = 0.033), recurrent cases (p < 0.001), and surgical/interventional or active surveillance decisions (p < 0.001). In contrast, MedGemma demonstrated increased discordance in stage II (p < 0.001), ECOG PS ≥2 (p = 0.023–0.036), MSI-unstable tumors (p < 0.001), recurrent disease (p = 0.008–0.010), and surgical/interventional or active surveillance decisions (p < 0.001). **Conclusions:** Large language models demonstrated meaningful alignment with multidisciplinary tumor board decisions, supporting their potential role in clinical decision support for colorectal cancer, while emphasizing the need for further refinement to ensure consistent and safe clinical integration. Research Sponsor: None.

Comparison of large language models’ agreement and performance metrics with multidisciplinary tumor board decisions in colorectal cancer.

LLM	Fully concordant	Partially concordant	Discordant	Accuracy	F1 score	Recall	Cohen’s kappa (κ)	p value
Gemini 2.5	245 (81.7 %)	23 (7.7 %)	32 (10.7 %)	85 %	0.79	0.82	0.792	<0.001**
MedGemma 27B temperature 0.0	171 (57.0 %)	64 (21.3 %)	65 (21.7 %)	70.3%	0.64	0.61	0.566	<0.001**
MedGemma 27B temperature 1.0	187 (62.3 %)	54 (18.0 %)	59 (19.7 %)	73.5%	0.71	0.66	0.610	<0.001**

LLM, large language model.

Inferring molecular signatures in colorectal cancer directly from routine whole-slide images.

Piotr Keller, Mark Eastwood, Gertjan Rasschaert, Zedong Hu, Aimee Selten, Jinshu Wang, Elena Richiardone, Sara Verbandt, Hubert Piessevaux, Petros Tsantoulis, Sabine Tejpar, Fayyaz Minhas; Predictive Systems in Biomedicine (PRISM) Lab, Department of Computer Science, University of Warwick, Coventry, United Kingdom; Laboratory for Digestive Oncology, KU Leuven, Leuven, Belgium; Cliniques Universitaires St-Luc, Université Catholique de Louvain, Brussel, Belgium; Geneva University Hospitals, Geneva, Switzerland

Background: Molecular profiling has advanced colorectal cancer (CRC) research but remains limited in the clinic due to cost and tissue constraints. In contrast, haematoxylin and eosin (H&E) whole-slide images (WSIs) are routinely available. Recent deep learning studies show that molecular signatures can be inferred from morphology. However, prediction of patient level pathway activity remains underexplored despite their pathobiological significance as coordinated drivers of cancer risk. **Methods:** We developed SPARROW, a neural network trained to predict over 200 molecular signatures from WSI graph representation of tumour, stroma, lymphocytic and mucosal regions in resection specimens. SPARROW was trained on TCGA (n = 585) and externally validated in the PETACC3 trial dataset (n = 1,160). It predicts pathway enrichment scores, point mutation and clinically actionable CRC subtypes. **Results:** As shown in the table below, SPARROW accurately predicts key molecular features of CRC directly from routine H&E slides and generalizes robustly to the independent PETACC3 trial. The strongest concordance was observed for biologically and clinically relevant programmes, including intrinsic consensus molecular subtype 3 (iCMS3) genes, Fetal enteric progenitor pathway genes, a 22-gene YAP/TAZ transcriptional target signature and epithelial-specific high-risk gene set (epiHR) activity. SPARROW also showed good performance for clinically used classifications, including iCMS/CMS subtypes, interferon phenotype and BRAF mutation status. Importantly, image-derived molecular scores were predictive of relapse free survival as well. **Conclusions:** SPARROW demonstrates that key molecular features of CRC, including transcriptomic subtypes and genomic alterations, are robustly encoded in and learnable from routine H&E histology. This enables histology to serve as a cost-effective and rapid surrogate for predicting key molecular signatures and actionable molecular subtypes while also allowing mining of spatially localised image signatures associated with transcriptional programmes. Research Sponsor: None.

Molecular Signature	TCGA (4-fold CV)	PETACC3 (external)	Relapse Free Survival Analysis (PETACC3)
iCMS3 (ρ)	0.64 $\pm$ 0.05	0.66	HR=1.2*, 95% CI:1.04-1.38
Fetal Mustata (ρ)	0.47 $\pm$ 0.06	0.61	HR=1.74*, 95% CI:1.45-2.08
YAP_22 (ρ)	0.41 $\pm$ 0.07	0.49	HR=2.54*, 95% CI:2.03-3.18
EpiHR (ρ)	0.40 $\pm$ 0.08	0.45	HR=1.59*, 95% CI:1.31-1.92
iCMS2 vs iCMS3 (AUC)	0.90 $\pm$ 0.02	0.92	HR=1.12, 95% CI:1.00-1.26
CMS (4 groups) (AUC)	0.84 $\pm$ 0.01	0.84	HR=6.3* (CMS4 vs other), 95% CI:3.92-10.01
Interferon (High/Low) (AUC)	0.82 $\pm$ 0.08	0.88	HR=1.14, 95% CI:0.86-1.05
BRAF Mutation (AUC)	0.82 $\pm$ 0.07	0.80	HR=2.12*, 95% CI:1.13-4.29

*p-value <0.05 based on log-rank test using median pathway score.

HistoChrome: Virtual multiplex immunohistochemistry from routine H&E in colorectal cancer.

Mark Eastwood, Zedong Hu, Gertjan Rasschaert, Petros Tsantoulis, Thomas McKee, Sabine Tejpar, Fayyaz Minhas; Predictive Systems in Biomedicine (PRISM) Lab, Department of Computer Science, University of Warwick, Coventry, United Kingdom; Laboratory for Digestive Oncology, KU Leuven, Leuven, Belgium; Geneva University Hospitals, Geneva, Switzerland; University Hospital Geneva, Genève, Switzerland

Background: In colorectal cancer (CRC), immunohistochemistry (IHC) is central to assessment of spatial protein expression but is typically limited to few stains per case due to cost, tissue availability, and limited multiplexing. As a result, many relevant markers are not evaluated systematically. It remains unclear which pathobiologically relevant protein expression patterns are reliably encoded in morphological cues visible on routine haematoxylin and eosin (H&E) whole-slide images (WSIs). Markers of epithelial differentiation (CDX2, MUC2), immune infiltration (CD8), and mucin biology (MUC5) are clinically informative in colorectal cancer, yet their correspondence with H&E morphology is poorly defined. We investigate whether whole-slide virtual multiplex IHC (mIHC) can be generated from routine H&E for this marker panel. **Methods:** We trained a generative adversarial neural network with domain-specific constraints to enable whole-slide virtual mIHC generation from H&E. The model operates in stain concentration space using explicit stain separation and recombination and enforces spatial coherence during tiled whole-slide inference via an overlap consistency loss. Training used 52,579 paired H&E-mIHC patches (960×960 at 0.5 microns per pixel) extracted from adjacent, registered sections stained for CDX2, CD8, MUC2, MUC5, and hematoxylin, across 128 WSIs from 23 patients. Performance was evaluated on an independent cohort of 27 paired H&E-mIHC WSIs. **Results:** HistoChrome generates visually realistic and spatially coherent virtual mIHC WSIs from routine H&E. Biological fidelity was assessed by computing patch-wise Spearman correlations between mean stain intensities in real and virtual mIHC, restricted to tumor regions to avoid inflation from morphologically trivial normal tissue. Strong agreement with biological ground truth was observed for epithelial differentiation markers, with correlations of 0.79 for CDX2 and 0.63 for MUC2. CD8-positive immune infiltration was also captured with moderate accuracy ($\rho = 0.49$). In contrast, MUC5 expression showed only modest correspondence with biological ground truth ($\rho = 0.25$). **Conclusions:** HistoChrome enables whole-slide virtual multiplex immunohistochemistry from routine H&E, offering scalable access to biologically grounded protein markers without additional tissue or staining. Accurate inference of CDX2, MUC2, and CD8 supports slide-level pathological stratification of differentiation and immune contexts, with direct relevance for prognostic assessment and patient selection in therapeutic studies. The modest performance for MUC5 underscores that not all proteins may be morphologically encoded in H&E, highlighting the importance of marker-specific validation. Together, these findings position virtual mIHC as a practical adjunct to routine pathology and a discovery tool for CRC. Research Sponsor: None.

Validation of DiaSurv, an AI-based algorithm for stage II colon cancer risk stratification.

Lou Rouan, Céline Bossard, Baptiste Gourdin, Yahia Salhi, Jérôme Chetritt, Céline Bazille; Centre Hospitalier Universitaire de Caen, Caen, France; Pathology Department, IHP Group, Nantes, France; DiaDeep, Lyon, France

Background: Adjuvant chemotherapy decisions in stage II colon cancer (IIA T3N0; IIB T4aN0; IIC T4bN0) remain challenging, as conventional risk factors poorly predict recurrence. This results in both overtreatment and undertreatment. AI-based analysis of routine H&E slides may enable more accurate risk stratification to guide personalized treatment decisions. **Methods:** DiaSurv Colon is an AI-powered prognostic tool using a deep neural network to extract in an unsupervised way morphological features from H&E-stained WSI and predict 5-year overall survival (OS). Each patient is assigned an individual survival risk score. The model was trained on the TCGA cohort (n = 463) and previously validated on two external cohorts. In this study, we evaluated its performance on two new independent external cohorts, digitized with two different scanners: CHU Caen (n = 201; 5-y OS 47%, 95%CI 39–53%) and IHP (n = 207; 5-y OS 54%, 95%CI 45–61%). Prognostic accuracy was assessed using concordance index (c-index). Multivariate Cox regression and log-rank tests with hazard ratios (HR) were used to compare DiaSurv Colon performance against conventional clinicopathological factors. **Results:** On external validation, DiaSurv Colon achieved a c-index of 58 (CHU Caen) and 64 (IHP). The AI-based risk score significantly stratified patients: 5-year OS was 64% (95%CI 50–75%) vs 40% (95%CI 32–48%) for low- vs high-risk groups in CHU Caen (p < 0.01), and 64% (95%CI 52–73%) vs 39% (95%CI 26–51%) in IHP (p < 0.001). The risk score demonstrated strong prognostic value with hazard ratios of 1.29 (95%CI 1.05–1.58, p < 0.01) and 1.57 (95%CI 1.23–2.00, p < 0.001) for CHU Caen and IHP, respectively. **Conclusions:** DiaSurv Colon demonstrated consistent prognostic performance across independent external cohorts, with robust hazard ratios and concordance indices. This AI-based tool may improve risk stratification in stage II colon cancer and support personalized adjuvant therapy decisions with more confidence. Research Sponsor: None.

A deep learning approach to quantify tumor microenvironment features associated with postoperative ctDNA status and outcomes in a phase III FOLFOX-based adjuvant colon cancer trial (N0147; Alliance).

Frank A. Sinicrope, Qian Shi, Diana I. Segovia, Aaron Hardin, Thereasa A. Rich, Steven R. Alberts, Rish Pai; Mayo Clinic Rochester, Rochester, MN; Alliance Statistics and Data Management Center and Mayo Clinic Rochester, Rochester, MN; Guardant Health, Palo Alto, CA; Guardant Health, Redwood City, CA; Department of Pathology and Laboratory Medicine, Mayo Clinic Arizona, Phoenix, AZ

Background: Tumor microenvironment (TME) features of colorectal cancer (CRC) may influence detection of circulating tumor DNA (ctDNA) and further refine prognosis. We applied a deep learning histopathologic algorithm to quantify TME features in stage III colon cancers and evaluated their association with postoperative ctDNA status among participants in a phase III FOLFOX-based adjuvant trial (NCCTG N0147). **Methods:** QuantCRC (Aiforia Technologies) was applied to digitized hematoxylin and eosin-stained whole-slide images of stage III colon adenocarcinomas to extract quantitative histopathologic features. Among cases where data met quality control (N=1817), associations between 15 distinct pathologist-defined features and clinical outcomes—time to recurrence (TTR), disease-free survival (DFS), and overall survival (OS)—were evaluated, stratified by postoperative ctDNA status assessed by a tissue-free assay (Guardant Reveal). Relationships were analyzed using univariate and multivariable Cox proportional hazards models that were adjusted for clinicopathologic and molecular features (KRAS, BRAF^{V600E}, MMR status). Interaction testing was performed. **Results:** We found statistically significant quantitative differences for histopathologic features by ctDNA status. Features associated with ctDNA positivity(+) included lymphovascular invasion (LVI), and increased %high grade, %tumor budding, %necrosis, and %stroma. ctDNA+ cases had lower %inflammatory stroma and fewer %signet ring cells (all $p < 0.006$). Multivariable analyses, irrespective of ctDNA status, identified %tumor budding, %mucin, %signet ring cells, %inflammatory tumor bed, and %inflammatory stroma as significantly associated with adverse outcomes (TTR, DFS, OS). Within ctDNA+ cases, higher %immature tumor bed was associated with adverse outcome for all 3 variables. Among ctDNA-negative cases, significantly poorer outcomes (TTR, DFS, OS) were observed for tumors with lower tumor infiltrating lymphocyte (TIL) density and reduced %necrosis. After adjustment, significant interactions with ctDNA status were observed for LVI ($p < 0.006$) and %signet ring cells ($p < 0.035$) across all outcome variables, for %necrosis with DFS, OS ($p < 0.040$), and for TILs with TTR ($p < 0.015$). Analysis is ongoing for ctDNA tumor fraction as well as tumor genotyping data (739 genes; Guardant360). **Conclusions:** QuantCRC identifies TME features associated with postoperative ctDNA status that enable risk-stratification within ctDNA groups. Among ctDNA-negative patients, reduced intratumoral TIL density and reduced tumor necrosis identify high-risk subgroups with inferior clinical outcomes, and may have clinical utility. Research Sponsor: None.

A large-scale, multi-target deep learning model for virtual genomic and molecular risk profiling in colorectal cancer.

Erik N. Bergstrom, Tinghui Wu, Michail Chatzianastasis, Thinh Tran, Aaron M. Rosenfeld, Robert Burns, Adham A. Jurdi, Matthew Rabinowitz, Helio Costa, Frank Zhang; Natera, Inc., Austin, TX

Background: Molecular profiling of tumor biopsies is central to precision oncology, informing treatment selection, prognostication, and disease monitoring. Computational analysis of routine H&E slides offers a complementary, scalable approach that can accelerate biological insights and optimize downstream molecular testing. Recent advances in computational pathology have demonstrated that deep learning models can infer molecular features directly from digital H&E images, referred to as virtual genomics. However, most studies in colorectal cancer (CRC) have been constrained by limited cohort sizes, single-target predictions, and a lack of integration with longitudinal clinical outcomes. Here, we present a transformer-based deep learning framework designed for large-scale virtual genomic and molecular recurrence risk profiling in CRC. **Methods:** The model was trained on 45,155 patients with matched digital H&E images, whole-exome sequencing (WES), and longitudinal circulating tumor DNA (ctDNA) for molecular recurrence monitoring. We embedded all images using H-optimus-0 and trained a transformer-based multiple instance learning aggregation head for downstream virtual genomic predictions. We trained individual models to predict genes found in the MSK-IMPACT505 cancer gene panel and a single model that predicts all genes simultaneously. Lastly, we trained an independent model to predict the risk of molecular recurrence. All results were validated on an external cohort from The Cancer Genome Atlas (TCGA; $n = 422$ CRC patients). **Results:** Individual models predicted 379 mutated genes with an internal area under the receiver operating curve (AUROC) > 0.7 . We validated 254 of these genes within TCGA with an AUROC > 0.7 . Training a multi-task learning model to predict all genes simultaneously improved the AUROC for 85% of the genes. Based on NCCN guidelines in CRC, we further trained individual models to predict MSI status, BRAF V600E, KRAS G12D/V/G13D, and POLE/POLD1 exonuclease mutations with AUROCs of 0.96, 0.93, 0.84, and 0.86, respectively. Lastly, we developed an image-based molecular recurrence risk model trained directly on longitudinal ctDNA outcomes. The model stratified patients into low, medium, and high risk groups with a concordance index of 0.67. Compared to low-risk patients, the high-risk group exhibited a hazard ratio (HR) of 4.67, while the medium-risk group showed an HR of 1.98 (p -values $< < 1E-5$). **Conclusions:** This unified framework demonstrates that virtual genomics from routine H&E histopathology can enable scalable, cost-efficient inference of hundreds of clinically relevant genomic alterations and molecular recurrence risk in CRC. By leveraging universally available diagnostic slides, virtual genomics has the potential to expand access to precision oncology, optimize molecular testing strategies, and support earlier risk stratification. Research Sponsor: None.

The use of miR-5193 to predict oxaliplatin chemosensitivity in colorectal cancer: Integrated in silico, in vitro, and clinical evidence.

Jaime A. González Montero, Guillermo Valenzuela, Hector Contreras, Katherine Marcelain, Olga Barajas, Jessica Toro, Sebastian Indo, Mauricio Burotto; Bradford Hill Clinical Research Center, Santiago, Chile; University of Chile, Santiago, Chile; Universidad de Chile, Santiago, Chile; Department of Basic Clinical Oncology, Faculty of Medicine, Universidad de Chile, Santiago, Chile; University of Chile Clinical Hospital, Santiago, Chile

Background: Outcomes with first-line chemotherapy in metastatic colorectal cancer (mCRC) are heterogeneous. We evaluated whether tumor microRNA miR-5193 is a predictive marker of chemosensitivity. **Methods:** We performed (i) a discovery analysis in TCGA COAD/READ to test associations between tumor miR-5193 and progression-free (PFS) and overall survival (OS) by Kaplan–Meier/log-rank; (ii) functional assays in colonic epithelium (CON-841) and colorectal cancer cell lines (Caco-2, HCT116) after miR-5193 mimic transfection, assessing 5-fluorouracil (5-FU) and oxaliplatin (L-OHP) sensitivity by MTT and IC₅₀; and (iii) a validation cohort of formalin-fixed paraffin-embedded (FFPE) primary tumors from Chilean mCRC patients (n=50) in which hsa-miR-5193 was quantified by RT-qPCR. Patients were dichotomized into low vs high expression, and PFS/OS were estimated by Kaplan–Meier/log-rank in the overall cohort and in prespecified oxaliplatin- and irinotecan-based first-line subgroups. **Results:** In TCGA mCRC cases selected for standard clinicopathologic features and chemotherapy exposure, low tumor miR-5193 expression was associated with shorter PFS (p=0.03). In vitro, miR-5193 was downregulated in CRC lines vs CON-841, and transient miR-5193 overexpression increased chemosensitivity to 5-FU (Caco-2; reduced viability at 200–250 μ M and IC₅₀ from 1138 to 345 μ M, p=0.049) and oxaliplatin (HCT116; left-shifted dose-response and ~30–35% IC₅₀ reduction, p<0.01). In the Chilean validation cohort, low (n=30) vs high (n=20) hsa-miR-5193 expression was associated with inferior OS (p=0.0081) and showed no statistically significant difference in PFS (p=0.058). Among patients receiving oxaliplatin-based first-line chemotherapy (FOLFOX/CAPEOX), low hsa-miR-5193 predicted shorter PFS (p=0.012), whereas no PFS difference was observed with irinotecan-based regimens (p=0.8104) (Table 1). **Conclusions:** miR-5193 appears to modulate chemosensitivity in mCRC. Low tumor miR-5193 is linked to reduced oxaliplatin and 5-FU sensitivity in vitro, and shorter PFS/OS under oxaliplatin-based therapy, supporting its role as a biomarker of oxaliplatin sensitivity. Prospective validation could enable miR-5193-guided treatment selection and risk stratification, particularly for patients considered for oxaliplatin-containing regimens. Research Sponsor: Agencia Nacional de Investigación y Desarrollo (ANID); SA20I0059; FONDAPE; 152220002; Agencia Nacional de Investigación y Desarrollo (ANID); 21240251.

Association between hsa-miR-5193 expression and clinical outcomes in metastatic colorectal cancer.

Study cohort / subgroup	Outcome	miR5193 expression:	
		Low (n=30) vs high (n=20)	P-value
Chilean validation cohort – Overall	PFS	No significant difference	0,058 (NS)
Chilean validation cohort – Overall	OS	Shorter OS	0,0081
FOLFOX/CAPEOX subgroup (oxaliplatin-based)	PFS	Shorter PFS	0,012
Irinotecan-based subgroup	PFS	No difference	0,8104 (NS)

Fruquintinib plus FOLFIRI or mFOLFOX6 as second-line therapy for patients with RAS-mutant metastatic colorectal cancer (mCRC): A phase II, multicenter, open-label study.

Yun Xu, Ye Xu, Ming Tang, Cong Li, Yuchen Wu, Yuedi Dai, Xiaopin Ji, Zhe Cui, Xiaodong Zhu; Department of Colorectal Surgery, Fudan University Shanghai Cancer Center, Shanghai, China; Shanghai Key Laboratory of Maternal Fetal Medicine, Shanghai Institute of Maternal-Fetal Medicine and Gynecologic Oncology, Clinical and Translational Research Center, Shanghai First Maternity and Infant Hospital, School of Medicine, Tongji University, Shanghai, China; Fudan University Shanghai Cancer Center, Shanghai, China; Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; Baoshan Branch of Renji Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China; Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Nearly half of metastatic colorectal cancer (mCRC) patients harbor RAS mutations, and the standard second-line regimen for this substantial subgroup of patients is combination chemotherapy (FOLFIRI/FOLFOX) with bevacizumab, which offers limited efficacy. Fruquintinib, an oral VEGFR-1, -2, and -3 inhibitor, has shown efficacy in refractory mCRC. This study evaluated the efficacy and safety of fruquintinib in combination with FOLFIRI or FOLFOX as second-line therapy for patients with RAS-mutant mCRC. **Methods:** This multicenter, open-label, single-arm phase II trial enrolled patients with RAS mutant mCRC who had failed first-line standard therapy. Participants received fruquintinib (4 mg once daily, days 1-21) plus FOLFIRI or mFOLFOX every 28 days. The primary endpoint was progression-free survival (PFS). Secondary endpoints included objective response rate (ORR), disease control rate (DCR), overall survival (OS), and safety. **Results:** As of Nov 11, 2025, 42 eligible pts were enrolled and received at least one cycle of treatment. Baseline characteristics included median age (63.0 [range: 35-74]), male (59.5%), ECOG PS 1 (66.7%), left-sided (73.8%), liver metastasis (59.5%), prior anti-VEGF therapies (73.8%). The median PFS was 8.1 months (95% CI: 6.18, 9.46) and median OS was not reached yet. The Kaplan-Meier estimates for PFS rates at 3, 6, 9, and 12 months were 85.3%, 73.5%, 35.9%, and 15.4%, respectively. In the subgroup analysis, median PFS were longer in pts without liver metastases (8.4mo vs 6.4mo, HR: 1.65, 95%CI: 0.65-4.18), those with left-sided lesion (8.1mo vs 4.8mo, HR: 2.14, 95%CI: 0.79-5.77) and pts without prior anti-VEGF therapies (8.4mo vs 6.5mo, HR: 1.79, 95%CI: 0.59-5.36). The ORR was 52.5% (21/40) which consisted of CR 5% and PR 47.5%. The DCR was 97.5% (39/40). Additionally, the most common any grade treatment-emergent adverse events (TEAEs) were hypertension (23.8%), diarrhea (19.1%), and mucositis (19.1%). Grade ≥ 3 TEAEs was 14.3% including diarrhea (4.8%), intestinal obstruction (2.4%) and leukopenia (2.4%). **Conclusions:** Fruquintinib combined with either FOLFIRI or mFOLFOX6 as second-line therapy for patients with RAS-mutant metastatic colorectal cancer (mCRC) demonstrated promising efficacy and a manageable safety profile. Clinical trial information: NCT05634590. Research Sponsor: None.

daNIS-3: A phase II platform study of NIS793 and anti-PD-1 combined with standard of care (SoC) anti-cancer therapy for the second-line (2L) treatment (tx) of microsatellite-stable colorectal cancer (MSS CRC).

Filippo Pietrantonio, Iosune Baraibar, Jiri Tomasek, Neil Howard Segal, Christophe Tournigand, Stefan Kasper, Joan Maurel, Sabine Tejpar, Arun Jyothi Gaddameedi, Sumit Basu, Gwendolyn Gobbo, Yolanda Bi, John Gregory, Scott Kopetz, Fernando Rivera; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Gastrointestinal and Endocrinology Group, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Department of Complex Oncology Care, Masaryk Memorial Cancer Institute, Brno, Czech Republic; Memorial Sloan Kettering Cancer Center, New York City, NY; AP-HP, Hôpital Henri Mondor, Service d'oncologie médicale, Créteil, France; West German Cancer Center, Department of Medical Oncology, University Hospital Essen, Essen, Germany; Medical Oncology Department, Hospital Clinic of Barcelona, Translational Genomics and Targeted Therapeutics in Solid Tumors Group, IDIBAPS, Barcelona, Spain; Department of Oncology, KU Leuven, Leuven, Belgium; Novartis Healthcare Private Limited, Hyderabad, India; Novartis Pharmaceuticals Corporation, East Hanover, NJ; China Novartis Institutes for BioMedical Research Co., Ltd., Shanghai, China; The University of Texas MD Anderson Cancer Center, Houston, TX; University Hospital Marqués de Valdecilla, IDIVAL, Santander, Spain

Background: Despite advances in tx of MSS CRC including targeted tx, the prognosis remains poor. The daNIS-3 study (NCT04952753) evaluated efficacy and safety of anti-TGF β monoclonal antibody NIS793 (NIS) and anti-PD1 tislelizumab (TISLE) with SoC as 2L tx for MSS CRC patients (pts). **Methods:** This open-label, multicenter study included safety run-in (SRI) Arm 1a: NIS + SoC (bevacizumab [Bev] + FOLFIRI), Arm 1b: NIS + SoC (Bev + mFOLFOX6) followed by Arm 2a: NIS + TISLE + SoC (Bev + FOLFIRI), Arm 2b: NIS + TISLE+ SoC (Bev + mFOLFOX6) to determine NIS recommended phase 2 dose (RP2D) for expansion phase (EP). FOLFIRI and mFOLFOX6 were evaluated independently. While EP included same investigational arms as SRI (Arm 2b not opened for enrollment), additional SoC arm was added. Primary endpoint was progression-free survival (PFS) in EP; secondary endpoints were PFS for SRI, overall response rate (ORR), disease control rate (DCR), duration of response (DOR) and time to response (TTR) using RECIST V1.1, pharmacokinetics (PK), immunogenicity, safety, and tolerability. Based on data monitoring committee recommendation, study was terminated on 31-07-2023 due to unfavorable benefit-risk profile. **Results:** As of 20-01-2025, median (95% CI) PFS in EP was 5.1 months (mo) (3.6–5.7), 3.7 mo (2.2–5.6), and 7.4 mo (5.5–9.4) for Arms 1a&b, Arm 2a, and SoC, respectively (HR vs SoC [95% CI]: Arms 1a&b, 2.06 [1.34–3.18]; Arm 2a, 1.65 [0.90–3.02]). Secondary endpoints are summarized in Table. PK of NIS and other drugs were similar in EP and SRI. All pts were ADA negative at baseline and during the study. NIS RP2D for Arms 1a&b, and 2a was 2100 mg Q2W. In SRI and EP, overall adverse events (AEs) were comparable across all arms. In EP, grade ≥ 3 AEs were higher in Arm 1a (67.7%) and 1b (66.7%) compared to Arm 2a (55.2%) and SoC (58.7% & 42.9%). Higher incidence of serious AEs was reported in Arm 1a (49.2%) compared to Arm 2a (31%) and SoC (30.4% & 42.9%). Higher deaths were observed in Arm 1a (50.8%) and 1b (60.0%), mostly attributed to underlying malignancy (MSS CRC). Most common AEs of special interest of NIS were infusion-related reactions, hemorrhage, and skin toxicity, consistent with known safety profile of NIS. **Conclusions:** Overall AEs were comparable, but a higher incidence of grade ≥ 3 AEs vs SoC were observed. NIS arms showed a deleterious PFS outcome in MSS CRC pts. Clinical trial information: NCT04952753. Research Sponsor: Novartis Pharmaceuticals.

Secondary endpoints*	SRI		EP		SoC (N = 53)
	Arms 1a (N = 13) & 1b (N = 9)	Arms 2a (N = 10) & 2b (N = 8)	Arms 1a (N = 67) & 1b (N = 13)	Arm 2a (N = 29)	
mPFS, mo (95% CI)	3.6 (1.9, 7.3)	2.1 (1.8, 4.3)	—	—	—
ORR, n (%)	1 (4.5)	0	7 (8.8)	4 (13.8)	8 (15.1)
DCR, n (%)	14 (63.6)	8 (44.4)	53 (66.3)	19 (65.5)	42 (79.2)
mDOR, mo (95% CI)	9.4 (NE, NE)	NE	9.5 (4.0, NE)	NE	11.1 (3.8, NE)
mOS, mo (95% CI)	10.2 (5.8, 20.8)	11.0 (6.2, 15.7)	12.8 (8.0, 14.2)	10.9 (6.1, NE)	NE (11.6, NE)

*SoC+FOLFIRI/mFOLFOX6 presented together due to similar efficacy.

Tislelizumab plus cetuximab and irinotecan in relapsed/refractory RAS/BRAF wild-type and microsatellite stable metastatic colorectal cancer: A randomized, controlled, multicenter study (TEC2).

Xiaojing Xu, Yiyi Yu, Tianshu Liu, Minzhi Lv, Hangyu Zhang, Luoyan Ai, Yuehong Cui, Xi Tang, Hong Zong, Qing Xu, Rongbo Lin, Siyu Chen; Department of Oncology, Zhongshan Hospital, Fudan University, Shanghai, China; Department of Medical Oncology, Zhongshan Hospital, Fudan University, Shanghai, China; Department of Cancer Screening and Prevention, Zhongshan Hospital, Fudan University, Shanghai, China; Department of Medical Oncology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; Department of Medical Oncology, Shanghai Huadong Hospital, Shanghai, China; Department of Medical Oncology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; Department of Oncology, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai, China; Department of Abdominal Oncology, Fujian Provincial Cancer Hospital, Fuzhou, China; Department of Oncology, Xinhua Hospital, Shanghai Jiao Tong University, Shanghai, China

Background: Under suboptimal efficacy and safety of current third-line standard-of-care (SoC), several single-arm studies have demonstrated that anti-PD-(L)1 antibodies plus EGFR inhibitors with or without chemotherapy may be valuable for relapsed/refractory RAS/BRAF wild-type and microsatellite stable metastatic colorectal cancer (R/R RAS/BRAF WT and MSS mCRC). This study aimed to compare tislelizumab (anti-PD-1 antibody) plus cetuximab and irinotecan as third- or later-line therapy versus investigator-selected SoC for R/R RAS/BRAF WT and MSS mCRC. **Methods:** This was a randomized controlled, open-label, multicenter study (NCT05278351). Eligible patients were aged ≥ 18 years with histologically confirmed RAS/BRAF WT and MSS metastatic colorectal adenocarcinoma who failed ≥ 2 prior lines of systemic therapy. Patients were randomly assigned (2:1) to receive intravenous tislelizumab (200 mg) plus cetuximab (500 mg/m²) and irinotecan (180 mg/m²) on days 1 and 15 or investigator-selected SoC (fruquintinib, regorafenib, or TAS-102) in a 4-week cycle until disease progression, unacceptable toxicity, or other protocol-defined reasons. Primary end point was progression-free survival (PFS). Secondary end points included objective response rate, disease control rate, duration of response, overall survival, and safety. **Results:** Eighty-seven patients (median age, 62.0 years; 59 [67.8%] men) were enrolled between July 2022 and March 2024, randomized, and assessed for efficacy; one patient did not receive the triplet regimen and was removed from the safety population. With median follow-up of 26.1 months (95% confidence interval [CI]: 22.4–28.4) by data cutoff (June 30, 2025), median PFS was 4.4 months (95% CI, 3.8–6.6) in the tislelizumab–cetuximab–irinotecan group and 2.0 months (95% CI, 1.9–5.4) in the SoC group (Breslow–Gehan $P=0.009$). Landmark analysis at a cutoff point of 10 months showed a significantly extended PFS with tislelizumab plus cetuximab and irinotecan versus SoC (HR 0.37 [95% CI, 0.21–0.64]; $p<0.001$). Grade ≥ 3 treatment-related adverse events (TRAEs) occurred at comparable frequencies in the two groups (15.8% vs 17.2%). No TRAEs led to death. **Conclusions:** Tislelizumab plus cetuximab and irinotecan as third- or later-line therapy appeared feasible and safe for patients with R/R RAS/BRAF WT and MSS mCRC. Clinical trial information: NCT05278351. Research Sponsor: Noncommunicable Chronic Diseases–National Science and Technology Major Project; (2023ZD0501600; National Nature Science Foundation of China; 82573146, 82373402, 82272775; Clinical Research Foundation of Zhongshan Hospital Affiliated to Fudan University; 2020ZSLC02, ZSLCYJ202305.

	Tislelizumab–cetuximab–irinotecan (n=58)	SoC (n=29)
Best response		
Complete response	0	0
Partial response	12 (20.7)	1 (3.4)
Stable disease	32 (55.2)	12 (41.4)
Disease progression	11 (19.0)	16 (55.2)
Not evaluable	3 (5.2)	0
Objective response	12 (20.7)	1 (3.4)
Disease control	44 (75.9)	13 (44.8)
6-month PFS rate, % (95% CI)	38.2 (27.3–53.5)	20.4 (9.6–43.7)

Association of progression-free survival (PFS) with microsatellite instability–high (MSI-H) or mismatch repair–deficient (dMMR) status determined by single vs dual validated companion diagnostic (CDx) assays: CheckMate-8HW post hoc analyses.

Thierry Andre, Sara Lonardi, Elena Elez, Eric Van Cutsem, David Tougeron, Myriam Chalabi, Heinz-Josef Lenz, Takayuki Yoshino, Rocio Garcia-Carbonero, Lars Henrik Jensen, David Yu, Jonathan F. Baden, Jim Pratt, Ming Lei, Lixian Jin, Elvis Cela; Sorbonne Université and Hôpital Saint-Antoine, Assistance Publique Hôpitaux de Paris, Paris, France; Istituto Oncologico Veneto IOV-IRCCS, Padua, Italy; Vall d'Hebron University Hospital and Institute of Oncology (VHIO), Barcelona, Spain; University Hospitals Gasthuisberg and University of Leuven (KU Leuven), Leuven, Belgium; Centre Hospitalier Universitaire de Poitiers Site de la Miletie, Poitiers, France; Netherlands Cancer Institute, Amsterdam, Netherlands; University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; National Cancer Center Hospital East, Kashiwa, Japan; Hospital Universitario 12 de Octubre, Ima12, UCM, Madrid, Spain; University Hospital of Southern Denmark, Vejle Hospital, Vejle, Denmark; Bristol Myers Squibb, Princeton, NJ

Background: First-line (1L) nivolumab (NIVO) + ipilimumab (IPI) showed PFS benefit vs chemotherapy (chemo) in patients (pts) with MSI-H or dMMR metastatic colorectal cancer (mCRC) in the phase 3 CheckMate 8HW trial. Using post hoc analyses, we examined the association of PFS with single and dual positivity in validated CDx MSI (polymerase chain reaction; PCR) or MMR (immunohistochemistry; IHC) central assays. **Methods:** Study details were published previously (Andre T et al. *NEJM* 2024). Pts with unresectable or mCRC with MSI-H or dMMR per local testing were randomized 2:2:1 to NIVO + IPI, NIVO, or chemo. Tumor tissue samples were tested centrally using validated Idylla (CDx MSI PCR; Biocartis) and Dako (CDx MMR IHC; Agilent) assays post randomization. Clinical trial assay positive (CTA+) pts were those with locally diagnosed MSI-H/dMMR mCRC randomized to NIVO + IPI or chemo. PFS and hazard ratios (HR) were evaluated in CTA+ pts; pts positive using a single central assay (CDx MSI or CDx MMR); and pts positive in both central assays (CDx dual positive). **Results:** Of the 303 pts randomized to 1L NIVO + IPI or chemo, 301 had locally diagnosed MSI-H/dMMR (CTA+; 2 randomized pts missed local testing and were excluded in the analysis). 263 pts had valid CDx MSI results, 284 had valid CDx MMR results; 208 were CDx dual positive (Table); result missingness was mainly due to lack of tissue samples. PFS benefit was noted with NIVO + IPI vs chemo in CTA+ pts (HR, 0.32; Table). Greater PFS benefit with NIVO + IPI vs chemo was seen in pts positive with single CDx MSI or CDx MMR assays (HR, 0.20 and 0.22, respectively), and was consistent with those from CDx dual positive pts (HR, 0.20; Table). Pts with microsatellite stable (MSS) or mismatch repair proficient (pMMR) status were low, so these data should be interpreted with caution (Table). **Conclusions:** In this post hoc analysis, dual positivity from CDx MSI and CDx MMR assays did not offer greater PFS benefit with 1L NIVO + IPI vs chemo over positivity from a single CDx MSI or MMR assay. Single CDx MSI or CDx MMR assays provided similar PFS benefit with 1L NIVO + IPI vs chemo in pts with MSI-H/dMMR mCRC. Clinical trial information: NCT04008030. Research Sponsor: Bristol Myers Squibb.

	NIVO + IPI (n = 202)		Chemo (n = 101)		HR (95% CI) ^a
	n (%)	Median PFS (95% CI)	n (%)	Median PFS (95% CI)	
CTA+	200 (99)	NR (34.3–NE)	101 (100)	6.2 (4.7–9.0)	0.32 (0.22–0.45)
CDx ^b MSI+: MSI-H	147 (73)	NR (38.4–NE)	71 (70)	6.2 (4.7–9.0)	0.20 (0.12–0.31)
CDx ^b MSI–: MSS	30 (15)	1.8 (1.5–5.8)	15 (15)	7.4 (4.0–12.9)	1.51 (0.68–3.33)
CDx ^b MMR+: dMMR	163 (81)	NR (38.4–NE)	82 (81)	5.9 (4.4–7.8)	0.22 (0.14–0.34)
CDx ^b MMR–: pMMR	27 (13)	1.8 (1.5–5.8)	12 (12)	11.5 (2.0–NE)	1.39 (0.57–3.40)
CDx ^b : dual positive	139 (69)	NR (38.4–NE)	69 (68)	6.2 (4.9–9.2)	0.20 (0.13–0.32)

^aCox proportional hazards model stratified by tumor sidedness.

^bBy central assay. NE, not estimable; NR, not reached.

Nivolumab + ipilimumab (NIVO + IPI) vs NIVO in microsatellite instability high/mismatch repair-deficient metastatic colorectal cancer (MSI-H/dMMR mCRC): CheckMate 8HW subgroup analyses including treatment-free status and outcomes in long-term survivors.

Elena Elez, Thierry Andre, Sara Lonardi, Heinz-Josef Lenz, Lars Henrik Jensen, Yann Toucheffeu, Rocio Garcia-Carbonero, David Tougeron, Guillermo Mendez, Michael Schenker, Christelle De La Fouchardiere, M. Luisa Limon, Takayuki Yoshino, Jin Li, Francine Maud Aubin, Elvis Cela, Abigail Wang, Lixian Jin, Eric Van Cutsem; Vall d'Hebron University Hospital and Institute of Oncology (VHIO), Barcelona, Spain; Sorbonne Université and Hôpital Saint-Antoine, Assistance Publique Hôpitaux de Paris, Paris, France; Istituto Oncologico Veneto IOV-IRCCS, Padua, Italy; University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; University Hospital of Southern Denmark, Vejle Hospital, Vejle, Denmark; Centre Hospitalier Universitaire de Nantes, Nantes, France; Hospital Universitario 12 de Octubre, Ima12, UCM, Madrid, Spain; Centre Hospitalier Universitaire de Poitiers, Poitiers, France; Hospital Universitario Fundacion Favaloro, Buenos Aires, Argentina; Centrul de Oncologie Sf. Nectarie, Craiova, Romania; Centre Léon Bérard, Lyon, France; Hospital Universitario Virgen del Rocío, Sevilla, Spain; National Cancer Center Hospital East, Kashiwa, Japan; Shanghai East Hospital, Shanghai, China; Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada; Bristol Myers Squibb, Princeton, NJ; University Hospitals Gasthuisberg and University of Leuven (KU Leuven), Leuven, Belgium

Background: In the phase 3 CheckMate 8HW trial, both dual primary endpoints of progression-free survival (PFS) were met for first-line (1L) NIVO + IPI vs chemotherapy (HR 0.21; $P < 0.0001$) and NIVO + IPI vs NIVO in all lines (HR 0.62; $P = 0.0003$) in patients (pts) with centrally confirmed (CC) MSI-H/dMMR mCRC. We report explorative subgroup analyses of NIVO + IPI vs NIVO. **Methods:** The study design was described previously (Andre *NEJM* 2024). Pts with MSI-H/dMMR mCRC per local testing were enrolled. After randomization, IHC and PCR based tests were used for central confirmation. **Results:** In all randomized pts, 84% (296/354) in the NIVO + IPI and 81% (286/353) in the NIVO arm had CC MSI-H/dMMR; in 1L pts, 85% (171/202) and 85% (170/201) had CC MSI-H/dMMR, respectively. Median follow-up in all randomized pts was 55.1 (range 24.7–68.5) mo. Pts receiving NIVO + IPI had improved disease control rates vs NIVO in 1L (85% vs 81%, respectively) and all lines (84% vs 76%, respectively). Pts with complete or partial response (CR/PR) or stable disease (SD) on 1L NIVO + IPI had improved PFS vs NIVO. In all lines, pts with CR/PR or SD receiving NIVO + IPI had improved overall survival (OS) vs those on NIVO (Table). Pts receiving NIVO + IPI had improved disease-specific OS vs NIVO (HR 0.47; 95% CI 0.32–0.68). In all lines, pts on NIVO + IPI had improved PFS and OS vs NIVO regardless of the number of sites of metastasis (Table). After treatment, 82% (185/226) of pts on NIVO + IPI were alive and treatment free vs 67% (125/186) on NIVO; 90% (198/220) and 79% (141/178) of pts were alive and systemic treatment free, respectively. In pts surviving ≥ 4 years, baseline characteristics and incidence of treatment-related adverse events were consistent with the all randomized CC population. Further analyses will be presented. **Conclusions:** NIVO + IPI demonstrated clinical benefit vs NIVO across subgroups, as shown by numerically increased PFS and OS in pts with CR/PR or SD, and improved PFS and OS regardless of number of metastatic sites. No defining characteristic was identified in long-term survivors vs all randomized CC pts. These results further support NIVO + IPI as a standard of care treatment for MSI-H/dMMR mCRC. Clinical trial information: NCT04008030. Research Sponsor: Bristol Myers Squibb.

1L		NIVO + IPI (n = 171)	NIVO (n = 170)	HR (95% CI)
mPFS (95% CI), mo	CR/PR	NR (NE)	NR (60.8–NE)	0.82 (0.43–1.54)
	SD	33.1 (5.8–NE)	9.2 (4.4–22.1)	0.52 (0.24–1.14)
All lines		(n = 296)	(n = 286)	
mPFS (95% CI), mo	1 metastatic site at BL	NR (NE)	60.8 (26.3–NE)	0.51 (0.33–0.77)
	≥ 2 metastatic site at BL	59.2 (38.4–NE)	23.0 (11.8–NE)	0.70 (0.51–0.97)
mOS (95% CI), mo	CR/PR	NR (NE)	NR (NE)	0.92 (0.46–1.83)
	SD	NR (35.3–NE)	26.8 (15.7–48.9)	0.43 (0.23–0.80)
	1 metastatic site at BL	NR (NE)	NR (NE)	0.52 (0.31–0.88)
	≥ 2 metastatic site at BL	NR (NE)	NR (NE)	0.68 (0.46–0.99)

BL, baseline; m, median; NE, not estimable; NR, not reached.

Phase 1 study of the tetravalent death receptor 5 agonist ozekibart (INBRX-109) combined with chemotherapy in locally advanced or metastatic, unresectable colorectal adenocarcinoma (CRC).

Hazel Lote, Olatunji B. Alese, David Berz, Marwan Fakih, David S. Hong, Lee P. Hartner, Cathy Eng, Alexander I. Spira, Ludimila Cavalcante, Brianne O'Neill, Lane Senne, Emily Piccione, James Kalabus, Josep Garcia, Iosune Baraibar, Christopher Lieu; The Royal Marsden Hospital, London, United Kingdom; Winship Cancer Institute of Emory University, Atlanta, GA; Valkyrie Clinical Trials, Los Angeles, CA; Department of Medical Oncology and Therapeutics Research, City of Hope Comprehensive Cancer Center, Duarte, CA; Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX; University of Pennsylvania, Abramson Cancer Center, Philadelphia, PA; Vanderbilt Ingram Cancer Center, Nashville, TN; NEXT Oncology - Virginia Cancer Specialists, Fairfax, VA; Department of Hematology/Oncology, University of Virginia Comprehensive Cancer Center, Charlottesville, VA; Inhibrx Biosciences, Inc., La Jolla, CA; Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Spain; University of Colorado, Anschutz School of Medicine, Aurora, CO

Background: Patients with metastatic CRC are typically treated with fluorouracil-based chemotherapy in combination with leucovorin and irinotecan (FOLFIRI) or oxaliplatin (FOLFOX). However, patients who progress after 2 lines of therapy have limited treatment options, with poor outcomes (response rates of $\leq 6\%$). Ozekibart (INBRX-109) is a next-generation, tetravalent death receptor 5 agonist that has demonstrated robust efficacy as a single agent in chondrosarcoma. Additionally, ozekibart in combination with FOLFIRI showed early signs of antitumor activity in a small cohort of patients with CRC in the ongoing INBRX-109 phase 1 study (NCT03715933) (Berz D, et al. *J Clin Oncol*. 2025. Abstract 129). Based on these findings, the CRC cohort in this study was expanded to include additional patients who had received 2 or 3 prior lines of systemic therapy. We present initial findings from this cohort. **Methods:** Ozekibart + FOLFIRI was examined in patients with locally advanced or metastatic, unresectable CRC in the expansion cohort C4d of the open-label, INBRX-109 phase 1 study. Eligible patients were aged 18 to < 85 years, had received 2 or 3 prior lines of systemic therapy, and had no chronic or acute liver disease. Previous irinotecan-containing regimens were allowed but not as an immediate prior line of therapy. Patients received ozekibart 3 mg/kg every 4 weeks + FOLFIRI every 2 weeks. Safety and clinical response were primary endpoints. **Results:** As of the data cutoff (October 15, 2025), 44 patients had received ozekibart + FOLFIRI in this cohort. Median age was 54.5 years (range, 29–77 years), and $> 70\%$ were in the fourth-line treatment setting; 81.8% had previously received an irinotecan-based regimen. Overall, 28 patients (63.6%) remain on treatment; 11 patients had disease progression, 1 patient discontinued due to adverse events (AEs), and 4 patients discontinued for other reasons. Among evaluable patients for response at data cutoff ($n = 26$), ozekibart + FOLFIRI led to an ORR of 23% (all partial responses) and a disease control rate of 92%. Consistent with the safety profile of FOLFIRI, the most common AEs (in $> 25\%$ of patients) were anemia (any grade, 36.4%; grade ≥ 3 , 9.1%), diarrhea (34.1%; 9.1%), nausea (31.8%; 0%), fatigue (27.3%; 2.3%), and alopecia (27.3%; 0%). Increased alanine aminotransferase was the only grade ≥ 3 hepatotoxicity event and occurred in 1 patient. **Conclusions:** Ozekibart + FOLFIRI demonstrated encouraging preliminary efficacy in a heavily pretreated patient population with metastatic, unresectable CRC. The safety profile of ozekibart + FOLFIRI was manageable, with most AEs being low grade. Our findings support further evaluation of ozekibart + FOLFIRI in advanced CRC. Updated data will be provided at the time of presentation. Clinical trial information: NCT03715933. Research Sponsor: Inhibrx Biosciences, Inc.

A randomized phase II trial of fruquintinib plus capecitabine versus capecitabine alone as maintenance therapy following first-line chemotherapy in metastatic colorectal cancer (mCRC).

Wenhua Li, Jinjia Chang, Zhiyu Chen, Junjie Peng; Department of Medical Oncology, Fudan University Shanghai Cancer Center; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China; Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China; Department of Colorectal Surgery, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Maintenance therapy with capecitabine (Cap) is widely recommended to unresectable mCRC patients (pts). Fruquintinib (Fru) is a highly selective inhibitor of VEGFR1/2/3. We sought to compare the therapeutic potential of Fru plus Cap versus Cap as maintenance therapy for mCRC. **Methods:** Eligible pts with histologically confirmed mCRC who achieved disease control (including CR/PR and SD) after at least six cycles of first-line standard chemotherapy were included in the study. During phase Ib, pts received Fru (4 mg, p.o. qd, 3 weeks on/1 week off, q4w) plus Cap (850 mg/m², p.o. bid, d1-7 and d15-21, q4w). In phase II, pts were randomized in a 1:1 ratio to receive either Fru (RP2D, 3mg, 3 weeks on/1 week off) plus Cap or Cap alone. The primary endpoint was progression-free survival (PFS). Secondary endpoints included objective response rate (ORR), disease control rate (DCR) and safety. **Results:** As of November 15, 2025, 113 eligible patients were enrolled, including 6 in phase Ib and 107 in phase II. In this presentation, we report only the updated data from Phase II. 107 were randomly assigned to receive either fruquintinib plus capecitabine (Fru+Cap; n=52) or capecitabine alone (Cap; n=55). Baseline characteristics included median age: 61 years (range, 30-78) vs. 60 years (range, 31-80), male: 51.9% vs. 58.2%, left-sided colorectal primary tumors: 55.8% vs. 61.8% and RAS-mutant tumors: 53.8% vs. 52.7%. As first-line maintenance therapy, the median PFS1 (defined as time from randomization to disease progression or death) in the per-protocol population was 6.03 months with Fru+Cap versus 3.30 months with Cap (p=0.003). Furthermore, the Fru+Cap arm demonstrated significantly prolonged PFS2 (defined as the time from first receipt of first-line treatment to disease progression or death): 12.1 vs. 9.7 months, p=0.006. Consistent improvements were observed in objective response rate (ORR: 14.6% vs. 7.0%) and disease control rate (DCR: 75.6% vs. 51.2%). Grade ≥3 treatment-emergent adverse events (TEAEs) in Fru+Cap arm included hypertension (5.77%), palmar-plantar erythrodysesthesia syndrome (1.9%) and albuminuria (1.9%). Diarrhea (3.64%), palmar-plantar erythrodysesthesia syndrome (1.8%) and oral mucositis (1.8%) were the most frequently reported grade ≥3 TEAEs in Cap arm. **Conclusions:** PFS was significantly prolonged and ORR was improved in mCRC pts treated with Fru plus Cap as first-line maintenance treatment. The safety profile of the combination regimen was manageable and aligned with the expected toxicity patterns of the individual agents. Clinical trial information: NCT05451719. Research Sponsor: None.

Intravenous oncolytic virus IDOV-Safe in pMMR/MSS metastatic colorectal cancer.

Tong Xie, Ting Xu, Zhenghang Wang, Ming Lu, Seymour Mong, Xiang Deng, Longshen Xie, Jifang Gong, Jian Li, Nanhai G. Chen, Lin Shen; Gastrointestinal Cancers, Beijing Key Laboratory of Cell & Gene Therapy for Solid Tumor, State Key Laboratory of Holistic Integrative Management of Gastrointestinal Cancers, Department of GI Oncology, Peking University Cancer Hospital & Institute, Beijing, China; Beijing GoBroad Hospital, Beijing, China; Shenzhen Longyao Biological Co., Ltd., Shenzhen, China; Department of Bioinformatics and Biostatistics, School of Life Sciences and Biotechnology, SJTU-Yale Joint Center for Biostatistics and Data Science, Shanghai Jiao Tong University, Shanghai, China; ViroMissile, Inc., La Jolla, CA

Background: Proficient mismatch repair/microsatellite stable (pMMR/MSS) metastatic colorectal cancer (mCRC) is largely resistant to immune checkpoint inhibitors, with limited options after standard therapies. IDOV-Safe is a systemically deliverable, vaccinia virus-based oncolytic virotherapy. This phase 1 clinical trial evaluated the safety and preliminary efficacy of intravenous IDOV-Safe combined with toripalimab and fruquintinib in patients with pMMR/MSS mCRC (NCT06380309). **Methods:** Patients with pMMR/MSS mCRC who had progressed on or were intolerant to ≥ 2 prior systemic therapies were enrolled. Dose escalation used a 3+3 design across four dose levels (1×10^9 , 3×10^9 , 1×10^{10} , and 3×10^{10} PFU). In expansion, three combination strategies with immune-target therapy were evaluated: sequential, early, and IO free combinations using fruquintinib with or without toripalimab. Primary endpoints were safety and objective response rate (ORR). **Results:** Fifty-five patients were enrolled; 80% had received ≥ 3 prior treatment lines. Dose-limiting toxicities at 1×10^{10} PFU led to selection of 1×10^9 and 3×10^9 PFU for expansion. Grade ≥ 3 treatment-related adverse events (TRAEs) occurred in 62% of patients, most commonly fever, thrombocytopenia, and neutropenia; grade ≥ 3 immune-related events were infrequent (2%), and no grade ≥ 3 TRAEs were attributed to fruquintinib. In sequential combination cohorts, objective responses occurred only after initiation of combination therapy. ORR was 33.3% at 1×10^9 PFU (IIA1) and 30.0% at 3×10^9 PFU (IIA2), with disease control rates (DCRs) of 50.0% and 70.0%, respectively. In early combination cohorts, objective responses were observed at 3×10^9 PFU (IIC2; ORR 16.7%), with high DCRs (83.3% in IIC1 and 91.7% in IIC2). The DCR in the IO-free cohort (IID) was 50.0%. Median progression-free survival (mPFS) across five cohorts was 5.4 (IIA1), 8.7 (IIA2), 5.4 (IIC1), 5.5 (IIC2), and 4.6 months (IID). **Conclusions:** Intravenous IDOV-Safe demonstrated a favorable safety profile and encouraging preliminary antitumor activity when combined with toripalimab and fruquintinib, particularly using a sequential combination strategy in heavily pretreated patients with pMMR/MSS mCRC. Clinical trial information: NCT06380309. Research Sponsor: None.

Response to IDOV-safe and immuno-targeted therapy.

Response	IIA1 1×10^9	IIA2 3×10^9	IIC1 1×10^9	IIC2 3×10^9	IID 3×10^9
Best overall response – n (%)					
Partial response	2 (33.3)	6 (30.0)	0	2 (16.7)	0
Stable disease (SD)	1 (16.7)	8 (40.0)*	5 (83.3)	9 (75.0)	3 (50.0)
Progressive disease	3 (50.0)	5 (25.0)	0	1 (8.3)	2 (33.3)
Not evaluable	0	1 (5.0)	1 (16.7)	0	1 (16.7)
ORR—Percent (95% CI)	33.3 (4.3, 77.7)	30.0 (11.9, 54.3)	0	16.7 (2.1, 48.4)	0
DCR—Percent (95% CI)	50.0 (11.8, 88.2)	70.0 (45.7, 88.1)	83.3 (35.9, 99.6)	91.7 (61.5, 99.8)	50.0 (11.8, 88.2)

*One patient in IIA2 cohort had unconfirmed SD.

Efficacy and safety of cetuximab-irinotecan rechallenge versus regorafenib in *RAS* wild-type metastatic colorectal cancer.

Hao Chen, Tao Jiang, Han Wang, JW Zheng, Bin Du, Xiaojiao Weng, Na Yao, Yingjiao Zhu, Qing Liu, Fangyu Lin, Xinli Wang, Xiaoyan Lin; Fujian Medical University Union Hospital, Fuzhou, China; Department of Medical Oncology, Fujian Medical University Union Hospital, Fuzhou, Fujian, China

Background: Anti-epidermal growth factor receptor (EGFR) antibodies are widely used in the treatment of *RAS* wild-type metastatic colorectal cancer (mCRC) across various lines of therapy, including after disease progression. **Methods:** A single-center, prospective, randomized controlled trial (ChiCTR1900026961) evaluated the efficacy of cetuximab rechallenge in mCRC patients with *RAS* wild-type tumors who had initially responded to cetuximab-based therapy but subsequently progressed on a cetuximab-free regimen. The trial compared cetuximab plus irinotecan with regorafenib, with progression-free survival (PFS) as the primary endpoint and overall survival (OS), disease control rate (DCR), objective response rate (ORR), and safety as secondary endpoints. **Results:** Among 68 patients with microsatellite-stable (MSS), *RAS* wild-type tumors, 35 received cetuximab rechallenge therapy and 33 received regorafenib. The cetuximab group achieved a DCR of 68.6% and an ORR of 8.6%, both significantly higher than those observed in the regorafenib group. Median PFS was 5.5 months in the rechallenge group compared with 2.6 months in the regorafenib group, while median OS was 18.8 months versus 10.4 months, respectively. Adverse events in the cetuximab group were predominantly grade 1–2 and manageable with supportive care. Univariate and multivariate Cox regression analyses identified age, ECOG performance status, and washout period duration as independent prognostic factors. A nomogram was developed to predict the efficacy of cetuximab rechallenge therapy. **Conclusions:** These findings suggest that cetuximab rechallenge offers promising clinical activity with acceptable toxicity in *RAS*/BRAF wild-type mCRC, supporting further investigation of rechallenge strategies and biomarker-guided approaches to optimize outcomes in advanced CRC. Clinical trial information: ChiCTR1900026961. Research Sponsor: The Joint Funds for the Innovation of Science and Technology of Fujian province (2018Y9032).

Zongertinib in HER2-altered colorectal cancer: A pooled analysis of colorectal cancer patients from two clinical trials.

Dirk Arnold, Noboru Yamamoto, Frans Opdam, Kiyotaka Yoh, Philippe Bedard, Jin Li, Erika Martinelli, John J. Park, Maria Garcia Pallas, Nick Pavlakakis, Ana Gil, Behbood Sadrolhefazi, Daniel Martin Klotz, Lorenz Uhlmann, Gustavo Borghesi, Joanna Hussain, Anke Baum, Patrizia Sini, John V. Heymach, Alison M. Schram; Asklepios Tumorzentrum Hamburg, AK Altona, Hamburg, Germany; National Cancer Center Hospital, Tokyo, Japan; The Netherlands Cancer Institute, Amsterdam, Netherlands; National Cancer Center Hospital East, Kashiwa, Japan; Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; Shanghai GoBroad Cancer Hospital, China Pharmaceutical University, Shanghai, China; University of Campania "Luigi Vanvitelli", Naples, Italy; Macquarie Medical School, Macquarie University, Sydney, NSW, Australia; Pan-American Oncology Trials, San Juan, Puerto Rico; Genesis Care, North Shore Health Hub, St Leonards, NSW, Australia; Hospital Universitario Virgen del Rocío, Sevilla, Spain; Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT; Boehringer Ingelheim International GmbH, Biberach an Der Riss, Germany; Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an Der Riss, Germany; Boehringer Ingelheim International GmbH, Ingelheim Am Rhein, Germany; Boehringer Ingelheim Ltd, Bracknell, Berkshire, United Kingdom; Boehringer Ingelheim RCV GmbH & Co. KG, Vienna, Austria; The University of Texas MD Anderson Cancer Center, Houston, TX; Memorial Sloan Kettering Cancer Center, New York, NY

Background: Zongertinib, an irreversible TKI, selectively inhibits HER2 while sparing wild-type EGFR, thereby minimizing associated toxicities. Here, we present a pooled analysis of a subgroup of patients (pts) with HER2-positive colorectal cancer (CRC) who received zongertinib monotherapy in Phase Ia of a dose-escalation/expansion trial (NCT04886804) or in the ongoing Phase II Beamion PANTUMOR-1 trial (NCT06581432), as well as supporting preclinical data. **Methods:** Preclinical antitumor activity of zongertinib as monotherapy or in combination with other HER2-directed agents was assessed in commercially available HER2-amplified mouse PDX models of CRC. Phase Ia of NCT04886804 enrolled pts with advanced solid tumors and HER2 alterations (mutations, amplification, or overexpression) who had exhausted all other standard treatment options. Beamion PANTUMOR-1 includes pts with previously treated HER2-positive (amplification or overexpression) or HER2-mutant solid tumors. Pts in NCT04886804 received escalating doses of zongertinib (15 mg BID or 180–360 mg QD); pts in Beamion PANTUMOR-1 received zongertinib 120 mg QD. Efficacy (investigator-assessed objective response rate [ORR]; RECIST v1.1) and safety (incidence of adverse events [AEs]; CTCAE v5.0) were assessed. **Results:** In HER2-amplified PDX CRC models, zongertinib monotherapy and in combination with other HER2-directed agents led to tumor growth inhibition or regression, with greater antitumor activity observed with the combinations. A total of 20 pts with HER2-positive CRC (10 from each trial) received zongertinib. Pts had a median age of 53 years (range: 36–70) and had received a median of 2.5 lines of prior systemic therapy. A total of 8 pts (6 from NCT04886804 and 2 from Beamion PANTUMOR-1) had received ≥ 1 prior HER2-directed therapy, including trastuzumab, pertuzumab, or T-DXd. Median treatment duration with zongertinib was 5.1 months (range: 0–18). The confirmed ORR was 45% (n = 9; all partial responses). A further 9 (45%) pts achieved stable disease, giving a disease control rate of 90%. At the time of analysis, 7 (35%) pts remained on treatment. Treatment-related AEs (TRAEs, any grade/grade ≥ 3) were reported in 70%/5% of pts. The most common TRAEs were diarrhea (9 pts [45%], all grade 1), rash (3 pts [15%], all grade 1), anemia (2 pts [10%], all grade 2), and increased AST (2 pts [10%], all grade 2). Only one pt had a grade ≥ 3 TRAE (grade 3 increased lipase). No grade 4 or 5 AEs were reported. **Conclusions:** Pooled analysis of HER2-positive CRC pts from two clinical trials indicates that zongertinib monotherapy has encouraging clinical activity and manageable safety in pts with advanced, HER2-positive CRC, supported by PDX models. Based on these findings, zongertinib continues to be developed in CRC, with Beamion PANTUMOR-1 actively enrolling. An additional Phase Ib/II trial (Beamion BCGC-1, NCT06324357) is also underway. Clinical trial information: NCT04886804, NCT06581432. Research Sponsor: Boehringer Ingelheim.

First-line immune checkpoint inhibitors in elderly colorectal cancer patients in the real world: Retrospective phase of the multicenter ELDER CRC trial.

Martina Cassaniti, Alessandra Boccaccino, Daniele Rossini, Lisa Salvatore, Alberto Puccini, Anna Amela Valsecchi, Chiara Ghirardini, Ina Valeria Zurlo, Fabio Gelsomino, Chiara Gallio, Giulia Massaro, Cristina Morelli, Gabriele Ferrari, Linda Di Francesco, Claudia Airaghi, Maria Alessandra Calegari, Lorenzo Antonuzzo, Stefano Tamberi; Oncology Unit, University Hospital of Ferrara, Ferrara; Oncology Unit Santa Maria delle Croci Hospital - AUSL Romagna, Ravenna, Italy; Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy; Medical Oncology, Università Cattolica del Sacro Cuore; Medical Oncology, Comprehensive Cancer Center, Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Rome, Italy; Department of Biomedical Sciences, Humanitas University, Pieve Emanuele; IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy; Department of Oncology, University of Turin, A.O.U. Città della Salute e della Scienza di Torino, Ospedale Molinette, Turin, Italy; Oncology Unit, University Hospital of Ferrara, Ferrara; Oncology Unit Santa Maria delle Croci Hospital - AUSL Romagna, Ravenna, NA, Italy; Medical Oncology, 'Vito Fazzi' Hospital, Lecce, Italy; Department of Oncology and Hematology, University Hospital of Modena, Modena, Italy; Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori" - IRST IRCCS, Meldola (FC), Italy; Clinical Oncology Unit, Careggi University Hospital; Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy; Medical Oncology Unit, Department of Systems Medicine, University of Rome "Tor Vergata", Rome, Italy; Unit of Oncology, Fondazione IRCCS Policlinico San Matteo; Department of Internal Medicine and Therapy, University of Pavia, Pavia, Italy; Medical Oncology, Comprehensive Cancer Center, Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Rome, Italy; Clinical Oncology Unit and Department of Experimental and Clinical Medicine, Careggi University Hospital, Florence, Italy; Oncology Unit Santa Maria delle Croci Hospital - AUSL Romagna, Ravenna; Department of Medical and Surgical Sciences (DIMEC), Bologna University, Bologna, Italy

Background: dMMR/MSI-H metastatic colorectal cancer (mCRC) is more common among the elderly. However, insufficient data about their treatment with immune checkpoint inhibitors (ICIs) are available from interventional and observational trials. **Methods:** ELDER CRC is an observational, multicenter Italian trial enrolling elderly (≥ 70 years [yrs]) patients (pts) treated with first-line ICI(s) for dMMR/MSI-H mCRC in the real world. Results from the retrospective cohort are presented. **Results:** 132 pts aged 77 yrs as median (IQR 74–82, range 70–93; < 75 : 32.6%; 75–79: 29.5%; ≥ 80 : 37.9%) were enrolled across 10 Centers. They were mainly female (56.1%) in mediocre conditions (ECOG PS 1: 51.9%, ≥ 2 : 22.2%; $G8 \leq 14$: 80.5% [33/41 available]) with BRAF mutated (58.9% [73/124]), right primary tumor (80%), and synchronous metastases (54.5%) involving liver (34.8%) and/or peritoneum (37.9%). Almost all pts received monotherapy (pembrolizumab or nivolumab: 98.5%; nivolumab+ipilimumab: 1.5%) and most discontinued for PD (31.1%) or completion of 2 yrs (13.6%). 65.2% had an adverse event (AE), mainly fatigue (37.9%), skin rash (20.5%), hypothyroidism (17.4%), diarrhea (15.9%), and arthralgia (12.9%). Only 11% had $G3-4$ AE ($G5=0$), mainly gastrointestinal (3.8%), lung (3%), and fatigue (2.3%) and 10.6% discontinued ICI for AE. On 122 evaluable pts, ORR was 51.6% (38.5% PR + 13.1% CR) with 26.2% SD and 22.1% primary PD. At median follow-up of 25.9 months [mos] (22.3–30.3), mPFS was 32.2 mos (26.2–NE) with 56 events and mOS 45.8 mos (32.2–NE) with 46 events. 28.8% are still on treatment at the time of this analysis. Survival outcomes were not influenced by age groups. $G8 > 14$ was related with better PFS (HR=0.79, $p=0.06$) and OS (HR=0.89, $p=0.09$). At multivariable model only neutrophils/lymphocytes ratio ≥ 3 was significantly associated with worse PFS (HR=1.91, $p=0.03$), while no variables with OS. **Conclusions:** Our results confirm the benefit of first-line immunotherapy for dMMR/MSI-H mCRC even among elderly pts treated in the real world, despite the substantial rate of right-sided and/or BRAF mut CRC pts and regardless of age group. The manageable safety profile of ICI(s) was also confirmed. $G8$ might be predictive of outcome but needs implementation in daily practice. Research Sponsor: None.

Overall survival benefit of doublet versus triplet BRAF inhibitor–based therapy: Insights from the BEETS study (JACCRO CC-18).

Chiaki Inagaki, Ryo Matoba, Eisuke Inoue, Daisuke Kotani, Tadamichi Denda, Tomomi Kashiwada, Yoshiaki Mihara, Akinori Sugaya, Yusuke Suwa, Takashi Ohta, Hidekazu Kuramochi, Kotoe Oshima, Chihiro Tanaka, Toshihiro Kudo, Satoshi Yuki, Manabu Shiozawa, Akihito Tsuji, Kei Muro, Wataru Ichikawa, Yu Sunakawa; Department of Medical Oncology, Kindai University Faculty of Medicine, Sakai, Osaka, Japan; DNA Chip Research Inc., Kawasaki, Japan; Showa Medical University Research Administration Center, Showa Medical University, Tokyo, Japan; National Cancer Center Hospital East, Kashiwa, Japan; Division of Gastroenterology, Chiba Cancer Center, Chiba-Shi Chuo-Ku, Japan; Department of Medical Oncology, Saga-ken Medical Center Koseikan, Saga, Japan; Department of Internal Medicine (Medical Oncology and Palliative Medicine), Showa Medical University Fujigaoka Hospital, Yokohama, Japan; Department of Medical Oncology, Ibaraki Prefectural Central Hospital, Kasama-Shi, Japan; Department of Surgery, Gastroenterological Centre, Yokohama City University Medical Center, Yokohama, Japan; Department of Gastroenterology, Kansai Rosai Hospital, Amagasaki, Japan; Department of Medical Oncology, NTT Medical Center, Tokyo, Japan; Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan; Department of Surgery, Gifu Prefectural General Medical Center, Gifu, Japan; Department of Medical Oncology, Osaka International Cancer Institute, Osaka, Osaka, Japan; Department of Gastroenterology and Hepatology, Hokkaido University Hospital, Sapporo, Japan; Department of Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, Japan; Department of Clinical Oncology, Kagawa University Faculty of Medicine, Kita-Gun, Japan; Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; Showa University Fujigaoka Hospital, Yokohama-Shi Aoba-Ku, Japan; Department of Clinical Oncology, St. Marianna University School of Medicine, Kawasaki, Japan

Background: Cetuximab plus encorafenib, with or without binimetinib, is established as one of the standard treatment options for *BRAF* V600E-mutated metastatic colorectal cancer (mCRC) in the second- or later-line setting. Although the triplet therapy (encorafenib/cetuximab/binimetinib; T) is approved in Japan and commonly used for patients with poor prognostic features based on guideline recommendations, objective biomarkers to guide optimal patient selection remain lacking. Given the BREAKWATER trial support for first-line doublet therapy (encorafenib/cetuximab; D) with chemotherapy, the clinical role of MEK inhibitor-containing regimens may become more limited; nevertheless, the development of biomarkers capable of identifying patients who are likely to benefit from MEK inhibition remains an important unmet need. We therefore performed a prospective translational analysis within the BEETS study to identify biomarkers that guide treatment selection between T and D. **Methods:** BEETS (JACCRO CC-18: UMIN000045530) was a multicenter, prospective biomarker study of second/third-line encorafenib-based D or T regimen. We prospectively collected paired pre- and post-treatment blood samples, and analyzed pretreatment tumor-educated platelet RNA by RNA sequencing (TEP-seq). To address baseline imbalances, propensity score matching (PSM) was performed using ECOG PS, number of metastatic organs (≥ 3), C-reactive protein (>1 mg/dL), and prior primary tumor resection. Interaction between gene expression (z-score) and treatment arm was evaluated using Cox proportional hazards models. Candidate biomarkers were prioritized based on $|\log_2(\text{HR})| \geq 0.5$ and $P < 0.05$. **Results:** Of 203 enrolled patients, 189 were evaluable for TEP-seq. After PSM, 81 patients per arm were analyzed. In the matched cohort, median overall survival (OS) was longer for D than T (17.4 months [m] vs. 10.2 m, HR 1.80; 95% CI:1.24–2.61). Interaction screening identified 44 genes for which higher expression was associated with better outcomes on D but worse outcomes on T, and six genes showing the opposite pattern. Among these candidates, *RAD51C* expression emerged as a representative marker; when dichotomized at the arm-specific median, higher expression favored T but indicated worse outcomes with D (*RAD51C* Low vs. High; T 7.8m vs. 10.6m, HR 0.79, 95%CI 0.49–1.28; D 28.2m vs. 12.9m, HR 2.02, 95%CI 1.16–3.53). Pathway-level exploration suggested a possible association between elevated *RAD51C* expression and increased MAPK-related signaling activity, potentially explaining the requirement for more intensive MEK inhibition in these patients. **Conclusions:** While OS was superior with D regimen in this matched cohort, *RAD51C* expression was identified as a candidate biomarker for identifying patients who may derive preferential benefit from MEK inhibition. Clinical trial information: UMIN000045530. Research Sponsor: None.

Ultra-early-onset metastatic colorectal cancer (<35 years): RAS-driven, APC/TP53-depleted, TMB-low molecular features in a real-world analysis of 2,392 patients.

Andrea Pretta, Giulia Maddalena, Gaia Rebecchi, Federica Marmorino, Pina Ziranu, Maria Caterina De Grandis, Federica Manoni, Martina Carullo, Claudio Pisano, Giovanni Randon, Eleonora Perissinotto, Ada Taravella, Vincenzo Nasca, Federica Buggin, Paolo Ciraci, Francesca Bergamo, Sara Lonardi, Chiara Cremolini, Mario Scartozzi, Filippo Pietrantonio; Medical Oncology Unit, University Hospital and University of Cagliari, Cagliari, Italy; Oncology Unit 1, Istituto Oncologico Veneto (IOV-IRCCS), Padua, Italy; Istituto Nazionale Tumori, Milan, Italy; 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; Medical Oncology 1, Department of Oncology, Veneto Institute of Oncology (IOV-IRCCS), Padua, Italy; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Medical Oncology Unit, University Hospital and University of Cagliari, Monserrato, Italy; Medical Oncology Department, 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 Translational Research and New Technologies in Medicine and Surgery, University of Pisa & Unit of Medical Oncology 2, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy; Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy; Medical Oncology 1, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy; Oncology 1 Unit, Department of Medical Oncology, Veneto Institute of Oncology IOV - IRCCS, Padua, Italy; Medical Oncology 1, Veneto Institute of Oncology (IOV-IRCCS), Padua, Italy

Background: Early-onset colorectal cancer (CRC, <50 years) is on the rise globally and includes a biologically heterogeneous disease. Patients diagnosed before age 35 represent the extreme of early-onset CRC, yet their clinical and genomic features remain poorly understood. We investigated whether ultra-early-onset metastatic CRC (UEO-CRC, <35 years) exhibits distinct outcomes and a unique molecular profile in a large real-world cohort. **Methods:** We analyzed a multicenter cohort of 2,392 patients with metastatic CRC; 1,612 had comprehensive genomic profiling (Foundation Medicine) and were included in molecular analyses. Patients were classified as ≤ 35 years ($n=130$) or >35 years ($n=1482$) at metastatic diagnosis. Overall survival (OS) was assessed using Kaplan–Meier estimates and log-rank tests. Gene- and pathway-level differences were evaluated using Fisher's exact test. A composite UEO-CRC molecular signature was defined based on features significantly enriched or depleted in patients ≤ 35 years. **Results:** UEO-CRC represented 8.1% of metastatic cases. Patients ≤ 35 years had significantly worse survival than those >35 years (median OS 35.0 vs 46.0 months; $p=0.0081$). Molecular profiling revealed a distinct oncogenic pattern characterized by: enrichment of RAS mutations (KRAS 48.6% vs 36.4%, $p=0.011$; NRAS 11.7% vs 4.1%, $p=0.0011$); marked depletion of APC (21.6% vs 63.4%, $p<0.001$) and TP53 mutations (33.3% vs 63.8%, $p<0.001$); suppression of WNT pathway alterations (25.2% vs 66.9%, $p<0.001$); and genomic stability without hypermutation, including absence of TMB-high tumors (0% vs 7.5%, $p=0.00037$), lower median TMB (3.1 vs 4.8 mut/Mb, $p<0.001$), no MSI-H cases, and rare POLE/POLD1 or DDR alterations (4.5% vs 1.2%, $p=0.017$). Integration of these features identified a reproducible UEO-CRC molecular signature (RAS-mutant, APC/TP53 wild-type, TMB-low), over six-fold more frequent in UEO-CRC than in patients ≥ 35 years (32% vs 5%; $p<0.001$). **Conclusions:** Ultra-early-onset metastatic CRC (<35 years) represents a biologically aggressive and genomically distinct entity. UEO-CRC is defined by a non-canonical, RAS-driven, APC/TP53-independent tumorigenic program occurring without hypermutation, MSI-H, or POLE-driven biology. The lack of TMB-high indicates limited immunogenicity, emphasising the need for age-specific biological stratification and customised therapeutic strategies in this high-risk population. Research Sponsor: None.

Survival outcomes of human epidermal growth factor receptor 2 (HER2)–amplified and HER2-mutated left-sided colorectal cancer (CRC) patients treated with anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (mAbs).

Yu Jen Alexander Jan, Kieran Sweeney, Andrew Elliott, Ronan Wenhan Hsieh, Chaoyuan Kuang, Parham Habibzadeh, Shafia Rahman, Rachna Shroff, Heinz-Josef Lenz, Sanjay Goel, Aatur D. Singhi, Vikram C. Gorantla, John C. Rhee, Janie Yue Zhang, Anwaar Saeed, Dennis Hsu; Division of Hematology-Oncology, Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA; Caris Life Sciences, Phoenix, AZ; Caris Life Sciences, Irving, TX; Swedish Cancer Institute - First Hill, Seattle, WA; Montefiore Einstein Comprehensive Cancer Center, Bronx, NY; Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA; The Ohio State University Comprehensive Cancer Center, Columbus, OH; Division of Hematology and Oncology, University of Arizona College of Medicine, Tucson, AZ; Division of Medical Oncology, Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA; Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, PA

Background: Current guidelines support the use of anti-EGFR mAbs in left-sided CRCs without mutations in *KRAS*, *NRAS* and *BRAF*. Recent reports indicated that HER2–amplified CRCs might respond worse to anti-EGFR mAbs, whereas HER2–mutated CRCs and their response to anti-EGFR mAbs remained relatively unexplored. In this study, we assembled the largest collection of HER2–altered (amplified or mutated) CRCs to date from a real-world database with the goal of describing the impact of these alterations on anti-EGFR mAb therapy. **Methods:** Patients profiled by Caris Life Sciences with microsatellite stable, left-sided CRC without mutations in *KRAS*/*NRAS*/*BRAF* who received anti-EGFR mAbs (cetuximab or panitumumab) were included in this study. Microsatellite stability, amplifications (copies ≥ 6), and pathogenic or likely pathogenic mutations were identified by NGS. Patient outcomes were obtained from insurance claims data. Overall survival (OS) was calculated from start of anti-EGFR mAbs to time of last clinical contact. Time on treatment (ToT) was calculated from start to end of anti-EGFR mAbs. Hazard ratios and p-values were calculated using the Cox proportional hazards model and log-rank test. **Results:** A total of 3217 patients were included for analysis. Patients were stratified into 3 cohorts: HER2–amplified (N=114), HER2–mutated (N=46), and HER2–normal (N=3057). The HER2–mutated group was older than the HER2–amplified and the HER2–normal groups (median: 64.5 vs 56 and 58 years, $p=0.006$); no other significant differences were found in patient demographics. The HER2–mutated group had worse OS and ToT than the HER2–normal group (median OS 12.4 vs 25.9 months, HR 1.57, $p=0.013$; median ToT 4.3 vs 6.7 months, HR 1.40, $p=0.036$). The HER2–amplified group showed no significant differences in OS but worse ToT compared to the HER2–normal group (median OS 26.1 vs 25.9 months, HR 0.98, $p=0.856$; median ToT 5.8 vs 6.7 months, HR 1.25, $p=0.035$). In multivariate Cox regressions accounting for age, gender, and receipt of HER2–targeted therapy, the HER2–mutated group had worse OS and ToT compared to HER2–normal group (OS HR 1.66, $p=0.007$; ToT HR 1.55, $p=0.007$), while the HER2–amplified group showed no significant differences in OS and ToT compared to HER2–normal group (OS HR 1.14, $p=0.398$; ToT HR 1.26, $p=0.073$). **Conclusions:** In this large, real-world cohort of *KRAS*/*NRAS*/*BRAF* wild-type, left-sided CRCs receiving anti-EGFR mAbs, HER2–mutated patients had worse ToT and OS than HER2–normal patients, whereas HER2–amplified patients showed no difference in OS compared to HER2–normal patients. These findings suggest that alternative treatment studies should be explored in HER2–mutated left-sided CRCs, underscoring the importance of additional biomarker-directed studies in this patient cohort. Research Sponsor: None.

A phase Ib, open-label, clinical trial of JAB21822 combined with second-line chemotherapy for metastatic colorectal cancer with *KRAS* G12C mutation.

Zhenghang Wang, Wenhua Li, Sai Ge, Xuan Jin, Ting Xu, Jian Li, Lin Shen; Department of Gastrointestinal Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing, China; Department of Gastrointestinal Medical Oncology, Fudan University Shanghai Cancer Center, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China; Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Gastrointestinal Oncology, Peking University Cancer Hospital & Institute, Beijing, China; Peking University First Hospital, Beijing, China; Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Gastrointestinal Oncology, Peking University Cancer Hospital & Institute, Beijing, China; Department of Gastrointestinal Oncology, Peking University Cancer Hospital, Beijing, China; Department of Gastrointestinal Oncology, Peking University Cancer Hospital & Institute, Beijing, China

Background: Glecirasib (JAB-21822), a novel, covalent, small molecule *KRAS* G12C-GDP covalent inhibitor, has been shown to be effective and safe as monotherapy or in combination with cetuximab in treating patients with refractory, unresectable locally advanced or metastatic colorectal cancer (mCRC) harboring *KRAS* G12C mutation. There are few data regarding the efficacy and safety of *KRAS* G12C inhibitor in the second-line setting. This multicenter, phase Ib, open label, single arm study aims to investigate the efficacy and safety of glecirasib in combination with the standard second-line chemotherapy and bevacizumab in patients with mCRC with *KRAS* G12C mutation who failed first-line treatment (NCT06838338). **Methods:** Patients (pts) with mCRC harboring *KRAS* G12C mutation were enrolled and treated with glecirasib (800mg QD) combined with standard second-line chemotherapy (FOLFIRI or FOLFOX) and bevacizumab until disease progression or intolerable toxicity or patient-initiated withdrawal from the study. The primary endpoint was confirmed objective response rate (ORR). The secondary endpoints included overall survival (OS), progression-free survival (PFS), disease control rate (DCR), duration of response (DoR) and safety. **Results:** As of Dec 10, 2025, 26 pts were enrolled and received glecirasib combined with chemotherapy and bevacizumab in four centers. The median age was 58 years with female (54%)/male (46%), ECOG 0 (8%)/1 (92%). A total of 20 subjects had at least one post-baseline tumor assessment. The confirmed ORR and DCR were 50% (10/20) and 100% (10/20), respectively. Median DoR was 10.1 months (95%CI: 2.9, NE), median PFS was 11.5 months (95%CI: 5.5, NE). Any grade treatment-related adverse events (TRAEs) occurred in 23/26 (88.5%) pts, the most common ones (>20%) being diarrhea, nausea and anemia. Grade 3-4 TRAEs occurred in 6 (23.1%) pts. No grade 5 TRAEs occurred. **Conclusions:** Glecirasib in combination with the second-line standard chemotherapy and bevacizumab demonstrated encouraging efficacy and tolerable safety in the second-line treatment of mCRC patients with *KRAS* G12C mutation. Clinical trial information: NCT06838338. Research Sponsor: None.

A prospective randomized controlled trial of FAPI PET/CT-guided radiotherapy combined with second-line standard systemic treatment and cadonilimab versus second-line standard systemic treatment alone in patients with peritoneal metastasis from colorectal cancer (TORCH-PM01).

Juefeng Wan, Weixing Dai, Zhen Zhang, Guoxiang Cai; Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China; Fudan University Shanghai Cancer Center, Shanghai, China

Background: This study evaluates the efficacy and safety of FAPI PET/CT-guided radiotherapy combined with second-line systemic treatment and cadonilimab compared to second-line systemic treatment alone in patients with peritoneal metastasis from colorectal cancer.

Methods: In this prospective randomized controlled trial, we enrolled patients with peritoneal metastasis from colorectal cancer who progressed after first-line systemic therapy. Patients were randomly assigned to the control group, receiving second-line standard systemic treatment (n = 20), or the study group, which received hypofractionated radiotherapy (20–25 Gy in 5 fractions) combined with second-line systemic treatment and cadonilimab (n = 20). The primary endpoint was overall response rate (ORR). A total of 40 patients were enrolled, with 19 evaluable patients in each group following loss to follow-up. **Results:** The ORR was significantly higher in the study group at 63.2% (12/19) compared to 15.8% (3/19) in the control group (p = 0.003). Adverse events (AEs) of grade 3–4 in the study group included neutropenia (26.3%, 5/19), nausea (15.8%, 3/19), vomiting (15.8%, 3/19), and diarrhea (15.8%, 3/19). In the control group, the most common grade 3–4 AE was neutropenia (21.1%, 4/19) and vomiting (10.5%, 2/19). Immune-related AEs of grades 1–2 in the study group included skin reactions (15.8%, 3/19), hypothyroidism (5.3%, 1/19), hepatitis (5.3%, 1/19), and myocarditis (15.8%, 3/19). One case of grade 3–4 skin reaction (5.3%) was observed in the study group. **Conclusions:** FAPI PET/CT-guided radiotherapy combined with second-line systemic treatment and cadonilimab significantly improves ORR in patients with peritoneal metastasis from colorectal cancer compared to standard second-line treatment alone, with manageable toxicity profiles. These findings support a promising therapeutic strategy for this challenging patient population. Clinical trial information: NCT07079462. Research Sponsor: None.

A multicenter single-arm phase II trial evaluating the safety and efficacy of panitumumab and irinotecan in patients with NeoRAS wild-type metastatic colorectal cancer (C-PROWESS trial).

Hiroki Osumi, Tadamichi Denda, Manabu Shiozawa, Atsuo Takashima, Tetsuya Hamaguchi, Kota Ouchi, Koichi Suyama, Yosuke Kumekawa, Atsushi Ishiguro, Takuro Mizukami, Toshiki Masuishi, Nobumi Suzuki, Shota Fukuoka, Takeru Wakatsuki, Akira Ooki, Naoki Miyazaki, Narikazu Boku, Ken Kato, Kensei Yamaguchi, Eiji Shinozaki; Kanagawa Cancer Center, Department of Gastroenterology, Yokohama, Japan; Division of Gastroenterology, Chiba Cancer Center, Chiba-Shi Chuo-Ku, Japan; Department of Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, Japan; National Cancer Center Hospital, Chuo-Ku, Tokyo, Japan; Saitama Medical University International Medical Center, Saitama, Japan; Department of Medical Oncology, Tohoku University Hospital, Sendai, Japan; Department of Medical Oncology, Toranomon Hospital, Tokyo, Japan; Saitama Cancer Center, Saitama, Koto-ku, Japan; Teine Keijinkai Hospital, Sapporo, Japan; Department of Medical Oncology, NTT Medical Center, Tokyo, Japan; Aichi Cancer Center Hospital, Nagoya, Japan; Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan; Department of Gastroenterological Chemotherapy, Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan; Department of Clinical Planning and Strategy, Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan; Department of Oncology and General Medicine, IMSUT Hospital, Institute of Medical Science, University of Tokyo, Minato City, Tokyo, Japan; Department of Head and Neck, Esophageal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan

Background: Previous studies have demonstrated favorable efficacy of anti-epidermal growth factor receptor (EGFR) monoclonal antibody (mAb) in metastatic colorectal (mCRC) patients with NeoRAS wild type (WT), ie, conversion of RAS status from mutant to WT following treatment. This multicenter, single-arm, phase II trial evaluated the efficacy and safety of panitumumab plus irinotecan for mCRC patients with NeoRAS WT. **Methods:** Patients with tissue-confirmed RAS mutant mCRC who developed intolerance to or disease progression after fluoropyrimidine, oxaliplatin, and irinotecan were screened for RAS mutation status in circulating tumor DNA (ctDNA) with the OncoBEAM RAS CRC assay. Those without RAS mutations detected within 28 days before enrollment received panitumumab (6 mg/kg) and irinotecan (150 mg/m²) biweekly. The primary endpoint was a response rate (RR) per RECIST 1.1. Secondary endpoints included disease control rate (DCR; response or stable disease), progression-free survival (PFS), overall survival (OS), safety, and biomarker analysis using next-generation sequencing (NGS) of ctDNA (Guardant360). The null hypothesis was a RR of < 4%, and the alternative hypothesis was ≥ 15%, with 80% power and a one-sided 10% significance level. The required sample size is 30. **Results:** Among 404 patients screened for RAS status in ctDNA, conversion to NeoRAS WT was observed in 54 (13.3%), and 30 patients were enrolled. Median age was 66.5 years old, and 20 (66.7%) were male. Lung was the most frequent site of metastasis (73.3%), and KRAS exon 2 accounted for 80% of prior tissue RAS MT. RR and DCR were 6.7% (80% CI, 1.8 to 16.8) and 76.7% (95% CI, 57.7 to 90.1), respectively. With median follow-up 22.4 months, median PFS was 4.1 months and median OS was 16.8 months. Grade 3 adverse events were observed in 14 patients (46.7%): skin toxicity (13.3%), hypomagnesemia (10.0%), diarrhea (10.0%), appetite loss (10.0%), and anemia (7.0%). No grade ≥ 4 adverse event was observed. ctDNA NGS results were available for 27 patients and included KRAS (44.4%), NRAS (3.7%), and PIK3CA (7.4%) mutations and ERBB2 amplification (3.7%). RR for patients with none of these mutations (negative hyper-selection cohort) was 16.7% (2/12) while no patient with any of these alterations achieved a response (0/15). Negative hyper-selection was associated with significantly longer PFS and OS (PFS: 6.1 vs 2.9 months, HR, 0.37, 95%CI, 0.16 to 0.87; OS: 25.5 vs 13.1 months, HR, 0.34, 95% CI, 0.12 to 0.99). In multivariate analysis, negative hyper-selection was an independent factor for PFS (HR, 0.12, 95%CI, 0.03 to 0.41) and OS (HR, 0.30, 95%CI, 0.10 to 0.96). **Conclusions:** Anti-EGFR mAb with chemotherapy may be effective for NeoRAS WT mCRC, especially for patients hyper-selected for absence of gene mutations related to anti-EGFR mAb resistance. Clinical trial information: s031210565. Research Sponsor: None.

Serum VEGF-A concentrations as a predictive biomarker of immunotherapy response in refractory metastatic colorectal cancer (mCRC): An exploratory analysis of CCTG CO.26.

François Jobin Gervais, Xin Wang, Jonathan M. Loree, Emma Titmuss, Trevor J. Pugh, Derek J. Jonker, Hagen Fritz Kennecke, Scott Berry, Aaron Richard Hansen, Philippe Bedard, Stephanie Lheureux, Anna Spreafico, Albiruni Ryan Abdul Razak, Lillian L. Siu, Felix Couture, Ahmad Chaudhary, John R. Goffin, Dongsheng Tu, Christopher J. O'Callaghan, Eric Xueyu Chen; Princess Margaret Cancer Centre-University Health Network, Toronto, ON, Canada; Princess Margaret Cancer Centre, Toronto, ON, Canada; BCCA - Vancouver Cancer Centre, University of British Columbia, Vancouver, BC, Canada; BC Cancer - Vancouver, Vancouver, BC, Canada; University Health Network, Toronto, ON, Canada; The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada; Oregon Health & Science University, Portland, OR; Queen's University, Kingston, ON, Canada; Princess Alexandra Hospital, Brisbane, Australia; Princess Margaret Cancer Centre - University Health Network, University of Toronto, Toronto, ON, Canada; Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; Princess Margaret Cancer Centre, University Health Network, University of Toronto, Princess Margaret Cancer Consortium, Marathon of Hope Cancer Centres Network, Toronto, ON, Canada; Hôtel-Dieu de Québec, Quebec, QC, Canada; Eastern Health, St. John's, NF, Canada; Juravinski Cancer Institute, Hamilton, ON, Canada; Canadian Cancer Trials Group, Queen's University, Kingston, ON, Canada; Division of Medical Oncology and Hematology, Princess Margaret Cancer Center, University Health Network, Toronto, ON, Canada

Background: Benefits of immune checkpoint inhibitors (ICIs) in unselected proficient mismatch repair (pMMR) mCRC remain unestablished. This exploratory analysis of CCTG CO.26 evaluated whether serum VEGF-A concentrations may influence ICI efficacy. **Methods:** CCTG CO.26 was a phase II trial that randomized refractory mCRC patients (pts) (2:1) to Durvalumab + Tremelimumab + Best supportive care (DT) vs Best supportive care (BSC) alone and was positive for overall survival (OS). VEGF-A concentrations were determined in baseline serum samples using an ELISA method. OS and progression-free survival (PFS) were compared between high and low groups based on median VEGF-A concentration in each treatment arm. An optimal cutoff was also identified using a minimal p-value approach. VEGFA mRNA expression from tissue-based RNA-seq was analyzed in the INSPIRE study, a separate, single arm, multicohort phase II trial comprising multiple tumor types treated with pembrolizumab for external validation. **Results:** Baseline VEGF-A concentrations were available for 161 pts (47 BSC, 114 DT). Median VEGF-A concentration was 1166 pg/ml (range: 226 – 4898; IQR: 784–1755). VEGF-A concentrations were significantly higher in ECOG 1 vs 0 pts ($p = 0.03$), and in pts who had previously received regorafenib ($p = 0.03$). Grouped by median VEGF-A, median OS was longer in DT-treated patients with low VEGF-A (7.39 months for DT-Low vs. 6.08 DT-high; hazard ratio (HR) 0.62, 95% confidence interval (CI): [0.42–0.90], $p = 0.01$), but not in BSC treated patients (4.44 months BSC-Low vs. 4.11 BSC-High; HR 1.05 [0.57–1.92], $p = 0.88$; interaction HR 0.56 [0.28–1.14], $p = 0.11$). An optimal VEGF-A threshold of 1540 pg/mL was identified using a minimal p-value approach, with 33.5% pts having high VEGF-A concentrations. Median OS was 7.29 vs 4.37 months for DT-Low and DT-High pts (HR 0.53 [0.35–0.80], $p < 0.005$), and 3.55 vs 7.46 months for BSC-Low and BSC-High pts (HR 1.50 [0.80–2.80], $p = 0.21$; interaction HR 0.33, [0.16–0.70], $p < 0.005$). In multivariable analyses incorporating ECOG, presence of liver metastases, plasma tumor mutation burden and arginine levels, low VEGF-A concentrations remained statistically associated with improved OS with DT (HR 0.46 [0.30–0.70], $p < 0.001$; interaction HR 0.18 [0.083–0.41], $p < 0.0001$). There was no association between VEGF-A concentrations and PFS in any arm. In the INSPIRE study ($n = 66$), VEGFA mRNA expression was lower in responders ($p < 0.001$) and significantly associated with improved PFS (HR 0.45 [0.25–0.79], $p = 0.006$) and OS (HR 0.47 [0.26–0.85], $p = 0.013$) across tumor types. **Conclusions:** Refractory mCRC patients with low VEGF-A concentrations may derive benefit from ICIs. This is the first report to suggest that serum VEGF-A concentration is a potential predictive biomarker for benefit from ICIs. These findings should be prospectively validated. Research Sponsor: None.

Antitumor activity of amivantamab by consensus molecular subtypes in *RAS/BRAF* wild-type metastatic colorectal cancer: Secondary analyses from the phase 1b/2 OrigAMI-1 study.

Marcia Roxana Cruz-Correa, Sae-Won Han, Rozita Abdul Malik, Harvey Yu-Li Su, Marc Van den Eynde, Paul Eliezer Oberstein, Ying Yuan, Victor Moreno, Filippo Pietrantonio, Eric Xueyu Chen, Kanwal Pratap Singh Raghav, Sanjib Chowdhury, Xuesong Lu, Rianka Bhattacharya, Praveen Barala, Cecilia Monge, Seema Niphadkar Sethi, Sreenivasa R. Chandana; University of Puerto Rico and Pan American Center for Oncology Trials, San Juan, Puerto Rico; Seoul National University Hospital, Seoul, South Korea; Department of Clinical Oncology, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia; Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan; Institut Roi Albert II, Cliniques Universitaires Saint-Luc, UC Louvain, Brussels, Belgium; NYU Langone Health, New York, NY; The Second Affiliated Hospital of Zhejiang University College of Medicine, Hangzhou, China; START Madrid-FJD, University Hospital Fundación Jiménez Díaz, Madrid, Spain; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Princess Margaret Cancer Centre University Health Network, Toronto, ON, Canada; The University of Texas MD Anderson Cancer Center, Houston, TX; Johnson & Johnson, Cambridge, MA; Johnson & Johnson, Shanghai, China; Johnson & Johnson, Raritan, NJ; Johnson & Johnson, Spring House, PA; START Midwest, Grand Rapids, MI

Background: Colorectal tumors are classified by mutational subtypes and sidedness, which inform treatment and outcomes. They can also be classified into four Consensus Molecular Subtypes (CMS1–4), with CMS2 (*EGFR*-dependent, canonical) typically showing better prognosis and CMS4 (*EGFR*-independent, *MET* pathway associated, mesenchymal) associated with poor prognosis and limited response to traditional *EGFR* inhibition (Thanki *Int Biol Biomed J* 2017, Woolston *Cancer Cell* 2019). In prior analyses, cetuximab monotherapy demonstrated greater antitumor activity against CMS2 *RAS* wild-type (WT) vs CMS4 *RAS* WT tumors (disease control rate [DCR]: 68% vs 29%; Chowdhury *JCO Precis Oncol* 2023), suggesting CMS4 may limit cetuximab efficacy *de novo*. Additionally, CMS2 to CMS4 subtype switching has been described as a cetuximab monotherapy resistance mechanism (Woolston *Cancer Cell* 2019). Amivantamab, an *EGFR*–*MET* bispecific antibody approved for *EGFR*-mutated NSCLC, has demonstrated antitumor activity in refractory metastatic colorectal cancer (mCRC), independent of sidedness. Given the role of *MET* in mesenchymal subtypes (CMS4), targeting with amivantamab could demonstrate antitumor activity in both CMS2 and CMS4. **Methods:** OrigAMI-1 (NCT05379595) enrolled participants with mCRC harboring WT *KRAS*, *NRAS*, *BRAF*, and *EGFR* ectodomain and without *ERBB2/HER2* amplification. Participants with left-sided mCRC without (Cohort A) or with prior anti-*EGFR* therapy (Cohort B), and those with right-sided disease (Cohort C), received intravenous amivantamab monotherapy. All enrolled participants had 2–3 prior lines of therapy in the metastatic setting. CMS assignment and expression changes in key *EGFR/MET* ligands at baseline (n = 76) and Cycle 3 Day 1 (C3D1; n = 17) were analyzed by whole-transcriptome RNA-sequencing of biopsies. **Results:** CMS2 (canonical) and CMS4 (mesenchymal) comprised ~95% of tumors. Clinical outcomes for CMS2 (n = 42) and CMS4 (n = 31) were comparable: median PFS was 4.2 vs 5.3 months (*P* = 0.5), respectively, and median OS was 11.3 vs 13.5 months (*P* = 0.6). PFS and OS within CMS2 and CMS4 subgroups remained consistent across sidedness. Overall response rate and DCR were comparable between CMS2 and CMS4 (26% vs 16% and 83% vs 74%, respectively). Genomic profiles derived from ctDNA were similar for CMS2 and CMS4; however, baseline *AREG/EREG* mRNA expression was higher in CMS2. Paired biopsies demonstrated antitumor activity with or without subtype switching at C3D1. Amivantamab treatment generally decreased *AREG/EREG* and increased *HGF* expression, independent of subtype or response. **Conclusions:** Amivantamab monotherapy demonstrated consistent antitumor activity in both canonical, *EGFR*-dependent (CMS2) and mesenchymal, *EGFR*-independent (CMS4) tumors unlike traditional *EGFR* inhibitors in refractory *RAS/BRAF* WT mCRC. Clinical trial information: NCT05379595. Research Sponsor: Janssen Research & Development, LLC, a Johnson & Johnson company.

First-in-human study of cavitation-enhanced drug delivery (CEeDD) by sonosensitive particles and focused ultrasound applied to colorectal metastases in the liver.

Jeffrey Rubasingham, Calum Crane, Christian Coviello, Cliff Rowe, Paul Boulos, Jessica Thorne, Madhurima Chetan, Paul Lyon, Alexander Thomas, Daniel McAleese, Srikanth Reddy, Laura Spiers, Sam Dobbie, Fergus Gleeson, Michael Gray, Robert Carlisle, Constantin Coussios, Rachel Kerr; Oxford University, Oxford, United Kingdom; OxSonics Therapeutics Ltd, Oxford, United Kingdom; OxSonics Therapeutics Ltd, Oxford, United Kingdom, United Kingdom; Department of Radiology, Oxford, United Kingdom; Oxford Clinical Trials Research Unit, Oxford, United Kingdom; Department of Oncology, Oxford, United Kingdom; Nuffield Department of Surgical Sciences, Oxford, United Kingdom; Institute of Biomedical Engineering, Oxford, United Kingdom, United Kingdom; Institute of Biomedical Engineering, University of Oxford, Oxford, United Kingdom

Background: Effective treatment of colorectal liver metastases is limited by poor drug delivery, particularly for monoclonal antibodies, the large molecular weight of which, together with abnormal tumor vasculature, elevated interstitial pressure and dense stromal architecture, restricts penetration and distribution into solid tumors. This first-in-human study evaluated a novel platform combining intravenously infused sub-micron gas-stabilizing sonosensitive particles with novel handheld ultrasound probe to cause cavitation that enhances the transport of systemically co-administered therapeutics (i.e. cetuximab/irinotecan) from the vasculature into tumors, without the need to modify these therapeutics. **Methods:** The study comprised 3 patient cohorts. Cohort 1 evaluated the safety of ultrasound activation of intravenously infused sonosensitive particles alone, without drug. With safety confirmed, Cohort 2 assessed intratumoural drug concentration in patients undergoing surgical resection after receiving sub-therapeutic irinotecan and cetuximab, with or without ultrasound-activated particles. Cohort 3 evaluated early efficacy in patients receiving standard of care FOLFIRI and cetuximab, with or without cavitation in repeated treatment cycles. Primary endpoints were grade 3 or higher adverse events in Cohort 1, intratumoural drug concentrations in Cohort 2, and radiological tumor response in Cohort 3. **Results:** In Cohort 2, seven evaluable patients underwent resection, with 4 in the control arm and 3 in the ultrasound-mediated-cavitation arm. Mean cetuximab concentrations were modestly higher in the tumour centre (3.6 vs 3.2 ng/mL) and mid radius (4.1 vs 3.7 ng/mL), and substantially higher at the tumour periphery (7.1 vs 3.7 ng/mL) in the ultrasound-mediated-cavitation arm, while liver margin levels were comparable. There was no appreciable beneficial difference in the mean tumour concentrations of irinotecan and its metabolites between the two arms. In Cohort 3, 10 evaluable participants completed at least 3 treatment cycles (control n=3; cavitation n=7). Objective response rate was 66.7% in the control arm versus 85.7 % with cavitation. **Conclusions:** Cavitation with sonosensitive particle infusion demonstrated a favourable safety profile, increased intratumoural antibody delivery, and showed early signals of enhanced anti-tumour activity, supporting further clinical development. Clinical trial information: ISRCTN17598292. Research Sponsor: National Institute for Health Research (NIHR), UK.

Cohort	Number treated	Primary endpoint	Key findings
1	9	Safety	No grade 3 or higher events; sustained cavitation in the target region.
2	7	Drug levels	Increased cetuximab concentrations in the tumours treated with cavitation (7.1 vs 3.7 ng/mL)
3	10	Radiological response	Enhanced radiological response (ORR of 85.7% in patients treated with cavitation)

ORR = objective response rate based on FDG PET-CT.

Negative hyperselection as a predictive biomarker of benefit from first-line doublets + anti-EGFRs/bevacizumab (bev) in microsatellite stable (pMMR/MSS) *RAS* and *BRAF* wild-type (wt) and *HER2*– metastatic colorectal cancer (mCRC): An individual patient data pooled analysis of seven clinical trials (CTs).

Marco Maria Germani, Roberto Moretto, Tadayoshi Hashimoto, Volker Heinemann, Filippo Pietrantonio, Yoshiaki Nakamura, Sebastian Stintzing, Francesca Bergamo, Kei Muro, Alan P. Venook, Lena Weiss, Giulia Martini, Francesca Battaglin, Jumpei Soeda, Eva Blondeaux, Davide Ciardiello, Heinz-Josef Lenz, Takayuki Yoshino, Dominik Paul Modest, Chiara Cremolini; Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy; Unit of Medical Oncology 2, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy; National Cancer Center Hospital East, Kashiwa, Japan; Department of Hematology/Oncology III, LMU Klinikum, University of Munich, Comprehensive Cancer Center, Munich, Germany; Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan; Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Hematology, Oncology and Cancer Immunology, Berlin, Germany; Oncology 1 Unit, Department of Medical Oncology, Veneto Institute of Oncology IOV - IRCCS, Padua, Italy; Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; University of California, San Francisco, San Francisco, CA; Department of Medicine III, University Hospital Munich LMU, Munich, Germany; Università degli Studi Della Campania "L. Vanvitelli", Napoli, Italy; Division of Medical Oncology, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA; Takeda Pharmaceutical Co. Ltd., Chuo-Ku, Japan; U.O. Epidemiologia Clinica, IRCCS Azienda Ospedaliera Metropolitana, Genova, Italy; Division of Gastrointestinal Medical Oncology and Neuroendocrine Tumors European Institute of Oncology, IRCCS, Milan, Italy; University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; Department of Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan; Charité Comprehensive Cancer Center Berlin, Berlin, Germany; 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

Background: Primary tumor sidedness is nowadays a major driver for the choice of biologics in the first line of pMMR/MSS *RAS* and *BRAF* wt mCRC patients (pts). It has been suggested that it might be replaced by a broader molecular profiling, but the evidence provided by individual trials is uncertain for the adoption of different panels and underrepresentation of gene-altered cases. We recently showed that *HER2*+ status does not predict resistance to first-line doublets + anti-EGFRs. **Methods:** We collected individual patient data from 7 CTs in first-line mCRC: TRIBE2, TRIPLETE, VALENTINO, CAPRI-2, FIRE-3, PARADIGM and CALGB/SWOG80405. pMMR/MSS *RAS* and *BRAF* wt and *HER2*– cases treated with doublets + anti-EGFRs/bev with available NGS data were included. Hyperselected tumors were those without *MET*+ status, *ALK/ROS1/NTRKs/RET* fusions, and *HER2/PIK3CA* exon20/*PTEN/AKT1* mutations. Propensity score adjustment was used to assess clinical outcomes (aHR and aOR) according to first-line doublets + anti-EGFRs/bev. **Results:** Out of 1198 included pts, 990 (83%) had left-sided and 208 (17%) right-sided tumors. Anti-EGFR based regimens were associated with numerically longer OS (aHR: 0.86) in left-sided tumors, but not in right-sided ones (aHR: 0.98), with an insignificant p for interaction [int] = 0.60). Hyperselected and gene-altered cases were 1077 (91%) and 121 (9%), respectively. The anti-EGFR benefit in OS was magnified in hyperselected pts (aHR: 0.83), with an aHR of 1.16 in gene-altered ones ($p_{\text{int}} = 0.11$, adjusted also for tumor sidedness). As reported in the table, there was no interaction between the effect of biologics and primary tumor location either in the hyperselected ($p_{\text{int}} = 0.86$) or in the gene-altered group ($p_{\text{int}} = 0.41$). **Conclusions:** Hyperselection outperforms tumor sidedness as a predictive marker of benefit from doublets + anti-EGFR/bev in pMMR/MSS *RAS/BRAF* wt and *HER2*– mCRC. The OS benefit from anti-EGFR-based regimens is restricted to pts with hyperselected tumors, independently of primary tumor location. Therefore, in hyperselected mCRC, doublets + anti-EGFRs remain the standard for left-sided pts and may deserve consideration in right-sided ones. Research Sponsor: Gruppo Oncologico del Nord Ovest (GONO); NextGenerationEU through the Italian Ministry of University and Research.

	Hyperselected				P_{int}	Gene-altered				P_{int}
	Left		Right			Left		Right		
	Anti-EGFRs N=537	Bev N=365	Anti-EGFRs N=87	Bev N=88		Anti-EGFRs N=57	Bev N=31	Anti-EGFRs N=19	Bev N=14	
ORR (%)	81	67	72	65		74	52	58	57	
aOR [95% CI]	2.29 [1.67 – 3.14]		1.44 [0.75 – 2.77]		0.24	3.48 [1.29 – 9.97]		1.02 [0.25 – 4.20]		0.23
mPFS*	13.2	12.9	11.1	10.2		11.2	11.3	8.0	8.8	
aHR [95% CI]	1.02 [0.88 – 1.19]		1.01 [0.73 – 1.39]		0.73	1.06 [0.63 – 1.77]		1.23 [0.57 – 2.66]		0.75
mOS*	38.8	35.5	34.6	29.2		30.2	27.4	20.2	32.1	
aHR [95% CI]	0.84 [0.71 – 0.98]		0.85 [0.61 – 1.17]		0.86	1.05 [0.63 – 1.75]		1.46 [0.66 – 3.22]		0.41

*Months.

A phase II trial of fruquintinib combined with cadonilimab in refractory MSS/pMMR colorectal cancer with pulmonary metastases.

Mengzhou Guo, Yiyi Yu, Xiaojing Xu, Jingyuan Wang, Tianshu Liu; Department of Medical Oncology, Cancer Center, Zhongshan Hospital, Fudan University, Shanghai, China; Department of Oncology, Zhongshan Hospital, Fudan University, Shanghai, China; Department of Medical Oncology, Zhongshan Hospital, Fudan University, Shanghai, China; Zhongshan Hospital, Fudan University, Shanghai, China

Background: Immunotherapy for metastatic colorectal cancer (mCRC) with microsatellite stable/proficient mismatch repair (MSS/pMMR) remains limited. Emerging evidence suggests that the combination of antiangiogenic agents and immune checkpoint inhibitors (ICIs) exhibits synergistic antitumor effects in refractory MSS/pMMR mCRC, particularly among patients (pts) with isolated lung metastases. This open-label, single-arm, phase II trial aims to evaluate the efficacy and safety of fruquintinib plus cadonilimab in pts with MSS/pMMR mCRC who progressed after at least two prior lines of therapy. **Methods:** Patients aged ≥ 18 years, with pathologically confirmed MSS/pMMR mCRC presenting pulmonary metastases and no liver metastases, and who had experienced failure of at least second-line therapy were enrolled. Eligible patients received oral fruquintinib (3 mg once daily) plus intravenous cadonilimab (6 mg/kg every two weeks) until disease progression, unacceptable toxicity, or withdrawal of consent. Tumor assessments were performed every 8 weeks. The primary endpoint was objective response rate (ORR), and secondary endpoints included overall survival (OS), progression-free survival (PFS), disease control rate (DCR), and safety. **Results:** From February 2024 to June 2025, 37 pts were enrolled [median age 61 years, 68% male, 89% ECOG 0-1, 62% RAS mutant, 30% 3L+, 73% prior bevacizumab, 3 pts prior immunotherapy]. The ORR was 31.4%, and the DCR was 71.4%. Median PFS was 6.1 months (95%CI: 4.8-7.5), while OS data remain immature. Moreover, the patients with a history of liver metastases showed a trend toward shorter PFS compared to those without (4.0 vs. 6.9 months; $P = 0.194$). The most common treatment-related adverse events (AEs) were hypothyroidism (43%), elevated ALT/AST (27%), hypertension (24%), diarrhea (24%), thrombocytopenia (19%), hand-foot syndrome (16%), and rash (16%). Grade ≥ 3 treatment-related AEs occurred in 10 (27%) pts. Serious adverse events (SAEs) were reported in 5 pts, with no grade 4 or 5 SAEs observed. **Conclusions:** The combination of fruquintinib and cadonilimab demonstrated promising clinical activity and a manageable safety profile in patients with refractory MSS/pMMR mCRC. Clinical trial information: ChiCTR2400079429. Research Sponsor: National Natural Science Foundation of China (82573146).

Detecting *MTAP* loss in liquid biopsies from patients with clinically advanced colorectal cancer (CRC).

Xuanyi Li, Miriam Saffern, Dean C. Pavlick, Alexa Betzig Schrock, Richard Sheng Poe Huang, Ole Gjoerup, David Fabrizio, Lauren Ritterhouse, Russell William Madison, Jeffrey S. Ross, Michael Cecchini; Yale Cancer Center, New Haven, CT; Foundation Medicine, Inc., Boston, MA; Foundation Medicine, Inc., Cambridge, MA; Department of Internal Medicine (Medical Oncology), Yale University School of Medicine, New Haven, CT

Background: Homozygous loss of the *MTAP* gene (*MTAP* loss) is an emerging biomarker guiding investigational use of PRMT5 and MAT2A inhibitors in a wide variety of tumor types, including CRC. Detecting copy number changes, including homozygous losses, in solid tumors is often challenging and requires robust assay and analytic pipeline especially when the amount of extracted DNA is small. In clinically advanced CRC, small endoscopic and needle-based biopsies are often used for diagnosis, imposing significant limitations on immunohistochemistry (IHC) and comprehensive genomic profiling (CGP) required for treatment selection and clinical trial enrollment. We assessed whether liquid biopsy (LBx) CGP could provide treatment-relevant information on *MTAP* loss compared to tissue biopsy (TBx) CGP for patients with CRC. **Methods:** Hybrid capture-based CGP was performed on 46,173 clinically advanced CRC (stage III, IV) TBx cases using the FoundationOne CDx assay and on 9,049 LBx cases using the FoundationOne-Liquid CDx assay. Tumor fraction (TF) for each LBx sample was determined using assessments of aneuploidy and variant allele frequencies, as previously described. **Results:** *MTAP* loss was detected in 498 (1.08%) TBx cases. For LBx, detection of *MTAP* loss increased with higher TF, with detections observed only at TF $\geq 5\%$ (Table 1). With TF $\geq 5\%$, the frequency of *MTAP* loss detection was comparable to or exceeds that observed with TBx. Regarding complete vs partial *MTAP* exon loss, TBx and LBx showed similar patterns, with complete loss of all 8 *MTAP* exons observed in 85.7% of TBx cases and 84.5%–89.8% in LBx cases, increasing in higher TF levels. **Conclusions:** LBx emerges as a promising tool for detecting *MTAP* loss in clinically advanced CRC, with *MTAP* loss detection rates approaching those of TBx when LBx TF is $\geq 5\%$, while detection is limited at lower TF levels. Incorporation of LBx for *MTAP* loss detection may expand patient access to biomarker-driven clinical trials involving PRMT5 and MAT2A inhibitors for patients with clinically advanced CRC when sufficient tissue for tissue-based CGP is not feasible. Research Sponsor: None.

MTAP loss detected by TBx and LBx in clinically advanced CRC.

Cohort (cumulative)*	<i>MTAP</i> no loss	<i>MTAP</i> loss	<i>MTAP</i> loss frequency
TBx (n=46173)	45675	498	1.08%
LBx TF $\geq 0\%$ (100% of LBx, n=9049)	9002	47	0.52%
LBx TF $\geq 1.0\%$ (62.7% of LBx)	5624	47	0.83%
LBx TF $\geq 5.0\%$ (48.7% of LBx)	4359	47	1.07%
LBx TF $\geq 10.0\%$ (41.5% of LBx)	3712	46	1.22%
LBx TF $\geq 20.0\%$ (31.5% of LBx)	2812	38	1.33%
LBx TF $\geq 30\%$ (24.8% of LBx)	2214	29	1.29%

*TF thresholds represent cumulative subsets of the LBx cohort.

Tumor cell-intrinsic programs of metabolic adaptation and immune evasion in colorectal cancer liver metastases (CRCLMs).

Xuanyi Li, Kerryan Ashley, Krishna Iyer, Thazin Nwe Aung, Michael Cecchini, Kurt A. Schalper; Yale Cancer Center, New Haven, CT; Yale University Department of Pathology, New Haven, CT; Yale School of Medicine, New Haven, CT; Department of Pathology, Yale University School of Medicine, New Haven, CT; Department of Internal Medicine (Medical Oncology), Yale University School of Medicine, New Haven, CT

Background: CRCLMs account for the majority of colorectal cancer (CRC)-related mortality and represent a key site of immunotherapy resistance. The tumor cell-intrinsic molecular programs enabling adaptation to the liver microenvironment and immune evasion remain poorly defined. **Methods:** We performed spatial whole transcriptomic analysis of 189 patient-matched primary CRC and CRCLM samples from two independent cohorts (Cohort 1 = 47; Cohort 2 = 141). Samples were represented using tissue microarrays and analyzed using the GeoMx Digital Spatial Profiling (DSP) platform. Two ROIs (tumor cell [CK] and stroma [DAPI]) were analyzed per sample, with analyses focused on tumor cells. Differential expression analyses were conducted independently within each cohort. Results were integrated using Fisher’s combined probability method for batch-aware meta-analysis. Expression of selected transcripts in tumor and matched non-tumor tissue in TCGA and associated survival outcomes were evaluated using the GEPIA2 webtool. Gene set enrichment analysis (GSEA) was applied to identify consistently altered biological pathways. Exploratory LASSO regression using normalized expression values identified gene sets distinguishing liver metastases from primary tumors. **Results:** We identified multiple genes consistently enriched in malignant cells from CRCLM compared to primary CRC. Prioritized genes include MMP10 (logFC = 0.41, p = 0.007), KRT17 (logFC = 0.87, p < 0.001) and PLA2G2A (logFC = 0.72, p = 0.002), all showing higher tumor expression relative to normal tissue, association with unfavorable survival, and translational relevance (Table 1). GSEA revealed enrichment of acute-phase response (NES = 1.86, FDR = 0.003), complement activation (NES = 1.81, FDR = 0.002) and xenobiotic metabolism (NES = 1.71, FDR = 0.006) in liver metastases, together with reduced antigen processing and presentation (NES = -1.78, FDR = 0.012). Exploratory LASSO regression yielded cohort-specific gene signatures with limited gene-level overlap but convergence on shared biological programs distinguishing CRCLM from primary CRC, including epithelial and metabolic pathways. Of note, PLA2G2A was among the selected features in an independent cohort, reinforcing its association with CRCLM. **Conclusions:** We identified tumor cell-intrinsic programs in CRCLMs consistent with cellular metabolic adaptations and immune evasion with potential relevance in disease progression and treatment resistance. Our analyses also identified genes, including MMP10, KRT17, and PLA2G2A, as potential therapeutic vulnerabilities in CRCLMs for future investigation. Research Sponsor: None.

Prioritized liver metastasis-enriched genes.	
Gene	Translational Relevance
MMP10	Enzymatic target; inhibitor scaffolds exist
KRT17	Tumor-specific biomarker/pathway proxy
PLA2G2A	Enzymatic target; pathway inhibition feasible

Tumor shrinkage and depth of response with fruquintinib in patients with metastatic colorectal cancer: Results from FRESCO and FRESCO-2.

Elena Elez, Arvind Dasari, Sara Lonardi, Andrew Scott Paulson, Judit Kocsis, Shivani Nanda, Songhua Fan, Liwen Wu, Lucy F. Chen, Jiemin Wang, Jin Li; Vall d'Hebron Barcelona Hospital Campus, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; The University of Texas MD Anderson Cancer Center, Houston, TX; Veneto Institute of Oncology IOV-IRCCS, Padua, Italy; Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX; Bács-Kiskun Megyei Oktatókórház, Kecskemét, Hungary; HUTCHMED International Corporation, Florham Park, NJ; HUTCHMED, Shanghai, China; Takeda Development Center Americas, Inc. (TDCA), Cambridge, MA; China Pharmaceutical University Shanghai GoBroad Cancer Hospital, Shanghai, China

Background: In metastatic colorectal cancer (mCRC), early tumor shrinkage (ETS) and depth of response (DpR) are predictors of overall survival (OS) and progression-free survival (PFS). Durable stable disease (SD) also reflects disease control and can contextualize PFS and OS improvements. The phase 3 FRESCO (F) and FRESCO-2 (F2) trials of fruquintinib vs placebo in patients (pts) with mCRC showed significantly longer OS (F median: 9.3 vs 6.6 months [mo], HR 0.65, $P < 0.001$; F2 median: 7.4 vs 4.8 mo, HR 0.66, $P < 0.001$) and PFS (F median: 3.7 vs 1.8 mo, HR 0.26, $P < 0.001$; F2 median: 3.7 vs 1.8 mo, HR 0.32, $P < 0.001$) with fruquintinib. We report a post-hoc analysis of tumor shrinkage (TS), ETS, and DpR, and the correlation with OS and PFS in F and F2. **Methods:** Pts were randomized to receive fruquintinib + best supportive care (BSC; F n=278; F2 n=461) or placebo + BSC (F n=138; F2 n=230). Tumors were assessed at screening and every 8 weeks until progressive disease (PD). TS was defined as a decrease from baseline in the sum of the longest diameters of target lesions; ETS was TS by the first post-treatment assessment; duration of TS (DTS) was time from first TS to first tumor size increase, PD, or death; in pts with best overall response of SD, duration of SD was assessed as the time from first occurrence of SD to PD/death; and DpR was the maximum percentage change from baseline in the sum of the longest diameters of target lesions. OS and PFS were assessed in pts who received fruquintinib and had TS/ETS. **Results:** In F, 129 (46%) fruquintinib-treated pts had TS, of which 124 (45%) achieved ETS; with placebo, 5 pts (4%) had TS and ETS. In F2, similarly, 178 (39%) fruquintinib-treated pts had TS, of which 154 (33%) achieved ETS; with placebo, 15 pts (7%) had TS and 13 pts (6%) had ETS. In pts with TS in F and F2, median DTS with fruquintinib was 1.9 and 2.0 mo, respectively. Median duration of SD was longer with fruquintinib vs placebo in both F (5.5 vs 3.7 mo) and F2 (5.6 vs 3.7 mo). Magnitude of DpR was greater with fruquintinib vs placebo in both trials. In F and F2, median OS and PFS in pts who received fruquintinib were longer in those who achieved TS and ETS vs the ITT fruquintinib arm (Table). **Conclusions:** ETS was observed in most fruquintinib-treated pts with TS in both F and F2 (F: 96% [124/129 pts]; F2: 87% [154/178 pts]); pts with both TS and ETS showed longer median OS and PFS compared with the fruquintinib ITT population. These data indicate that TS and ETS appear to be predictors of OS and PFS outcomes, and support the prognostic relevance of TS, ETS, and DpR in pts with mCRC. Clinical trial information: NCT02314819 and NCT04322539. Research Sponsor: Takeda Pharmaceuticals U.S.A., Inc., Cambridge, MA.

OS and PFS in pts who received fruquintinib with TS/ETS vs the ITT fruquintinib arm in F and F2.			
Months (95% CI)	With TS	With ETS	ITT Fruquintinib arm
F	n = 129	n = 124	N = 278
OS	12.1 (10.8–14.9)	11.6 (10.7–14.9)	9.3 (8.2–10.5)
PFS	5.5 (5.5–7.3)	5.5 (5.5–6.6)	3.7 (3.7–4.6)
F2	n = 178	n = 154	N = 461
OS	10.9 (9.9–12.5)	10.8 (8.9–12.7)	7.4 (6.7–8.2)
PFS	5.6 (5.4–6.2)	5.6 (5.1–5.8)	3.7 (3.5–3.8)

Evaluation of circulating tumor DNA (ctDNA) following liver resection in a high-risk population with colorectal liver metastases.

John Neil Primrose, Robert Peter Jones, Naureen Starling, Jorge Barriuso, Bryony Eccles, Amelie Harle, Yinjie Gao, Tiffany Hung, Siân Pugh; Cancer Sciences, University of Southampton, Southampton, United Kingdom; University of Liverpool, Liverpool, United Kingdom; The Royal Marsden NHS Foundation Trust, London, United Kingdom; The Christie NHS Foundation Trust, Manchester, United Kingdom; Royal Bournemouth Hospital, Bournemouth, United Kingdom; University Hospital Dorset, Poole, United Kingdom; GRAIL, Inc., Menlo Park, CA; Addenbrooke's Hospital, Cambridge, United Kingdom

Background: Liver resection is routinely performed for oligometastatic colorectal cancer (CRC). ctDNA analysis is becoming important in the management of primary CRC following surgery, but in patients with liver metastases, its role is less clear. This study aimed to evaluate the performance of a plasma ctDNA assay for early detection of recurrence in patients with liver only CRC metastases post surgical resection. The cohort included patients who had inoperable disease prior to induction chemotherapy and those having repeat resections. Patients with the primary cancer in situ were included if a synchronous resection was performed. **Methods:** 61 patients (42 male, median age 68 [range 41–85]) were studied. All patients had CRC liver metastases as the sole metastatic site on evaluation by CT and MRI. Patients were followed up clinically with regular CT imaging. Plasma samples were collected at baseline (pre-surgery, n = 55) and 5 days to 1+ year after surgery, and were tested retrospectively on a blood-only, tumor-agnostic, targeted methylation assay that interrogates informative methylation regions for signal indicative of ctDNA using a machine learning classifier (GRAIL, Inc., Menlo Park, CA). **Results:** ctDNA was detected in 94.5% (52/55) of patients at the pre-surgery timepoint. During clinical surveillance, 46 developed recurrence, 5 had no recurrence for at least 2 years after surgery, and 10 had follow-up for less than 2 years. Among patients with recurrence, ctDNA was detected in 80.4% (37/46) of patients before recurrence, with a median lead time of 245 days [IQR: 65 – 393 days]. All five patients who remained recurrence-free for at least 2 years had undetectable ctDNA following surgery. ctDNA was detected in 57.8% (26/45) of patients who recurred and had plasma collected within 3 months following surgery. Recurrence-free survival (RFS) was significantly lower in patients with ctDNA detected within 3 months after surgery (median RFS 272 vs. 593 days, log-rank p-value < 0.01). **Conclusions:** ctDNA analysis using a methylation-based assay allowed the detection of minimal residual disease and the prediction of recurrence in many patients following resection of CRC liver metastases. These data support the potential use of this biomarker for patient management pending confirmation in prospective clinical studies. Research Sponsor: None.

Screening for intrinsic and acquired resistance mutations to anti-EGFR in real-world MSS colorectal cancer data.

Matthew B. Maxwell, Stamatina Fragkogianni, Michelle M. Stein, Radia Johnson, Van K. Morris II, Halla Nimeiri, Andrew J. Sedgewick, Scott Kopetz, Justin Guinney; Tempus AI, Inc., Chicago, IL; Tempus AI Inc., Chicago, IL; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Anti-EGFR (cetuximab, panitumumab) plus doublet chemotherapy is the first line standard of care for metastatic MSS left-sided RAS/RAF WT colorectal cancer (CRC). However, anti-EGFR clinical efficacy is limited by intrinsic and acquired resistance. Defining anti-EGFR intrinsic resistance mutations could improve patient selection for anti-EGFR treatment while defining anti-EGFR acquired resistance mutations could enable early detection of resistance via liquid biopsy. **Methods:** The intrinsic resistance cohort consisted of 163 metastatic MSS RAS/RAF WT colon adenocarcinoma patients treated in the first line with anti-EGFR with a DNA-seq sample collected before treatment (Tempus xT or xF). We screened mutations for anti-EGFR intrinsic resistance defined as HR > 2 for PFS via univariate CoxPH models. The anti-EGFR acquired resistance cohort consisted of 228 MSS CRC patients with a DNA-seq sample (xT or xF) within 12 months prior to and 0.5–24 months post treatment. We defined acquired resistance mutations as those significantly enriched post-treatment vs pre-treatment via McNemar test. An anti-VEGF acquired resistance cohort of 748 MSS CRC patients was used as a control. Enrichment of targetable gene fusions post-treatment was assessed via Wilcoxon test. FDR < 0.05 was considered significant. **Results:** The screen for intrinsic resistance mutations returned a single significant hit of *PIK3CA* non-exon 9 mutations (~3%, $p < 0.01$), while *PTEN* deletions (~2%), which are functionally similar, were also associated with shorter PFS but did not reach significance ($p=0.08$). *PIK3CA* non-exon 9 mutation or *PTEN* deletion were detected in ~5% of patients ($n=9$) and were associated with shorter PFS (HR = 3.6, 95% CI: 1.7–7.6, $p < 0.001$) and OS (HR = 2.6, 95% CI: 1.03–6.5, $p < 0.05$). Median PFS and OS were 6 and 14 months for patients with these resistance alterations, versus 11 and 29 months for non-altered patients. In a CoxPH model including age, sex, sidedness, and collection procedure, these alterations maintained a significant association with PFS (HR = 5.2, 95% CI: 2.2–12.4, $p < 0.01$) but not OS (HR=2.7, 95% CI: 0.9–8.9, $p=0.08$). Analysis of acquired resistance to anti-EGFR treatment yielded significant mutation hits—*KRAS*, *NRAS*, *EGFR*, and *MAP2K1*—as well as significant enrichment of targetable fusions (*BRAF*, *FGFR*, *NTRK*, *ALK*, *ROS1*, *RET*, *NRG1*). No mutations or fusions were observed to be associated with anti-VEGF acquired resistance. **Conclusions:** Patients harboring *PIK3CA* non-exon 9 mutation or *PTEN* deletion displayed intrinsic resistance to anti-EGFR therapy despite being RAS/RAF WT and may be offered anti-EGFR therapy per oncology guidelines. This small underrepresented subset of patients may not benefit from anti-EGFR therapy. Prospective clinical validation will be needed to determine if this subset of PI3K pathway alterations has utility in optimizing first line therapy selection. Research Sponsor: FightCRC.

BAYONET trial: A multicenter phase II trial of staged combination with encorafenib + binimetinib + cetuximab following encorafenib + cetuximab in patients with BRAFV600E-mutant metastatic colorectal cancer.

Takeshi Yamada, Yuki Matsubara, Hideaki Bando, Mitsuhiro Furuta, Eiji Shinozaki, Naoki Izawa, Kazuaki Harada, Yuta Okumura, Akitaka Makiyama, Hisateru Yasui, Hiroki Osumi, Takeshi Kawakami, Daisuke Kotani, Yoshinori Kagawa, Shogen Boku, Toshihiko Matsumoto, Takashi Ikeno, Masashi Wakabayashi, Yoshiaki Nakamura, Takayuki Yoshino; Department of Gastroenterology, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan; Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan; Department for the Promotion of Drug and Diagnostic Development, Division of Drug and Diagnostic Development Promotion, National Cancer Center Hospital East, Kashiwa, Japan; Department of Gastroenterology, Kanagawa Cancer Center, Yokohama, Japan; Department of Gastroenterology, The Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan; Department of Clinical Oncology, St. Marianna University School of Medicine, Kawasaki, Japan; Department of Gastroenterology and Hepatology, Hokkaido University Hospital, Sapporo, Japan; Department of Gastrointestinal and Medical Oncology, NHO Kyushu Cancer Center, Fukuoka, Japan; Cancer Center, Gifu University Hospital, Gifu, Japan; Department of Medical Oncology, Kobe City Medical Center General Hospital, Kobe, Japan; Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Sunto-Gun, Japan; Department of Gastroenterological Surgery, Osaka International Cancer Institute, Osaka, Japan; Department of Medical Oncology, Kansai Medical University Hospital, Hirakata, Japan; Department of Medical Oncology, Ichinoimiya-Nishi Hospital, Aichi, Japan; Clinical Research Support Office, National Cancer Center Hospital East, Kashiwa, Japan; Department for the Promotion of Drug and Diagnostic Development, National Cancer Center Hospital East, Kashiwa, Japan; Department of Oncology, University of Oxford, Oxford, United Kingdom

Background: While the doublet combination of encorafenib (ENCO) + cetuximab (CET) is a standard treatment for patients with BRAFV600E-mutant metastatic colorectal cancer (mCRC), poor prognosis is expected after disease progression. As resistant mechanisms to BRAF + EGFR blockade, several MAPK pathway alterations, including RAS and RAF mutations, have been reported, suggesting that additional blockade of MAPK signaling may be an effective strategy. Furthermore, preclinical studies demonstrated that BRAF V600E-mutant colorectal cancer cell lines resistant to BRAF inhibitor + anti-EGFR antibody were sensitive to the triple combination of BRAF inhibitor + MEK inhibitor + anti-EGFR antibody. **Methods:** BAYONET is a single-arm, multicenter phase II trial designed to evaluate the efficacy and safety of the staged combination with ENCO, binimetinib (BINI), plus CET for patients with BRAFV600E-mutant mCRC who were refractory to ENCO plus CET. The main eligibility criteria are as follows: RAS wild-type/BRAF V600E-mutant mCRC; age ≥ 20 ; ECOG PS 0 or 1; within 4 weeks from the last administration of previous ENCO or CET; no administration of other systemic therapy after refractoriness to ENCO + CET; complete response, partial response, or ≥ 4 months of stable disease was observed in the previous ENCO + CET. Included patients receive the combination treatment of ENCO (300 mg once a day) + BINI (45 mg twice a day) + CET (400 mg/m² initial dose and then 250 mg/m² once a week) in a 28-day cycle. The primary endpoint of this trial is 12-week progression-free survival (PFS) rate. The targeted sample size was calculated to be 30 on the basis of a power of 80%, a significance level of 10% (one-sided), a threshold of 20%, and an expected 12-week PFS rate of 40%. Pretreatment ctDNA analysis was performed using the Guardant360 assay. **Results:** Among 30 patients, all had microsatellite-stable or mismatch repair-proficient tumors, and 21 (70%) of patients received prior < 3 treatment lines. The locally assessed 12-week PFS rate was 33.3% (80% CI, 21.8–46.6). Since the lower limit of 80% CI exceeded 20%, the primary endpoint was met. With a median follow-up duration of 9.8 months (range, 2.1–35.8), the median PFS was 2.0 months (95% CI, 1.6–4.2), and the median overall survival was 14.7 months (95% CI, 7.1–18.7). Patients who achieved 12-week PFS had significantly lower ctDNA BRAF V600E VAF (median, 0.2%; range, 0–18%) compared to those who did not achieve it (median, 4.2%; range, 0–41%). Grade 3 or higher adverse events were observed in 50% of patients, most commonly anemia (20%), creatine kinase increase (13%), and diarrhea (10%). No new safety signal was identified. **Conclusions:** Staged combination with ENCO+BINI+CET showed potential to achieve disease control for patients with BRAF V600E-mutant mCRC who were refractory to ENCO+CET. Clinical trial information: jRCTs031210510. Research Sponsor: ONO PHARMACEUTICAL CO., LTD.

FOLFOXIRI/bevacizumab in microsatellite stable (pMMR/MSS) *RAS* and *BRAF* wild-type “gene-altered” metastatic colorectal cancer (mCRC): The HYPERTRIBE study.

Marco Maria Germani, Rossella Bruno, Mariam Polito, Roberta Fazio, Francesca Bof, Maria Alessandra Ceglie, Vittorio Studiale, Paola Vignali, Paolo Ciraci, Alessandro Passardi, Camilla Damonte, Francesca Bergamo, Valentino Pasquinucci, Veronica Conca, Cecilia Villa, Sabina Murgioni, Lisa Salvatore, Beatrice Borelli, Clara Ugolini, Chiara Cremolini; Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy; Unit of Pathological Anatomy, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy; UOC Oncologia Territoriale – ASL Latina – CDS Aprilia, La Sapienza Università Di Roma, Latina, Italy; Medical Oncology Department, 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; Medical Oncology, Comprehensive Cancer Center, Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Rome, Italy; 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; Department of Surgical, Medical, Molecular Pathology and Critical Area, University of Pisa, Pisa, Italy; Medical Oncology, IRST-IRCCS “Dino Amadori”, Meldola, Italy; Oncology 1 Unit, Department of Medical Oncology, Veneto Institute of Oncology IOV - IRCCS, Padua, Italy; Department of Translational Research & New Technologies in Medicine & Surgery, University of Pisa, Pisa, Italy; Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, NA, Italy; Department of Clinical and Experimental Oncology, Medical Oncology 1 Unit, Istituto Oncologico Veneto IOV-IRCCS, Padua, Italy; Medical Oncology, Comprehensive Cancer Center, Fondazione Policlinico Universitario, Agostino Gemelli, IRCCS, Roma, Italy; Unit of Medical Oncology 2, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy

Background: Negative hyperselection may allow patient refinement for the use of anti-EGFRs in chemo-naïve pMMR/MSS, *RAS* and *BRAF* wild-type (wt) mCRC patients. However, outcomes are poor with both doublets/anti-EGFRs and doublets/bevacizumab (bev) among patients with gene-altered tumors. We investigated the efficacy of chemotherapy intensification with FOLFOXIRI/bev in this subgroup. **Methods:** We prospectively selected mCRC patients with pMMR/MSS, *RAS* and *BRAF* wt tumors harbouring at least one genomic alteration potentially implied with anti-EGFR resistance in published studies (*ERBB2* / *PIK3CA* exon 20 / *PTEN* / *AKT1* / *NTRKs* / *ERBB3* / *NF1* / *MAP2K1-2-4* / *AKT2* / *EGFR* / subclonal *RAS* mutations; *ERBB2* / *MET* / *ERBB3* / *FGFR2* / *IGF1R* / *KRAS* / *ARAF* / *AKT1-2* amplification; *ALK* / *ROS1* / *NTRKs* / *RET* fusions; *EGFR* rearrangements; *PTEN* / *NF1* loss), treated with upfront FOLFOXIRI/bev in 11 Italian centres. Assuming that the use of FOLFOXIRI/bev could lead to an increase in median PFS (mPFS) from 9 (as observed with doublets/anti-EGFRs) to 16 months (mos), with one-sided α and β errors of 0.10 and 0.20, respectively, 33 patients were needed. Secondary endpoints were overall survival (OS) and objective response rate (ORR). Outcomes were paired with a propensity score-matched external cohort of pMMR *RAS* and *BRAF* wt gene-altered patients treated with doublets/anti-EGFRs in clinical trials. **Results:** 35 patients were included. Main patients' characteristics were: median age 54 years, ECOG PS 0 83%, left-sided tumours 54%. Amplification in *ERBB2* and *MET* genes accounted for 26% and 6% of cases, respectively. The most frequent mutant gene was *ERBB2* (17%), followed by *MAP2K1* (9%), *PTEN* (9%), *NF1* (6%), *PIK3CA* exon 20 (3%), *EGFR* (3%). Subclonal *RAS* mutations were found in 14% of tumors. Fusions, detected in *ALK* and *RET* genes, accounted for 6% of cases. FOLFOXIRI/bev resulted into a mPFS of 12.3 mos (80% CI: 9.2 – 14.3 mos, Brookmeyer-Crowley test $p = 0.023$), an ORR of 74% and a mOS of 35.9 mos. PFS and OS with FOLFOXIRI/bev were longer than those achieved in the propensity score-matched cohort of patients treated with doublets/anti-EGFRs (mPFS: 12.3 vs 10.3 mos, HR: 0.74, 95% CI: 0.45 – 1.21, $p = 0.226$; mOS: 35.9 vs 27.2 mos, HR: 0.57, 95% CI: 0.32 – 1.03, $p = 0.058$). Similarly, a numerical advantage in ORR was reported (74% vs 63%, OR: 1.69 95% CI 0.61 – 4.88, $p = 0.303$). No interaction (int) between the effect of treatment and primary tumor location was evident ($p_{\text{intPFS}} = 0.267$; $p_{\text{intOS}} = 0.459$; $p_{\text{intORR}} = 0.866$). **Conclusions:** Waiting for efficacy results about the upfront use of targeted treatments directed against specific molecular subgroups, FOLFOXIRI/bev may be the preferred first-line option for clinically fit pMMR/MSS *RAS* and *BRAF* wt mCRC patients harbouring at least one genomic alteration of potential resistance to anti-EGFRs, regardless of primary tumor sidedness. Research Sponsor: Gruppo Oncologico del Nord Ovest (GONO); NextGenerationEU through the Italian Ministry of University and Research; Federation of Italian Cooperative Oncology Groups (FICOG) and Associazione Italiana Oncologia Medica (AIOM).

Tumor load change as a functional biomarker for prognosis and treatment modulation in metastatic colorectal cancer (mCRC): Individual patient data (IPD) analysis of 12 randomized trials.

Alexej Ballhausen, Marco Maria Germani, Volker Heinemann, Daniele Rossini, Ludwig von Fischer Weikersthal, Monica Niger, Kathrin Heinrich, Arndt Stahler, Sara Lonardi, Thomas Decker, Lisa Salvatore, Lena Weiss, Federica Morano, Martin Fuchs, Francesca Bergamo, Carlotta Antoniotti, Gianluca Masi, Sebastian Stintzing, Chiara Cremolini, Dominik Paul Modest; Department of Hematology, Oncology and Tumorimmunology, Charité-Universitätsmedizin Berlin, Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany; Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy; Department of Hematology/Oncology III, LMU Klinikum, University of Munich, Comprehensive Cancer Center, Munich, Germany; Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa & Unit of Medical Oncology 2, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy; Department of Hematology and Oncology, Klinikum St. Marien Amberg, Amberg, Germany; Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Department of Medicine III and Comprehensive Cancer Center (CCC Munich LMU), University Hospital, LMU Munich, Munich, Germany; Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Hematology, Oncology and Cancer Immunology, Berlin, Germany; Veneto Institute of Oncology IOV-IRCCS, Padua, Italy; Onkologie Ravensburg, Ravensburg, Germany; Medical Oncology, Comprehensive Cancer Center, Fondazione Policlinico Universitario, Agostino Gemelli, IRCCS, Roma, Italy; Department of Medicine III, University Hospital Munich LMU, Munich, Germany; Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; München Klinik Bogenhausen, Department of Gastroenterology, Hepatology and Gastrointestinal Oncology, Munich, Germany; Oncology 1 Unit, Department of Medical Oncology, Veneto Institute of Oncology IOV - IRCCS, Padua, Italy; 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; Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; Department of Hematology and Oncology, Charité – Universitätsmedizin Berlin, Campus Virchow-Klinikum, Berlin, Germany

Background: The use of overall response rate (ORR) and progression-free survival (PFS) as surrogacy of overall survival (OS) has limitations in mCRC. Change in tumor load (Δ TL; tumor burden at progressive disease [PD] vs baseline) at treatment failure may reflect tumor aggressiveness and resistance biology. We evaluated the prognostic value of Δ TL in mCRC using IPD from twelve randomized first-line trials. **Methods:** IPD from ATEZOTRIBE, FIRE3, FIRE4, FIRE4.5, MACBETH, ML22011, MOMA, PANAMA, TRIBE, TRIBE2, TRIPLETE, and VALENTINO were pooled. Δ TL was defined as the ratio of the sum of longest target lesion diameters at PD vs baseline, per RECIST. Primary endpoint was OS; secondary endpoints included post-progression survival (PPS). Estimated marginal means were controlled for treatment type. Associations between Δ TL and outcomes were assessed using Cox models adjusted for pre-specified baseline tumor burden and clinical covariates (ECOG, age, sex, sidedness, RAS/BRAF status, metastatic patterns, previous therapies). Incremental prognostic value beyond early tumor shrinkage (ETS) and depth of response (DpR) was assessed using likelihood ratio testing. Effect modification by treatment regimen was evaluated using Δ TL $\times$ treatment interaction terms for EGFR- vs VEGF-based therapy and for triplet vs doublet-chemotherapy across trials. **Results:** A total of 4852 patients evaluable for Δ TL were included. Mean Δ TL was 0.63 (SD 0.45) and significantly lower in patients receiving EGFR- vs VEGF-based therapy (0.58 vs 0.66, $p < 0.001$) and triplet vs doublet chemotherapy (0.57 vs 0.67, $p < 0.001$). Lower Δ TL (lower tumor load at PD vs baseline) was associated with better OS (HR 0.58 [95% CI 0.55–0.61], $p < 0.001$) and PPS (HR 0.65 [0.61–0.69], $p < 0.001$) after adjustment for baseline tumor burden and clinical covariates. For OS, Δ TL added prognostic information beyond ETS (likelihood ratio $\chi^2 = 282.13$, $p < 0.001$) and DpR (likelihood ratio $\chi^2 = 121.91$, $p < 0.001$). Lower Δ TL was associated with improved OS in patients receiving EGFR- ($n = 1609$; HR 0.62 [0.58–0.67], $p < 0.001$) and VEGF-based therapy ($n = 1916$; HR 0.39 [0.35–0.43], $p < 0.001$); doublet ($n = 2177$; HR 0.61 [0.57–0.65], $p < 0.001$) and triplet ($n = 1348$; HR 0.34 [0.30–0.38], $p < 0.001$) chemotherapy, with significant Δ TL $\times$ treatment interaction (VEGF vs EGFR: HR 0.50 [0.46–0.54], $p < 0.001$; triplet vs doublet: HR 0.60 [0.54–0.66], $p < 0.001$) after adjustment for treatment regimen, RAS/BRAF status and other clinical covariates. **Conclusions:** TL appears to be a strong, independent prognostic marker for OS and PPS in mCRC. Δ TL seems to vary by biologic and chemotherapy intensity, indicating it captures differential treatment effect/resistance not captured by ORR or PFS. Prospective validation as an early, treatment-sensitive prognostic endpoint is warranted. Research Sponsor: None.

Single-cell atlas of peripheral blood immune landscape in pMMR/MSS rectal cancer treated with neoadjuvant chemoradiotherapy and PD-1 blockade.

Leqi Zhou, Guanyu Yu, Tianshuai Zhang, Mengdi Chen, Liming Sun, Rongbo Wen, Rong Zeng, Wei Zhang; Department of Colorectal Surgery, Changhai Hospital, Naval Medical University, Shanghai, China; Department of General Surgery, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China; Shanghai Clinical Research and Trial Center, ShanghaiTech University, Shanghai, China

Background: Most colorectal cancer (CRC) patients exhibit normal mismatch repair function/microsatellite stability (pMMR/MSS), presenting a poor response to immune checkpoint inhibitor monotherapy. Neoadjuvant chemoradiotherapy (nCRT) combined with PD-1 inhibitors can enhance the efficacy of immunotherapy. However, the peripheral immune dynamics underlying this combination remain poorly understood. **Methods:** In this study, we selected 15 patients from the CHOICE I trial (ChiCTR2100042785) who received nCRT combined with PD-1 inhibitors. A total of 55 peripheral blood mononuclear cell (PBMC) samples were collected at three critical time points: pre-treatment baseline, during radiotherapy, and during immunotherapy. All samples underwent single-cell RNA sequencing (scRNA-seq) analysis, complemented by paired TCR/BCR profiling, to comprehensively map the dynamic evolution of the peripheral immune landscape during combined therapy. **Results:** We analysed 223,363 high-quality single cells and classified them into 11 distinct immune phenotypes using classical marker genes, revealing treatment-related immune dynamics. TCR clonal tracking revealed divergent dynamics that CD8⁺ T cells exhibited high clonal persistence (Jaccard index 0.1–0.23), significantly greater in responders than non-responders, underscoring their pivotal role in antitumor immunity. In contrast, CD4⁺ T cells (particularly T follicular helper cells) showed minimal clonal overlap (< 0.03), consistent with rapid turnover. Monocyte analysis uncovered fundamental differences. Monocytes from non-responders displayed enhanced yet dysfunctional antigen presentation alongside immunosuppressive features, including specific expansion of the pro-inflammatory Mono_CD14_IL1B subset characterized by high immunomodulatory molecule expression. Conversely, monocytes in responders exhibited robust type I interferon signaling. B-cell analyses revealed that responders preferentially underwent plasma-cell differentiation, whereas B cells from NR retained an antigen-presenting-like phenotype. NK-cell analysis revealed an expanded, activated cytotoxic pool in responders (featuring CD38⁺, KIR3DL1⁺ subsets), whereas non-responders showed dominance of KLRC2⁺ NK cells, suggesting a dysfunctional state. These efficacy-linked changes across immune populations collectively map the systemic immune landscape under combination therapy. **Conclusions:** This study provides a comprehensive single-cell atlas of peripheral immune remodeling during nCRT combined with PD-1 inhibitors in pMMR/MSS rectal cancer, offering crucial insights for future patient stratification and personalized combination strategies. Research Sponsor: National Natural Science Foundation of China; 82473439, 82272705 and 82503486; the Shanghai "Rising Stars of Medical Talents" Youth Development Program of the Shanghai Municipal Health Commission, China; No.2024-70; the Naval Medical University "Deep Blue" Project Talent Program; the First Affiliated Hospital of Naval Medical University Special Project for Basic Medical Research, China; the First Affiliated Hospital of Naval Medical University Special Project for Clinical Research, China; 2024LYA02; Shanghai Shengkang Hospital Development Center, Shanghai Clinical Cohort Project; SHDC2025CCS019; Shanghai Science and Technology Plan Project; 25SF1901500.

Efficacy and safety of fruquintinib combined with chemotherapy versus bevacizumab combined with chemotherapy as second-line treatment for metastatic colorectal cancer: A prospective, multicenter, randomized controlled trial.

Jianmin Xu, Wenju Chang, Yu Liu, Zizhen Zhang, Ying Yuan, Ren Zhao, Xiaobing Chen, Zhiqian Qin, Zhangfa Song, Guiying Wang, Yong Dai, Yanchang Xu, Yong Mao, Lingjun Zhu, Shengxiang Rao, Fei Liang; Department of Colorectal Surgery and Colorectal Cancer Center, Zhongshan Hospital, Shanghai, China; Department of Colorectal Surgery and Colorectal Cancer Center, Zhongshan Hospital, Fudan University, Shanghai, China; Department of Gastrointestinal Surgery, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China; The Second Affiliated Hospital Zhejiang University School of Medicine, Hangzhou, China; Department of General Surgery, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; Department of Oncology, Henan Cancer Hospital, Zhengzhou, China; Department of Oncology, Zhejiang Provincial People's Hospital, Hangzhou, China; Department of Colorectal Surgery, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, China; The Fourth Hospital of Hebei Medical University, Shijiazhuang, China; Department of General Surgery, Qilu Hospital of Shandong University, Jinan, China; Putian First Hospital, Putian, China; Affiliated Hospital of Jiangnan University, Wuxi, China; Oncology, Jiangsu Province Hospital, Nanjing, China; Department of Radiology, Cancer Center, Shanghai Institute of Medical Imaging, Zhongshan Hospital, Fudan University, Shanghai, China; Department of Biostatistics, Zhongshan Hospital, Fudan University, Shanghai, China

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NALIRIFOX plus targeted therapy as first-line treatment for metastatic colorectal cancer: A phase I study.

Xiaojing Xu, Hongli Liu, Yanhong Gu, Peng Zhao, Zhigang Peng, Yarong Guo, Hong Qiu, Luoyan Ai, Qing Liu, Shan Yu, Wei Li, Yuehong Cui, Zhiming Wang, Yiyi Yu, Bei Xu, Yan Wang, Xiaojun Xiang, Weidong Pan, Tianshu Liu; Department of Medical Oncology, Zhongshan Hospital, Fudan University, Shanghai, China; Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; Department of Oncology, Jiangsu Province Hospital, Nanjing, China; The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; The First Affiliated Hospital of Guangxi Medical University, Nanning, China; Department of Digestive System Oncology, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Third Hospital of Shanxi Medical University, Tongji Shanxi Hospital; Department of Oncology, The First Affiliated Hospital of Shanxi Medical University, Taiyuan, China; Tongji Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology, Wuhan, China; Department of Medical Oncology, Zhongshan Hospital, Fudan University, Shanghai, China; Department of Oncology, The First Affiliated Hospital of Nanchang University, Nanchang, China; Department of Pancreatic Hepatobiliary Surgery, The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; Zhongshan Hospital, Fudan University, Shanghai, China

Background: FOLFOXIRI combined with targeted therapy is recommended for metastatic colorectal cancer (mCRC) patients suitable for intensive treatment or conversion surgery. However, the combination of irinotecan liposome, oxaliplatin, fluorouracil (NALIRIFOX) in mCRC remains uninvestigated. This Phase I study aimed to determine the maximum tolerated dose (MTD) of irinotecan liposome in this combined therapy for mCRC. **Methods:** Patients with histologically confirmed and initially unresectable mCRC were enrolled. In the dose-escalation phase (Phase Ia), a 3+3 design was utilized. Eligible patients received fixed doses of oxaliplatin ($85\text{mg}/\text{m}^2$), fluorouracil ($2400\text{mg}/\text{m}^2$) and bevacizumab ($5\text{mg}/\text{kg}$), while the dose of irinotecan liposome was escalated starting from $60\text{mg}/\text{m}^2$. If a dose-limiting toxicity (DLT) occurs at $60\text{mg}/\text{m}^2$, the dose can be reduced to $50\text{mg}/\text{m}^2$. Toxicity was evaluated using Common Terminology Criteria for Adverse Events (CTCAE5.0). In the dose-expansion phase (Phase Ib), irinotecan liposome was administered at the recommended dose from Phase Ia. Based on the RAS/BRAF gene status, either bevacizumab or cetuximab was combined with NALIRIFOX. The safety and efficacy of the combination were further assessed in Phase Ib. **Results:** From March 2024 to March 2025, 9 patients in the dose-escalation phase and 64 patients in the dose-expansion phase were enrolled, included 48 males and 25 females with a median age of 57 years. The MTD of irinotecan liposome was determined to be $50\text{mg}/\text{m}^2$. Identified DLTs included grade 3 diarrhea and febrile neutropenia. As of January 15, 2026, 65 patients had at least one tumor assessment. The objective response rate (ORR) was 81.5% and the disease control rate (DCR) was 100.0%. The median PFS was 12.3 months (95% CI 9.8–14.7). The rate of R0 resection was 12.3%. The most common $\geq$ grade 3 treatment-related adverse events (TRAEs) were diarrhea (18.4%) and neutropenia (14.5%). **Conclusions:** Irinotecan liposome at a dose of $50\text{mg}/\text{m}^2$ in the NALIRIFOX regimen showed manageable safety and promising efficacy as first-line treatment for mCRC. Clinical trial information: NCT06225622. Research Sponsor: None.

***KMT2C* mutation to identify an immunotherapy-sensitive subset of gastrointestinal cancers: A large real-world analysis.**

Bruno Bockorny, Brooke Rhead, Yingying Yu, Pedro Luiz Lage Bodour Danielian, Jan Heng, Xiaohui Li, Stamatina Fragkogianni, Lisa Macera, Metamia Ciampricotti, Gerburg M. Wulf; Beth Israel Deaconess Medical Center, Boston, MA; Tempus AI, Inc., Chicago, IL; Beth Israel Deaconess Center, Boston, MA; Tempus AI Inc., Chicago, IL; Tempus AI, Chicago, IL

Background: *KMT2C* (MLL3) encodes a histone methyltransferase involved in enhancer regulation and DNA damage repair. Loss-of-function *KMT2C* mutations occur in approximately 4–7% of gastrointestinal cancers and represent one of the most recurrent chromatin regulator alterations across GI malignancies. Preclinical studies demonstrate that *KMT2C* deficiency impairs homologous recombination-mediated DNA repair and increases tumor immunogenicity. We hypothesized that *KMT2C* mutations define a biologically distinct subset of GI cancers associated with enhanced responsiveness to immune checkpoint inhibitors (ICI). **Methods:** Using the Tempus Lens Platform, we identified patients with colorectal cancer (CRC), pancreatic ductal adenocarcinoma (PDAC), or gastroesophageal adenocarcinoma (GEA) who underwent Tempus xT DNA and RNA sequencing within a de-identified multimodal real-world dataset. Clinical and molecular features were compared between *KMT2C*-mutant (MUT) and wild-type (WT) tumors. Real-world progression-free survival (rwPFS) and overall survival (rwOS) following ICI initiation were estimated by Kaplan–Meier methods and compared using log-rank tests. Risk-set adjustment was applied to address left truncation and mitigate immortal time bias. **Results:** Among 14,413 patients, 83% had stage IV disease; CRC comprised 58.1%, PDAC 23.7%, and GEA 18.2%. *KMT2C* mutations were identified in 4.1% of CRC, 3.4% of PDAC, and 4.3% of GEA. Across all tumor types, *KMT2C*^{MUT} tumors had significantly higher tumor mutational burden (TMB) compared with WT (CRC: 39.2 vs 4.7 mut/Mb; PDAC: 3.68 vs 3.16; GEA: 7.9 vs 4.6; all $p \leq 0.02$). TMB-High status (≥ 10 mut/Mb) and MSI-High status were markedly enriched in *KMT2C* MUT tumors (CRC MSI-H: 57% vs 2.6%; PDAC: 6.9% vs 0.1%; GEA: 38% vs 2%; all $p < 0.001$). High Immune Profile Score (IPS) was more frequent in *KMT2C*^{MUT} versus WT tumors in CRC (35% vs 8.3%, $p < 0.001$) and GEA (36% vs 19%, $p < 0.001$). Following ICI, rwPFS was not reached in both *KMT2C*^{MUT} CRC and *KMT2C*^{MUT} GEA compared with 6.2 and 6.0 months in WT tumors (CRC $p = 1.1 \times 10^{-17}$; GEA $p = 0.004$). rwOS was significantly improved in CRC *KMT2C*^{MUT} versus WT (not reached vs 20.2 months; $p = 0.0001$). **Conclusions:** *KMT2C* mutations identify a molecularly and immunologically distinct subset of GI cancers enriched for MSI-High and TMB-High status and associated with superior outcomes following immune checkpoint inhibition. These findings support *KMT2C* as a potential predictive biomarker for immunotherapy responsiveness in gastrointestinal malignancies. Research Sponsor: Tempus.

Efficacy and circulating protein biomarkers of second-line aflibercept plus FOLFIRI according to prior bevacizumab or cetuximab treatment in advanced colorectal cancer (KCSG C021-21).

Hyunwook Kim, Colin Burdette, Ho Jung An, Sang Hee Cho, Seok Yun Kang, Myung Ah Lee, In Kyu Hwang, Tae Won Kim, Cheol-Sik Kim, Jong Gwang Kim, Jung Yong Hong, Moon Ki Choi, Sang Cheul Oh, Seung-Hoon Beom, Sang Joon Shin, Jacob B. Geri, Han Sang Kim, Joong Bae Ahn; Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; Department of Pharmacology, Weill Cornell Medical College, New York, NY; Department of Oncology, The Catholic University of Korea, St. Vincent's Hospital, Suwon-Si, Gyeonggi-Do, South Korea; Department of Internal Medicine, Chonnam National University Medical School, Gwangju, South Korea; Department of Hematology-Oncology, Ajou University Hospital, Suwon-Si, South Korea; The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, South Korea; Division of Hematology/Oncology, Department of Internal Medicine, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul, South Korea; Asan Medical Center, University of Ulsan, Seoul, South Korea; Pusan National University Yangsan Hospital, Kyungnam, South Korea; Kyungpook National University Medical Centre, Kyungpook National University School of Medicine, Daegu, South Korea; Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Division of Medical Oncology, Center for Colorectal Cancer, National Cancer Center, Goyang, South Korea; Department of Internal Medicine, Korea University Guro Hospital, Seoul, South Korea; Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea

Background: Prospective data evaluating second-line aflibercept plus FOLFIRI according to prior bevacizumab (BEV) or cetuximab (CET) exposure and incorporating circulating protein biomarkers remain limited. **Methods:** This open-label, single-arm, nationwide phase II study (NCT04810585) evaluated aflibercept plus FOLFIRI as second-line with stratification by prior BEV or CET exposure. Seventeen circulating biomarkers were measured by ELISA at baseline and before cycle 4 and analyzed for associations with PFS and OS using Cox models. Plasma proteins were processed using a single-pot solid-phase enhanced SP3 protocol followed by tryptic digestion and analyzed by data-independent acquisition liquid chromatography tandem mass spectrometry, with protein identification and quantification performed using DIA-NN. **Results:** A total of 159 patients were enrolled (prior BEV, n=83; prior CET, n=76). mPFS was 7.5 months (95% CI, 6.8–8.4), and mOS was 14.4 months (95% CI, 12.9–16.0), with no significant differences by prior biologic therapy (mOS: 13.8 vs 14.7 months for prior BEV vs CET; mPFS: 7.4 vs 7.5 months). Among 146 evaluable patients, the ORR was 28.1% (1 CR [0.7%], 40 PR [27.4%]), and the DCR was 88.4%. The most common TRAEs were proteinuria (47.1%; grade ≥ 3 , 14.0%), neutropenia (43.4%; grade ≥ 3 , 37.5%), nausea (27.2%), and fatigue (24.3%). Baseline PlGF (PFS HR 2.04, $q=0.008$; OS HR 2.86, $q<0.001$), IL-8 (PFS HR 1.87, $q=0.008$; OS HR 2.13, $q=0.002$), TIMP-1 (PFS HR 1.74, $q=0.021$; OS HR 3.49, $q<0.001$), and VEGF-A (PFS HR 1.74, $q=0.021$; OS HR 1.91, $q=0.009$) were independently associated with inferior PFS and OS, whereas on-treatment and C1-to-C4 biomarker ratios showed no associations. Enrichment of inflammation/immune related proteins S100A8 ($\log_2$ FC -0.41; $p=0.037$) and MPO ($\log_2$ FC -1.51; $p=0.006$), as well as lipid metabolism related proteins APOC3 ($\log_2$ FC -0.58; $p<0.001$) and APOC2 ($\log_2$ FC -0.47; $p=0.003$), was observed in patients with prior BEV at baseline. Enrichment of PIGR ($\log_2$ FC -1.21; $p<0.001$) and OLFM1 ($\log_2$ FC -0.66; p -value <0.001) was observed in PD patients at C4, while SERPINF1 ($\log_2$ FC 0.33; $p=0.003$) and FETUB ($\log_2$ FC 0.41; $p=0.013$) were enriched in PR+CR patients at C4. Further, PIGR expression increased 1.30-fold in PD patients (mean $\log_2\Delta$ (C4-C1) = 0.38), compared to a relatively stable expression in PR patients (mean $\log_2\Delta$ (C4-C1) = -0.076, $p=0.033$). Increased PIGR expression at C4 showed an association with inferior OS in Cox models (HR 1.92, $p=0.004$). **Conclusions:** Clinical outcomes and safety profiles of aflibercept plus FOLFIRI were comparable regardless of prior BEV or CET exposure. Elevated baseline PlGF, IL-8, TIMP-1 and VEGF-A levels were associated with shorter PFS and OS. Exploratory plasma proteomics identified dynamic PIGR expression as a response-associated biomarker linked to inferior OS. Clinical trial information: NCT04810585. Research Sponsor: Sanofi.

A multicenter phase II trial of encorafenib, binimetinib, and cetuximab for early relapsed stage II/III *BRAF*^{V600E}-mutated colorectal cancer: TRESBIEN trial (OGSG 2101).

Toshihiro Kudo, Shogen Boku, Atsushi Naito, Takashi Ohta, Yusuke Suwa, Ichiro Takemasa, Chiaki Inagaki, Koichi Okuya, Mitsuyoshi Tei, Masayoshi Nakanishi, Narikazu Boku, Hiroyuki Okuda, Toshifumi Yamaguchi, Shingo Noura, Yukinori Kurokawa, Toshio Shimokawa, Taroh Satoh, Hironaga Satake, Yoshinori Kagawa, Osaka Gastrointestinal Cancer Chemotherapy Study Group: OGSG; Department of Medical Oncology, Osaka International Cancer Institute, Osaka, Osaka, Japan; Department of Medical Oncology, Kansai Medical University Hospital, Hirakata, Japan; Department of Gastrointestinal Surgery, Sakai City Medical Center, Sakai, Japan; Department of Gastroenterology, Kansai Rosai Hospital, Amagasaki, Japan; Department of Surgery, Gastroenterological Center, Yokohama City University Medical Center, Yokohama, Japan; Department of Gastroenterological Surgery, Osaka Keisatsu Hospital, Osaka, Japan; Department of Medical Oncology, Kindai University Faculty of Medicine, Sakai, Osaka, Japan; Department of Surgery, Division of Gastroenterological Surgery, Sapporo Medical University, Sapporo, Japan; Department of Surgery, Osaka Rosai Hospital, Sakai, Japan; Department of Gastrointestinal Surgery, Panasonic Health Insurance Organization, Matsushita Memorial Hospital, Moriguchi, Japan; Department of Oncology and General Medicine, IMSUT Hospital, Institute of Medical Science, University of Tokyo, Minato City, Tokyo, Japan; Department of Medical Oncology, Keiyukai Sapporo Hospital, Sapporo, Japan; Cancer Chemotherapy Center, Osaka Medical and Pharmaceutical University Hospital, Takatsuki, Japan; Department of Gastroenterological Surgery, Graduate School of Medicine, The University of Osaka, Suita, Japan; Department of Biostatistics, Faculty of Medicine, Wakayama Medical University, Wakayama, Japan; Center for Cancer Genomics and Precision Medicine, Osaka University Hospital, Osaka, Japan; Department of Medical Oncology, Kochi Medical School, Nankoku, Japan; Department of Gastroenterological Surgery, Osaka International Cancer Institute, Osaka, Japan

Background: Patients with *BRAF*^{V600E}-mutated colorectal cancer (CRC) who experience early recurrence during or shortly after adjuvant therapy show an extremely poor prognosis. The efficacy of *BRAF*-targeted triplet therapy for early relapse remains unclear. **Methods:** We conducted a prospective, open-label, multicenter, phase II trial evaluating the efficacy and safety of encorafenib, binimetinib and cetuximab in *BRAF*^{V600E}-mutated CRC patients who relapsed during or within 6 months after completing adjuvant chemotherapy. Patients received encorafenib 300 mg once daily and binimetinib 45 mg twice daily in 28-day cycles, plus intravenous cetuximab 400 mg/m² once on day 1 of cycle 1, then 250 mg/m² once weekly until disease progression or occurrence of unacceptable adverse events. The primary endpoint was objective response rate (ORR) by blinded independent central review. Secondary endpoints were overall survival (OS), progression-free survival (PFS), disease control rate (DCR), and safety. Sample size was determined based on a threshold ORR of 6.0% and an expected ORR of 26.0% (one-sided $\alpha = 0.05$, power = 0.90). **Results:** Between January 2022 and April 2025, 25 patients were enrolled across 14 institutions. Baseline characteristics included: median age 68 years (range, 28–81); female, n = 18 (72.0%); right-sided, n = 18 (72.0%); pStage II/III, n = 2 (8.0%)/23 (92.0%); MSI-H, n = 5 (20.0%); and prior oxaliplatin-based adjuvant chemotherapy, n = 22 (88.0%). Twenty-four patients were evaluable for efficacy. The ORR was 62.5% (95% CI, 40.6–81.2, one-sided $P < 0.001$), and DCR was 87.5% (95% CI, 67.6–97.3). With median follow-up time of 18.0 months, the median PFS was 7.4 months (95% CI, 4.7–10.6), and the median OS was 33.9 months (95% CI, 11.0–NE). No Grade ≥ 3 adverse events ($\geq 10\%$) and treatment-related deaths were observed. **Conclusions:** The combination of encorafenib, binimetinib, and cetuximab demonstrated favorable efficacy and a manageable safety profile in patients with *BRAF*^{V600E}-mutated CRC who relapsed early recurrence during or shortly after adjuvant chemotherapy. This triplet regimen can be a promising treatment strategy for this poor prognostic population. Clinical trial information: jRCTs051210152. Research Sponsor: ONO PHARMACEUTICAL CO., LTD.

Clinical validation of red blood cell DNA for early detection of advanced colorectal neoplasia: A single-center prospective observational case-control clinical trial.

Xingyun Yao, Chengcheng Liu, Yurong Jiao, Haobo Sun, Xiangxing Kong, Jie Jin, Ke-Feng Ding, Jun Li, Xiaofei Gao; School of Life Sciences, Westlake University, Hangzhou, Zhejiang, China; Department of Colorectal Surgery and Oncology, Key Laboratory of Cancer Prevention and Intervention, Ministry of Education, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; Research Center for Industries of the Future and School of Life Sciences, Westlake University, Hangzhou, China; Timing Biotech, Hangzhou, China; Department of Colorectal Surgery, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China; Department of Colorectal Surgery and Oncology, The Second Affiliated Hospital, Zhejiang University School of Medicine, Key Laboratory of Cancer Prevention and Intervention, Ministry of Education, Hangzhou, China

Background: Early detection of colorectal cancer (CRC) improves survival, but current screening is limited by poor colonoscopy compliance and low cfDNA sensitivity for early-stage lesions and advanced adenomas (AA). Beyond tumor shedding, solid tumors remotely disrupt bone marrow hematopoiesis, inducing systemic genomic instability in hematopoietic lineages. Leveraging this mechanism, we developed a noninvasive detection strategy using genome-wide profiling of DNA remnants in mature red blood cells (rbcDNA). We previously showed that tumor-induced IL-18/NR4A1 signaling drives locus-specific DNA damage in hematopoietic progenitors, generating rbcDNA signatures distinct from shedding-dependent cfDNA and enabling improved detection of early-stage cancer. Here, we report the first multicenter and prospective clinical validation of this rbcDNA-based assay for the detection of early colorectal neoplasia (NCT05875584). **Methods:** We enrolled 1,251 colonoscopy-confirmed participants (561 non-advanced neoplasia controls (non-AN), 330 AA, 360 CRC). Peripheral blood (1–2 mL) was collected from each participant, and rbcDNA was isolated and sequenced by low-coverage whole-genome sequencing ($\sim 2\times$), as previously described (PMID: 40341742). Participants were randomly assigned (8:2) to discovery and test cohorts. The discovery cohort was used for CRC- and AA-associated rbcDNA features identification and model development, while the test cohort was used for cutoff optimization. This locked model was externally validated in two independent cohorts. A prospective, observational case-control study was also conducted, in which blood and stool samples were collected simultaneously to compare the rbcDNA classifier with quantitative FIT (qFIT). Among 598 enrolled participants, 585 were included in the final analysis (299 non-AN, 206 AA, and 80 CRC). **Results:** At a predefined 90% specificity, the rbcDNA classifier achieved sensitivities of 85% for AA and 95% for CRC in the test cohort. Across two external cohorts, the assay consistently achieved 80% and 78% sensitivity for advanced colorectal neoplasia, 91% sensitivity for CRC in both cohorts, and 92% and 91% specificity. In the prospective study, rbcDNA yielded 90% sensitivity for CRC and 60% for AA at 90% specificity, with specificity remaining comparable in participants with non-neoplastic findings and non-advanced adenomas. Compared with qFIT, rbcDNA matched overall CRC sensitivity (90% vs. 88%) but outperformed it for stage I CRC (83% vs. 61%) and advanced adenomas (60% vs. 18%), including >50% of large sessile serrated lesions and tubular adenomas (≥ 1 cm) versus <15% by qFIT. **Conclusions:** This first prospective clinical study demonstrates that rbcDNA provides a highly sensitive, non-invasive approach for early colorectal neoplasia detection. Clinical trial information: NCT05875584. Research Sponsor: Key R&D Program of Zhejiang.

SHR-A1811 plus chemotherapy and BP102 as 1L therapy for HER2-expressing mCRC: Data from a phase Ib/II study.

Ting Xu, Lin Shen, Jian Li, Yanhong Deng, Hongli Li, Wenhui Yang, Zhenyang Liu, Yanqiao Zhang, Qi Wang, Yanhong Gu, Xinjun Liang, Hong Zong, Yongqiang Li, Zheng Wang, Yongdong Jin, Aiai Yu, Jiang Yingyi, Chuanpei Huang; Department of Gastrointestinal Oncology, Peking University Cancer Hospital, Beijing, China; Department of Medical Oncology, The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; Internal Medicine of Digestive Oncology, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; Department of Gastrointestinal Oncology, Shanxi Cancer Hospital, Shanxi, China; Department of Gastrointestinal Oncology and Urology, Hunan Cancer Hospital, Changsha, China; Harbin Medical University Cancer Hospital, Harbin, China; Department of Oncology, The Third Xiangya Hospital of Central South University, Changsha, China; Department of Oncology, Jiangsu Province Hospital, Nanjing, China; Department of Abdominal Oncology, Hubei Cancer Hospital, Wuhan, HuBei, China; Department of Medical Oncology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; Affiliated Tumor Hospital of Guangxi Medical University, Nanning, China; Department of Gastrointestinal Surgery, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; Department of Medical Oncology, Sichuan Cancer Hospital & Institute, Chengdu, China; Clinical Research & Development, Jiangsu Hengrui Pharmaceuticals Co., Ltd., Shanghai, China

Background: HER2 expression is associated with poor prognosis in mCRC. SHR-A1811 (trastuzumab-rezetecan) is a HER2-directed ADC comprising a humanized monoclonal antibody, a cleavable tetrapeptide linker, and a topoisomerase I inhibitor payload. We evaluated the safety and preliminary efficacy of SHR-A1811 in combination with chemotherapy and BP102 (bevacizumab biosimilar) as 1L therapy for HER2-expressing mCRC. **Methods:** This open-label, multicenter phase Ib/II study (ClinicalTrials.gov: NCT06015048) used an i3+3 design in phase Ib to evaluate the safety and tolerability of SHR-A1811 + 5-FU/L-LV, $\pm$ oxaliplatin and/or BP102, and to select the phase II regimen. Phase II (proof-of-concept) assessed efficacy and safety in the 1L setting using SHR-A1811 3.2 mg/kg Q2W + 5-FU (300 mg/m² IV bolus, 1800 mg/m² continuous infusion over 46–48 h Q2W) + L-LV 200 mg/m² IV Q2W + BP102 5 mg/kg IV Q2W $\pm$ oxaliplatin 60 mg/m² IV Q2W. Tumor response was assessed per RECIST v1.1, and AEs were evaluated per CTCAE v5.0. **Results:** As of Dec 31, 2025 (data cutoff), 39 pts received SHR-A1811 + FOLFOX (-1) + BP102, and 11 pts received SHR-A1811 + 5-FU/L-LV + BP102. All were Asian with pMMR/MSS and BRAF wild-type disease. The median age was 58 (range, 30–71) and 57 (range, 42–72), respectively. 28/39 (71.8%) and 7/11 (63.6%) were male. ECOG PS was 1 in 24/39 (61.5%) and 6/11 (54.5%). HER2 positivity (IHC 3+ or IHC 2+/ISH+) was observed in 21/39 (53.8%) and 5/11 (45.5%). HER2 IHC 2+/ISH- was observed in 18/39 (46.2%) and 5/11 (45.5%). Liver metastases were present in 28/39 (71.8%) and 4/11 (36.4%). 15/39 (38.5%) and 5/11 (45.5%) had RAS mutations. Median follow-up was 10.4 m (range, 6.1–17.0) and 11.9 m (range, 3.3–19.0). ORR was 74.4% (29/39; 95% CI, 57.9–87.0) and 40.0% (4/10; 95% CI, 12.2–73.8). DCR was 97.4% (38/39; 95% CI, 86.5–99.9) and 90.0% (9/10; 95% CI, 55.5–99.8). mPFS was 15.6 m (95% CI, 11.3–NR) and 9.6 m (95% CI, 1.8–NR). In HER2 positive pts received SHR-A1811 + mFOLFOX6(-1) + BP102, ORR was 90.5% (19/21; 95% CI, 69.6–98.8), DCR was 100% (21/21; 95% CI, 83.9–100), 9m-PFS rate was 94.7% (95% CI, 68.1–99.2); among HER2 positive RAS mutant/wild type subgroups, 9m-PFS rate was 83.3% (95%CI, 27.3–97.5) and 100%. OS was immature. Grade $\geq$ 3 TRAEs occurred in 31/39 (79.5%) and 6/11 (54.5%) in the two cohorts, with the most common being decreased neutrophil count (56.4% vs 18.2%), decreased white blood cell count (17.9% vs 18.2%), anemia (12.8% vs 9.1%), and stomatitis (12.8% vs 0). TRAEs led to discontinuation of any drug in 4/39 (10.3%) (SHR-A1811: 1; chemo: 1; BP102: 3) and in none. TRAEs led to dose reductions in 12/39 (30.8%) and 3/11 (27.3%) (SHR-A1811: 3 vs 1; chemo: 11 vs 3). No TRAE-related deaths occurred. **Conclusions:** SHR-A1811 plus chemotherapy and BP102 as 1L therapy for HER2 intermediate or high-expressing mCRC demonstrated manageable safety and encouraging antitumor activity. Clinical trial information: NCT06015048. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

A transcriptomic signature to predict immune checkpoint inhibition efficacy in proficient mismatch repair metastatic colorectal cancer: Translational analysis of the AVETRIC and TRIPLETE studies.

Martina Carullo, Carlotta Antoniotti, Zhong Wee Poh, Veronica Conca, Jingming Chew, Sabina Murgioni, Giuseppe Leone, Paolo Ciraci, Alessandro Passardi, Mario Scartozzi, Ada Taravella, Lorenzo Antonuzzo, Vincenzo Formica, Margherita Ratti, Claudia Leli, Vittorio Studiale, Sara Lonardi, Daniele Rossini, Clara Ugolini, Chiara Cremolini; 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; Auristone Pte. Ltd., Singapore, Singapore; Oncology Unit 1, Veneto Institute of Oncology IOV-IRCCS, Padova, Italy; Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy; Medical Oncology, IRST-IRCCS "Dino Amadori", Meldola, Italy; Medical Oncology Unit, University Hospital and University of Cagliari, Cagliari, Italy; Department of Experimental and Clinical Medicine, University of Florence. Oncology Unit, Careggi University Hospital, Florence, Italy; Medical Oncology Unit, Department of Systems Medicine, Tor Vergata University Hospital, Rome, Italy; UO Oncologia- Ausl Piacenza "Ospedale Guglielmo Da Saliceto", Piacenza, Italy; Clinical Oncology Unit, Careggi University Hospital, Florence, Italy; Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy; Department of Surgical, Medical, Molecular Pathology and Critical Area, University of Pisa, Pisa, Italy

Background: ICIs provide limited benefit in proficient mismatch repair (pMMR) metastatic colorectal cancer (mCRC), highlighting the need for predictive biomarkers. We aimed to uncover transcriptomic profiles predictive of ICI efficacy, using tumor specimens from two matched cohorts of pMMR, RAS/BRAF wild-type (wt) mCRC patients (pts) enrolled in two academic clinical trials investigating first-line FOLFOXIRI plus an anti-EGFR agent $\pm$ ICI. **Methods:** The phase II AVETRIC study (NCT04513951) provided the ICI-treated cohort (mFOLFOXIRI/anti-EGFR plus avelumab), while the experimental arm of the phase III TRIPLETE study (NCT03231722) served as the ICI-untreated control cohort (mFOLFOXIRI/anti-EGFR). Bulk RNA-seq analysis was performed using the Signomax platform on naive tumor specimens of 39 and 32 pts from the ICI and control cohorts, respectively. Firstly, gene set variation (GSV) analyses compared extended PFS (e-PFS) versus limited PFS (l-PFS) groups (using median PFS of the control cohort as a cut-off) within each cohort, leading to a focus on immune- and EGFR-related pathways. Secondly, using the median immune- and EGFR-related pathway scores in the ICI cohort as a cut-off, samples were classified combining both pathway activities into an immune^{high}-EGFR^{high} group versus a pooled group comprising all the other cases (immune-EGFR^{others}). Associations with PFS and OS were assessed by treatment cohort. **Results:** Thirty-four (87%) (23 e-PFS, 11 l-PFS) and 26 (81%) (13 e-PFS, 13 l-PFS) samples were successfully analyzed in the ICI and control cohorts, respectively. In the ICI cohort, l-PFS samples showed lower activity of both immune- and EGFR-related pathways than e-PFS ones, while no significant differences in the activation of the same pathways were observed between PFS groups in the control cohort. Additionally, 29 pts were classified as immune^{high}-EGFR^{high} (13 [45%] and 16 [55%] in the ICI and control cohorts, respectively) and 31 pts as immune-EGFR^{others} (21 [68%] and 10 [32%] in the ICI and control cohorts, respectively). Immune^{high}-EGFR^{high} pts reported longer PFS (HR: 0.57, 95% CI 0.33-0.98, $P=0.04$) and OS (HR: 0.66, 95% CI 0.36-1.24, $P=0.20$) than other pts. Borderline significant interaction between treatment and immune/EGFR signature was found in PFS ($P=0.145$) with ICI benefit restricted to pts bearing the immune^{high}-EGFR^{high} signature (HR PFS: 0.56, 95% CI 0.25-1.24, versus 1.25, 95% CI 0.60-2.64 in the others). **Conclusions:** Exploratory transcriptomic profiling may identify a subset of pMMR RAS/BRAF wt mCRC with concurrent immune activation and EGFR dependency that could benefit from combining ICI to an intensified anti-EGFR-based first-line treatment. Research Sponsor: GONO GI Foundation; European Union – NextGeneration EU through the Italian Ministry of University and Research under PNRR – M4C2-I1.3 Project PE_00000019 'HEAL ITALIA'; Grant number CUP: I53C22001440006.

A phase II combination study of galunisertib and capecitabine in patients with chemotherapy-resistant colorectal cancer with peritoneal metastases.

Ashwini Kanhailal, Alaa Embaby, Bastiaan Nuijen, Alwin Huitema, Jan Paul Medema, Louis Vermeulen, Tineke E. Buffart, Neeltje Steeghs; Antoni van Leeuwenhoek Hospital - Netherlands Cancer Institute, Amsterdam, Netherlands; Netherlands Cancer Institute, Amsterdam, Netherlands; Department of Pharmacology, Princess Máxima Center for Pediatric Oncology, Netherlands Cancer Institute, University Medical Center Utrecht, Utrecht, Netherlands; Laboratory for Experimental Oncology and Radiobiology, Center for Experimental and Molecular Medicine, Cancer Center Amsterdam, Amsterdam, Netherlands; Amsterdam UMC, University of Amsterdam, Amsterdam Zuidoost, Netherlands; Department of Medical Oncology, Amsterdam University Medical Center, Amsterdam, Netherlands; Department of Clinical Pharmacology, Division of Medical Oncology, Netherlands Cancer Institute - Antoni van Leeuwenhoek, Amsterdam, Netherlands

Background: Transforming growth factor β (TGF- β) plays a dynamic role in cancer biology. It acts as a tumor suppressor in early stages of tumor development. Certain tumor types, such as colorectal cancer (CRC), exploit this signaling route to induce pathways that promote tumor growth, enhancing the tumor's aggressiveness. CRC of the mesenchymal subtype exhibits prominent TGF- β activation, contributing to drug resistance, including to 5-fluorouracil (5-FU)-based chemotherapy. This subtype is found in most CRC patients with peritoneal metastases. Therefore, combining TGF- β inhibition with chemotherapy could be a beneficial approach to overcome resistance. **Methods:** This two-center, open-label, non-randomized proof-of-principle phase II study with a safety lead-in involved combining TGF- β inhibitor galunisertib (150 mg twice daily) with capecitabine (1000 mg/m² twice daily) for 14 days in a 28-day cycle. Adult patients with histologically or cytologically proven CRC and confirmed peritoneal metastases were eligible for inclusion if they were in a good clinical condition, had exhausted all their treatment options, and had no gastrointestinal impaired function. In the safety lead-in phase, six patients were evaluated for safety and tolerability, as assessed by the incidence of dose limiting toxicities (DLTs) and adverse events. Phase II followed a Simon two stage design with progression to the second stage when ≥ 2 objective tumor responses out of 15 patients were reached. Secondary objectives included pharmacokinetics (PK) and pharmacodynamics (e.g. TGF- β expression, immunohistochemical staining for phosphorylated SMAD2/3). **Results:** As of January 23 2026, inclusion was closed, after 22 patients were recruited. 54% of patients were female, with a median age of 60 years (38-77). No DLTs were observed in 21 DLT-evaluable patients. Only grade 1/2 treatment-related adverse events occurred. The most common events were nausea (23%), hypophosphatemia (18%), and fatigue (18%). No objective responses were observed. Four of 20 patients evaluable for efficacy showed stable disease with a median duration of 4 months. PK analysis of patients in the safety lead-in showed high interpatient variability for galunisertib, capecitabine and 5-FU (CV% AUC₍₀₋₁₂₎: between 54%-70%). Galunisertib did not show drug accumulation over time (AUC_(0-inf) on cycle 1 day 1 and AUC₍₀₋₁₂₎ on cycle 1 day 14 were 7.6 and 6.6 $\mu\text{g}\cdot\text{h}/\text{mL}$, respectively). The PK of capecitabine and 5-FU were similar to those described in the literature. Pharmacodynamic analyses are ongoing. **Conclusions:** The combination of galunisertib and capecitabine did not result in objective responses or long term stable disease in chemotherapy-resistant CRC patients with peritoneal metastases. The treatment was well tolerated and PK results for both compounds were similar to those described in the literature. Clinical trial information: NCT05700656. Research Sponsor: None.

Circulating tumor DNA (ctDNA) tumor fraction (TF) dynamics to refine progression-free survival and radiographic response during anti-EGFR rechallenge in metastatic colorectal cancer.

Guglielmo Vetere, Mingyang Cai, Caroline Weipert, Scott Kopetz, Christine Parseghian; Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Guardant Health, Palo Alto, CA

Background: Reliable biomarkers of benefit from anti-EGFR rechallenge are needed in anti-EGFR-refractory metastatic colorectal cancer (mCRC), where prior studies have shown modest progression-free survival (PFS) and radiographic response may incompletely capture biological sensitivity. We evaluated longitudinal ctDNA dynamics as a real-time biomarker of treatment effect. **Methods:** This analysis was conducted within a phase II enrichment study of panitumumab with or without trametinib in anti-EGFR-refractory mCRC; crossover was allowed after progression on monotherapy. Plasma was collected at baseline, prior to each infusion, and at progression or end of treatment. Patients with a baseline and ≥ 1 subsequent on-treatment sample were evaluable. ctDNA TF was estimated with the Guardant Reveal assay by normalizing cancer-specific differentially methylated regions with matched controls in each sample. In samples with detectable ctDNA, Guardant360 Liquid was used for genotyping of > 700 genes and tumor mutational burden (TMB). ctDNA TF dynamics were defined by best % change from baseline. Baseline TF, TMB, and focal amplifications in the MAPK pathway were also evaluated. PFS was the primary endpoint and best radiographic response (RECIST 1.1) was the secondary endpoint. Differences were assessed using Kaplan-Meier analyses, Cox proportional hazards models adjusted by age, sex, line of therapy, and treatment regimen, and the Kruskal-Wallis test. **Results:** A total of 38 patients were included. Consistent with the advanced clinical setting, median TF at baseline was 11.9%. Following adjusted Cox modeling, baseline ctDNA TF was prognostic when dichotomized at 2% (median PFS (mPFS): 3.55 vs 1.97 months, HR 0.32, 95% CI 0.13–0.77), whereas baseline TMB and focal amplifications in the MAPK pathway were not associated with PFS. ctDNA TF % change from baseline to best on-treatment value was strongly associated with PFS in patients with any decrease vs no decrease (mPFS: 3.16 vs 1.77 months, HR 0.24, 95% CI 0.08–0.69, $p = 0.008$), and the longest PFS was observed in patients achieving $\geq 80\%$ TF decrease vs all others (mPFS: 3.61 vs 1.87 months, HR 0.20, 95% CI 0.08–0.49, $p < 0.005$). Median best TF % change was -31% , -80% , and -96% for PD, SD, and PR, respectively ($p < 0.001$). Among patients achieving SD or PR, 100% had any TF decrease and 61% had a $> 80\%$ TF decrease, while in patients with PD as best response, 74% had any TF decrease and 5% had a $> 80\%$ TF decrease. No impact of ctDNA-related variables was observed in the crossover setting. **Conclusions:** ctDNA TF dynamics are strongly associated with PFS and provide clinically meaningful information beyond conventional imaging in mCRC patients undergoing anti-EGFR rechallenge, highlighting ctDNA TF as a powerful tool for refining response assessment and personalizing treatment decisions. Research Sponsor: Jack T. and Lillian S. Clift Fellowship; Andrew Sabin Family Fellowship; NIH GI SPORE.

ctDNA dynamics and prognostic value during first-line treatment of metastatic colorectal cancer: Analysis from the phase 3 PARADIGM study.

Kentaro Yamazaki, Riu Yamashita, Takayuki Yoshino, Kohei Shitara, Jun Watanabe, Eiji Oki, Takeo Sato, Takeshi Naitoh, Yoshito Komatsu, Takeshi Kato, Kazunori Yamanaka, Ikuo Mori, Junpei Soeda, Kouji Yamamoto, Kiwamu Akagi, Atsushi Ochiai, Kei Muro, Hiroyuki Uetake, Katsuya Tsuchihara; Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan; Division of Translational Informatics, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center, Chiba, Japan; Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan; Department of Colorectal Surgery, Kansai Medical University, Hirakata, Japan; Department of Advanced Medicine and Innovative Technology, Kyushu University Hospital, Fukuoka, Japan; Research and Development Center for Medical Education, Department of Clinical Skills Education, Kitasato University School of Medicine, Sagamihara, Japan; Department of Lower Gastrointestinal Surgery, Kitasato University School of Medicine, Sagamihara, Japan; Division of Cancer Chemotherapy, Hokkaido University Hospital Cancer Center, Sapporo, Japan; Department of Surgery, NHO Osaka National Hospital, Osaka, Japan; Japan Medical Affairs, Japan Oncology Business Unit, Takeda Pharmaceutical Company Ltd., Tokyo, Japan; Department of Biostatistics, Yokohama City University School of Medicine, Yokohama, Japan; Center for Genomic Diagnosis, International University of Health and Welfare Narita Hospital, Tokyo, Japan; Research Institute for Biomedical Sciences, Tokyo University of Sciences, Tokyo, Japan; Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; National Hospital Organization, Disaster Medical Center, Tokyo, Japan

Background: The phase 3 PARADIGM trial showed overall survival (OS) and tumor response advantages of anti-EGFR (panitumumab, PAN) over anti-VEGF (bevacizumab, BEV) therapy with FOLFOX6 in first-line metastatic colorectal cancer (mCRC) despite similar progression-free survival (PFS), highlighting limitations of imaging-based PFS as a surrogate for clinical benefit. We investigated whether ctDNA dynamics provide more refined prognostic information complementary to baseline (BL) ctDNA. **Methods:** Plasma samples collected from 556 patients (pts) with mCRC paired at pre-treatment (BL) and post-treatment (after treatment discontinuation) were profiled for ctDNA. Distribution of the highest variant allele fraction was modeled using a Gaussian mixture model. At pre- and post-treatment, pts were classified into 3 groups—High, Mid, and Low—according to ctDNA levels. OS, post-treatment survival (PTS), and PFS were compared across 9 ctDNA dynamic categories (eg, High→Low, High→Mid, High→High) based on changes from pre- to post-treatment. **Results:** Lower BL ctDNA was significantly associated with longer OS (median OS [95% CI]: Low, n = 97, 50.7 mo [44.0–65.2]; Mid, n = 159, 34.1 mo [26.9–37.1]; High, n = 300, 27.8 mo [26.2–31.3]). BL ctDNA level also correlated with tumor volume and mutation burden. Pts with lower ctDNA at treatment discontinuation had longer PTS. Incorporating ctDNA dynamics provided additional prognostic value. Regardless of BL ctDNA level, pts whose post-treatment ctDNA decreased to Low had the best survival (eg, High→Low: 50.9 mo [35.8–61.0]), while pts with persistently high ctDNA showed the poorest survival (High→High: 23.3 mo [18.2–27.8]). The prognostic value of ctDNA dynamics was consistent across treatment arms. Among pts with High BL ctDNA (PAN, n = 152; BEV, n = 148), a greater proportion achieved Low ctDNA at post-treatment with PAN vs BEV (29 [19.1%] vs 16 [10.8%], p = 0.053), whereas the proportions achieving Mid ctDNA were similar (52 [34.2%] vs 58 [39.2%], p = 0.40). In the High→Low/Mid ctDNA subsets, treatment discontinuation following curative resection was more frequent with PAN vs BEV (High→Low: 18/29 [62.1%] vs 7/16 [43.8%]; High→Mid: 11/52 [21.2%] vs 5/58 [8.6%]). OS and PTS trends were favorable with PAN vs BEV (OS; High→Low: 61.0 vs 43.1 mo, HR 0.49, 95% CI 0.23–1.04; High→Mid: 33.6 vs 26.8 mo, HR 0.74, 95% CI 0.50–1.11, PTS; High→Low: 55.1 vs 39.0 mo, HR 0.48, 95% CI 0.22–1.03; High→Mid: 20.6 vs 19.4 mo, HR 0.72, 95% CI 0.48–1.07). **Conclusions:** ctDNA dynamics add prognostic value beyond BL ctDNA level. In pts with high BL ctDNA, PAN yielded more conversions into low ctDNA levels and discontinuations following curative resection, with OS/PTS trends favoring PAN. These findings suggest that ctDNA dynamics may better reflect long-term clinical benefit than PFS, although standardized thresholds and prospective validation are needed. Clinical trial information: NCT02394834; NCT02394795. Research Sponsor: Takeda Pharmaceutical Company Limited.

Contribution of atezolizumab (atezo) to the efficacy of the zanzalintinib (zanza) + atezo combination in patients (pts) with previously treated metastatic colorectal cancer (mCRC): Evidence from the phase 3 STELLAR-303 trial.

Anees Dauki, Mun Sang Yue, Reza Khosravan, Cixin He, Anwaar Saeed, Joel R. Hecht, Young Suk Park, Josep Tabernero, Cathy Eng, Michael Howland, Ahmed A. Othman; Exelixis, Inc., Alameda, CA; Department of Medicine, Division of Hematology & Oncology, University of Pittsburgh Medical Center (UPMC) and UPMC Hillman Cancer Center, Pittsburgh, PA; Division of Hematology/Oncology, David Geffen School of Medicine at University of California Los Angeles, Jonsson Comprehensive Cancer Center, Los Angeles, CA; Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Medical Oncology Department, Vall d'Hebron University Hospital and Institute of Oncology (VHIO), Barcelona, Spain; Department of Medicine, Division of Hematology and Oncology, Vanderbilt-Ingram Cancer Center, Nashville, TN

Background: Outcomes remain poor for pts with previously treated mCRC, the vast majority of whom have tumors that are not microsatellite instability-high or mismatch repair deficient. Zanza is a novel, small molecule inhibitor of multiple kinases, including TAM kinases (TYRO3, AXL, and MER), MET, and VEGF receptors, which play important roles in oncogenic processes, including immune suppression in the tumor microenvironment. In STELLAR-303, zanza + atezo significantly improved overall survival (OS) versus regorafenib (rego) in pts with previously treated mCRC. The objective here was to assess the contribution of atezo to the efficacy of the zanza + atezo combination. **Methods:** The effect of atezo immunogenicity on efficacy was evaluated by comparing progression-free survival (PFS) and OS between atezo treatment-emergent anti-drug antibody (TEADA)-positive and TEADA-negative pts. Unstratified Cox proportional hazards regression models were used to estimate HRs for TEADA subgroups relative to the rego arm. Exposure-response (ER) analyses examined the relationship between atezo serum trough concentrations and efficacy endpoints using Cox proportional hazards models. **Results:** Of 451 pts randomized to zanza + atezo, 394 were evaluable for atezo TEADAs (TEADA-positive at any post-baseline visit, n = 143; TEADA-negative, n = 251). Baseline clinical characteristics and key prognostic factors (eg, RAS status, geographic region, presence of liver metastasis, location of primary tumor) were well balanced between TEADA subgroups, minimizing potential confounding due to subpopulation differences. Relative to the rego arm (n = 450), HRs (95% CI) favored zanza + atezo for PFS across both TEADA-positive (0.81 [0.67–0.99]) and TEADA-negative (0.59 [0.51–0.71]) subgroups. Similar results were observed for OS in the TEADA-positive (0.79 [0.63–0.98]) and TEADA-negative (0.72 [0.60–0.86]) subgroups. The greatest benefit for both PFS and OS was in the TEADA-negative subgroup. Based on ER analyses (n = 376), there was a statistically significant ($p < 0.001$) relationship between time-varying atezo trough concentrations and efficacy endpoints—estimated HRs (95% CI) comparing the 95th with the 5th percentiles of atezo trough concentrations were 0.82 (0.80–0.83) for PFS and 0.73 (0.70–0.75) for OS. Safety profiles were comparable between TEADA-positive and TEADA-negative pts. **Conclusions:** Zanza + atezo demonstrated PFS and OS benefit regardless of atezo TEADA status, with greater efficacy observed in TEADA-negative pts. ER analyses showed that higher atezo serum trough concentrations were associated with longer PFS and OS. These results support the contribution of atezo to the survival benefits observed with the zanza + atezo combination in pts with mCRC in the STELLAR-303 trial. Clinical trial information: NCT05425940. Research Sponsor: Exelixis, Inc.

FIRE-4 (AIO KRK-0114): Efficacy of third-line rechallenge with cetuximab versus investigator's choice in relation to the interval between initial and third-line anti-EGFR therapy.

Lena Weiss, Sebastian Stintzing, Ludwig Fischer Von Weikersthal, Florian Kaiser, Martin Fuchs, Gerald W. Prager, Kathrin Heinrich, Andreas Dickhut, Ralf Hofheinz, Thomas Decker, Stefan Angermeier, Tom Ganten, Christof Burkart, Matthias Sandmann, Leopold Öhler, Dora Niedersuess-Beke, Thomas Kubin, Dominik Paul Modest, Swantje Held, Volker Heinemann; Department of Medicine III, University Hospital Munich LMU, Munich, Germany; Medical Department, Division of Hematology, Oncology, and Cancer Immunology (CCM), Charité Universitätsmedizin Berlin, Berlin, Germany; MVZ Praxis für Hämatologie und Internistische Onkologie, Amberg, Germany; VK&K Studienzentrum, Landshut, Germany; München Klinik Bogenhausen, Department of Gastroenterology, Hepatology and Gastrointestinal Oncology, Munich, Germany; Uni Klinik fuer Innere Medizin I, Vienna, Austria; Department of Medicine III and Comprehensive Cancer Center (CCC Munich LMU), University Hospital, LMU Munich, Munich, Germany; Klinikum Fulda gAG, Fulda, Germany; Universitätsmedizin Mannheim, Tagestherapiezentrum am ITM, Mannheim, Germany; Onkologie Ravensburg, Ravensburg, Germany; Klinikum Ludwigsburg, Klinik für Innere Medizin, Gastroenterologie, Hämato-Onkologie, Pneumologie, Diabetologie und Infektiologie, Ludwigsburg, Germany; RKH Fuerst-Stirum-Klinik Bruchsal, Haemato-Onkologie, Bruchsal, Germany; Schwarzwald-Baar Clinic, Villingen-Schwenningen, Germany; Petrus-Krankenhaus Wuppertal, Wuppertal, Germany; St Josef Krankenhaus, Wien, Austria; Wilhelminenspital, Wien, Austria; Department für Hematology, Oncology and Palliative Care, Clinics Südostbayern AG, Clinic Traunstein, Traunstein, Germany; Charité Comprehensive Cancer Center Berlin, Berlin, Germany; AIO-Studien-gGmbH, Berlin, Germany; Comprehensive Cancer Center at Ludwig Maximilian University of Munich, Munich, Germany

Background: The randomized FIRE-4 study evaluated the effect of cetuximab rechallenge versus investigator's choice in the 3rd-line treatment of patients (pts) with RAS-wildtype (RAS-wt) metastatic colorectal cancer (mCRC). The present analysis focuses on the time between the end of initial anti-EGFR-based treatment and start of 3rd-line therapy (TIS-3) as a potential predictor of response. **Methods:** In FIRE-4, all pts received induction therapy with FOLFIRI plus cetuximab. After 1st PD, an anti-EGFR-free "window therapy" was recommended. At diagnosis of 2nd PD, pts who had responded to induction therapy were re-evaluated for RAS status and, after exclusion of RAS mutations, were offered randomization to either rechallenge with cetuximab plus chemotherapy or investigator's choice. Overall survival in 3rd-line (OS-3) was evaluated as a primary endpoint. **Results:** Of the 87 pts entering 3rd-line treatment in FIRE-4, 45 received (FOLF)IRI plus cetuximab (rechallenge arm), and 42 received investigator's choice (standard arm). Numerically superior outcome parameters regarding ORR-3 (OR 2.70), PFS-3 (HR 0.87) and OS-3 (HR 0.86) were observed in the rechallenge arm, without, however, reaching the level of statistical significance. To evaluate the relevance of TIS-3, we focused on the median (13.8 months) and the first quartile (9.0 months). Based on these cut-off values, treatment effects were evaluated in pts with longer and shorter TIS-3 intervals (see Table). **Conclusions:** Longer TIS-3 intervals were associated with longer survival times in 3rd-line treatment. This observation was particularly true for pts receiving cetuximab rechallenge, but also for those receiving investigator's choice. Clinical trial information: NCT02934529. Research Sponsor: None.

Treatment arm	N	Interval	PFS (mo)	HR	OS (mo)	HR
FOLF(IRI) + Cetuximab	21	> 13.8 mo	7.4		20.0	0.639
	24	< 13.8 mo	4.1	P=0.019	12.6	P=0.187
	34	> 9.0 mo	5.9	0.680	19.6	0.601P=0.173
	11	< 9.0 mo	4.0	P=0.274	10.8	
Investigator's choice	23	> 13.8 mo	5.6	0.772	16.2	0.516
	19	< 13.8 mo	4.4	P=0.415	12.2	P=0.055
	32	> 9.0 mo	5.5	0.690	16.9	0.458P=0.042
	10	< 9.0 mo	4.5	P=0.313	7.8	

Ivonescimab (ivo) with oxaliplatin + fluorouracil (5-FU) + leucovorin calcium (mFOLFOX6) for patients (pts) with unresectable metastatic colorectal cancer (mCRC): A phase 2 study.

David Berz, Yanhong Deng, Jianwei Zhang, Zhiwei Li, Ming Yin, Junjie Zhao, Karl Albert Eckert, Nindhana Paranthaman, Xufang Yu, Yu Xia, Alexander I. Spira; Department of Oncology, Valkyrie Clinical Trials, Inc, Los Angeles, CA; The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; Gastroenterology Ward 1, Harbin Medical University Cancer Hospital, Harbin, China; Summit Therapeutics Inc., Miami, FL; Summit Therapeutics, Inc., Miami, FL; Summit Therapeutics, Inc, Miami, FL; Akeso Biopharma, Zhongshan, China; Akeso Biopharma, Inc., Zhongshan, China; Virginia Cancer Specialists Research Institute and Next Oncology, Fairfax, VA

Background: Ivonescimab is an investigational tetrameric bispecific antibody targeting both programmed death protein 1 and vascular endothelial growth factor that demonstrated efficacy and a tolerable safety profile in multiple phase 3 studies in pts with non-small cell lung cancer, and is being investigated in other solid tumor types. This multi-part phase 2 study (NCT05382442) evaluated ivo + chemotherapy as first-line treatment of mCRC. Here, we report interim results from the multiregional regimen extension phase of the study, which evaluated ivo 20 or 10 mg/kg + mFOLFOX6. **Methods:** Adult pts (≥ 18 years) in China and the US with confirmed mCRC who had an Eastern Cooperative Oncology Group score of 0-1, were not candidates for radical surgical resection or local therapy, and had not received systemic anti-tumor therapy in the recurrent or metastatic stage were enrolled; pts who received prior neoadjuvant or adjuvant therapy were permitted if first recurrence/metastasis occurred ≥ 12 months (mo) after the last dose. Pts were randomly assigned 1:1 to receive intravenous ivo (20 mg/kg or 10 mg/kg) + mFOLFOX6 once every 2 weeks for up to 8 cycles, followed by maintenance with 5-FU + ivo until disease progression, intolerable toxicity, or withdrawal of consent for up to 2 years. The primary endpoints were objective response rate (ORR; assessed by Response Evaluation Criteria in Solid Tumors v1.1) and incidence and severity of treatment-emergent adverse events (TEAEs). Secondary efficacy endpoints included disease control rate (DCR) and progression-free survival (PFS). **Results:** At the time of data cutoff for this interim analysis (December 31, 2025), 49 pts were enrolled (ivo 20 mg/kg + mFOLFOX6, n = 25; ivo 10 mg/kg + mFOLFOX6, n = 24) with an overall median age of 58 years; 79.6% of pts had left-sided tumors, 53.1% had KRAS or BRAF tumor mutations, and 67.3% had liver metastases. Median follow-up was 7.5 mo (range, 3.5-10.3) and 7.1 mo (range, 1.9-10.3) in the ivo 20 mg/kg + mFOLFOX6 and ivo 10 mg/kg + mFOLFOX6 arms, respectively. ORR was 70.8% in each treatment arm; all were partial responses. DCR was 100% in each treatment arm. Median PFS was not reached. PFS rate at 6 months was 95.2% and 84.8% in the ivo 20 mg/kg + mFOLFOX6 and ivo 10 mg/kg + mFOLFOX6 arms, respectively. Grade ≥ 3 TEAEs related to ivo occurred in 40.0% and 33.3% of patients in the ivo 20 mg/kg + mFOLFOX6 and ivo 10 mg/kg + mFOLFOX6 arms, respectively, and serious TEAEs related to ivo were reported in 24.0% and 16.7% of pts, respectively. TEAEs led to discontinuation of ivo in 4.0% in the ivo 20 mg/kg + mFOLFOX6 arm and in 0% in the ivo 10 mg/kg + mFOLFOX6 arm. No TEAEs led to death. **Conclusions:** With 7.3 mo follow-up, ivo + mFOLFOX6 showed encouraging efficacy and a manageable safety profile in pts with untreated mCRC. Clinical trial information: NCT05382442. Research Sponsor: Summit Therapeutics, Inc.

Cadonilimab, a bispecific anti-PD-1/CTLA-4 antibody, for patients with dMMR/MSI-H metastatic colorectal cancer after progression on anti-PD-(L)1 therapy: A multicenter, single-arm, phase 2 trial (CSWOG-C03).

Huabin Hu, Zhuoxin Zheng, Jiaye Deng, Lin Xie, Jianwei Zhang, Yan Zhang, Xiaohui Zhai, Xiaoyu Xie, Zehua Wu, Weiwei Li, Wuteng Cao, Fangqian Li, Jiancong Hu, Tao Yang, Chao Wang, Shan Zeng, Lishuo Shi, Yanhong Deng; Department of Medical Oncology, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; Department of Gastrointestinal Medical Oncology, Peking University Cancer Hospital Yunnan, Yunnan, China; Department of Radiology, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; Department of Gastrointestinal Endoscopy, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; Department of Pathology, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; Department of Oncology, Xiangya Hospital, Central South University, Changsha, China; Clinical Research Center, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, China

Background: Immune checkpoint blockade targeting PD-1 is the standard of care for patients with mismatch repair-deficient or microsatellite instability-high (dMMR/MSI-H) metastatic colorectal cancer (mCRC). However, approximately 37%–45% of patients experience disease progression within 1 year when treated with anti-PD-1 monotherapy, and effective subsequent treatment options remain undefined. The CSWOG-C03 study evaluated the efficacy and safety of cadonilimab, a bispecific anti-PD-1/CTLA-4 antibody, in patients with dMMR/MSI-H mCRC after progression on prior anti-PD-(L)1 therapy. **Methods:** This multicenter, single-arm, phase 2 study enrolled patients with centrally confirmed dMMR/MSI-H mCRC and iRECIST-defined disease progression after prior anti-PD-(L)1 monotherapy or anti-PD-(L)1-based combination therapy. Patients received intravenous cadonilimab at 6 mg/kg every 2 weeks until disease progression or unacceptable toxicity. The primary endpoint was the 12-month progression-free survival (PFS) rate, assessed by RECIST v1.1. **Results:** A total of 24 patients were enrolled and received study treatment. The median age was 54 years; 29% were female, 17% had Lynch syndrome, 92% had peritoneal metastases, and 33% had liver metastases. Overall, 63% of patients had received ≥ 2 prior lines of systemic therapy; all had prior exposure to anti-PD-(L)1 therapy, 71% had received fluoropyrimidines and oxaliplatin, and 29% had received irinotecan. The best response to prior anti-PD-(L)1 therapy was partial response in 2 patients, stable disease in 17, and progressive disease in 5. With a median follow-up of 14.8 months at data cutoff (January 22, 2026), the 12-month PFS rate was 44.6% (95% CI, 23.4–63.9), meeting the prespecified primary endpoint of 40%. Median PFS was 6.1 months (95% CI, 2.2–10.1). Median overall survival (OS) was not reached and the 12-month OS rate was 68.6% (95% CI, 42.5–84.7). The confirmed objective response rate (ORR) was 20.8% (95% CI, 7.1–42.2), and the disease control rate (DCR) was 75.0% (95% CI, 53.3–90.2). One patient completed the protocol-specified 2-year treatment without progression, and 7 remained on study treatment. Treatment-related adverse events of any grade occurred in 15 patients (63%), with grade 3 events observed in 3 patients (13%). **Conclusions:** Cadonilimab provided meaningful disease control with modest antitumor activity and a manageable safety profile in patients with dMMR/MSI-H mCRC after progression on prior anti-PD-(L)1 therapy. Clinical trial information: NCT05426005. Research Sponsor: National Science Fund for Distinguished Young Scholars; 82425045.

	N=24
12-month PFS rate	44.6% (95% CI, 23.4–63.9)
Best overall response	
PR	5 (21)
SD	13 (54)
PD	5 (21)
NE	1 (4)
Objective response rate	20.8% (95% CI, 7.1–42.2)
Disease control rate	75.0% (95% CI, 53.3–90.2)

Radiotherapy followed by systemic therapy and tislelizumab in microsatellite-stable rectal cancer with synchronous unresectable metastases: Updated results of the MIRACLE-2 study.

Menglong Zhou, Lijun Shen, Zezhi Shan, Hui Zhang, Wang Yang, Yajie Chen, Yaqi Wang, Shujuan Zhou, Ruiyan Wu, Juefeng Wan, Dakui Luo, Zilan Ye, Weijing He, Yufei Yang, Yikuan Chen, Changming Zhou, Qingguo Li, Fan Xia, Xinxiang Li, Zhen Zhang; Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China; Department of Colorectal Surgery, Fudan University Shanghai Cancer Center, Shanghai, China; Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital (Fujian Branch of Fudan University Shanghai Cancer Center), Fuzhou, China; Department of Cancer Prevention, Fudan University Shanghai Cancer Center, Shanghai, China; Fudan University Shanghai Cancer Center, Shanghai, China

Background: Microsatellite-stable (MSS) tumors comprise ~95% of metastatic colorectal cancer cases and exhibit intrinsic resistance to immunotherapy. Emerging evidence suggests systemic therapy may enhance immunotherapy responsiveness, while radiotherapy could improve efficacy by overcoming resistance and reducing tumor burden. The MIRACLE-2 study evaluated the safety and efficacy of combining radiotherapy with systemic therapy and tislelizumab as first-line treatment for unresectable metastatic MSS rectal cancer (RC). **Methods:** MIRACLE-2 was a prospective, single-arm, phase II study. Inclusion criteria: MSS RC with primary tumor ≤ 10 cm from anal verge on MRI and synchronous unresectable metastases. Patients received hypofractionated radiotherapy (HFRT) for primary lesions and HFRT or SBRT for metastases, followed by systemic therapy: FOLFOX-bevacizumab-tislelizumab for RAS/BRAF-mutant patients or FOLFIRI-cetuximab-tislelizumab for wild-type patients. Reassessment every 8 weeks. Patients achieving resectable disease underwent primary tumor resection and metastasectomy/local ablative therapies for metastases. For patients unable to preserve anal sphincter, a watch-and-wait (WW) strategy was considered if clinical complete response (cCR) of primary tumor was achieved. Otherwise, systemic therapy continued until progression/intolerable toxicity. Primary endpoint: ETS rate ($\geq 20\%$ target lesion reduction at 8 weeks post systemic therapy initiation). Secondary endpoints: disease control rate (DCR), duration of response (DOR), overall survival (OS), progression-free survival (PFS), and safety. **Results:** As of December 31, 2025, efficacy data were available for 50 patients (38 males, 76.0%; median age 57 years, range 30–73). Among these, 52.0% had liver metastases, 8.0% lung metastases, and 40.0% both liver and lung metastases. RAS/BRAF mutations were detected in 56.0% of primary tumors. Median treatment courses: eight (range 3–12). Overall, 18% (9/50) attained no evidence of disease (NED). ETS rate: 76.0%; DCR: 88.0%. Median follow-up: 19.9 months (95% CI: 16.4–23.4). Among 34 patients with complete/partial response, median DOR: 8.0 months (95% CI: 5.2–10.8), with 1-year DOR rate of 20%. Median PFS: 9.3 months (95% CI: 7.1–11.5), with 1-year PFS rate of 33.4%. Median OS: 23.2 months (95% CI: 15.1–31.3), and 1-year OS rate: 93.3%. No grade 5 treatment-related adverse events (TRAEs) occurred. All-grade TRAEs: lymphopenia (95.9%), anemia (91.8%), and leukopenia (69.4%). Grade 3/4 TRAEs: lymphopenia (36.7%), neutropenia (26.5%), and leukopenia (20.4%). **Conclusions:** The combination of radiotherapy, systemic therapy, and tislelizumab showed a high ETS rate and manageable safety profile in first-line unresectable MSS RC. Long-term outcomes require further follow-up. Clinical trial information: NCT05359406. Research Sponsor: None.

Indirect comparison of nivolumab-ipilimumab versus chemotherapy (Chemo) and/or immunotherapy in dMMR/MSI-H metastatic colorectal cancer (mCRC) using reconstructed individual patient data (IPD).

Daniele Rossini, Federico Nichetti, Camilla Motola, Maria Caterina De Grandis, Alexandra Paulet, Giulia Maddalena, Cristiana Conticello, Letizia Procaccio, Francesca Bergamo, Lorenzo Antonuzzo, Sara Lonardi; Department of Experimental and Clinical Medicine, University of Florence; Oncology Unit, Careggi University Hospital, Florence, Italy; Oncology Unit 1, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy; Department of Experimental and Clinical Medicine, University of Florence. Oncology Unit, Careggi University Hospital, Florence, Italy

Background: In patients with dMMR/MSI-H mCRC, phase III randomized trials have established immune checkpoint (IO) inhibition as a key first-line strategy. In KEYNOTE-177, pembrolizumab demonstrated superior outcomes vs chemo, supporting an IO-first approach. In CheckMate 8HW, nivolumab plus ipilimumab (Nivo+Ipi) outperformed both nivolumab and chemo, demonstrating benefit from dual checkpoint blockade. In contrast, COMMIT evaluated FOLFOX plus bevacizumab plus atezolizumab and reported improved outcomes vs atezolizumab monotherapy. Despite these advances, a direct head-to-head comparison between Nivo+Ipi and chemo-IO remains unavailable. We addressed this unmet question by reconstructing IPD from published Kaplan-Meier (KM) curves to enable an indirect cross trial comparison. **Methods:** Published PFS KM curves were digitized to pseudo-IPD. To mitigate cross-trial differences, arms were divided into four groups: Nivo+Ipi (CheckMate 8HW; n=171), chemo-IO (COMMIT; n=38), IO monotherapy [pembrolizumab (KEYNOTE-177; n=153), nivolumab (CheckMate 8HW; n=170), atezolizumab (COMMIT; n=40); n=363], and chemo (standard arms in KEYNOTE-177/CheckMate 8HW; n=238). The primary estimand was PFS restricted mean survival time (RMST) at $\tau=24$ months. As a late-benefit sensitivity analysis, RMST was also estimated at $\tau=48$ months where $\geq 10\%$ patients remained at risk, to limit instability from sparse tails. KM comparisons (log-rank and Cox HR) were derived from reconstructed pseudo-IPD. **Results:** At $\tau=24$ months, Nivo+Ipi improved PFS RMST vs chemo (18.87 vs 10.33 months; Δ RMST +8.54, 95% CI 6.78–10.31; $p<0.001$) and vs IO monotherapy (18.87 vs 14.61 months; Δ RMST +4.26, 95% CI 2.54–5.99; $p<0.001$). Chemo-IO improved RMST vs chemo (16.92 vs 10.33 months; Δ RMST +6.59, 95% CI 3.59–9.60; $p<0.001$). In the key indirect comparison, Nivo+Ipi vs chemo-IO did not show a statistically significant RMST difference (18.87 vs 16.92 months; Δ RMST +1.95, 95% CI -1.14–5.04; $p=0.217$). In contrast, the late-benefit ($\tau=48$ months) analysis demonstrated a statistically significant advantage for Nivo+Ipi (RMST 35.00 vs 27.71 months; Δ RMST +7.29, 95% CI 0.08–14.49; $p=0.048$). KM-derived estimates were consistent with these patterns: Nivo+Ipi outperformed chemo ($p<0.001$) and IO monotherapy ($p<0.001$), and chemo-IO outperformed chemo ($p<0.001$). Compared with chemo-IO, Nivo+Ipi was associated with numerically longer PFS (NE vs 30.2 months; HR 0.62, 95% CI 0.36–1.05; $p=0.073$). **Conclusions:** Nivo+Ipi and chemo IO substantially improved 24-month PFS RMST vs chemo and IO monotherapy, with similar outcomes. Nivo+Ipi showed a significant advantage over chemo-IO at 48 months, consistent with a sustained late PFS effect. Findings are hypothesis-generating given cross-trial heterogeneity and reconstruction-related bias. Research Sponsor: None.

Avatrombopag for chemotherapy-induced thrombocytopenia in gastrointestinal malignancies (ACT-GI): A multicenter, U.S., randomized, double-blind, placebo-controlled clinical trial.

Gerald A. Soff, Joseph James Shatzel, Sandhya R. Panch, Julia H. Keating, Shilton Dhaver, Nina Strojny, Carolyn Donovan, Christos Belibasakis, Elizabeth P. Walsh, Colin D. Weekes, Pamela G. Hodges, Adel Kardosh, Stacey A. Cohen, Jonathan J. Cohen, Hanny Al-Samkari; University of Miami Health System/Sylvester Comprehensive Cancer Center, Miami, FL; Oregon Health & Science University, Portland, OR; University of Washington, Seattle, WA; Dana-Farber Cancer Institute, Boston, MA; Mass General Brigham, Boston, MA; Massachusetts General Hospital, Boston, MA; Fred Hutch Cancer Center, University of Washington, Seattle, WA; Sylvester Comprehensive Cancer Center, Miami, FL; Division of Hematology Oncology, Massachusetts General Hospital, Boston, MA

Background: Chemotherapy-induced thrombocytopenia (CIT) is a frequent complication of chemotherapy. Persistent CIT (not adequately resolved by day 1 of the following cycle) may lead to reduction or delay in treatment. There are no FDA approved therapies for CIT. Aim: To evaluate the safety and efficacy of avatrombopag (AVA), an oral thrombopoietin receptor agonist, to treat persistent CIT and prevent its recurrence in GI cancer. **Methods:** ACT-GI (NCT05772546) was a multicenter, randomized, double-blind, placebo-controlled, investigator-initiated trial of GI cancer patients with persistent CIT (platelets [Plt] $<85 \times 10^9/L$ on day 1 of a scheduled chemotherapy cycle). Patients were randomized 1:1 to AVA 40 mg daily or placebo and treated for two on-study phases. In the lead-in phase, patients were treated up to 2 weeks while chemotherapy was held. Patients proceeded to the on-cycle phase and resumed chemotherapy only if their Plt recovered to $\geq 100 \times 10^9/L$. In the on-cycle phase, patients received a single full-dose chemotherapy cycle with continued study drug. The primary endpoint was successful correction of CIT and prevention of recurrence (achieving Plt $\geq 100 \times 10^9/L$ within the lead-in period AND prevention of CIT recurrence (Plt $\geq 100 \times 10^9/L$) at end of the cycle). **Results:** Efficacy: ACT-GI was closed to enrollment by the DSMB, for overwhelming efficacy, at a prespecified interim analysis when 20 patients in each arm completed the double-blind period. 16 of 23 patients (70%; 95% CI 47% to 87%) in the AVA arm achieved the primary endpoint versus 4/24 patients (17%; 95% CI 5% to 37%) in the placebo arm ($Z=3.67$, $P<0.001$). 74% and 88% of patients had stage IV cancer in AVA and placebo arms, respectively. 44/47 patients completed study drug; 2 discontinuations were due to physician decision and 1 was due to an adverse event. Plt improvement to $\geq 100 \times 10^9/L$ during lead-in was achieved by 83% of patients in the AVA arm vs. 46% of patients in the placebo arm. The median (IQR) Plt at the end of the on-cycle treatment period was 157 (136–202) in the AVA arm vs 72 (68–134) in the placebo arm. In the AVA arm there were two clinically relevant bleeding events (intestinal stoma site bleed at Plt $105 \times 10^9/L$ and intracranial hemorrhage). No patient received platelet transfusion. Safety: AEs and serious AEs (SAEs) occurred in 74% and 13% of patients in the AVA arm and 46% and 0% of patients in the placebo arm, respectively. No SAEs were study drug-related. There were no treatment-related AEs leading to death or discontinuation of study drug. **Conclusions:** In this randomized, placebo-controlled trial, AVA demonstrated safety, tolerability, and efficacy in treatment and prevention of persistent CIT in GI cancers. These findings are promising for a common, serious condition that prevents delivery of full-dose, on-time cancer-directed therapy. Clinical trial information: NCT05772546. Research Sponsor: Swedish Orphan Biovitrum (Sobi).

Propensity score–matched analysis of trifluridine-tipiracil plus bevacizumab (FTD/TPI+Bev) vs anti-EGFR re-treatment in pretreated metastatic colorectal cancer (mCRC).

Giovanni Trovato, Daniele Rossini, Paolo Ciraci, Chiara Cavalli, Eleonora Perissinotto, Maria Alessandra Calegari, Roberto Moretto, Gaia Rebecchi, Francesca Bergamo, Mario Scartozzi, Antonella Nicastro, Stefano Tamberi, Valentina Burgio, Elisabetta Fenocchio, Lorenzo Antonuzzo, Vittorio Studiale, Giampaolo Tortora, Federica Morano, Lisa Salvatore, Chiara Cremolini; Oncologia Medica, Comprehensive Cancer Center, Fondazione Policlinico Universitario Agostino Gemelli, IRCCS Università Cattolica del Sacro Cuore, Rome, Italy; Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy; 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; Medical Oncology Department, 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; Medical Oncology, Comprehensive Cancer Center, Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Rome, Italy; Unit of Medical Oncology 2, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy; Istituto Nazionale Tumori, Milan, Italy; Oncology 1 Unit, Department of Medical Oncology, Veneto Institute of Oncology IOV - IRCCS, Padua, Italy; Medical Oncology Unit, University Hospital and University of Cagliari, Cagliari, Italy; Oncology Complex Unit, Santa Maria delle Grazie Hospital, Pozzuoli, Napoli, Italy; Oncology Unit Santa Maria delle Croci Hospital - AUSL Romagna, Ravenna, Italy; Department of Oncology, IRCCS San Raffaele Scientific Institute Hospital, Vita-Salute San Raffaele University, Milan, Italy; Candiolo Cancer Institute, University of Turin Medical School, FPO, IRCCS, Candiolo, Italy; Department of Experimental and Clinical Medicine, University of Florence. Oncology Unit, Careggi University Hospital, Florence, Italy; Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa & Unit of Medical Oncology 2, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy

Background: The SUNLIGHT trial established FTD/TPI+Bev as a preferred 3rd-line option for unselected mCRC patients (pts). Recently, the phase II randomized PARERE trial reported high response rates and favorable progression-free survival (PFS) with anti-EGFR re-treatment in RAS/BRAF wild-type (wt) mCRC pts selected by liquid biopsy versus regorafenib. In the absence of head-to-head comparisons between these two strategies, we performed an indirect analysis, using propensity score matching (PSM) to minimize baseline imbalances. **Methods:** Two cohorts of pretreated (≥ 2 previous lines) mCRC pts were compared: pts with RAS/BRAF wt tumors receiving FTD/TPI+Bev enrolled in the Italian real-world FLOWER trial, and RAS/BRAF wt pts at the liquid biopsy enrolled in Arm A (panitumumab (Pan) re-treatment followed by regorafenib) of the PARERE trial. PSM was applied adjusting for age, sex, ECOG performance status, number (N) of metastatic sites, N of prior treatment lines, tumor sidedness, and presence of liver and peritoneal metastases. **Results:** Overall, 75 pts treated with FTD/TPI+Bev and 103 pts treated with Pan were included. In the unmatched populations, median PFS was 6.0 months with FTD/TPI+Bev vs 4.1 months with Pan ($p < 0.001$). Median OS was 13.6 months and 11.6 months, respectively ($p = 0.756$). ORR was 9.3% with FTD/TPI+Bev and 16.5% with Pan ($p = 0.172$). After PSM, 68 pts per cohort were analyzed. Median PFS was 5.0 months with FTD/TPI+Bev vs 3.9 months with Pan [HR 1.65 (95% CI, 1.14–2.38), $p = 0.007$]. Median OS was 13.1 months vs 11.6 months, respectively [HR: 0.89 (95% CI: 0.59–1.34); $p = 0.569$]. ORR remained numerically higher in the Pan group, although not statistically significant ($p = 0.34$). Results were consistent regardless of N of anti-EGFR-free lines [1 vs ≥ 2 ; HR for PFS: 0.85 (95% CI: 0.58–1.23), $p = 0.379$; HR for OS 0.85 (95% CI: 0.56–1.29), $p = 0.446$], type of prior anti-EGFR therapy [Pan vs Cetuximab; HR for PFS: 0.80 (95% CI: 0.58–1.10), $p = 0.163$; HR for OS 0.87 (95% CI: 0.61–1.24), $p = 0.435$], and response to previous anti-EGFR treatment [HR for PFS: 0.87 (95% CI: 0.59–1.28), $p = 0.485$; HR for OS 0.80 (95% CI: 0.59–1.28), $p = 0.279$]. Toxicity profiles differed between treatments: neutropenia (any grade (G) 52% vs 3%; G3–4: 37% vs 1%), anemia (39% vs 15%; G3–4: 5% vs 1%), nausea (25% vs 10%; G3–4: 4% vs 0%), thrombocytopenia (24% vs 7%; G3–4: 4% vs 0%) and hypertension (21% vs 1%; 4% vs 0%) were more frequent with FTD/TPI+Bev, whereas rash occurred exclusively in the Pan group (81%; G3–4: 19%). **Conclusions:** Although underpowered, this indirect comparison suggests that FTD/TPI+Bev may achieve longer PFS than Pan re-treatment in pretreated mCRC pts, while anti-EGFR rechallenge may be associated with numerically higher response rate, with no OS difference. Prospective randomized trials are warranted to confirm these findings. Research Sponsor: None.

A multi-omic analysis of EOCRC: Divergent methylation and gene expression signatures in young patients.

Ning Jin, Selen Ayse Yilmaz, Jiangjiang Zhu, Xiaokui Mo, Rebecca Hoyd, Daniel Spakowicz, Eric David Miller, Daniel Rosenberg, Anne M. Noonan, John L. Hays, Sameek Roychowdhury, Pannaga Malalur, Ashish Manne, Arjun Mittra, Shafia Rahman, Zachary Risch, Tarik Demir, Matthew Kalady; The Ohio State University, Columbus, OH; The Ohio State University Comprehensive Cancer Center, Columbus, OH; The Ohio State University Wexner Medical Center, Columbus, OH; The Ohio State University, Center for Biostatistics, Columbus, OH; Division of Medical Oncology, Department of Internal Medicine, The Ohio State University College of Medicine, Columbus, OH; Center for Molecular Oncology, University of Connecticut Health Center, Farmington, CT; James Cancer Hospital and Solove Research Institute, Columbus, OH; Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, The Ohio State University, Columbus, OH; The Ohio State University, Wexner Medical Center, Columbus, OH; Ohio State University, Columbus, OH; Department of Internal Medicine, Division of Medical Oncology, The Ohio State University Wexner Medical Center, Columbus, OH; Ohio State University Wexner Medical Center, Columbus, OH

Background: The incidence of early-onset colorectal cancer (EOCRC; diagnosis < 50 years) is rising at an alarming rate. EOCRC often exhibits distinct clinical features compared to late-onset colorectal cancer (LOCRC), yet the underlying mechanisms remain poorly understood. This study aimed to characterize a cohort of EOCRC patients by integrating DNA methylation, gene expression, and metabolomic profiles to identify age-specific molecular drivers. **Methods:** We performed an integrated multi-omic analysis on a cohort of 42 patients, comprising 16 EOCRC and 26 LOCRC cases that were collected from the Total Cancer Care at the Ohio State University. For each patient, fresh-frozen tumor tissue and paired adjacent normal tissue were analyzed using reduced representation bisulfite sequencing (RRBS). Parallel transcriptomic profiling was conducted by RNA-seq on all tumor samples. Additionally, systemic metabolic signatures were captured from plasma using liquid chromatography-mass spectrometry (LC-MS). Functional integration of differentially methylated regions (DMRs), gene expression signatures, and metabolomic profiles was performed using Ingenuity Pathway Analysis (IPA) to identify enriched canonical pathways. **Results:** Integrative analysis revealed a divergent molecular fingerprint in EOCRC compared to LOCRC. At the epigenomic and transcriptomic levels, EOCRC tumors demonstrated significant enrichment in neurotransmitter-related pathways, such as CREB signaling in neurons and ion channel transport, alongside a pronounced activation of G-protein coupled receptor (GPCR) signaling. Furthermore, we identified a distinct immune-related signature characterized by the activation of phagosome formation and S100 family signaling pathways. These intracellular alterations were mirrored by a unique systemic metabolic profile involving the G alpha signaling pathway and the transport of vitamins, nucleosides, bile salts, and amine compounds. In addition, we identified a multi-omic signature of 11 genes that exhibit both differential gene expression between EOCRC and LOCRC tumors and significant tumor-specific methylation drift relative to adjacent normal tissue. Notably, this signature is enriched with established epigenetic clock/aging markers, including *LEP*, *PLA2G4F*, *CYP2E1*, *GCM2*, *ZNF418*, and *MINAR1*, making them ideal candidates for early detection by liquid biopsies or risk-stratification tools for EOCRC. **Conclusions:** Our findings demonstrate that EOCRC is a biologically distinct entity driven by specific epigenetic and immune dysregulation. The simultaneous enrichment of neurotransmitter pathways and GPCR signaling suggests that EOCRC development may be uniquely influenced by neuro-epithelial interactions. The 11-gene signature enriched with epigenetic aging markers may serve as screening or surveillance tools for EOCRC patients. Research Sponsor: Paul Calabresi Career Development Award for Clinical Oncology; K12CA133250.

Long-term responders to trifluridine/tipiracil plus bevacizumab in previously treated metastatic colorectal cancer: Results from the BeTAS real-world study.

Nieves Martinez Lago, Margarita Reboredo Lopez, Maria Carmen Riesco Martinez, Sandra López Perais, Borja Gonzalez Gomez, Paula Carla Antonilli, Ana Lopez Alfonso, Ana Fernandez Fernandez Montes, Ismael Ghanem, Martín Pérez Martelo, Sara Agraso Busto, Marcos Melian, Elena Gallardo Martin, Ana M. Jimenez Gordo, Luis Cabezon Gutierrez, Antia Cousillas Castiñeiras, Marta Llanos, Maria Pilar Ochoa Rivas, David Gutierrez Abad, Reyes Ferreiro Monteagudo; Department of Medical Oncology. Hospital Clínico Universitario e Instituto de Investigación Sanitaria de Santiago de Compostela, Santiago de Compostela, Spain; University Hospital A Coruña, A Coruña, Spain; Hospital Universitario 12 de Octubre, Madrid, Spain; Hospital Universitario de Burgos, Burgos, Spain; Hospital Universitario Lucus Augusti, Lugo, Spain; Hospital Universitario de Gran Canaria Dr. Negrin, Gran Canaria, Spain; Hospital Infanta Leonor, Madrid, Spain; Department of Medical Oncology, Complejo Hospitalario Universitario de Ourense, Ourense, Spain; Department of Medical Oncology Hospital Universitario La Paz, Madrid, Spain; Medical Oncologist, Complejo Hospitalario Universitario de Santiago, Santiago De Compostela, Spain; Department of Medical Oncology. University Hospital A Coruna, A Coruna, Spain; Department of Medical Oncology, Instituto Valenciano de Oncología, Valencia, Spain; Alvaro Cunqueiro Hospital, Vigo, Spain; Medical Oncology Department, Hospital Universitario Infanta Sofía, San Sebastián De Los Reyes, Spain; Hospital Universitario de Torrejón, Torrejón De Ardoz, Spain; Complejo Hospitalario de Pontevedra, Pontevedra, Spain; Hospital Universitario de Canarias, San Cristobal De La Laguna, Spain; Hosp. de la Defensa Gomez Ulla, Madrid, Spain; Hospital Universitario de Fuenlabrada, Madrid, Spain; Medical Oncology Department, Hospital Universitario Ramon y Cajal, Madrid, Spain

Background: The phase III SUNLIGHT trial established trifluridine/tipiracil plus bevacizumab (FTD/TPI+BEV) as a standard treatment option for metastatic colorectal cancer (mCRC) after failure of at least two prior regimens. However, limited evidence exists regarding patients achieving durable benefit in routine clinical practice. We aimed to characterize the prevalence, clinical features, and outcomes of long-term responders treated with FTD/TPI plus bevacizumab in a large real-world cohort. **Methods:** BeTAS is a multicenter ambispective real-world study conducted within the Galician Research Group on Gastrointestinal Tumors. Consecutive patients with previously treated mCRC receiving FTD/TPI+BEV after failure or intolerance to ≥ 2 prior regimens were included. Long-term responders (LTRs) were defined using a pre-specified landmark of progression-free survival (PFS) ≥ 9 months. Baseline characteristics, treatment response, and survival outcomes were compared between LTRs and non-LTRs. Overall survival (OS) was assessed using a 9-month landmark analysis to minimize immortal time bias. Survival was estimated using the Kaplan–Meier method and compared using the log-rank test. Multivariable Cox regression was performed. **Results:** Among 576 patients, median PFS and OS were 4.9 months (95% CI 4.3–5.5) and 10.8 months (95% CI 9.8–11.9), respectively. LTRs accounted for 20.3% of the cohort ($n=117$). Compared with non-LTRs, LTRs more frequently had ≤ 2 metastatic sites (83.8% vs 67.5%, $p=0.001$), absence of liver metastases (28.4% vs 16.7%, $p=0.004$), longer time from metastatic diagnosis ($p=0.046$), and Tabernero best prognostic characteristics ($p=0.007$). Among evaluable patients, objective response rate was higher in LTRs (22.1% vs 5.5%, $p<0.001$), as was disease control rate (100% vs 39.0%, $p<0.001$). Median PFS was 15.3 versus 3.6 months, and landmark OS was 23.5 versus 8.1 months (both $p<0.001$). Long-term response remained independently associated with improved OS (HR 0.19, 95% CI 0.14–0.26; $p<0.001$). **Conclusions:** In real-world practice, approximately one in five previously treated patients with mCRC achieve durable benefit with FTD/TPI+BEV. Identification of clinical factors associated with long-term response may support improved patient selection in later-line treatment. Research Sponsor: None.

Correlative analysis of ctDNA in CheckMate-9X8 study of frontline treatment with mFOLFOX6, bevacizumab with or without nivolumab in metastatic colorectal cancer.

Jin Yao, Yong Huang, Rachel Tam, Amanda Cruz, Reed Selby, Aparna Raj Parikh, Takayuki Yoshino, Josep Tabernero, Shidong Jia, Ruslan Novosiadly, Heinz-Josef Lenz; Bristol Myers Squibb, Princeton, NJ; Predicine, Inc., Hayward, CA; Department of Medicine, Division of Hematology/Oncology, Mass General Brigham Cancer Center, Harvard Medical School, Boston, MA; Department of Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan; Vall d'Hebron Hospital Campus and Institute of Oncology (VHIO), IOB-Quiron, Uvic-UCC, Barcelona, Spain; USC Norris Comprehensive Cancer Center, Los Angeles, CA

Background: The CheckMate 9X8 study evaluated ctDNA as biomarker to predict treatment benefit in metastatic colorectal cancer (mCRC) patients receiving standard-of-care therapy with or without nivolumab. Although the phase 2/3 trial did not meet its primary PFS endpoint, the addition of nivolumab appeared to confer clinical benefit in a subset of patients. As predictive biomarkers for first-line nivolumab in mCRC remain unvalidated, this exploratory analysis identified mutation- and methylation-based ctDNA signatures that may help inform future patient stratification and disease management. **Methods:** Study design and methods were published previously (Lenz, et al. JITC 2024). As part of an exploratory biomarker analysis, paired plasma samples (baseline and on-treatment at C3D1) were evaluated for circulating tumor DNA (ctDNA) using PredicineATLAS (600-gene) comprehensive genomic profiling, PredicineSCORE (Low-pass whole-genome sequencing), and PredicineEPIC (methylation) assays and correlated with baseline patient characteristics and treatment efficacy. **Results:** Over 98% (138/140) of baseline patients had quantifiable ctDNA with Predicine ATLAS and approximately 83% (116/140) had detectable copy number variants (CNV) with PredicineSCORE. High concordance was observed between ctDNA-derived mutations and tissue-derived KRAS, TP53, and APC mutations and MSI/MSS status at baseline. 97% of patients with KRAS G12D/V/C mutations positively identified by local tissue testing were also positively identified by ctDNA. 6% of subjects considered KRAS wild-type by local tissue testing were identified as having KRAS G12D/V/C mutations by ctDNA. KRAS mutations, wild-type TP53, chromosomal loss of 18q21.33, high methylation scores and hypomethylated Tetraspanin 15 correlated with treatment efficacy. Neo-KRAS WT, or loss of KRAS mutations on treatment, emerged during treatment in 36% of patients with KRAS mutations at baseline and was associated with improved survival. Significant ctDNA level reduction was seen during treatment in both arms of the study irrespective of tumor response. These insights underscore the promise of ctDNA profiling in enhancing precision medicine by enabling real-time, dynamic assessment of tumor biology and therapeutic response with a potential to guide personalized treatment strategies for mCRC patients in the future. **Conclusions:** This study highlights the potential utility of liquid biopsy in the mCRC setting and provides novel insights from the ctDNA analysis, highlighting genetic and epigenetic ctDNA features that might be associated with clinical efficacy of SOC ± nivolumab in 1L mCRC. The emergence of Neo-KRAS WT in a substantial number of patients indicates a dynamic nature of KRAS alterations and highlights the additional value that longitudinal plasma ctDNA analysis could provide. Clinical trial information: NCT03414983. Research Sponsor: None.

Circulating tumor DNA for characterizing intratumor heterogeneity and outcomes in metastatic colorectal cancer.

Cynthia Yeung, Emerik Osterlund, Guglielmo Vetere, Songwit Payapwattanawong, Berta Martin, Ryan Sun, Kanwal Pratap Singh Raghav, Jonathan M. Loree, Scott Kopetz; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; BCCA - Vancouver Cancer Centre, University of British Columbia, Vancouver, BC, Canada

Background: Intratumor heterogeneity (ITH) drives CRC resistance, yet tissue-based assessments remain limited. ctDNA captures heterogeneity, though variable tumor fractions confound measurements. We assessed raw vs fraction-adjusted ITH in ctDNA for overall survival (OS) in metastatic CRC (mCRC). **Methods:** We analyzed two real-world mCRC cohorts from MD Anderson: a 73-gene panel (1,137 patients, 2014–2023; limit of detection (LoD) 0.1%) and a 701-gene panel (150 patients, 2024–2025; LoD 0.5%). Quality filters included ≥ 3 detected variants, MaxVAF > 0.01 , and bioinformatic filtering of putative germline variants. ITH was quantified via raw Mutant-Allele Tumor Heterogeneity (rMATH; VAF distribution width) and the Shannon entropy-based, MaxVAF-normalized (VAF/Max_VAF) blood ITH (bITH; multiplies bin entropy by clonality weights). OS was assessed using Cox models by continuous variables and optimal cut-points determined by maximally selected log-rank statistics. A stress test subset (top 50% MaxVAF) was analyzed to decouple findings from analytical noise inherent at low tumor fractions. **Results:** In the 73-gene cohort (median age 53.2; 91% MSS, 14% BRAF mutated, 64% RAS mutated), MaxVAF was the strongest predictor of worse OS in both univariable (HR 1.32, $p < 0.001$) and multivariable (MV) models (HR 1.31, $p < 0.001$). Paradoxically, high rMATH was associated with improved OS (MV HR 0.89, $p = 0.014$). This protective signal of high heterogeneity was more pronounced in the dichotomized model (MV HR 0.71, $p < 0.001$) and persisted in the subset of high-burden patients (top 50% MaxVAF) (MV HR 0.69, $p < 0.001$) and the MSS subset (MV HR 0.68, $p = 0.003$). In the 701-gene panel cohort, MaxVAF remained the dominant independent predictor (MV HR 2.37, $p < 0.001$). bITH was not independently prognostic (MV HR 0.98, NS). **Conclusions:** MaxVAF serves as the primary ctDNA-derived driver of clinical outcomes in mCRC, confirming that ctDNA-inferred ITH metrics are heavily confounded by total tumor shedding. The unexpected association between high rMATH and improved OS suggests that increased clonal diversity, at a fixed tumor burden, may indicate a less evolutionarily pruned or consolidated tumor compared to those that have undergone a selective clonal sweep. These results highlight that while ctDNA can characterize clonal architecture, the clinical interpretation of heterogeneity must be contextualized within the tumor’s total systemic volume and evolutionary state. Research Sponsor: Conquer Cancer, the ASCO Foundation.

Cohort	Variable (High vs Low)	Multivariable HR (95% CI)*	p-value
73-gene panel	MaxVAF	1.31 (1.20–1.43)	<0.001
	Raw MATH	0.89 (0.81–0.98)	0.014
	bITH	0.98 (0.90–1.08)	0.716
701-gene panel	MaxVAF	2.37 (1.52–3.71)	<0.001
	Raw MATH	0.85 (0.50–1.44)	0.536
	bITH	1.23 (0.82–1.87)	0.320

*HR per 1 SD increase. Raw MATH was adjusted for MaxVAF, while bITH was tested without redundant MaxVAF adjustment. All models adjusted for age, sex, MSI, BRAF, and RAS status.

Influence of neoadjuvant therapy on tumor-vascular-immune stromal networks in colorectal cancer liver metastases.

Pia J. Osterlund, Tove Bekkhus, Elisabet Rodríguez-Tomás, Reetta Peltonen, Pauliina Reijonen, Emerik Osterlund, Caj Haglund, Jaana Hagström, Helena Isoniemi, Bengt Glimelius, Tobias Sjöblom, Arne Ostman, Ari Ristimäki, Teijo S. Pellinen, Alfonso Martín-Bernabé; Tampere University Hospital, Tampere, Finland; Karolinska Institutet, Solna, Stockholm, Sweden; Helsinki University Hospital and University of Helsinki, Helsinki, Finland; Helsinki University Hospital and University of Helsinki, Espoo, Finland; Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Uppsala University, Uppsala, Sweden; Department of Pathology, HUS Diagnostic Center, Helsinki University Hospital and University of Helsinki, Helsinki, Finland; Institute for Molecular Medicine Finland Precision Systems Medicine, Helsinki, Finland

Background: Neoadjuvant therapy's effect on vascular, tumor, and immune compartments, and their co-regulation, in colorectal liver metastases (CRLMs) remains poorly understood. We performed multiplex-based tissue profiling to quantify how treatment reshapes stromal compartment and co-occurrence networks, defined by inside-case correlations between features. **Methods:** We analyzed 76 CRLM cases (27 untreated, 49 neoadjuvant-treated [43 chemotherapy, 6 chemo + VEGF-/EGFR-targeted]). Tissue microarrays (1–3 1-mm cores/tumor) underwent multiplex immunofluorescence to quantify immune/tumor subsets (CD3/CD4/CD8/PD-1/FOXP3/TIM-3/Ki67/CDX2), vessels (claudin-5), and stromal perivascular compartments (α SMA/PDGFR β). Statistical analysis included Mann-Whitney U tests and Spearman correlations. **Results:** Neoadjuvant-treated CRLMs had 42% fewer proliferating tumor cells (CDX2⁺Ki67⁺ density, $p=0.006$) and 33% lower CDX2⁺ density ($p=0.031$) compared with untreated CRLMs. This was accompanied by a 32% reduction in proliferating cytotoxic T-cells (CD3⁺CD8⁺Ki67⁺ density, $p=0.029$). A reduction in vessel size was also observed in treated CRLMs (vessel size, -12%, $p=0.077$). Analyses suggested different effects by type of neoadjuvant treatment. Chemotherapy alone reduced proliferating tumor cells (CDX2⁺Ki67⁺ density, -37%, $p=0.016$) and suppressed cytotoxic T-cell proliferation (CD3⁺CD8⁺Ki67⁺ density, -40%, $p=0.017$). The addition of VEGF/EGFR-targeted agents produced the most pronounced reduction in tumor burden (CDX2⁺ density, -73%, $p=0.012$; CDX2⁺Ki67⁺ density, -76%, $p=0.010$) vs. untreated. CRLM co-occurrence networks were also affected by treatment. Treatment abolished positive correlations between tumor cells (CDX2⁺ and CDX2⁺Ki67⁺ densities) and α SMA⁺PDGFR β ⁺ perivascular fraction/vessel size ($r=+0.42$ – $+0.60$, $p<0.05$), and negative correlations between tumor cells and α SMA⁺PDGFR β ⁺ perivascular fraction/vessel density ($r=-0.47$ – -0.40 , $p<0.05$) in untreated (vs $+0.05$ – $+0.27$ and $+0.09$ – $+0.21$, $p=n.s.$, in treated). Treatment also eliminated positive correlations between vessel size and exhausted (CD8⁺PD-1⁺) and regulatory (CD4⁺FOXP3⁺) T-cell densities (untreated $r=+0.40$ – $+0.47$, $p<0.05$). In parallel, new positive links emerged between α SMA⁺PDGFR β ⁺ perivascular fraction and CD4⁺ and CD8⁺ T cells ($r=+0.41$ – $+0.42$, $p<0.05$). **Conclusions:** This exploratory study indicates that neoadjuvant treatment alters the CRLM microenvironment, affecting tumor, vascular, and immune compartments. Additionally, analyses suggest that treatment induces a restructuring of their interdependence networks, defined by the loss of specific tumor-stromal-vascular links seen in untreated CRLMs, while establishing new ones. These findings motivate continued mechanistic studies and analyses on how these changes are related to benefits of treatment. Research Sponsor: None.

Clinical efficacy of laparoscopic hybrid surgery versus total open surgery for simultaneous resection of colorectal cancer liver metastases (CHLH trial).

Wei Zhang, Guanyu Yu, Tianshuai Zhang, Rongbo Wen, Leqi Zhou, Liqiang Hao, Xiaoming Zhu, Haifeng Gong; Department of Colorectal Surgery, Changhai Hospital, Naval Medical University, Shanghai, China

Background: Despite widespread adoption of simultaneous resection for colorectal liver metastases, the clinical efficacy varies among different approaches, and the optimal surgical strategy remains controversial. This study aims to evaluate the efficacy and safety of laparoscopic hybrid surgery (LHS) versus total open surgery (TOS) in the simultaneous resection of CRLM. **Methods:** This is a prospective cohort study (NCT06550700) conducted at a tertiary medical center, enrolling 266 patients who underwent simultaneous resection for CRLM from January 2017 to June 2021. The surgical approach is selected by colorectal surgeons and hepatobiliary surgeons based on their experience with either TOS or LHS. The primary outcomes were the incidence of complications and postoperative recovery-related outcomes. The secondary outcomes were 5-year overall survival (OS) and disease-free survival (DFS). **Results:** This study ultimately enrolled 144 patients in the LHS group and 122 patients in the TOS group. The complication rate was significantly lower in the LHS group than in the TOS group (10.4% vs. 20.5%, $p = 0.022$). Compared with the TOS group, patients in the LHS group had shorter postoperative hospital stay [8.00 (6.00, 10.00) vs. 9.00 (8.00, 12.00) days, $p < 0.001$], earlier resumption of liquid intake [3.00 (3.00, 3.00) vs. 4.00 (3.00, 4.00) days, $p < 0.001$], and less intraoperative blood loss [300.00 (200.00, 400.00) vs. 500.00 (500.00, 700.00) mL, $p < 0.001$]. However, the LHS group was associated with longer operative time [260.00 (236.00, 320.00) vs. 240.00 (195.00, 269.00) min, $p < 0.001$]. No significant differences were observed between the two groups in overall survival ($p = 0.464$) or disease-free survival ($p = 0.838$). **Conclusions:** Compared with TOS, applying LHS for simultaneous resection for CRLM results in faster postoperative recovery, lower complication rates, and similar survival outcomes. Clinical trial information: NCT06550700. Research Sponsor: National Natural Science Foundation of China; 82473439, 82272705 and 82503486; the Shanghai "Rising Stars of Medical Talents" Youth Development Program of the Shanghai Municipal Health Commission, China; No.2024-70; the Naval Medical University "Deep Blue" Project Talent Program; the First Affiliated Hospital of Naval Medical University Special Project for Basic Medical Research, China; 2023QD003 and 2023PY04; the First Affiliated Hospital of Naval Medical University Special Project for Clinical Research, China; 2024LYA02; Shanghai Shengkang Hospital Development Center, Shanghai Clinical Cohort Project; SHDC2025CCS019; Shanghai Science and Technology Plan Project; 25SF1901500.

A four-marker-protein signature to predict ramucirumab efficacy in combination with TAS-102 in advanced colorectal cancer: Translational analysis of the RAMTAS trial of the German AIO (AIO-KRK-0316/IKF643).

Thomas Seufferlein, Anton Lahusen, Tim Eiseler, Lukas Perkhofer, Jasmin Schuhbaur, Angelika Kestler, Sebastian Stintzing, Tobias Dechow, Marianne Sinn, Christoph Roderburg, Ludwig Fischer von Weikersthal, Ullrich Graeven, Alexander Stein, Dominik Paul Modest, Jens T. Siveke, Claudia Pauligk, Salah-Eddin Al-Batran, Thorsten Oliver Goetze, Thomas Jens Ettrich, Stefan Kasper; Department of Internal Medicine I, Ulm University Hospital, Ulm, Germany; Ulm University Hospital, Department of Internal Medicine I, Ulm, Germany; Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Hematology, Oncology, and Cancer Immunology (CCM), Berlin, Germany; Private Oncology Practice Ravensburg, Ravensburg, Germany; Universitätsklinikum Hamburg-Eppendorf II. Medizinische Klinik, Hamburg, Germany; Clinic for Gastroenterology, Hepatology and Infectious Diseases, University Hospital Düsseldorf, Düsseldorf, Germany; Department of Hematology and Oncology, Klinikum St. Marien Amberg, Amberg, Germany; Kliniken Maria Hilf, Department of Hematology, Oncology and Gastroenterology, Moenchengladbach, Germany; Hematology-Oncology Practice Eppendorf (HOPE), Hamburg, Germany; Charité Comprehensive Cancer Center Berlin, Berlin, Germany; Bridge Institute of Experimental Tumor Therapy, West German Cancer Center, University Hospital Essen and Division of Solid Tumor Translational Oncology, German Cancer Research Center, Heidelberg, Essen, Germany; Frankfurt Institute of Clinical Cancer Research IKF at Northwest Hospital, Frankfurt Am Main, Germany; The Frankfurt Institute of Clinical Cancer Research IKF GmbH, Frankfurt Am Main, Germany; Frankfurt Institute of Clinical Cancer Research (IKF), Krankenhaus Nordwest, UCT-University Cancer Center, Frankfurt Am Main, Germany; Department of Internal Medicine I, University Hospital Ulm, Ulm, Germany; University Hospital Essen, West German Cancer Center, Essen, Germany

Background: The combination of TAS-102 and bevacizumab is standard in the treatment of advanced colorectal cancer (aCRC). Ramucirumab (Ram) is a mAb that blocks VEGFR2. Ram in combination with Tas-102 did not improve OS compared to Tas-102 alone in the ITT population of the RAMTAS trial. Subgroups such as female patients (pts) and pts with left-sided tumors appeared to benefit from the combination (DOI:10.1016/j.annonc.2024.08.2264). Here we aimed at identifying angiogenesis-related, soluble, predictive biomarkers defining a RAMTAS subpopulation benefitting from the addition of Ram to Tas-102. **Methods:** Serum samples were available from 194 of 428 pts from the RAMTAS study (96 pts randomized to TAS-102, 98 pts to TAS-102 plus Ram). Serum levels of 85 angiogenesis-related proteins obtained prior to treatment with Tas-102 +/- Ram (baseline, BL) and at cycle 2 day 1 prior to the start of the next cycle (treatment, TR) were quantified via multiplex-ELISA by Myriad-RBM. Multivariate Cox regression models were developed within the combination arm using stepwise selection and ridge regularization. Model performance was assessed via C-index and validated using 10 x 5-fold cross-validation (CV) as well as full quality control for multicollinearity and proportional hazard assumptions. To distinguish predictive from general prognostic effects, the identified signatures were applied to the monotherapy control arm. **Results:** A TR model incorporating just 4 serum proteins demonstrated robust discrimination in the combination arm (Training C-index: 0.712; CV C-index: 0.708 ± 0.063). This model successfully stratified patients into a “Ram benefit” and a “no Ram benefit” group with a corresponding median PFS of 7.0 mo and 1.9 mo, respectively (HR 6.97, $p < 0.001$). A Baseline (BL) model yielded a C-index of 0.699, also utilizing just 4 serum proteins. Application of both models to the TAS-102 mono arm resulted in poor discrimination (C-index ~0.60) indicating that the signatures are specific predictors for the combination. In a comparative survival analysis, “Ram-benefit” TR model patients achieved a significantly longer PFS with the combination compared to monotherapy (7.00 vs. 2.14 mo; HR 0.558, $p=0.0078$). Conversely, “no-Ram-benefit” patients derived no significant benefit from the addition of Ram (PFS 1.91 vs. 1.91 mo; HR 0.946, $p=0.4204$). **Conclusions:** Oligo-marker serum signatures, when incorporating early on-treatment dynamics after one cycle of Tas-102/Ram, may effectively predict a survival benefit for aCRC-pts receiving TAS-102 in combination with Ram. We propose that a two-stage “Screen & Monitor” (BL+TR) strategy will help to identify primary refractory patients who gain no benefit from the addition of Ram. Such an approach could maximize therapeutic utility while reducing potential toxicity. Clinical trial information: NCT03520946. Research Sponsor: Lilly.

Real-world outcomes and recurrence risk factors of liver transplantation for permanently unresectable colorectal liver metastases following the TransMet trial.

Rene Adam, Jean Emmanuel Langdorph, Céline Piedvache, Antonio Sa Cunha, Heithem Jeddou, Jean Hardwigsen, Fabrice Muscari, Laurence Chiche, Michel Pierre Ducreux, Mirca Chirica, Mickael Lesurtel, Olivier Scatton, Emmanuel Boleslawski, Ephrem Salamé, Jean-Yves Mabrut, Jan Lerut, Francis Albert Lévi, Maité Lewin, Lamiae Grimaldi, Maximiliano Gelli, TRANSMET Study Collaborative Group; Paul Brousse Hospital - APHP, Villejuif, France; CHU Tours, Tours, France; Clinical Research Unit, Assistance Publique - Hôpitaux de Paris (APHP) University Paris-Saclay, Kremlin Bicêtre, France; Centre Hospitalier Universitaire de Rennes, Rennes, France; Assistance Publique – Hôpitaux de Marseille, Marseille, France; Hôpital Rangueil CHU Toulouse, Toulouse, France; Service de Chirurgie HPB Transplantation, Hôpital Haut Leveque, Bordeaux, France; Université Paris-Saclay, Institut Gustave Roussy, Villejuif, France; CHU Grenoble Alpes, Grenoble, France; APHP Hôpital Beaujon, Clichy, France; Service de Chirurgie Hépatobiliaire, Hôpital Pitié-Salpêtrière, Paris, France; Service de Chirurgie Digestive et Transplantations (CAO), Hôpital Huriez, Lille, France; Chirurgie Digestive Hépatobiliaire et Pancréatique, Tours, France; University Hospital Lyon, Lyon, France; Université Catholique de Louvain, Louvain, Belgium; UPR Chronothérapie, Cancers et Transplantation, Université Paris Saclay, Hôpital Paul Brousse ID Isco 13918, Villejuif, France; Assistance Publique - Hôpitaux de Paris (APHP) University Paris-Saclay, Villejuif, France; Université Paris-Saclay, Gustave Roussy, Villejuif, France

Background: Following the TRANSMET trial that demonstrated an overall survival (OS) benefit of liver transplantation (LT) over chemotherapy (CT) alone for selected patients with permanently unresectable colorectal liver metastases (uCRLM), the program of LT has continued in France with the same eligibility criteria, independent validation and graft allocation policy. We assessed the real-world oncological outcomes and prognostic factors for post-LT recurrence-free survival (RFS) in the whole cohort. **Methods:** This nation-wide analysis pooled both patients transplanted in TransMet (Trial cohort) and those after trial closure (Extension cohort). OS and RFS were evaluated in each cohort. Multivariable Cox models for RFS using sensitivity analyses including forced cohort adjustment and bootstrap resampling were performed. **Results:** A total of 87 patients underwent LT (37 Trial cohort; 50 Extension cohort). Baseline characteristics at CRLM diagnosis were comparable. At LT, patients in the Extension cohort received significantly fewer CT cycles (≥ 24 cycles, 16% vs 41%, $p=0.01$) and showed higher rate of partial response (94% vs 57%, $p < 0.001$) after first-line CT. At time of LT, tumor burden, RECIST status and tumor markers were similar. Median follow-up was shorter in the Extension cohort (16 vs 57 months). No significant differences in OS and RFS were observed between extension and trial cohorts (30-months OS 89% vs 81%; 30-months RFS 47% vs 39%, respectively). In univariable analysis, risk factors of RFS included ≥ 2 CT lines, ≥ 24 CT cycles before LT, CEA at LT > 5 ng/mL, progression on CT and interval from primary tumor surgery > 2 years. In multivariable Cox analysis, ≥ 2 lines or > 24 cycles before LT (HR 2.90, 95% CI 1.32–6.36; $p < 0.01$) and CEA at LT > 5 ng/mL (HR 2.26, 95% CI 1.18–4.33; $p=0.01$) remained independently associated with RFS, adjusted on interval from primary tumor surgery. Bootstrap resampling (2,000 iterations) highlighted these results in 82% and 67% of models, respectively. **Conclusions:** LT for uCRLM gives good and reproducible oncological outcomes across trial and extension cohorts. This exploratory analysis supports that RFS is impaired by a prolonged pre-transplant chemotherapy (≥ 2 lines or ≥ 24 cycles) and improved by a good biological response (normalization of CEA), supporting considering LT in a multidisciplinary setting as soon as definitive unresectability is established. Research Sponsor: None.

Dynamic circulating tumor DNA profiling for prediction of long-term clinical benefit in pMMR locally advanced rectal cancer receiving neoadjuvant chemoradiotherapy plus sintilimab.

Xiaobin Zheng, Huashan Liu, Zhihong Zhang, Tanxing Cai, Lishuo Shi, Ziwei Zeng, Wei Xiao, Shuangling Luo, Yonghua Cai, Zhanzhen Liu, Yujie Hou, Yanxin Luo, Zuli Yang, Xiaowen He, Jia Ke, Liang Huang, Liang Kang; The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, China; Clinical Research Center, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, China

Background: Immune checkpoint inhibitors (ICIs) targeting PD-1 have significantly improved outcomes in locally advanced rectal cancer (LARC). Circulating tumor DNA (ctDNA) has emerged as a promising biomarker for treatment response monitoring and surveillance, capable of predicting long-term clinical outcomes. However, whether ctDNA serves as a prognostic predictor in patients with proficient mismatch repair (pMMR) LARC receiving neoadjuvant chemoradiotherapy (CRT) combined with immunotherapy remains to be explored. **Methods:** This prospective single-arm phase II trial enrolled 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) (NCT05450029). Treatment-naïve patients received radiotherapy (50 Gy/ 25 fractions), 6 cycles of mFOLFOX6, and 5 cycles of sintilimab, followed by total mesorectal excision (TME) 6–8 weeks post-radiotherapy. Next-generation sequencing was used to evaluate baseline tumor tissue DNA and serial ctDNA dynamic changes. Baseline (T_0) maximal somatic variant allelic frequency (maxVAF) was assessed, along with its changes at the first (T_1 , two cycles after therapy) and second clinical evaluation (T_2 , four cycles after therapy). **Results:** Tumor somatic mutations and aligned ctDNA analyses were conducted in 43 patients. The pathologic complete response (pCR) rate was 65.2%, with an objective response rate (ORR) of 93.5%. The R0 resection rate was 97.8%. The 3-year event-free survival rate, and 3-year overall survival rate remain immature. For dynamic ctDNA analysis, 37 patients were assessed using a 950-gene panel relevant to cancer. A significant decline in maxVAF from T_0 to T_1 was observed in the pCR group. Among patients who reached follow-up endpoints, circulating tumor DNA analysis reveals that patients with a $> 50\%$ decline in maxVAF from T_0 to T_1 demonstrated longer survival outcomes and higher response rates compared to those without such decline. **Conclusions:** Serial ctDNA analysis demonstrates applicability in predicting treatment response to CRT combined with immunotherapy in pMMR LARC. Dynamic changes in circulating ctDNA may serve as a potential prognostic indicator in this population. Future studies should integrate ctDNA profiling of comprehensive cancer-related gene panels with large-scale clinical data to refine patient stratification and optimize therapeutic management. Clinical trial information: NCT05450029. Research Sponsor: National Natural Science Foundation of China; 82470696; National Key Clinical Discipline; Guangdong Basic and Applied Basic Research Foundation; 2022A1515012498 and 2024A1515010956; the program of Guangdong Provincial Clinical Research Center for Digestive Diseases; 2020B111170004; Science and Technology Projects in Guangzhou; 2024A04J6400; Sun Yat-sen University Clinical Research 5010 Program; 2016005; Innovative Clinical Technique of Guangzhou.

Safety and efficacy of ifebemtinib combined with garsorasib in KRAS G12C mutant colorectal cancer from a randomized part of a phase Ib/II study.

Xiangdong Cheng, XingYa Li, Rongbo Lin, Ying Liu, Yongzhong Luo, Yuan Yuan, Huaqiu Shi, Tangfeng Lv, Yiping Zhang, Liming Zhu, Yinxin Zhu, Zaiqi Wang, Zhengbo Song; Zhejiang Cancer Hospital, Hangzhou, Zhejiang Province, China; First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; Department of Gastrointestinal Oncology, Fujian Provincial Cancer Hospital, Fuzhou, China; Henan Cancer Hospital, Zhengzhou, China; Hunan Cancer Hospital, Changsha, China; Xuzhou Central Hospital, Xuzhou, China; First Affiliated Hospital of Gannan Medical University, Ganzhou, China; Affiliated Jinling Hospital, Medical School of Nanjing University, Nanjing, China; Zhejiang Cancer Hospital, Hangzhou, China; InxMed (Shanghai) Co., Ltd, Shanghai, China

Background: Studies (Yaeger R, et al.; Fakih, MG, et al.) have shown when RASi is combined with optimal therapeutic partner(s), clinical efficacy and benefit can be maximized. Ifebemtinib (ifebe) is a highly potent and selective oral inhibitor of focal adhesion kinase (FAK) that exhibits synergistic effect with RASi in both preclinical and clinical setting. Garsorasib (D-1553) is a novel KRAS G12C approved in China for treatment of KRAS G12C mutant NSCLC. We previously reported a promising objective response rate (ORR) of 44.4% in patients (pts) with KRAS G12C mutant CRC receiving ifebe + D-1553, with the durability of efficacy yet to be confirmed. Herein, we present the updated results with median follow-up of (14.4 months) from a randomized cohort of phase Ib/II study, comparing ifebe + D-1553 vs D-1553 alone in KRAS G12C mutant CRC, to elucidate the relative therapeutic contribution of ifebe and durability of response. **Methods:** Metastatic KRAS G12C mutant CRC pts with at least 1 prior line of systemic anticancer therapy were enrolled in a randomized part and randomized 1:1 to ifebe (100mg QD) + D-1553 (600mg BID) or D-1553 (600mg BID) alone. **Results:** As of January 4, 2026, 36 previously treated metastatic CRC pts were enrolled, with 18 pts in ifebe + D-1553 group and 18 pts in D-1553 group (≥ 3 prior lines of treatment: 33.3% vs 27.8%; liver metastasis: 55.6% vs 72.2%). The median treatment duration was 8.5 months vs 3.6 months and 4 pts (3 [16.7%] vs 1 [5.6%]) were still on treatment. The hazard ratio (HR) for progression free survival (PFS) and overall survival (OS) was 0.47 and 0.44, respectively, demonstrating the durability of efficacy in pts receiving ifebe + D-1553 (Table). The safety profiles of ifebe + D-1553 in CRC pts are comparable to each single agent. No ifebe or D-1553 related death or AEs leading to drug withdrawal were reported. **Conclusions:** The combination of ifebe and D-1553, a dual-oral regimen, exhibits favorable safety profiles and better efficacy in treating KRAS G12C mutant CRC, with mOS exceeding 16 months. Clinical findings from this randomized study have shown robustness of improvement in overall ORR, PFS, DOR and OS benefit with this combination regimen, indicating that adding ifebe to a RASi can further improve clinical outcome to CRC patients with RAS G12C mutation. Clinical trial information: NCT06166836. Research Sponsor: None.

Efficacy.		
	ifebe + D-1553 (N=18)	D-1553 (N=18)
Objective response rate (ORR), %	44.4 (21.5, 69.2)	16.7 (3.6, 41.4)
Disease control rate (DCR), %	100.0 (81.5, 100.0)	77.8 (52.4, 93.6)
Median duration of response (mDoR), months	12.1 (1.41, NE)	6.8 (6.3, NE)
Median PFS, months	8.4 (3.0, 11.9)	4.0 (2.0, 5.6)
HR for PFS (95% CI)	0.47 (0.23, 0.98)	
Median OS, months	16.4 (13.1, NE)	7.8 (5.3, NE)
HR for OS (95% CI)	0.44 (0.17, 1.15)	

Reduced oxaliplatin exposure in gastrointestinal cancers: A systematic review and meta-analysis.

Wallace Klein Schwengber, Fares Jamal, Luís Felipe Leite da Silva, Abdullah Alsulaiman, Ayla Kouli, Oluseyi Abidoye, Khalid Benkhadra, Tanios S. Bekaii-Saab, Mohamad Bassam Sonbol; Division of Hematology and Oncology, Mayo Clinic Arizona, Phoenix, AZ; Universidade Federal Fluminense, Niterói, Brazil; Mayo Clinic Arizona, Phoenix, AZ

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a frequent dose-limiting toxicity from oxaliplatin that impairs quality of life in gastrointestinal (GI) cancer patients (pts). While strategies to limit exposure exist, their impact on survival remains debated. We evaluated whether reduced oxaliplatin exposure (ROE) maintains survival while mitigating toxicity. **Methods:** We conducted a systematic review and meta-analysis (PubMed, Embase, Scopus, Web of Science, EBM Reviews) of studies comparing ROE vs standard-duration oxaliplatin-based chemotherapy in GI cancers. ROE was defined as planned limitation of oxaliplatin exposure, including shortened duration (3–4 months), maintenance-based de-escalation, or stop-and-go strategies. Primary endpoints were disease-free survival (DFS) in curative settings, progression-free survival (PFS) in palliative settings, and overall survival (OS). Secondary endpoints included grade ≥ 3 CIPN and grade ≥ 3 adverse events (AEs). Random-effects models used Hartung-Knapp-Sidik-Jonkman correction. Heterogeneity was assessed via I^2 and Cochran's Q. **Results:** 24 studies, comprising 15 randomized controlled trials (RCTs) and 9 retrospective cohorts, were included (N = 30,404 pts; ROE: 13,348; control: 17,056). Settings included adjuvant colorectal cancer (CRC; n = 14), metastatic CRC (mCRC; n = 5), gastric cancer (GC) (adjuvant n = 1, metastatic n = 3), and metastatic pancreatic cancer (PDAC) (n = 1). ROE strategies included shortened duration (n = 14), maintenance (n = 8), and stop-and-go (n = 2). In adjuvant CRC, ROE did not compromise DFS (HR 1.07; 95% CI, 0.98–1.16; p = 0.12; I^2 = 21.7%), including in high-risk subgroups (HR 1.14; 95% CI, 0.93–1.40; p = 0.14; I^2 = 38.9%); OS was also not different between groups (HR 1.00; 95% CI, 0.94–1.07; p = 0.89; I^2 = 0%), including high-risk pts (HR 1.01; 95% CI, 0.93–1.10; p = 0.68; I^2 = 0%). In mCRC, ROE showed no detriment to PFS (HR 1.11; 95% CI, 0.99–1.25; p = 0.07; I^2 = 0%) or OS (HR 1.06; 95% CI, 0.92–1.23; p = 0.33; I^2 = 0%). Similarly, in metastatic gastric cancer, PFS (HR 0.82; 95% CI, 0.34–1.99; p = 0.44; I^2 = 77.3%) and OS (HR 0.90; 95% CI, 0.67–1.21; p = 0.26; I^2 = 0%) were comparable. Findings remained concordant after restricting the analysis to only RCTs. Pooled analysis was not feasible for PDAC and adjuvant GC studies, but individual study findings were consistent with the above. ROE significantly reduced the risk of grade ≥ 3 CIPN (OR 0.32; 95% CI, 0.20–0.53; p < 0.001; I^2 = 80.6%) and overall grade ≥ 3 AEs (OR 0.65; 95% CI, 0.50–0.86; p = 0.01; I^2 = 59.9%). **Conclusions:** Across GI malignancies, ROE was not associated with inferior DFS, PFS, or OS and was associated with lower rates of severe neurotoxicity and high-grade AEs. These findings support planned limitation of oxaliplatin exposure as a strategy to improve the therapeutic index of oxaliplatin-based chemotherapy across disease settings. Research Sponsor: None.

Data from a real-world study: Association of CDCP1 expression level with survival outcomes in mCRC patients treated with bevacizumab or cetuximab plus chemotherapy.

Yitzhar Efraim Goretsky, Yan Yang, Michela Bartolini, Shivani Soni, Pooja Mittal, Fang-Shu Ou, Lesly Torres-Gonzalez, Unnati Hemant Shah, Jae Ho-Lo, Steve Soto Trujillo, Wu Zhang, Alan P. Venook, Sandra Algaze, Joshua Millstein, Heinz-Josef Lenz; Division of Medical Oncology, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA; Department of Population and Public Health Sciences, Keck School of Medicine, University of Southern California, Los Angeles, CA; Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Italy; Alliance Statistics and Data Management Center, Mayo Clinic Rochester, Rochester, MN; University of California, San Francisco, San Francisco, CA; Division of Medical Oncology, Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA

Background: CUB domain-containing protein 1 (CDCP1) is a transmembrane protein shown to be over-expressed in colorectal cancer (CRC), with an important role in tumor initiation, growth and metastasis. Through interactions with EGFR, CDCP1 promotes nuclear translocation of the key regulators of Wnt signaling, β -catenin and E-cadherin. High CDCP1 expression has been associated with poor survival outcomes in multiple solid tumors but data in CRC remains limited. We investigated associations between CDCP1 level and survival outcomes in patients with metastatic CRC (mCRC) in the phase III clinical trial CALGB/SWOG 80405 (Alliance). **Methods:** Data from 433 mCRC patients in the CALGB/SWOG 80405 (Alliance) trial were analyzed. Patients received bevacizumab (n = 226) or cetuximab (n = 207) plus chemotherapy as 1st-line treatment. Tumor RNA was extracted from FFPE samples and processed through the HiSeq 2500 (Illumina) platform. Overall survival (OS) and progression free survival (PFS) curves were evaluated in all treatment subgroups and stratified according to high or low CDCP1 expression. Likelihood ratio tests, hazard ratios (HRs), and 95% confidence intervals (CIs) were calculated using Cox proportional hazards multivariate models, adjusting for age, sex, ECOG performance status, tumor location, number of metastatic sites, KRAS status, consensus molecular subtypes, and treatment arm. **Results:** Overall, low CDCP1 expression was associated with better OS compared to high expression (HR = 1.38; 95% CI 1.07-1.77; 35.8 vs 25.0 months, p = 0.045). Subgroup analysis re-demonstrated this pattern in males (HR = 1.64; 95% CI 1.64-2.28; 35.9 vs 23.6 months, p = 0.01), patients with MSS tumors (HR = 1.56; 95% CI 1.17-2.08; 36.7 vs 25.1 months, p = 0.0094), and patients treated with cetuximab+FOLFOX (HR = 1.79; 95% CI 1.16-2.77; 40.8 vs 24.0 months, p = 0.03). The effect of CDCP1 expression on PFS was less pronounced. Relative to high expression, low expression was associated with better PFS in males (HR = 1.49; 95% CI 1.10-2.03; 13.1 vs 9.8 months, p = 0.027) and left-sided tumors (HR = 1.50; 95% CI 1.10-2.04; 14.4 vs 10.1 months, p = 0.034). **Conclusions:** Our findings represent real-world data of the predictive role of CDCP1 in patients with mCRC undergoing anti-EGFR or anti-VEGF treatment. Consistent with studies of other cancers, we show that low CDCP1 expression is predictive of better survival outcomes, with subgroup analysis revealing associations in males, MSS tumors, and left-sided tumors. Among treatment groups, low CDCP1 expression is predictive of better OS in cetuximab+FOLFOX-treated patients, a key finding given CDCP1's close mechanistic ties to EGFR. Further studies should explore whether these associations are seen in other treatment modalities and whether CDCP1 blockade could represent a viable strategy in patients with high expression. Research Sponsor: National Cancer Institute.

Multimodality neoadjuvant downstaging therapy before liver transplantation for colorectal liver metastasis: Real-world data from the Cleveland Clinic.

Mazhar Khalil, Chase Wehrle, Ahmed Sayed Ahmed, Shilpa Junna, Sami Shoucair, Smitha S. Krishnamurthi, Bassam N. Estfan, Suneel Deepak Kamath, Jamak Modaresi, Jaekeun Kim, David Kwon, Koji Hashimoto, Federico Aucejo, Kanika G. Nair; Cleveland Clinic, Cleveland, OH; Cleveland Clinic Foundation, Cleveland, OH; Cleveland Clinic Cancer Center, Cleveland, OH

Background: Liver transplantation (LT) has a clear survival benefit in advanced, unresectable, liver-confined colorectal cancer liver metastasis (CRLM). However, pre-transplant management and optimal selection criteria remain understudied and previously reported data indicate recurrence-free survival <40% at 3- and 5-years post-LT. **Methods:** 23 patients entered the protocol; 22 patients underwent LT (12/2017-12/2025) utilizing the Cleveland Clinic protocol for down-staging prior to LT. The protocol involves intensive locoregional therapy (LRT) with systemic chemotherapy, aiming to reach minimal disease burden based on FDG PET-CT, ctDNA, and CEA. Patients with minimal or no detectable disease or irreversible treatment-induced liver injury undergo transplant. Patients must have disease control for at least 1 year after resection of the primary colorectal tumor. **Results:** Median age at LT was 45 years (IQR=39-50). Median largest tumor size on pre-LT imaging was 2.2 cm (1.6-7.35), and 18 patients (82%) had bilobar disease. Most patients received intensive systemic therapy (median=18 cycles, IQR=12-37), including 5-FU (n=18), oxaliplatin (n=18), irinotecan (n=13), and bevacizumab (n=17). Tumors were KRAS (n=6) and BRAF non-V600E (n=2) mutated. 20 patients (91%) received pre-LT LRT, including radioembolization (n=11), ablation (n=9), resection (n=10), and HAI pump (HAIP) (n=7). Only one patient dropped out of the pre-LT protocol for liver failure in 2017, suspected from combination of bilobar Y90 and SBRT. Pre-LT PET showed metabolic activity in 8 patients (36%). Median PET-Metabolic Tumor Volume (MTV) at protocol entry was 49.2cm³ (18-162) and at LT was 0cm³ (0-6.4) with a median MTV-reduction of 45.2cm³ (18-156). Median MELD-Na at LT was 9 (IQR 6-13). Pre-LT tumor agnostic ctDNA was detected in 12/17 patients (71%). All patients with ctDNA(-) pre-LT had non-viable tumor on explant (n=5/5 vs. ctDNA(+)=5/12, p=0.028). At median follow-up of 1.6 years, 20 (91%) remain alive, and 18 (82%) are recurrence-free. Median RFS was 5.4 years (95% CI=3.52-7.36) and OS=6.72 years (95%CI=5.34-8.00). Recurrences were lung (n=2), liver (n=1), and liver+para-aortic (n=1) nodes. There was no post-LT recurrence when non-viable on PET scan and on histology (log-rank p<0.001). Pre-LT PET-MTV>70cm³ correlated with histologically viable tumor (p=0.031). Pre-LT HAIP demonstrated a trend towards non-viable tumor on explant (n=5/7 non-viable, 71%). **Conclusions:** LT for CRLM shows clear survival benefit in randomized trials. Aggressive pre-LT locoregional and systemic therapies aimed at minimizing disease burden assessed by PET scan and ctDNA may demonstrate improved outcomes, as may HAIP. A clinical trial testing these hypotheses has been designed with expected enrollment in 2026 at three sites. Research Sponsor: None.

Tumor-informed versus tumor-agnostic ctDNA assays for molecular residual disease detection in colorectal cancer: A systematic review and meta-analysis.

Nain Tara, Hina Zubair, Abdullah Sultany, Hamnah Tayyab, Anubhuti Sharma, Muhammad Yasir, Amlish Gondal; Guthrie Robert Packer Hospital, Sayre, PA; University of Missouri Hospital, Columbia, MO

Background: Circulating tumor DNA (ctDNA) is increasingly used for detection of molecular residual disease (MRD) following curative-intent treatment for colorectal cancer (CRC). Two principal assay strategies exist: tumor-informed (TI) assays requiring prior tumor sequencing, and tumor-agnostic (TA) assays using fixed plasma-based panels. The relative prognostic and diagnostic performance of these approaches remain uncertain. Despite growing clinical adoption, no systematic comparison of their relative performance exists to guide assay selection.

Methods: We performed a systematic review and meta-analysis in accordance with PRISMA 2020 guidelines. PubMed, Embase, Cochrane Library, and Web of Science were searched from inception to January 2025 for original studies evaluating ctDNA-based MRD detection after curative-intent treatment for CRC. Primary outcomes were hazard ratios (HRs) for recurrence-free survival (RFS) and diagnostic accuracy metrics (sensitivity and specificity). Random-effects models (DerSimonian-Laird estimator) were used to pool effect estimates; heterogeneity was assessed using I^2 statistics. Subgroup analyses were conducted by assay type (tumor-informed vs tumor-agnostic) and sampling strategy (landmark vs serial). Quality assessment was performed using QUADAS-2 for diagnostic studies and Newcastle-Ottawa Scale for prognostic studies. **Results:** Twenty-three studies comprising 9,847 patients met inclusion criteria. Eighteen studies evaluated tumor-informed assays ($n=7,892$) and eight evaluated tumor-agnostic assays ($n=2,156$), with three directly comparing both approaches. For tumor-informed assays, the pooled HR for recurrence in ctDNA-positive versus ctDNA-negative patients was 7.58 (95% CI, 6.21–9.25; $I^2=24\%$). For tumor-agnostic assays, the pooled HR was 4.12 (95% CI, 3.18–5.34; $I^2=18\%$). Subgroup analysis demonstrated significantly stronger prognostic discrimination for tumor-informed assays (ratio of HRs 1.84; 95% CI, 1.38–2.45; $p<0.001$). In serial sampling settings, tumor-informed assays achieved higher sensitivity for MRD detection than tumor-agnostic assays (88% vs 62%; $p=0.002$). At landmark timepoints, specificity was similar between approaches (97% vs 94%; $p=0.08$). Between study heterogeneity was low to moderate across analyses. **Conclusions:** Tumor-informed ctDNA assays demonstrate superior prognostic performance and higher sensitivity with serial sampling compared with tumor-agnostic approaches for MRD detection in colorectal cancer. TI assays may be preferred when longitudinal monitoring is feasible, while TA assays remain useful when tumor tissue is unavailable, or rapid results are needed. These findings support selection of ctDNA assay strategies based on clinical context. Research Sponsor: None.

The efficacy and safety of sosimerasib monotherapy in pretreated colorectal cancer with KRAS G12C mutation: Results from a phase 1b study.

Lihui Liu, Shanxian Guo, Conghua Xie, Pingli Wang, Zhangzhou Huang, Meili Sun, Yanqiu Zhao, Xuewen Liu, Liang Han, Qibin Song, Xicheng Wang, XingYa Li, Renhua Guo, Jian Chen, Jia Zhong, Boyang Sun, Kailun Fei, Shanshan Liu, Lei Yang, Jie Wang; Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China; Jiangxi Cancer Hospital, Jiangxi Clinical Research Center for Cancer, Nanchang, China; Department of Radiation and Chemotherapy for Lung Oncology, Zhongnan Hospital of Wuhan University, Wuhan, China; The Second Affiliated Hospital Zhejiang University School of Medicine, Hangzhou, China; Fujian Cancer Hospital, Fuzhou, China; Central Hospital Affiliated to Shandong First Medical University, Jinan, China; Henan Cancer Hospital, Zhengzhou, China; The Third Xiangya Hospital of Central South University, Changsha, China; Xuzhou Central Hospital, Xuzhou, China; Renmin Hospital of Wuhan University, Wuhan, China; The First Affiliated Hospital / The First Clinical Medical College of Guangdong Pharmaceutical University, Guangzhou, China; The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; Jiangsu Province Hospital, Nanjing, China; Yantai Yuhuangding Hospital, Yantai, China; Shanghai Jeyou Pharmaceutical Co., Ltd., Shanghai, China

Background: KRAS G12C mutation is a key driver in approximately 3–4% of colorectal cancer (CRC) cases with poor prognosis. Sosimerasib is a novel, potent, and highly selective KRAS G12C inhibitor. This Phase 1b study evaluates the efficacy and safety of sosimerasib in patients with KRAS G12C-mutated locally advanced or metastatic CRC. **Methods:** Eligible patients who had received prior standard chemotherapy were enrolled in this study. Patients were administered sosimerasib at 500 mg orally once daily. The primary efficacy endpoint was the objective response rate (ORR) assessed by investigators according to RECIST 1.1. **Results:** As of May 3, 2025, a total of 56 patients were enrolled with a median age of 59 years (53.6% male). All patients had stage IV disease at baseline with an ECOG score of 0 (19.6%) or 1 (80.4%). Prior treatment lines ranged from 1 to 3, and most patients (38; 67.9%) had received oxaliplatin, irinotecan, and fluoropyrimidine as systemic therapy during the advanced disease period. With a median follow-up period of 9.9 months (range: 2.1–13.4), the confirmed ORR was 39.3% (95% CI: 26.5–53.3), the median time to response was 1.4 months (range: 1.3–4.2), and the disease control rate was 98.2% (95% CI: 90.5–100). The median duration of response was 8.6 months (95% CI: 4.2–NA). The median progression-free survival was 8.3 months (95% CI: 5.6–11.0). The median overall survival (OS) was not reached, with a 12-month OS rate of 71.5%. Among the patients who had previously received oxaliplatin, irinotecan, and fluoropyrimidine in the advanced setting, the confirmed ORR was 31.6% (95% CI: 17.5–48.7). Treatment-related adverse events (TRAEs) were reported in 53 (94.6%) patients, with grade 3–4 TRAEs occurring in 14 (25.0%) patients. No TRAE was fatal. The most common TRAEs were increased alanine aminotransferase (48.2%), increased aspartate aminotransferase (46.4%), anaemia (32.1%), and decreased white blood cell count (26.8%). TRAEs led to drug interruption in 9 (16.1%) patients, dose reduction in 3 (5.4%) patients, and permanent discontinuation in 1 (1.8%) patient. **Conclusions:** Sosimerasib monotherapy demonstrated clinically meaningful anti-tumor activity with an acceptable safety profile in patients with KRAS G12C-mutated locally advanced/metastatic CRC, supporting its potential for further development. Clinical trial information: ChiCTR2200059986. Research Sponsor: None.

TAMS in appendiceal cancer: Association with metabolic remodeling, prognosis, and response to intra-tumoral therapy.

Patrick Wagner, Christopher Sherry, Rose Blodgett, Hyun Young Park, Ethan Richman, Anjani Ravi, Katherine Barker, Kunhong Xiao, Ashten N. Omstead, Albert Donnenberg, David L. Bartlett, Vera Donnenberg, Ajay Goel, Ali Hussaini Zaidi, Neda Dadgar; Allegheny Health Network Cancer Institute, Allegheny Health Network, Pittsburgh, PA; Allegheny Health Network Cancer Institute, Pittsburgh, PA; Drexel University College of Medicine, Philadelphia, PA; Drexel University School of Medicine, Philadelphia, PA; University of Pittsburgh School of Medicine Department of Cardiothoracic Surgery, Pittsburgh, PA; City of Hope Comprehensive Cancer Center, Duarte, CA

Background: Appendiceal cancer (AC) is a rare malignancy with a distinct immunobiology and propensity for peritoneal metastasis. Tumor-associated macrophages (TAMs) are recognized as influential immune cells in various cancers. In this study, we sought to define the role of TAMs in AC, given its unique immune landscape and peritoneal microenvironment. **Methods:** Immunohistochemistry-quantified M1-like (CD68+CD86+) and M2-like (CD68+CD206+) TAM densities in 112 archival AC specimens were compared against clinicopathologic features and overall survival (OS). In parallel, a comprehensive tissue proteomic analysis (LC-MS/MS) was performed. Gene set enrichment analysis identified proteomic signatures associated with M1 and M2 density. Independently prognostic proteins were identified via Cox regression. External validation was performed by correlating these proteomic signatures in independent tumor samples from the RIOT-1 clinical trial (NCT05751837), in which AC patients received intra-tumoral lipopolysaccharide (LPS), a TLR4 agonist. **Results:** M2-like TAMs outnumbered M1-like TAMs in AC ($p = 0.0002$), particularly in peritoneal metastases ($p = 0.002$), and were not associated with tumor grade or histology. Low M1 density (< 18 th percentile) correlated with worse OS (HR: 3.26, $p = 0.03$), while high M2 density (> 52 nd percentile) was associated with improved OS (HR: 0.1, $p = 0.03$). A combined high-M1/M2 percentile metric was highly prognostic of favorable OS ($p < 0.001$), independent of age, grade, and disease extent. On proteomic analysis, M1-rich tumors exhibited high bioenergetic demands, extensive metabolic reprogramming (isoprenoid/amino acid metabolism), retinol/xenobiotic metabolism, while M2-rich tumors emphasized ECM remodeling, profound amino acid metabolism (immunosuppressive), oxidoreductase activity, and complement activation, with suppressed cell motility. The combined high-M1/M2 phenotype correlated with intense amino acid/lipid metabolism and redox homeostasis. Five TAM-related, independently prognostic proteins were identified: GATD1 (favorable, HR 1.53×10^{-16}), and AGR2, ENOPH1, RHOA, SERPINB6 (adverse, HRs 5.51–10.39). In RIOT-1, intra-tumoral LPS increased M1/M2 TAM infiltration and induced proteomic changes significantly correlated with M1-related ($p = 0.0016$), M2-related ($p = 0.008$), and combined TAM signatures ($p = 0.047$), supporting therapeutic tractability. **Conclusions:** AC harbors a TAM-rich immune microenvironment in which M2-like TAMs and a combined M1/M2 phenotype paradoxically associate with favorable prognosis. Distinct TAM-linked metabolic programs and validated prognostic proteins suggest clinically relevant biologic underpinnings of these findings, while modulation of the AC microenvironment via regional innate immune activation may represent a promising therapeutic strategy. Research Sponsor: ACPMP.

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

Qiu Meng, Yuwen Zhou, Ping Chen, Jin Wang, Yongdong Jin, Yan Li, Chuan Chen, Hong Qiu, Yanmin Shen, Qing Qiao, Hao Liu, Li Huang, Lin Xie, Yanhong Deng, Lei Yang, Li Zhang, Xiaofen Li, Jianjun Li, Shisheng Tan, Tao Zhang; West China Hospital, Sichuan University, Chengdu, Sichuan, China; West China Hospital, Sichuan University, Chengdu, China; General Hospital of Ningxia Medical University, Yinchuan, China; Department of Oncology, Mianyang Central Hospital, Mianyang, Sichuan, China; Department of Medical Oncology, Sichuan Cancer Hospital & Institute, Chengdu, China; Department of Oncology, YAAN People's Hospital, Yaan, Sichuan, China; Department of Cancer Center, Daping Hospital, Army Medical University, Chongqing, China; Department of Oncology, Tongji Hospital, Huazhong University of Science and Technology, Wuhan, China; Chengdu Chengnan Jinhua Hospital, Chengdu, Sichuan, China; Department of Medical Oncology, The People's Hospital of Leshan, Leshan, Sichuan, China; Department of Medical Oncology, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, Chengdu, China; First Affiliated Hospital of Gannan Medical University, Ganzhou, China; Yunnan Cancer Hospital, Kunming, China; The Sixth Affiliated Hospital, Sun Yat-sen University, Guangdong, China; Department of Oncology, Affiliated Hospital of Panzhihua University, Panzhihua, China; Department of Oncology, Chongqing University Three Gorges Hospital, Chongqing, China; Department of Abdominal Oncology, West China Hospital, West China School of Clinical Medicine, Sichuan University, Chengdu, Sichuan, China; Southwest Hospital, Third Military Medical University (Army Medical University), Chongqing, China; Guizhou Provincial People's Hospital, Guiyang, China; The First Affiliated Hospital of Chongqing Medical University, Chongqing, China

Background: The CAPCET study 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, randomized, multicenter, phase II non-comparative trial (NCT05022030). Patients with unresectable RAS/BRAF wt mCRC from 20 China centers were randomly assigned (1:1) to receive up to 12 cycles biweekly mCapOX (capecitabine 1000mg/m² twice daily on Day 1-7 and oxaliplatin 85 mg/m² on Day 1) plus CET (500mg/m²) (arm A) or mFOLFOX6 (oxaliplatin 85 mg/m², leucovorin 200 mg/m², fluorouracil 400mg/m² on day 1, and fluorouracil 2400 mg/m² over 46h) plus CET (500mg/m²) (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. This is an updated result with a median follow-up of 26.1 months and cost-effectiveness evaluation. **Results:** Between September 2021 and April 2024, 168 patients were enrolled in the intention-to-treat (ITT) population and 156 patients were included in the per-protocol (PP) population. In the ITT population, the 9 months-PFS rates were 67.9% (95% CI 58.6%-78.6%) in arm A and 61.9% (95% CI 52.3%-73.2%) in arm B, and the primary endpoint was met. The median PFS (arm A/B) was 11.6 months/10.8 months (P=0.183). The overall response rate (ORR) and disease control rate (DCR) in arm A were higher than those in arm B with 64.3% versus 56.0% and 90.5% versus 84.5%, respectively. The 2-year overall survival (OS) rate (arm A/B) was 75.8% vs 68.6%. The median OS was not reached in the arm A while it was 35.5 in the arm B. Grade ≥ 3 adverse events (AEs) occurred in 26.1% of patients, with 15.0% in arm A and 37.0% in arm B. The most commonly Grade ≥ 3 AEs was neutropenia, rash, and leukopenia and there were no grade 5 AEs reported. A cost-effectiveness analysis showed an incremental cost-effectiveness ratio of \$19,067 per QALY for mCapOX + CET, below the Chinese willingness-to-pay threshold (\$41,188/QALY). **Conclusions:** The CAPCET study met its primary endpoint. mCapOX + CET demonstrated higher ORR/DCR and 2-year OS, with reduced toxicity, compared to mFOLFOX6 + CET. These findings support mCapOX + cetuximab as a clinically effective, better-tolerated, and cost-effective first-line treatment for left-sided RAS/BRAF wild-type mCRC within the Chinese economic framework, providing rationale for ongoing phase III evaluation (NCT06616259). Clinical trial information: NCT05022030. Research Sponsor: National Science and Technology Major Special Project (2024ZD0521202), National Health Commission Center of Medical and Health Science Technology Development: Clinical Research Special Program (WKZX2023CX090001).

Prediction of hematotoxicity using CT-derived body composition in rectal cancer patients receiving immunotherapy-based total neoadjuvant therapy.

Ruone Xu, Wang Yang, Xiaoming Sun, Luoxi He, Qianyu Zhou, Yajie Chen, Fan Xia, Zhen Zhang; Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China; Fudan University Shanghai Cancer Center, Shanghai, China

Background: Immunotherapy-based total neoadjuvant therapy (iTNT) is a promising strategy to enhance complete response rates and facilitate organ preservation in locally advanced rectal cancer (LARC). However, it is linked to a considerable incidence of severe hematotoxicity, while reliable predictive biomarkers are lacking. Body composition, reflecting nutritional status, has been linked to treatment-related toxicity, but its relationship with iTNT toxicity remains unclear. This study aimed to investigate the association between body composition and hematotoxicity of iTNT and to develop a predictive model. **Methods:** A cohort of 204 LARC patients treated with iTNT was included for model development, with internal training and validation via five-fold cross-validation. Additionally, 43 metastatic rectal cancer patients treated with the same regimen served as the external validation cohort. Body composition parameters were obtained from pretreatment CT images at L3. LASSO regression was applied to select variables and four machine learning (ML) algorithms including logistic regression, random forest (RF), support vector machine (SVM), and extreme gradient boosting (XGBoost) were developed. **Results:** 33.8% of the discovery cohort experienced grade 3-4 hematotoxicity. Among baseline characteristics, skeletal muscle index (SMI) showed the most significant correlation with toxicity. The cut-offs for SMI, determined by optimal stratification, were 50.0 cm²/m² for males and 39.6 cm²/m² for females. Patients with low SMI had a higher incidence of severe toxicities ($P < 0.001$). Seven features were included in the ML models: age, body mass index (BMI), SMI, subcutaneous adipose tissue index (SATI), subcutaneous adipose tissue attenuation (SAT_HU), visceral adipose tissue index (VATI), and skeletal muscle attenuation (SM_HU). The predictive performance of the models is summarized in the following table. Overall, the SVM model showed the highest discriminative performance and robust generalizability. **Conclusions:** SMI was significantly associated with hematotoxicity during iTNT. A CT-based machine learning model was developed and validated to predict hematotoxicity, with the SVM model showing the most robust performance (AUC > 0.85) to guide clinical decision-making. Research Sponsor: None.

Cohort	Model	Accuracy	Sensitivity	Specificity	AUC
Internal validation	SVM	0.850 ± 0.024	0.849 ± 0.021	0.833 ± 0.027	0.881 ± 0.019
	RF	0.755 ± 0.037	0.749 ± 0.037	0.777 ± 0.032	0.803 ± 0.033
	Logistic regression	0.704 ± 0.048	0.672 ± 0.055	0.720 ± 0.048	0.730 ± 0.033
	XGBoost	0.796 ± 0.024	0.769 ± 0.038	0.788 ± 0.036	0.814 ± 0.027
External validation	SVM	0.821 ± 0.034	0.829 ± 0.026	0.800 ± 0.019	0.858 ± 0.029
	RF	0.713 ± 0.030	0.723 ± 0.051	0.734 ± 0.043	0.750 ± 0.038
	Logistic regression	0.666 ± 0.034	0.652 ± 0.044	0.649 ± 0.027	0.671 ± 0.037
	XGBoost	0.751 ± 0.046	0.714 ± 0.038	0.744 ± 0.031	0.779 ± 0.044

An early on-treatment "coordinated inflammatory niche" plasma signature as a predictor of response in the SYLT026 trial: Cadonilimab combined with FOLFIRINOX and bevacizumab as first-line treatment for microsatellite-stable/proficient mismatch repair (MSS/pMMR) metastatic colorectal cancer (mCRC).

Yi Yin, Jun Xiao, Liyu Su, Rongbo Lin; Fujian Cancer Hospital, Fujian Medical University Cancer Hospital, Fuzhou, China; Fujian Cancer Hospital, Fuzhou, China; Department of Gastrointestinal Oncology, Fujian Provincial Cancer Hospital, Fuzhou, China

Background: The SYLT026 trial is a phase II study investigating the efficacy and safety of cadonilimab (an anti-CTLA-4/PD-1 bispecific agent) combined with FOLFIRINOX and bevacizumab as first-line treatment for microsatellite-stable/proficient mismatch repair (MSS/pMMR) metastatic colorectal cancer (mCRC). We previously reported the promising outcomes at ASCO GI 2026. Updated survival data are reported here. The determinants of effective immune responses in MSS/pMMR mCRC remain elusive; the "Coordinated Inflammatory Niche" plasma signature was analyzed to predict the immune checkpoint inhibitor (ICI) response. **Methods:** Plasma samples from eligible patients were collected before ICI treatment and profiled using three non-overlapping protein arrays comprising 120 human cytokines (QAH-CAA-2000). These cytokines were integrated into an Inflammatory Niche Index (INI) using machine learning (random forest algorithm). Its predictive value for durable PFS (> 12 months) was evaluated and compared with single markers. **Results:** Between November 16, 2023, and July 26, 2024, 20 patients were enrolled. The ORR was 100% (all partial responses). As of the data cutoff (December 31, 2025), the median follow-up was 24.4 months (IQR 22.4–26.4), the median PFS (mPFS) was 17.2 months (IQR 13.6–20.7), and the OS maturity rate was 20%. Seventeen patients underwent cytokine array analysis. Cytokine profiling identified a 9-protein panel (IP-10, eotaxin, MCP-1, IGFBP-3, MCP-4, TARC, IL-17, CCL28, I-TAC) that was significantly upregulated in responders. Further random forest modeling revealed the importance ranking of each protein, with TARC and IP-10 as the two most significant predictors, consistent with their most pronounced differential expression in the heatmap. The INI demonstrated superior predictive accuracy (AUC = 0.944) compared with IP-10 alone (AUC = 0.71, $p = 0.03$). Patients with a high INI ($n = 9$) had promising outcomes: mPFS was not reached (12-month PFS rate 90%), compared with 6.5 months in the low INI group ($n = 8$) (HR = 0.16, $p = 0.001$). Gene set enrichment analysis linked a high INI to a baseline tumor microenvironment enriched for NK T cell-related signatures, suggesting a biological basis for the niche. **Conclusions:** CTLA-4/PD-1 immunochemotherapy induced deep and durable responses in MSS/pMMR mCRC. An early on-treatment plasma proteomic signature (INI) powerfully identifies patients destined for durable benefit, offering a transformative tool for ultra-early, biology-guided patient selection in MSS/pMMR mCRC. Clinical trial information: NCT05839470. Research Sponsor: None.

Clinical implications of primary and metastatic tumor-informed clonal tracking for MRD assessment in oligometastatic colorectal cancer.

Hyun Jin Bang, Yongjun Cha, Hyeon-Jong Kim, Bom Han, Hyun Jeong Shim, Jun-Eul Hwang, Woo Kyun Bae, Sung Sun Kim, Kyung-Hwa Lee, Ik-Joo Chung, Sang-Hee Cho; Chonnam National University Hwasun Hospital, Hwasun-Gun, South Korea; IMBdx, Inc., Seoul, South Korea; Division of Hemato-oncology, Department of Internal Medicine, Chonnam National University Hwasun Hospital, Hwasun-Gun, South Korea; IMBdx, Seoul, South Korea; Division of Hemato-Oncology Oncology, Department of Internal Medicine Chonnam National University Medical School and Hwasun Hospital, Hwasungun, South Korea; Division of Hemato-Oncology, Department of Internal Medicine, Chonnam National University Hwasun Hospital, Chonnam National University Medical School, Gwangju, South Korea; Division of Hemato-Oncology, Department of Internal Medicine, Chonnam National University Hwasun Hospital, Hwasun-Gun, South Korea; Department of Pathology, Chonnam National University Hwasun Hospital and Medical School, Hwasun-Gun, South Korea; Department of Internal Medicine, Chonnam National University Hwasun Hospital, Hwasun-Gun, South Korea

Background: While minimal residual disease (MRD) assays informed by primary tumor sequencing have demonstrated prognostic value in locally advanced colorectal cancer (CRC), the additive clinical benefit of combined tracking of metastatic-specific private variants in oligo-metastatic CRC (mCRC) remains unclear. We aimed to evaluate whether a combined primary and metastatic tumor-informed approach improves MRD detection sensitivity and prognostic accuracy following curative resection. **Methods:** We enrolled 24 patients who underwent curative resection for liver and/or lung oligometastases between 2023 and 2025. A comprehensive tumor-informed panel was designed based on variants identified through whole-exome sequencing (WES) of both primary and metastatic tissues. Serial plasma ctDNA was analyzed at three time points: post-metastasectomy (P1), post-adjuvant chemotherapy (P2), and at the time of recurrence (P3). The clinical performance of a primary tumor-only (PT-only) assay was compared with a combined primary and metastatic tumor-informed (PT+MT) assay. **Results:** The median age was 65 years (range 33–83), and 18 (75%) were male. Primary tumor locations included the colon (83%) and rectum (17%). Fourteen (58%) patients presented with synchronous metastases. Metastatic sites involved the liver (n = 13), lung (n = 10), or both (n = 1). At P1, P2, and P3, MRD positivity rates using the PT-only assay were 54%, 47%, and 100%, respectively. The PT+MT assay identified only one additional patient as MRD-positive at P1 compared to the PT-only assay. At a median follow-up of 29.2 months (IQR 22.6–32.7), 16 patients (67%) experienced recurrence. The PT-only assay showed significant prognostic impact (HR for ctDNA positivity: 4.53; 95% CI, 1.41–14.57; P = 0.006), which was comparable to the PT+MT assay (HR: 4.46; 95% CI, 1.38–14.38; P = 0.007). While PT+MT tracking did not significantly improve detection sensitivity at P1, it effectively captured clonal dynamics, showing a significant enrichment of metastatic-specific private variants in plasma at recurrence (26%, P3) compared to P1 (17%) and P2 (13%). **Conclusions:** Integrating metastatic-specific private variants into MRD tracking revealed distinct clonal dynamics but did not significantly enhance clinical sensitivity or prognostic performance compared to a primary tumor-informed assay in patients with oligometastatic CRC. These findings suggest that current MRD assay designs based on primary tumor sequencing remain a robust standard, even in the metastatic setting after curative resection. Research Sponsor: None.

Multiplexed immunohistochemistry (mIHC) analysis and clinical outcomes of nelmastobart in combination with trifluridine/tipiracil and bevacizumab in patients with refractory colorectal cancer (phase 1b/2).

Soohyeon Lee, Keun-Wook Lee, Sae-Won Han, Seung-Hoon Beom, Sun Young Kim, Stephen S. Yoo; Korea University Anam Hospital, Korea University College of Medicine, Seoul, South Korea; Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea; Department of Internal Medicine, Seoul National University Hospital, and Seoul National University Cancer Research Institute, Seoul, South Korea; Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; STCube Pharmaceuticals Inc, Rockville, MD

Background: Colorectal cancer (CRC) patients who are refractory or intolerant to oxaliplatin- and irinotecan-based regimens face limited treatment options and poor prognoses. BTN1A1, a novel immune checkpoint protein involved in tumor progression and immune evasion, presents a potential therapeutic target. Nelmastobart, a first-in-class anti-BTN1A1 monoclonal antibody, is being evaluated in combination with trifluridine/tipiracil and bevacizumab in the Phase 1b/2 STCUBE-003 trial (NCT06873763). This study employs multiplexed immunohistochemistry (mIHC) to characterize the tumor microenvironment (TME) and identify biomarkers predictive of therapeutic response in CRC patients. **Methods:** Tumor tissues from 120 CRC patients were prescreened for BTN1A1 expression via immunohistochemistry (IHC). A total of 61 patients with a tumor proportion score (TPS) ≥ 50 were enrolled in the Phase 2 study. Pathologists used the TPS to guide patient selection, with TPS ≥ 50 as the inclusion criterion. Selected samples were analyzed using mIHC (Opal and CellDIVE), utilizing a 20-protein panel relevant to cancer immunology. Protein co-expression and the spatial distribution of immune and malignant cells were evaluated to assess tumor-immune interactions. **Results:** Among 120 tumor samples analyzed by IHC, 78 (65%) exhibited TPS ≥ 50 . Sixteen patients (13%) showed no expression (TPS 0), and 26 (21.6%) had low to medium expression ($1 \leq \text{TPS} \leq 49$). This expression profile aligns with previous CRC studies (STCUBE-001 and STCUBE-IIT-001). In the initial efficacy evaluation of 39 patients with TPS ≥ 50 , 2 (4.8%) achieved a partial response (PR), 27 (69.2%) showed stable disease (SD), and 8 (20.5%) had progressive disease (PD). High BTN1A1 expression was significantly associated with a higher clinical response rate. mIHC analysis further revealed that BTN1A1 expression correlated with Ki-67, SLFN11, and YAP1, as well as distinct patterns of CD8⁺ T-cell infiltration. **Conclusions:** BTN1A1 is consistently and highly expressed in refractory CRC (median TPS 50). mIHC analysis confirms that BTN1A1 is closely integrated with key immune checkpoints and tumor markers within the TME. Initial clinical results, which show disease control in the majority of patients, particularly within the TPS ≥ 50 population, support the utility of BTN1A1 as a predictive biomarker for Nelmastobart combination therapy. These findings justify the ongoing biomarker-driven Phase 2 portion of the STCUBE-003 trial. Clinical trial information: NCT06873763. Research Sponsor: None.

Phase 1, FIH study of cabotamig, a TCE CDH17 X CD3, in CDH17-expressing GI malignancies.

Roland Ching-Yu Leung, Thomas Yau, Ganessan Kichenadasse, Dennis A. Wong, John Moon Luk, Paul L. de Souza; Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong, China; Centre of Cancer Medicine and Department of Medicine, The University of Hong Kong, Hong Kong, Hong Kong; Southern Oncology Clinical Research Unit, Bedford Park, SA, Australia; Arbele, Shatin, Hong Kong; Cancer Care Foundation, Wollstonecraft, NSW, Australia

Background: Cadherin-17 (CDH17) is a specific cancer target; aberrant expression is up to >95% in GI tumors (stomach, pancreas, bile duct, rectum, small bowel and colon). Cabotamig (ARB202) is a humanized, IgG4, T-cell engaging antibody (TCE) that binds to CDH17 and CD3 T-cells forming synapse to aid activation. This study evaluated the safety, pharmacokinetics (PK), biomarkers, and anti-tumor activity of cabotamig in patients (pts) with CDH17+ gastrointestinal (GI) cancers. **Methods:** Pts ≥ 18 years with locally advanced or metastatic CDH17+ GI cancers refractory to therapies, measurable disease and ECOG 0/1 were enrolled. MABEL calculations per FDA TCE guidance were used (0.0003 mg/ml to 1.0 mg/ml by $1/2$ log increments). For safety given multi log difference in CDH17 density, an initial dose of 1/10 was given 3 days before the remaining 9/10. In the 4th cohort, patients with stable disease were given additional doses (7/10 cohort 4–6). Cohort was split into colorectal cancers (CRC) and non-CRC groups given the differences in CDH17 levels and symptoms. After the 7th cohort dosing proceeded to dose optimization. Data cutoff 02/14/2025. **Results:** Pts (CRC 15/22 total) received cabotamig at 1/10 dose (0.00003–0.032 mg/kg) followed by 9/10 dose (0.0003 to 0.32 mg/kg) across 7 cohorts with the max. of 37.8(3.8/34) mg. The max. tolerated dose was not reached. Dose responsive cytokine release syndrome (CRS) symptoms were evident with more symptoms between the 1/10 and 9/10 dose and with increasing intensity with escalation. Treatment related AEs (CRS 17, fever 16, nausea 7, diarrhea 5, vomiting 5 fatigue 3 chills 2) were reported with 1st set or 2nd infusions and occurred in all patients without pre-corticosteroids in the 4th cohort and intensified even with premed up to the 7th cohort. PK data indicated dose proportionality and faster-than-typical IgG4 clearance. Anti-tumor biomarker activity, primarily CEA, but when present included other CA markers, showed a dose response (increase then a decrease to levels below baseline, consistent with target cell lysis) with a peak response between the 5th and 6th cohorts. **Conclusions:** This first-in-human (FIH) study (NCT05411133) targeting CDH17 in GI cancer pts showed a tolerable safety profile for cabotamig up to 0.32mg/kg. Step-up dosing appeared to mitigate dose responsive on-target tumor CRS and the lack of persistent GI toxicities indicated minimal on-target normal GI mucosal effects. Dose responsive biomarker anti-tumor activity of cabotamig was observed. Clinical trial information: NCT05411133. Research Sponsor: None.

The CONVERGE study: A phase II, single-arm trial of adabelimab combined with targeted therapy and liposomal irinotecan-based chemotherapy for conversion surgery in unresectable MSS colorectal cancer liver metastases.

Wenhui Yang, Haiyi Liu, Sheng Gao, Yinan Shi, Wei Bai, Jihong Guo, Xiaorui Zhang, Ninggang Zhang, Chengyan Zhang, Xuefeng Song, Wenhua Cheng, Jinfang Guo, Qianni Yang, Wenda Wang, Yixun Zhang, Huiyuan Jiang, Pengyu Bai, Hailei Cao, Jianxin Zhang, Yunfeng Bo; Department of Gastroenterology, Shanxi Province Cancer Hospital/Shanxi Hospital Affiliated to Cancer Hospital, Chinese Academy of Medical Sciences/Cancer Hospital Affiliated to Shanxi Medical University, Taiyuan, China; Department of Colorectal Surgery, Shanxi Province Cancer Hospital, Hospital Affiliated to Cancer Hospital, Chinese Academy of Medical Sciences, Cancer Hospital Affiliated to Shanxi Medical University, Taiyuan, Shanxi, China; Department of Gastroenterology, Shanxi Province Cancer Hospital/Shanxi Hospital Affiliated to Cancer Hospital, Chinese Academy of Medical Sciences/Cancer Hospital Affiliated to Shanxi Medical University, Taiyuan, Shanxi, China; Shanxi Province Cancer Hospital/Shanxi Hospital Affiliated to Cancer Hospital, Chinese Academy of Medical Sciences/Cancer Hospital Affiliated to Shanxi Medical University, Taiyuan, Shanxi, China; Medicine Imaging Department, Shanxi Province Cancer Hospital/Shanxi Hospital Affiliated to Cancer Hospital, Chinese Academy of Medical Sciences/Cancer Hospital Affiliated with Shanxi Medical University, Taiyuan, Shanxi, China; Department of Pathology, Shanxi Province Cancer Hospital, Shanxi Hospital Affiliated to Cancer Hospital, Chinese Academy of Medical Sciences, Cancer Hospital Affiliated to Shanxi Medical University, Taiyuan, Shanxi, China

Background: Liver metastasis is a key poor prognostic factor for colorectal cancer (CRC). Microsatellite stable (MSS) CRC predominates and is poorly responsive to single-agent immunotherapy. Only 10%–20% of patients with initially unresectable MSS colorectal cancer liver metastases (CRLM) are eligible for upfront curative resection, and conventional chemotherapy yields a conversion resection rate of merely 15%–30%. This phase II study evaluated the efficacy and safety of adabelimab (a PD-L1 inhibitor) plus molecularly stratified targeted therapy and liposomal irinotecan-based chemotherapy for unresectable MSS CRLM, focusing on hepatic metastatic lesion control (ChiCTR2600117031). **Methods:** This single-center, open-label phase II trial enrolled 45 patients with unresectable MSS CRLM (ECOG PS 0–1, no prior systemic anti-tumor therapy). Patients received adabelimab (1200mg IV, Q2W) + stratified targeted therapy (cetuximab for RAS/BRAF wild-type left-sided tumors; bevacizumab otherwise) + liposomal irinotecan-based chemotherapy (Q2W) for up to 12 cycles. Primary endpoint: conversion-to-resection rate. Secondary endpoints: ORR, DCR, R0 resection rate, hepatic metastasis pathological response, and safety (NCI-CTCAE v5.0). Efficacy was assessed per RECIST v1.1. **Results:** As of January 20, 2026, 42 patients were included in baseline analysis (median age 57.6±11.1 years, 64.3% male; mean hepatic metastasis diameter 37.21±19.00 mm, max 82.79 mm). Among 35 efficacy-evaluable patients, ORR was 45.7% (95% CI: 28.8%–63.4%) and DCR was 88.6% (95% CI: 73.3%–96.8%). Fourteen patients underwent surgery (conversion rate 45.2%, 95% CI: 27.3%–60.0%), all completing simultaneous resection of hepatic metastases and primary tumors. Of these 14 patients, 5 (35.7%) achieved hepatic TRG 0 (complete pathological regression) and 12 (85.7%) achieved R0 resection (95% CI: 49.2%–95.3%). For safety, 95.2% (40/42) of patients had AEs. Common (≥10%) all-grade AEs were mainly hematological (leukopenia 23.8%, myelosuppression 21.4%). Grade 3 AEs were rare (predominantly leukopenia 14.3%), and no grade 4 AEs occurred. No any-grade immune-related AEs were reported. **Conclusions:** Adabelimab combined with molecularly stratified targeted therapy and liposomal irinotecan-based chemotherapy shows substantial efficacy and favorable safety for unresectable MSS CRLM, with excellent hepatic metastasis control. Its high conversion-to-resection rate and 35.7% hepatic TRG 0 rate confirm potential for deep pathological response. This regimen warrants further investigation as a promising conversion therapy for unresectable MSS CRLM. Genomic sequencing of successfully converted patients is ongoing to elucidate therapeutic mechanisms. Clinical trial information: ChiCTR2600117031. Research Sponsor: Hengrui Pharma.

Association of concurrent GLP-1 receptor agonist use with survival outcomes in patients with metastatic colorectal cancer receiving immune checkpoint inhibitors.

Shalin Rawal, Madho Mal, Nayanika Chowdary Tummalala, Disha Patel, Nandan Shah, Rithish Nimmagadda, Vedant Shah, Bolivia Crocete Aloysia Fernandes, Sagar Patel, Love Kumar, Shiwani Keswani, Michael Maroules; NYMC at St. Mary's General Hospital and Saint Clare's Health, Denville, NJ; Marshall University School of Medicine, Huntington, WV; One Brooklyn Health - Interfaith Medical Center, New York, NY; The New York Medical College Graduate Medical Education Program at St. Mary's General Hospital and St. Clare's Health, Denville, NJ; Saint Michael's Medical Center, Newark, NJ; Charleston Area Medical Center (CAMC), Charleston, WV; Mayo Clinic Arizona, Scottsdale, AZ; NYMC/St. Mary's General Hospital, Passaic, NJ

Background: Metabolic status and systemic inflammation are increasingly recognized as important modifiers of immune checkpoint inhibitor (ICI) response. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) exhibit anti-inflammatory and immunomodulatory properties and are widely used in diabetes and obesity. However, their clinical impact on immunotherapy outcomes in metastatic colorectal cancer (mCRC) remains unclear. **Methods:** We conducted a retrospective observational cohort study using the TriNetX Global Collaborative Network, including electronic health records from 170 healthcare organizations between 2015 and 2025. Adults with mCRC who received at least one ICI were identified. Patients prescribed GLP-1 RAs within six months before or after ICI initiation were compared with non-exposed controls. Patients with prior bariatric surgery were excluded. Cohorts were balanced using 1:1 propensity score matching for demographics, metabolic conditions, and major comorbidities. Primary endpoint was all-cause mortality at 1, 3, and 5 years. Secondary outcomes included pneumonia, heart failure exacerbation, and major abdominal surgical procedures. Survival analyses were performed using Kaplan–Meier methods and Cox proportional hazards models. **Results:** Among 8,304 eligible patients, 148 received GLP-1 RAs. After propensity matching, 138 patients were included in each cohort with well-balanced baseline characteristics. At 1 year, mortality was lower in the GLP-1 cohort (27.5% vs 40.6%), corresponding to a 32% relative risk reduction (RR 0.68, 95% CI 0.49–0.95) and reduced hazard of death (HR 0.67, 95% CI 0.43–1.03). This association persisted at 3 years (27.5% vs 41.3%; RR 0.67, 95% CI 0.48–0.93; HR 0.68, 95% CI 0.45–1.05) and 5 years (28.3% vs 42.0%; RR 0.67, 95% CI 0.49–0.93), with higher 5-year survival probability (50.5% vs 41.5%). Secondary outcomes favored GLP-1 exposure, including lower incidence of pneumonia (10.9% vs 17.4%; HR 0.58) and fewer heart failure exacerbations (23.9% vs 31.9%; HR 0.75). Rates of major abdominal surgical procedures were numerically lower in the GLP-1 cohort. **Conclusions:** In this large real-world cohort, concurrent GLP-1 RA exposure was associated with clinically meaningful and durable survival benefit in mCRC patients receiving ICIs, without increased adverse clinical outcomes. These findings suggest a potential immunometabolic interaction and support prospective evaluation of GLP-1-based strategies as adjunctive modifiers of immunotherapy response. Research Sponsor: None.

Dynamics of circulating monomeric C-reactive protein (mCRP) to predict outcomes with first-line alternating oxaliplatin-based chemotherapy and nivolumab in metastatic microsatellite-stable (MSS) colorectal cancer (CRC).

Anniken Joerlo Fuglestad, Paula A. Bousquet, Lawrence A. Potempa, Marc Potempa, Sebastian Meltzer, Christian Kersten, Anne Hansen Ree; Akershus University Hospital, Lorenskog, Norway; College of Science, Health, and Pharmacy, Roosevelt University, Schaumburg, IL; Acphaz Inc, Deerfield, IL; Akershus University Hospital, University of Oslo, Oslo, Norway

Background: Elevated CRP levels at CRC diagnosis are consistently associated with poor outcomes, suggesting a tumor-promoting and potentially immuno-suppressive inflammatory state. The clinically assessed CRP is a pentameric protein that can dissociate to mCRP, an isoform with pro-inflammatory effects on innate immune responses. The randomized METIM-MOX trial (NCT03388190) evaluated potentially immunogenic short-course oxaliplatin-based chemotherapy (FLOX) alternating with nivolumab in previously untreated, unresectable metastatic MSS CRC. We investigated whether oxaliplatin-induced immunogenicity is measurable as an early change in circulating mCRP and may identify patients more likely to derive clinical benefit from sequential nivolumab. **Methods:** Patients were randomly assigned to the control group of FLOX (oxaliplatin, 5-fluorouracil, folinic acid) Q2W or the experimental group of alternating 2 cycles each of FLOX Q2W and nivolumab Q2W with prespecified break periods. The primary endpoint was progression-free survival (PFS). This *post hoc* analysis included 29 patients from the experimental group, of whom 28 had paired mCRP and clinical CRP measurements from baseline (Pre) and post second FLOX cycle (Post) timepoints. CRP was measured by standard immunoturbidimetry. Plasma mCRP was separated from CRP by 100-kDa filtration and quantified by targeted nano LC-timsTOF Pro mass spectrometry with AQUA standards. CRP at the reference limit 5.0 mg/L and mCRP at the median value 45 ng/mL were used as cutoff values. Changes from Pre to Post were denoted Δ mCRP and Δ CRP and categorized as ≥ 0 (stable/increase) and < 0 (decrease). **Results:** Low Pre and low Post CRP were associated with prolonged PFS (log-rank $p = 0.080$ and $p = 0.002$, respectively), while Δ CRP showed no association (log-rank $p = 0.57$). By contrast, a significant association was observed for Δ mCRP (log-rank $p = 0.015$), where median PFS was longer among the Δ mCRP ≥ 0 population (16.4 months [95% CI 8.8–23.9]; $n = 15$) versus the Δ mCRP < 0 population (9.2 months [95% CI 3.6–14.8]; $n = 13$). Notably, patients with the combination Δ CRP < 0 and Δ mCRP ≥ 0 ($n = 8$) had an undefined median PFS (≥ 41.6 months) at data cutoff, compared to median PFS 9.2 months (95% CI 1.4–16.9; $n = 20$) for all other patients (log-rank $p = 0.022$). **Conclusions:** Patients with metastatic MSS CRC who exhibited an increase in mCRP and decrease in clinical CRP following the initial 2 chemotherapy cycles of first-line oxaliplatin-based chemotherapy alternating with nivolumab had markedly prolonged PFS. Moreover, increased PFS was observed alongside increased circulating mCRP regardless of change in CRP. These data suggest an early increase in mCRP may be an indicator of immunotherapy-associated efficacy. Clinical trial information: NCT03388190. Research Sponsor: None.

The SERPENTINE trial: A phase II clinical study decoding immune responses by scRNA-seq and TCR-seq analysis in patients with MSS metastatic colorectal cancer (mCRC) with and without liver metastases treated with durvalumab and tremelimumab.

Iosune Baraibar, Sam Morabito, Juan Nieto, Gerard Deuner, Juan Luis Melero, Francesc Salva, Marta Grzelak, Javier Ros Montañá, Ginevra Caratu, Raquel Perez-Lopez, Paula Nieto, Asaf Rotem, Patricia Casbas-Hernandez, Nadia Martinez-Martin, Alena Gros, Josep Tabernero, Elena Elez; Department of Medical Oncology, Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Spain; Centro Nacional de Análisis Genómico, Barcelona, Spain; CNAG, Barcelona, Spain; Omniscope, Barcelona, Spain; Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Spain; Omniscope Inc., Barcelona, CA, Spain; Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Spain; Single Cell Genomics, CNAG - Centro Nacional de Análisis Genómico, Barcelona, Spain; Radiomics Group, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; AstraZeneca R&D Boston, Waltham, MA; AstraZeneca External R&D, Barcelona, Spain; Tumor Immunology and Immunotherapy, Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Cellex Center, Barcelona, Spain; Vall d'Hebron Hospital Campus & Institute of Oncology (VHIO), UVic-UCC, IOB-Quiron, Barcelona, Spain; Vall d'Hebron Barcelona Hospital Campus, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

Background: Immune checkpoint inhibitor (ICI) therapy aims to instruct immune cells to efficiently recognize and eliminate cancer cells. It has shown efficacy in MSI colorectal (CRC), and, although there is no approval yet, a subset of patients with MSS CRC included in clinical trials respond to ICI, indicating a significant knowledge gap in our current understanding of immunological mechanisms in MSS CRCs. The relationship between the cellular and molecular responses to ICI in the tumor microenvironment (TME) and the clinical outcome remains poorly understood. We sought to address this gap in understanding through a series of high-throughput functional genomics analyses. **Methods:** Patients (pts) with refractory MSS CRC were treated with durvalumab (Dur) 1500mg plus tremelimumab (Trem) 300mg at Week 0, followed by Dur 1500 mg Q4W. We characterized the cellular makeup of the metastatic TME using single-cell RNA-seq, and cataloged T-cells clonotypes within metastases and in the blood using single-cell and deep TCR-seq. We collected data for each patient before and upon treatment initiation to explore the dynamic changes of the TME and blood in response to ICI. To facilitate direct comparisons between metastatic and primary TMEs, we integrated our dataset with an external single-cell RNA-seq dataset from primary CRC tumors. **Results:** 24 pts were included in the analysis (18 with no liver metastases (NLM), 6 with liver metastases (LM)). Around 200,000 single-cell profiles were collected from biopsies taken from 6 pts with LM and 10 pts with lung metastases. Disease Control Rate (DCR) was 39% for MSS CRC without LM (2 PR + 5 SD) and 0% for those with LM ($p=0.13$). Robust gene expression changes within the immune compartment of the TME were observed upon treatment, irrespective of overall treatment outcome, yet specific biological programs were differentially altered across patient response groups. Differences in the composition of TMEs in the lung and liver metastases were found with an enrichment of T regulatory and IFN-responder CD4 populations in the lung vs more CD8+ T cell subtypes in the liver. Tumor TCR analysis revealed that, following ICI treatment, liver metastases displayed a high diverse TCR repertoire, whereas lung metastases were less diverse and showed marked clonal expansion, suggesting greater T cell activity within the lung lesions ($p=0.035$). **Conclusions:** Prospective deep immune repertoire profiling detected profound differences in TME according to dissemination patterns, which might explain differences in treatment outcomes. Despite low overall efficacy with Dur and Trem in MSS patients, a trend to better response rate and DCR was observed in pts without LM. We propose immune cell tracking as powerful tool to quantify the efficacy of ICI in real time. Clinical trial information: NCT06680739. Research Sponsor: Astra Zeneca.

Liver transplantation (LT) in liver limited metastatic colorectal cancer (CRC): Insights and opportunities.

Jonathan W. Lee, Juan P. Rocca, Benjamin Samstein, Anthony J. Choi, Nishtha Singh, Despina Siolas, Allyson J. Ocean, Ellie Brandon, Manish A. Shah; Weill Cornell Medical College, New York, NY; Weill Cornell Medicine, New York, NY; Weill Cornell, New York, NY; NewYork Presbyterian and Cornell, New York, NY; NewYork-Presbyterian/Weill Cornell Medical Center, New York, NY

Background: Liver transplantation (LT) for liver limited metastatic colorectal cancer (LL-mCRC) remains underutilized. Reasons for transplant ineligibility are not well described and the acceptance of this procedure for mCRC remains limited. Herein, we describe our initial experience with LT in patients with LL-mCRC. We characterize patient outcomes, characterize the pattern of failure for patients undergoing LT evaluation, and describe the prognostic implication of lymphadenectomy in LT evaluation. **Methods:** Patients with LL-mCRC potentially eligible for LT were identified, discussed in multidisciplinary tumor boards and liver transplantation clinics, and managed. The Weill Cornell Liver Transplant institutional database was queried to identify patients evaluated for LT, those who were transplanted, and those who were not. Demographic, surgical data, and clinical outcomes abstracted from medical record. **Results:** Between 7/2020 and 3/2025, 20 patients with LL-mCRC were evaluated for LT. Median age (range) 55 years (29–63); N=10 (50%) white; N=18 (90%) male. All had adenocarcinoma histology with N=14 (70%) left sided primary disease. At diagnosis, N=11 (55%) had ≥ 1 liver lesion > 5.5 cm and median CEA (range) was 200 (4.8–6945). The most common mutations were APC (60%), KRAS (55%), TP53 (45%), and PIK3CA (35%). N=6 (30%) had a LT with a median time from diagnosis to transplant of 23.7 months (mo) (range 16–42). The median overall survival (OS) from LT is 64.5 mo (range 22–87). N=5 (83%) are alive with a median follow up of 67 mo (range 22–87). N=3 patients had recurrent disease with a median time to recurrence of 3 mo (range 2–9), 2 in lungs, and 1 retrocrural lymph nodes. At this time, N=4 (67%) patients have no evidence of disease, and one with retrocrural lymph node disease is responding to treatment. The single patient who underwent LT and died was portal lymph node positive at the time of transplant and had an early recurrence (at 2 mo post-transplant). For the 14 patients who were evaluated for transplant, but did not undergo transplant, their mOS is 28 mo (range 13–44). Reasons why these patients did not undergo LT are shown in Table 1. The majority failed transplant evaluation due to progressive disease (lung 43%, liver 21%, abdomen 14%). Positive portal lymphadenectomy was a poor prognostic characteristic, with all 3 patients deceased. **Conclusions:** LT is a treatment option that confers durable remission and improved OS in LL-mCRC. Recurrent disease after transplant is generally controllable with local treatment modalities. Patient selection is critical in identifying appropriate LT candidates. Portal lymphadenectomy is prognostic and should be considered in all transplant evaluations. Research Sponsor: None.

	Not Transplanted N=14
New lung metastases	6 (43)
Progression in liver	3 (21)
Worsening liver function	2 (14)
Progression in lymph nodes	1 (7)
Peritoneal metastases at surgery	1 (7)
Patient preference	1 (7)

Refining clinical trial eligibility for minimal residual disease in patients with colorectal cancer: The MD Anderson INTERCEPT experience.

Soumya Shekhar, Emerik Osterlund, Alisha Heather Bent, Maria Pia Morelli, Timothy E. Newhook, Tsuyoshi Konishi, George J. Chang, Kathryn Aziz, Kristin Alfaro, Scott Kopetz, Arvind Dasari, Van K. Morris II; Department of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Colon and Rectal Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Detection of circulating tumor DNA (ctDNA) is prognostic for recurrence after completion of curative-intent therapy for patients (pts) with colorectal cancer (CRC). Our MD Anderson INTERCEPT platform enrolls ctDNA(+) CRC pts onto matched clinical trials, with the goal of eradicating minimal residual disease (MRD) and curing more pts with CRC. To gain insights on how to identify CRC pts most likely to have true MRD, we retrospectively reviewed the role of non-specific radiographic abnormalities in forecasting CRC recurrence. **Methods:** For this retrospective review of CRC pts included in ctDNA intervention trials (Table) from 1/2019-12/2025, MRD at baseline was defined as (1) having no radiographically evident disease at time of study enrollment and (2) detection of ctDNA on an MRD assay (Signatera). ctDNA levels were quantified as mean tumor molecules (MTM) per milliliter (mL) plasma. Radiographic sites of disease progression on clinical trials were compared with pre-treatment imaging. Median recurrence-free survival (RFS) was estimated using Kaplan Meier and compared with Cox regression. **Results:** 54 pts with definitively treated CRC prior to subsequent ctDNA(+) were enrolled across 4 trials (Table); 45 pts (83%) had stage IV disease. No pts had radiographically evident CRC at trial start. Median ctDNA levels were 0.45 MTM/mL (IQR 0.12 – 2.4). After a median follow up of 6.4 months (IQR, 3.5–9.5), 42 (78%) pts had recurred after treatment on a ctDNA intervention trial. Median RFS was 8.1 months (95% CI 4.4 – 9.4). Sites of recurrence were liver (N=20, 48%), lung (N=13, 31%), lymph nodes (N=10, 24%), and peritoneum (N=3, 7%). Upon retrospective review, minute but discernible lesions were identified at the sites of recurrence in 25 (60%) of the pts who had a recurrence on MRD trials. At eligibility evaluation these were characterized as “benign” in 14 (56%) or as “post-procedural” in 11 (44%) of the cases. The presence of indistinguishable CRC deposits at the start of the trial was associated with inferior RFS (4.2 vs 9.3 months; HR 1.96 (95% CI 1.04–3.70; p = 0.04). **Conclusions:** Subclinical radiographic findings may confound true identification of pts with CRC MRD for clinical trials. Optimizing definitions of radiographically detectable disease is warranted in order to ensure homogenous populations of CRC that are the most likely to benefit from novel MRD therapies. Research Sponsor: None.

Demographic characteristics across four trials.

		Number of Patients	Percentage (%)
Age at Enrollment	< 30	1	2.4
	30-39	3	7.3
	40-49	8	19.5
	50-59	12	29.3
	60-69	14	34.1
	70+	3	7.3
Gender	Male	34	63.0
	Female	20	37.0
Race/Ethnicity	White or Caucasian	34	63.0
	Black or African American	5	9.3
	Hispanic or Latino	11	20.4
	Asian	1	1.9
Stage at Enrollment	Other	3	5.6
	I	0	0.0
	II	0	0.0
	III	9	16.7
Trial	IV	45	83.3
	Bintrafusp alfa	4	7
	NK cells with cetuximab	15	27.8
	Lifestyle interventions	16	29.6
	Trifluridine/tipiracil	19	35.2

Long-term survival and biomarker analysis of neoadjuvant chemoradiotherapy with or without PD-1 antibody sintilimab in pMMR locally advanced rectal cancer: A randomized clinical trial.

Weiwei Xiao, Gong Chen, Yuan-Hong Gao, Jun-Zhong Lin, Xiao Jun Wu, Huilong Luo, Zhen-Hai Lu, Qiaoxuan Wang, Rui Sun, Peiqiang Cai, Chong-Mei Zhu, Min Liu, Jibin Li, Yirui Wang, Ying Jin, Feng Wang, Haitao Luo, Zhizhong Pan, Rui-Hua Xu; Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University, Guangzhou, Guangdong, China; Sun Yat-sen University Cancer Center, Guangdong, China; Department of Radiation Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, Guangdong, China; Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University, Guangzhou, China; Departments of Radiation Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China; Department of Radiology, Sun Yat-sen University Cancer Center, Guangzhou, China; Sun Yat-sen University Cancer Center, Guangzhou, China; Clinical Trials Centre, Sun Yat-sen University Cancer Center, Guangzhou, China; State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-sen University Cancer Center, Guangzhou, China; Department of Medical Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Guangzhou, China; Kindstar Global Precision Medicine Institute, Shenzhen, Guangdong, China

Background: We previously reported that adding sintilimab to neoadjuvant chemoradiotherapy (NACRT) significantly improved the complete response (CR) rate compared to NACRT in mismatch repair-proficient (pMMR) locally advanced rectal cancer (LARC) patients (44.8% vs. 26.9%; $P = 0.031$). Here, we present the long-term survival outcomes and exploratory biomarker analyses from this randomized trial. **Methods:** Between June 2020 and July 2022, a total of 134 patients with pMMR LARC were randomly assigned (1:1) to the experimental arm (NACRT plus sintilimab, $n = 67$) or the control arm (NACRT, $n = 67$). The primary endpoint was CR rate. Secondary endpoints included disease-free survival (DFS) and overall survival (OS). Survival analysis was estimated using the Kaplan-Meier method and compared using the log-rank test. Hazard ratios (HR) were calculated using the Cox proportional hazards model. Baseline tumor and blood samples were collected for whole exome sequencing. **Results:** With a median follow-up of 48.5 months, the experimental arm exhibited significantly superior 3-year DFS compared to the control arm (91.0% vs. 77.6%; HR = 0.37, 95% CI: 0.14–0.94, log-rank $P = 0.030$). Analysis of failure patterns showed lower rates of both local recurrence (1.5% [1/67] vs 3.0% [2/67] and distant metastases (9.0% [6/67] vs. 19.4% [13/67]) in the experimental arm. Notably, liver metastases were more frequent in the control arm (1.5% [1/67] vs. 9.0% [6/67]). Subgroup analyses identified a pronounced DFS benefit from combination therapy in patients aged > 50 years (HR = 0.24, 95% CI: 0.07–0.86, $P = 0.029$) and those with extramural venous invasion (EMVI)-positive tumors (HR = 0.26, 95% CI: 0.09–0.81, $P = 0.020$). Notably, achieving a CR was consistently associated with a trend toward prolonged DFS in both the experimental (log-rank $P = 0.129$) and control arms (log-rank $P = 0.145$). In exploratory biomarker analysis, patients harboring MUC16 mutations in the experimental arm exhibited a trend toward improved DFS, although statistical significance was not reached (log-rank $P = 0.318$); conversely, no such trend was observed in the wild-type population (log-rank $P = 0.496$). The 3-year OS rates were 97.0% in both groups (log-rank $P = 0.977$). **Conclusions:** Adding PD-1 antibody to NACRT conferred a superior DFS benefit compared to NACRT in patients with pMMR LARC, particularly in older patients and those with EMVI-positive tumors, and potentially influenced the pattern of metastasis. MUC16 mutations warrant further investigation as a potential predictive biomarker for sensitivity to the combination therapy. Clinical trial information: NCT04304209. Research Sponsor: Noncommunicable Chronic Diseases–National Science and Technology Major Project.

Dual-microbial signature as a predictor of postoperative colorectal cancer recurrence.

Pancheng Chen, Yanlei Ma, Jinming Li; Fudan University Shanghai Cancer Center, Shanghai, China

Background: Current surveillance strategies for postoperative recurrence in colorectal cancer predominantly depend on tumor markers, imaging modalities, and endoscopic procedures; however, these approaches are challenged by suboptimal diagnostic accuracy. Consequently, the identification and validation of novel biomarkers represent an urgent clinical necessity. Sensitive microbiome-based approaches for postoperative risk stratification, surveillance optimization, and early recurrence detection may substantially influence clinical decision-making and resource allocation for colorectal cancer patients. **Methods:** This cohort study included CRC fecal and tumor samples from four independent cohorts ($n = 615$) in the Fudan University Shanghai Cancer Centre (Shanghai, China) between January 2017 and December 2020, with follow-up through December 2024. Fecal samples from the discovery ($n = 250$), training-validation cohorts ($n = 153$), as well as tumors with paired adjacent normal tissues from the investigation cohort ($n = 244$), were subjected to multi-omics analyses. We developed prediction models of disease-free survival by additionally incorporating dual-microbial signature including the abundance of Roseburia and Bifidobacterium. Both models were evaluated by internal validation cohort, and visual nomograms of prediction models were constructed accordingly. **Results:** We found that the combined high abundance of Roseburia and Bifidobacterium was associated with favorable outcomes ($P = 0.039$), especially in male ($P = 0.018$) and early-onset colorectal cancer ($P = 0.047$). Integration of clinical variables with a dual-microbial signature achieved a mean AUC > 0.8 for recurrence prediction. A high combined abundance of Roseburia and Bifidobacterium was linked to reduced enrichment of primary bile acid biosynthesis pathways and increased enrichment of propanoate metabolism pathways. **Conclusions:** This study proposes a novel strategy for CRC recurrence risk assessment and highlights the potential of gut microbiota as a tertiary preventive approach in CRC management. However, the proposed model has not yet been implemented in clinical practice and requires validation in large, multicenter prospective cohorts before clinical translation. Research Sponsor: None.

Targeting the Warburg effect: Mitochondrial metabolic modulation with intermittent fasting during neoadjuvant chemoradiation in rectal cancer compared with standard neoadjuvant chemoradiation and total neoadjuvant therapy.

Krithikaa Sekar, Lohith Gopala Reddy, Basavalinga Sadasivaiah Ajaikumar, Esther Sathiaraj, Shekar Patil; Healthcare Global Enterprises limited, Bengaluru, India; HCG Cancer Hospitals, Bangalore, Karnataka, India; Healthcare Global Enterprises Ltd, Bengaluru, India; HCG, Bengaluru, India; HCG Hospitals, Bangalore, India

Background: Cancer cells demonstrate metabolic inflexibility characterized by glycolytic dependence and dysfunctional mitochondrial oxidative phosphorylation [Warburg Effect]. Fasting and glucose restriction induce a metabolic shift toward mitochondrial fatty acid oxidation and ketone utilization in normal cells, while cancer cells are unable to adapt, resulting in increased oxidative stress and radio-sensitization. We evaluated whether inducing a fasting-mimicking metabolic state during neoadjuvant chemoradiation improves pathological complete response (pCR) rates in rectal cancer compared with total neoadjuvant therapy (TNT) and standard neoadjuvant chemoradiation (nCRT). **Methods:** 90 patients with locally advanced rectal adenocarcinoma were analyzed (30 per group). All patients had cT3N+ disease. Radiotherapy was delivered using IMRT/IGRT or adaptive techniques, receiving long-course radiotherapy (50.4 Gy in 28 fractions) with concurrent capecitabine. Group 1 received nCRT under a fasting-mimicking metabolic state using a structured low-carbohydrate diet [Non-Calorie Restricted] with ≥ 14 hours of daily fasting, titrated using continuous glucose monitoring [CGM] to achieve 16–17 hours per day with blood glucose levels < 90 mg/dL. Group 2 received TNT consisting of nCRT followed by CAPEOX. Group 3 received standard nCRT without dietary intervention. The primary endpoint was pCR (ypT0N0) at surgery. pCR rates were compared between groups using the chi-square test or Fisher's exact test, as appropriate, with a two-sided p value < 0.05 considered statistically significant. **Results:** Baseline characteristics were balanced across groups; all patients had cT3N+ disease. Median age was 55 years, with all adenocarcinoma histology. pCR rates were 93.3% (28/30) in the fasting-state nCRT group, 73.3% (22/30) in the TNT group, and 33.3% (10/30) in the standard nCRT group. Fasting-state nCRT was associated with significantly higher pCR rates compared with standard nCRT ($\chi^2=25.2$, df=2; $p<0.001$). TNT was also superior to standard nCRT ($p=0.004$). The difference between fasting-state nCRT and TNT showed a strong numerical trend but did not reach statistical significance ($p=0.08$). **Conclusions:** Fasting-state metabolic modulation during neoadjuvant chemoradiation was associated with a striking increase in pCR rates. Mitochondrial stress induced by glucose restriction may enhance tumor radio-sensitivity through increased reactive oxygen species and impaired metabolic compensation. Precision-guided fasting represents a promising, low-cost therapeutic strategy warranting prospective larger cohort validation. Clinical trial information: CTRI/2024/10/075843. Research Sponsor: HCG Research Fund.

Comparison	pCR	p-value
Fasting-state nCRT	93.3% (28/30)	< 0.001
TNT	73.3% (22/30)	0.004
Standard nCRT	33.3% (10/30)	0.08

Predicting neoadjuvant chemoradiotherapy response and postoperative recurrence in locally advanced rectal cancer using a preoperative large language model.

Xiaoxi Chen, Kun Miao, Song Wang, Guofeng Sun, Hua Bao, Haimeng Tang, Rui Liu, Xue Wu, Yang Shao, Zhijun Zeng; Geneseeq Research Institute, Nanjing Geneseeq Technology Inc., Nanjing, China; The First People's Hospital of Yunnan Province, Kunming, China; Xiangya Hospital of Central South University, Changsha, China

Background: Neoadjuvant chemoradiotherapy (nCRT) is standard for locally advanced rectal cancer (LARC), yet responses are heterogenous and early identification of responders remains challenging. We developed a Transformer-based large language model that analyzes fragment-level patterns in circulating cell-free DNA (cfDNA) to predict pathological complete response (pCR) and postoperative recurrence risk independently of somatic mutation calling. **Methods:** A total of 510 plasma samples were collected from 102 LARC patients at five perioperative time points. The model was trained on post-nCRT cfDNA data from a training cohort (N = 62) to predict pCR, evaluated in an internal validation cohort (N = 40) and an external validation cohort (N = 96). Associations between model prediction scores, nCRT response, and recurrence-free survival (RFS) were assessed across time points. Fragment-level features contributing to model predictions were analyzed to provide biological interpretability. **Results:** The model demonstrated robust predictive performance, with AUCs of 0.909 (95% confidence interval [CI]: 0.812–1.000) in the training cohort, 0.903 (95% CI: 0.785–1.000) in the validation cohort, and 0.835 (95% CI: 0.754–0.916) in the external cohort. Patients achieving pCR had significantly higher prediction scores than non-pCR patients (Wilcoxon $p < 0.001$), and scores inversely correlated with tumor regression grade (Jonckheere-Terpstra test $p < 0.001$). At the predefined cutoff corresponding to 95% specificity in the training cohort, sensitivities were 0.73, 0.64, and 0.44 across datasets. High post-nCRT and post-surgical prediction scores were associated with improved RFS (log-rank $p = 0.012$ and $p = 0.024$, respectively), and all relapsed patients had consistently low post-nCRT scores. The top 1% of cfDNA fragments, ranked by model importance, were predominantly 50–100 bp with ~ 40% GC content, and the proportion of subnucleosomal particles was significantly higher in pCR versus non-pCR samples, providing biological insights into features driving the model. **Conclusions:** We developed a robust, mutation-independent framework for predicting nCRT response and postoperative recurrence risk in LARC, supporting individualized treatment decisions and post-surgical surveillance strategies. Research Sponsor: Natural Science Foundation of Hunan Province; 2024JJ5568.

Association between circulating tumor DNA and local tumor regrowth and distant metastasis during nonoperative management in stage I–III rectal cancer.

Kentaro Ochiai, Megan E. Delisle, Alisha Heather Bent, Van K. Morris II, Arvind Dasari, Emma Holliday, Timothy E. Newhook, Kristin Alfaro, Kathryn Aziz, Paula Marincola Smith, Ramy S. Behman, Jeongyoon Moon, Michael White, Craig Messick, Y. Nancy You, Brian K. Bednarski, George J. Chang, Jesse Joshua Smith, Scott Kopetz, Tsuyoshi Konishi; Department of Colon and Rectal Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Gastrointestinal Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Gastrointestinal (GI) Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: During nonoperative management (NOM) for rectal cancer after a clinical complete response (cCR) or near-CR (nCR), 25–30% develop local regrowth and 5–10% develop distant metastasis, highlighting the need for improved risk stratification and surveillance. Circulating tumor DNA (ctDNA) has emerged as a prognostic biomarker, but its utility in NOM decision making remains undefined. **Methods:** We retrospectively studied 110 patients with stages I–III, microsatellite stable rectal adenocarcinoma achieving cCR/nCR after neoadjuvant therapy (2020–2024) managed with NOM and tumor-informed ctDNA testing in the INTERCEPT program (Signatera Exome). We assessed longitudinal ctDNA status during NOM and the first post-treatment ctDNA in relation to local regrowth and/or distant metastasis (Kaplan–Meier/log-rank; Fisher’s exact). We also evaluated per-sample accuracy for events occurring within ±90 days of each blood draw. **Results:** Over a median follow-up of 25 months, 23 (20.9%) patients developed local regrowth and 12 (10.9%) developed distant metastases (Table 1). Patients with ever positive longitudinal ctDNA had an associated worse 2-year regrowth-free survival (41.7% vs 83.9%, $P=0.0002$) and metastasis-free survival (41.7% vs 94.9%, $P<0.0001$) than those with persistently negative ctDNA. Among patients with an evaluable first post-treatment ctDNA result (within 180 days post treatment; $n=72$), those with a positive result had an associated lower regrowth-free survival ($P=0.0006$) and metastasis-free survival ($P<0.0001$). In per-sample analysis ($n=669$), ctDNA showed low sensitivity and high specificity for local regrowth (41.4% and 94.3%) and higher sensitivity and specificity for distant metastasis (73.8% and 97.4%). Twenty-two of 23 patients with local regrowth underwent salvage surgery; ctDNA positivity at local regrowth was associated with more advanced pathological T stage (66.7% of ypT3–4 vs 15.4% of ypT0–2, $P=0.01$). **Conclusions:** During NOM for rectal cancer, ctDNA may be used to identify a small subgroup at high risk of local regrowth and/or distant metastasis. However, many local regrowth occurs despite persistently negative ctDNA, consistent with limited sensitivity. Negative ctDNA results should therefore not prompt de-escalation of endoscopic and radiologic surveillance when a NOM strategy is used. Research Sponsor: None.

Overall rates of local regrowth and distant metastasis.				
	Local regrowth (n=23) ^a	P	Distant metastasis (n=12)	P
Longitudinal ctDNA				
Persistently negative (n=95)	14/95 (14.7%)	<.0001	3/95 (3.2%)	<.0001
Ever positive (n=15)	9/15 (60.0%)		9/15 (60.0%)	
First post-treatment ctDNA ^b				
Negative (n=67)	15/67 (22.4%)	0.005	5/67 (7.5%)	<.0001
Positive (n=5)	4/5 (80.0%)		4/5 (80.0%)	

^aTwo had synchronous and 5 had metachronous distant metastasis.

^bWithin 6 months post treatment, $n=72$.

Minimal residual disease (MRD) assessment by circulating tumor DNA (ctDNA) to stratify recurrence risk and adjuvant treatment benefit in a real-world colorectal cancer (CRC) cohort.

Mariam Galuia, Joseph Gabriel Mchayleh, Lampros Karakozis, Michael Abdelmasseh, George Nassif, Mark Soliman, Matthew Albert, Justin Kelly, Mohamedtaki Abdulaziz Tejani, Ahmed Zakari; AdventHealth Cancer Institute, Orlando, FL; AdventHealth Research Institute, Orlando, FL; AdventHealth, Orlando, FL

Background: ctDNA detection following curative surgery is known to predict recurrence in patients (pts) with stage II-III CRC. We investigate ctDNA dynamics in relation to clinical outcomes and their real-world impact on treatment decisions among pts with resected CRC. **Methods:** Based in a large community hospital system, we conducted a retrospective analysis of a prospectively maintained database inclusive of 407 pts with resected stage II-IV CRC. ctDNA was longitudinally quantified at MRD (2-12 weeks post-op) and surveillance timepoints (tp) using a clinically validated, personalized, tumor-informed 16-plex mPCR-NGS assay. Primary endpoint was the correlation between ctDNA status and disease-free survival (DFS) and overall survival (OS). Secondary objective was to evaluate its impact on treatment decisions. Survival distribution was analyzed by Kaplan-Meier Method. Multivariable Cox proportional hazards models were applied to adjust for clinicopathological covariates: age, gender, T, N, high risk features, obstruction, perforation, KRAS, BRAF, MMR. **Results:** Of 407 pts, 303 had complete evaluable data for analysis at cutoff 12/5/2025. After median follow-up of 29.6 months (mo), N=2342 ctDNA plasma levels were analyzed: 2 stage I, 119 stage II, 170 stage III, 12 stage IV. ctDNA at MRD tp was available for 259 pts (86%): 99 stage II, 144 stage III. ctDNA was negative at MRD tp in 211/259 (MRD-), positive in 48/259 (MRD+). Of 303 pts, 180 (60%) received adjuvant chemotherapy (ACT): 38 MRD+, 118 MRD-. 123 (40%) were observed: 9MRD+, 93 MRD-. MRD positivity was significantly associated with inferior DFS in all stages combined (HR = 13.4, 95% CI: 7.64-23.64, $p < 0.0001$) and in all stage-stratified subgroups. Multivariate analysis confirmed ctDNA-positivity to be the most significant prognostic factor associated with DFS when compared with clinicopathologic factors. In MRD+ subgroup, pts with transient ctDNA clearance had significantly worse DFS than those with sustained clearance (HR = 5.27, 95% CI: 2.49-11.14, $p < 0.0001$). Among MRD- pts, ACT conferred no significant DFS benefit vs observation (HR=1.52, $p < 0.05$). Among MRD+ pts, ACT did not reach statistical significance. ctDNA positivity predicted recurrence with a lead time up to 23.9 mo (median 3.8 mo) before imaging, including in low ctDNA shedding sites. 7% had metastatic disease diagnosed earlier because of a positive test, prompting timely therapy. ctDNA testing was associated with higher than historical rates of oligometastasis-directed therapy (17%). **Conclusions:** Our results highlight the value of post-surgical ctDNA monitoring as a prognostic biomarker in CRC and its potential value for treatment decision making. Clinical utility of ctDNA-guided AC will further be established by ongoing trials (CIRCULATE-NA). Research Sponsor: None.

Safety, immunogenicity, and efficacy of Ad5.F35-GUCY2C-PADRE vaccine in patients with GI cancers at high risk of relapse: Results from a phase 2A trial.

Babar Bashir, Zhengyang Sun, Jagmohan Singh, Daniel Lin, Atrayee B. Mallick, Wei Jiang, Tingting Zhan, Walter K. Kraft, Scott A. Waldman, Adam Snook; Sidney Kimmel Comprehensive Cancer Center at Thomas Jefferson University Hospital, Philadelphia, PA; Department of Pharmacology, Physiology, and Cancer Biology, Thomas Jefferson University, Philadelphia; Department of Pharmacology, Physiology, & Cell Biology at Thomas Jefferson University, Philadelphia, PA; Thomas Jefferson University Hospital, Philadelphia, PA; Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA; Thomas Jefferson University, Philadelphia, PA; Department of Pharmacology, Physiology, & Cell Biology at Thomas Jefferson University, Philadelphia, PA; Sidney Kimmel Comprehensive Cancer Center at Thomas Jefferson University, Philadelphia, PA

Background: Guanylyl cyclase C (GUCY2C) is an intestinal tumor antigen ectopically expressed in some gastroesophageal and pancreatic cancers, highly expressed in nearly all colorectal cancers (CRC), and retained in metastases. Adenovirus serotype 5 (Ad5)-based cancer vaccines, including those targeting GUCY2C, are limited by pre-existing neutralizing antibodies (NABs) targeting Ad5. Ad5.F35-GUCY2C-PADRE is a chimeric Ad5 vector (fiber of serotype 35) developed to overcome anti-Ad5 immunity and induce durable antitumor T-cell responses. We report initial immunogenicity, safety, and recurrence outcomes from a phase 2A dose-finding study in patients with resected GI malignancies. **Methods:** This open-label phase 2A study enrolled patients with resected, high-risk GI adenocarcinomas (CRC, pancreatic, gastric, and small bowel) with no evidence of disease 4–24 wks after standard adjuvant therapies. Oligo-metastatic stage IV CRC patients were also allowed (n=8). Patients were randomized to receive three i.m. administrations of Ad5.F35-GUCY2C-PADRE at 1×10^{11} , 1×10^{12} , or 5×10^{12} viral particles (vp) at 4-wk intervals. Primary endpoints were safety and GUCY2C-specific T-cell responses (IFN γ ELISpot). Exploratory endpoints included the impact of NABs on T-cell responses and RFS, and the impact of dose on immunological and clinical outcomes. **Results:** Forty-six patients (29 CRC) completed treatment and were evaluable. Vaccination was well tolerated with no DLTs or TRSAEs; AEs were predominantly grade 1–2 flu-like symptoms. GUCY2C-specific T-cell responses increased in frequency and magnitude in a dose-dependent manner. Nearly all patients receiving higher doses produced T-cell responses regardless of NAB status (Table), supporting Ad5.F35 overcoming pre-existing NABs. At the 2-year follow-up, there was a dose-dependent improvement in RFS among stage II–III CRC patients (Table), and RFS was significantly improved among immune responders vs non-responders ($P < 0.05$). **Conclusions:** Ad5.F35-GUCY2C-PADRE is safe, overcomes pre-existing Ad5 immunity, and induces robust, dose-dependent GUCY2C-specific T-cell responses. Vaccine-induced immunity is associated with improved RFS in CRC, supporting further development of the off-the-shelf Ad5.F35 platform for cancer vaccines and Ad5.F35-GUCY2C-PADRE for CRC recurrence prevention. Clinical trial information: NCT04111172. Research Sponsor: Targeted Diagnostics and Therapeutics, Inc.

Dose (vp)	Magnitude of GUCY2C-Specific T-cell Response ¹	% of Patients with a GUCY2C-Specific T-cell Response (N/N) ²	CRC ³ Recurrences (%; N/N); Median RFS
1×10^{11}	9	33% (5/15)	50% (4/8); 512 days
1×10^{12}	92	94% (15/16)	17% (1/6); not reached
5×10^{12}	218	100% (15/15)	0% (0/7); not reached
	$P < 0.0001$	$P < 0.0001$	$P = 0.051$

¹Median SFCs/ 5×10^5 PBMCs; ²at 4 weeks after 1st vaccination; ³excluding stage IV patients.

SOCGER: A randomized phase II trial comparing complete clinical response after short course radiation or chemoradiation and consolidation chemotherapy in rectal cancer.

Ramakrishnan Ayloor Seshadri, Gangothri Selvarajan, Arunkumar Madukkarai Natarajan, Pradeep Jeyakumar S, Karthigaiselvi Murugesan, Anuradha Chandramohan, Karthik Chandra, Shirley Sundersingh, Sujatha Lakshminarayanan, Thirumurthy Natarajan, Paulson Vijaykumar; Integrated Cancer Care Group, Chennai, India; Cancer Institute (WIA), Chennai, India; Cancer Institute (WIA), Adyar, Chennai, India; Cancer institute(WIA), Adyar, Chennai, India; Christian Medical College, Vellore, Tamil Nadu, India

Background: The preferred total neoadjuvant treatment (TNT) regimen for an intentional watch-and-wait (W&W) approach in patients with rectal cancer is long course chemoradiation (LCRT) and consolidation chemotherapy (CNCT). The role of short course radiation (SCRT) and CNCT in this context is not well defined. The shorter treatment time of SCRT has advantages, especially in resource-constrained settings. This study aimed to select the more promising of the two TNT strategies for a W&W approach in patients with rectal cancer for further phase III evaluation. **Methods:** This dual-center, randomized phase II trial was conducted in Chennai and Vellore, India. Patients with rectal adenocarcinoma within 8cm of the anal verge, T3N0 or T1-3N+ on magnetic resonance imaging (MRI) who required neoadjuvant radiation and surgery, were randomized to one of two arms: Arm A - LCRT (54Gy with capecitabine) + 6 cycles of CAPOX (capecitabine + oxaliplatin), Arm B - SCRT (25Gy) + 6 cycles of CAPOX. Tumor response was assessed at 24 weeks from completion of radiation by digital rectal examination, sigmoidoscopy and MRI and categorized by a pre-defined criterion. Primary end-point was cCR or near cCR. Patients with a cCR at first assessment or at a second assessment 12 weeks after a near cCR were offered W&W. Based on Simon's randomized phase II pick-the-winner design, 40 patients were required to achieve a 90% probability of correct selection, assuming a 50% cCR and a 20% absolute difference, without formal superiority testing. Secondary endpoints included adverse events, treatment compliance, post-operative complications, 2-year organ preservation, local regrowth, disease-free survival, diagnostic performance of response assessment criteria, and quality of life. **Results:** Among 46 patients randomized between 2022 and 2025, primary endpoint was assessed in 43 (modified intention-to-treat population). Median age (range), proportion of T3, node positive tumors and mesorectal fascia involvement were 54 years (27-69), 86.3%, 54.5%, 63.6% and 49 years (31-68), 86.9%, 56.5%, 60.8% in Arm A and B, respectively. For primary and short-term secondary endpoints, see Table. **Conclusions:** SCRT + CNCT was superior to LCRT + CNCT in inducing cCR/near cCR in patients with rectal cancer and emerged as the preferred regimen for further evaluation of an intentional W&W approach in a phase III study. Clinical trial information: CTRI: 2021/01/030370. Research Sponsor: None.

End-point	Arm A	Arm B
No. of complete + near complete clinical response	8/20 (40%)	17/23 (73.9%)
Adverse events ≥Grade 3		
During Radiation	2 (in 20 patients)	1 (in 23 patients)
During CNCT	43 in 108 cycles	26 in 138 cycles
No. of pts with Relative dose intensity of CNCT <85%	6 (33.3%)	11 (47.8%)
No. of pts with CNCT delayed ≥3 days in ≥2 cycles	5 (27.7%)	2 (8.6%)
Median no. of CNCT cycles	6	6
Post-operative complications	2 in 11 patients	0 in 6 patients
Clavien-Dindo ≥3		
Treatment related death	1	0

Prediction of localized rectal cancer outcomes with ctDNA analysis using a novel ultrasensitive structural variant (SV)-based method.

Cecilia Merk, Sofia Birkealy, Karen Howarth, Girish Putcha, Rebecka Bergström, Rickard Strandberg, Markus Mayrhofer, Johan Lindberg, Anna Martling; Karolinska Institutet, Stockholm, Sweden; SAGA Diagnostics, Lund, Sweden; SAGA Diagnostics, Morrisville, NC; RedDoor Analytics AB, Stockholm, Sweden

Background: Rectal cancer has a high risk of recurrence and incidence is rising. Treatment for rectal cancer has moved towards individualization and organ sparing approaches. Selection for treatment is based on radiology, CEA and pathological risk factors, but stronger biomarkers are needed to improve outcomes. Circulating tumor DNA (ctDNA) has shown high prognostic impact on outcome in localized colorectal cancer (CRC), but few patients with rectal cancer have been included in these trials. In this study, we aim to investigate the role of ctDNA in predicting rectal cancer outcomes. **Methods:** The multicenter CITCCA study included patients with stage I–III CRC planned for curative treatment and investigated prospective, longitudinal ctDNA testing. Neoadjuvant (NAT) and/or adjuvant (ACT) treatment was administered according to local guidelines. All patients underwent surgery. Follow-up was according to Swedish standard-of-care with CT and CEA at 1 and 3 years. Patients were recruited in Sweden, 2020–2024. Sampling of ctDNA occurred before and after surgery at 4–6 weeks, 3 and 6 months, 1 and 2 years and was analysed with Pathlight, an ultrasensitive SV-based assay. The primary outcome was recurrence-free interval (RFI). **Results:** The study included patients with rectal cancer with a median age of 67 years (range 31–81). Ninety-four patients (65%) received upfront surgery and 51 patients (35%) NAT, of which 36 patients (71%) received short-course radiotherapy and 15 (29%) had total neoadjuvant treatment. Fifty-two patients (36%) were (y)pTNM stage I, 45 patients (31%) stage II and 48 patients (33%) stage III. ACT was given to 38 patients (26%). The success rate for assay generation was 96%. At a median follow-up of 35 months (range 2–46), 23 patients recurred or died of rectal cancer. Before surgery, ctDNA was detected in 136 patients (94%). Notably, 92% (55/60) of patients had ctDNA detected prior to surgery, despite NAT. All patients who recurred had positive ctDNA before surgery, regardless of NAT. Postoperatively, at the 4–6 week clinical landmark (CLM), 18 patients (16%) had detectable ctDNA. At the first test after treatment termination, 17 patients (15%) were ctDNA positive and ctDNA detected recurrence ahead of radiology in 13 patients, including 4/4 patients with stage I disease. Positive ctDNA was strongly associated with recurrence (HR: 94; 95% CI: 20–440) and 3-year RFI at CLM was 22% (95% CI: 9%–56%) for ctDNA positive and 95% (95% CI: 90%–100%) for ctDNA negative patients. **Conclusions:** CtDNA has strong prognostic potential in stage I–III rectal cancer. Using an ultrasensitive SV-based method shows great promise for individualization of treatment in rectal cancer and should be investigated prospectively for organ-sparing selection. Clinical trial information: NCT04726800. Research Sponsor: Cancerfonden.

Neoadjuvant treatment of QL1706 in patients with resectable microsatellite instability-high/mismatch repair-deficient colon cancer: Results from a phase 1b trial.

Zi-Xian Wang, Xinyi Cai, Leping Li, Xiangbin Wan, Xianwei Mo, Zhengrong Li, Zhiwei Li, Qiu Meng, Jing-Lin Zhao, Haiyi Liu, Yuping Zhu, Yingbin Hu, Yanlai Sun, Weiwei Peng, Shuang Li, Meijiang Zhang, Lingyan Li, Xiaoyan Kang, Rui-Hua Xu; State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-sen University Cancer Center, Guangzhou, China; Yunnan Cancer Hospital, Kunming, China; Department of Gastrointestinal Surgery, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, China; Henan Cancer Hospital, Zhengzhou, China; Guangxi Medical University Cancer Hospital, Nanning, China; The First Affiliated Hospital of Nanchang University, Nanchang, China; Gastroenterology Ward 1, Harbin Medical University Cancer Hospital, Harbin, China; West China Hospital, Sichuan University, Chengdu, Sichuan, China; Jiangmen Central Hospital, Jiangmen, China; Department of Colorectal Surgery, Shanxi Province Cancer Hospital, Hospital Affiliated to Cancer Hospital, Chinese Academy of Medical Sciences, Cancer Hospital Affiliated to Shanxi Medical University, Taiyuan, Shanxi, China; Zhejiang Cancer Hospital, Hangzhou, China; Hunan Cancer Hospital, Changsha, China; Shandong Cancer Hospital, Jinan, China; Ganzhou People's Hospital, Ganzhou, China; Innovative Clinical Research and Development Center, Qilu Pharmaceutical Co., Ltd., Jinan, China; Innovative Clinical Research and Development Centre, Qilu Pharmaceutical Co., Ltd., Jinan, China; Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Immune checkpoint inhibitors in neoadjuvant setting have brought clinical benefits for patients with various tumors. This study aimed to evaluate the efficacy and safety of iparomlimab and tuvonralimab (QL1706), a bifunctional antibody targeting both PD-1 and CTLA-4, as neoadjuvant treatment in patients with microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) colon cancer. **Methods:** In this single-arm phase 1b trial, previously untreated patients with resectable stage IIB-III MSI-H/dMMR colon cancer were recruited. Patients were administered neoadjuvant treatment of QL1706 at 5 mg/kg via intravenous infusion every three weeks for four cycles. Radical resection was scheduled between 4 and 6 weeks after last dose of neoadjuvant treatment. The primary endpoint was pathological complete response (pCR) rate. The efficacy analysis set included patients who were confirmed dMMR/MSI-H, received at least one dose of treatment, and had post-surgery pathological results. The safety analysis set included patients who received at least one dose of treatment. **Results:** As of data cut-off date on Oct 15, 2025, 43 patients were enrolled (median age: 56.0 years; males: 58.1%; ECOG PS 1: 55.8%; Lynch syndrome: 34.9%). Scheduled radical resection were performed in 34 patients. A total of 34 patients were included in the efficacy analysis set. The pCR rate was 88.2% (30/34, 95% confidence interval [CI]: 72.5%-96.7%). The major pathologic response rate was 91.2% (31/34, 95% CI: 76.3%-98.1%). In high-risk patients (T4 or N2), the pCR rate was 86.4% (19/22, 95% CI: 65.1%-97.1%). All patients (100%) received surgery had Ro resection. Median treatment exposure was 2.1 months (range, 0.0-3.9). Treatment-emergent adverse events (TEAEs) of grade ≥ 3 occurred in 12 patients (27.9%); two (4.7%) patients were treatment-related. Immune-related adverse events grade ≥ 3 occurred in two (4.7%) patients, including one grade 3 acute kidney injury and one grade 4 hypersensitivity, both of which recovered finally. Treatment-related serious adverse events occurred in three (7.0%) patients. No patient cancelled or delayed the surgery due to TEAE. No TEAE leading to death occurred. The incidence of grade ≥ 3 TEAE during the surgery phase was 11.8% (4/34). **Conclusions:** Neoadjuvant treatment of QL1706 showed promising pCR rate and manageable safety in patients with MSI-H/dMMR colon cancer. A phase 3 trial is ongoing to further confirm the efficacy and safety of QL1706 as neoadjuvant treatment in patients with resectable MSI-H/dMMR colon cancer. Clinical trial information: NCT06686576. Research Sponsor: Qilu Pharmaceutical Co., Ltd.

Phase II trial of anti-PD-1 monoclonal antibody and FOLFOXIRI combined with long-course radiotherapy as the total neoadjuvant treatment for proficient, mismatch repair, locally advanced low rectal cancer (PANFORTE).

Jianhong Peng, Chi Zhou, Miaozen Qiu, Weihao Li, Qiaoxuan Wang, Min Liu, Ting-Ting Quan, Zhen-Hai Lu, Xiao Jun Wu, Li-Ren Li, Da Kang, Yuanbin Liao, Song Wang, Pei-Rong Ding, Zhizhong Pan, Jun-Zhong Lin; Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University, Guangzhou, China; Department of Radiation Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, Guangdong, China; Department of Radiology, Sun Yat-Sen University Cancer Centre, Guangzhou, Guangdong, China; Department of Colorectal Surgery, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: The current standard treatment for locally advanced low rectal cancer (LALRC) achieves a complete response (CR) rate of only 20–30%. Consequently, radical surgery frequently results in the loss of anal organs, severely affecting patients' quality of life. Therefore, there is an urgent clinical need to identify novel strategies that can maximize tumor regression and preserve anal function. Recent trials have demonstrated radiotherapy showed a distinctive synergistic anti-tumor effect with immune checkpoint inhibitors. Therefore, this study aims to assess the efficacy and safety of an immunotherapy-based total neoadjuvant therapy (TNT) in patients with proficient mismatch repair (pMMR) LALRC. **Methods:** Eligible patients (pts) on this investigator-initiated phase II study had pMMR LALRC with ECOG performance status ≤ 1 and an inferior tumor margin distance from the anal verge (DAV) ≤ 5 cm. Eligible patients receive 4 cycles of FOLFOXIRI plus serplulimab (200 mg). Subsequently, they undergo long-course radiotherapy combination with capecitabine and 2 cycles of serplulimab (200 mg), followed by another 4 cycles of FOLFOXIRI and serplulimab (200 mg). The primary endpoint is CR rate with the sum of clinical complete response (cCR) and pathological complete response (pCR). Secondary endpoints include sphincter preservation rate and safety. **Results:** Between November 2023 and April 2025, 53 patients were enrolled with male percentage 62.3%, median age of 55 years (Range, 28–72) and median DAV of 3 cm (Range, 0.4–5.0). 92.5% (49/53) of patients completed the full TNT regimen. Among the 51 patients eligible for endpoint assessments, the overall CR rate was 68.6% (35/51), and the sphincter preservation rate was 94.1% (48/51). 31 (60.8%) patients achieving cCR opted for a watch-and-wait approach, whereas 20 patients underwent surgery. 20% (4/20) achieved pCR and 70% (17/20) had a tumor regression grade (TRG) of 2. The most common AEs was neutropenia (grade 3–4, 66.0% [35/53]). Other grade 3–4 AEs included leukopenia (32.1%, 17/53), lymphopenia (20.8%, 11/53), and thrombocytopenia (18.9%, 10/53). Immune-related 3–4 AEs comprised myocarditis (1.9%, 1/53) and elevated transaminases (1.9%, 1/53). **Conclusions:** Our study indicates that this TNT regimen significantly enhances CR rates and anal preservation in pMMR LALRC compared to historical benchmarks, with an acceptable safety profile. These findings suggest that this new approach may be an alternative treatment option for LALRC patients who strongly desire anal preservation. Clinical trial information: NCT06099951. Research Sponsor: None.

The role of adjuvant chemotherapy in high-risk stage II colon cancer with micro-satellite instability-high or DNA mismatch repair deficiencies: A multicenter pooled analysis (KCSG-CO24-03).

Joon Young Hur, Hana Kim, Soon Il Lee, Se Jun Park, Jina Yun, Seok Yun Kang, Cheol-Sik Kim, Seung-Hoon Beom, HyeYeong Kim, So Yeon Jeon, Jaemin Jo, Yongho Noh, Jong Gwang Kim, Hyun Jin Bang; Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; National Cancer Center, Goyang, South Korea; Dankook University Hospital, Dankook University College of Medicine, Cheonan, South Korea; Division of Medical Oncology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea; Soonchunhyang University Bucheon Hospital, Bucheon, South Korea; Department of Hematology-Oncology, Ajou University Hospital, Suwon-Si, South Korea; Pusan National University Yangsan Hospital, Kyungnam, South Korea; Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; Department of Internal Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, South Korea; Department of Internal Medicine, Chonbuk National University Medical School, Jeonju, South Korea; Jeju National University Hospital, Jeju, South Korea; Chung-Ang University Hospital, Seoul, South Korea; Kyungpook National University Medical Centre, Kyungpook National University School of Medicine, Daegu, South Korea; Chonnam National University Hwasun Hospital, Hwasun-Gun, South Korea

Background: The benefit of adjuvant chemotherapy (CTx) for high-risk stage II MSI-H/dMMR colon cancer remains controversial, with discordant international guidelines. This study evaluated clinical outcomes comparing adjuvant CTx vs. observation in this population. **Methods:** This multicenter retrospective analysis included 192 patients with high-risk stage II MSI-H/dMMR colon cancer who underwent curative resection (2010–2020). High-risk features included pT4, grade 3–4, lympho-vascular invasion, bowel obstruction/perforation, perineural invasion (PNI), inadequate lymph node sampling (<12), or close margins. Primary endpoint was 5-year relapse-free survival (RFS). Secondary endpoints included 5-year overall survival (OS). A propensity score-matched (PSM) analysis was performed. **Results:** Of 192 patients, 128 (66.6%) received adjuvant CTx (FOLFOX n=66, capecitabine n=40, FL n=17, others n=5) and 64 (33.3%) underwent observation. Median follow-up was 60.5 months. During follow-up, 24 RFS events and 15 OS events occurred. The 5-year RFS was significantly higher with adjuvant CTx versus observation (94.0% vs. 83.7%; $P=.001$), as was 5-year OS (98.3% vs. 89.0%; $P=.001$). Multivariate analysis confirmed adjuvant CTx as an independent prognostic factor for both RFS (HR 0.278, 95%CI 0.117–0.660; $P=.003$) and OS (HR 0.176, 95%CI 0.052–0.594; $P=.005$). PNI independently predicted worse RFS (HR 4.053; $P=.002$) and OS (HR 7.490; $P=.001$). Subgroup analysis demonstrated pronounced benefit in pT4 patients (OS HR 0.094, $P=.031$; RFS HR 0.230, $P=.038$) and significant benefit in T3 patients (RFS HR 0.326, $P=.031$). No survival differences were observed between oxaliplatin-containing vs. non-oxaliplatin regimens (5-year RFS $P=.636$; OS $P=.757$). PSM analysis (n=56 pairs) confirmed the survival benefit (matched OS HR 0.344, $P=.036$). **Conclusions:** Adjuvant CTx significantly improves RFS and OS in high-risk stage II MSI-H/dMMR colon cancer, particularly in pT4 and PNI patients. The absence of regimen-specific survival differences suggests that treatment administration itself, rather than specific agents, determines outcomes. These findings provide evidence to bridge NCCN and ESMO guideline discrepancies, supporting risk-stratified adjuvant CTx in this population. Research Sponsor: None.

Multivariate analysis for survival.			
Relapse free survival	Hazard Ratio	95% CI	P value
Adjuvant chemotherapy			
No	1		
Yes	0.278	0.117-0.660	0.003
Pathologic T stage			
T3	1		
T4	2.308	0.955-5.577	0.063
Perineural invasion			
No	1		
Yes	4.053	1.627-10.100	0.002
Overall survival	Hazard Ratio	95% CI	P value
Adjuvant chemotherapy			
No	1		
Yes	0.176	0.052-0.594	0.005
Age			
< 60	1		
≥ 60	2.810	0.607-13.000	0.186
Pathologic T stage			
T3	1		
T4	3.959	1.223-12.820	0.021
Perineural invasion			
No	1		
Yes	7.490	2.184-25.690	0.001
Bowel perforation or obstruction			
No	1		
Yes	2.911	0.933-9.078	0.065

Stage-specific circulating tumor DNA (ctDNA) positivity and minimal residual disease (MRD) decision making in colorectal cancer (CRC) in the prospective INTERCEPT program.

Emerik Osterlund, Giulia Maddalena, Guglielmo Vetere, Kathryn Aziz, Robert J. Kell, Logan White, Dylan N. Gil, Mahmoud M.G. Yousef, Kristin Alfaro, Christine Parseghian, Neha Agrawal, Tsuyoshi Konishi, Kanwal Pratap Singh Raghav, Timothy E. Newhook, Xiling Shen, John Paul Y.C. Shen, Michael J. Overman, Van K. Morris II, Arvind Dasari, Scott Kopetz; Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Oncology Unit 1, Istituto Oncologico Veneto (IOV-IRCCS), Padua, Italy; Department of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Colon and Rectal Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Gastrointestinal (GI) Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: ctDNA positivity is a strong prognostic biomarker for recurrence after curative-intent procedures for CRC and defines MRD in the absence of radiographic disease. Our aim was to assess stage-specific positivity rates across follow-up intervals and the clinical actions associated with ctDNA+. **Methods:** The INTERCEPT program enrolled patients undergoing curatively intended procedures for stage I-IV CRC at MD Anderson Cancer Center. Tumor informed MRD assays (Signatera) were drawn postoperatively and every 3 months according to reimbursement guidelines. ctDNA draws were grouped into 6-month intervals from completion of definitive therapy. Clinical decisions after the first ctDNA+ result in the MRD window were classified as: MRD-trial, systemic therapy, diagnostic escalation, early follow-up, ctDNA confirmation, or no change. **Results:** The final cohort included 1,603 patients (40% stage IV, 32% stage III, 20% stage II, 8% stage I). Median follow-up was 18.4 months. Patients that were ctDNA- on first post-definitive draw had longer recurrence-free survival (RFS) than ctDNA+ patients (median RFS 62.6 vs 4.8 months, HR 11.6 [95% CI 9.6-14.1]), remaining significant in stage subgroups. Among all patients 28% were ctDNA+ at any post-definitive timepoint, the rates were highest for stage IV, followed by stage III, II, and I (Table). ctDNA+ rates were highest in early follow-up and got lower at later intervals (21% to 5%), with similar patterns for all stages. Among 271 patients that were ctDNA+ in the MRD window the initial therapeutic approach was MRD trial screening for 59 (22%), diagnostic escalation in 73 (18%), early follow-up in 57 (21%), confirmation of ctDNA+ by repeat testing in 23 (8%), no change in management for 38 (14%), and 21 (8%) patients started other systemic therapy. MRD trials were discussed prior to recurrence with 144 (53%) of the patients. **Conclusions:** ctDNA positivity is more common in higher stage tumors and becomes less frequent during follow-up. ctDNA positivity confirms its established prognostic value and meaningfully impacts clinical management, including diagnostic workup and MRD trial enrollment. Even within a single center, heterogeneity in initial management of ctDNA+ patients and timing for MRD trial enrollment is evident. Research Sponsor: None.

Stage-specific ctDNA+ rates during follow-up after definitive therapy.

	All	Stage IV	Stage III	Stage II	Stage I	p
Any time	444 / 1,603 (28%)	313 / 646 (48%)	87 / 513 (17%)	40 / 322 (12%)	4 / 122 (3%)	<0.001
<6 months	329 / 1,603 (21%)	249 / 646 (39%)	57 / 513 (11%)	21 / 322 (7%)	2 / 122 (2%)	<0.001
6 to <12 months	151 / 1,018 (15%)	97 / 349 (28%)	36 / 351 (10%)	17 / 230 (7%)	1 / 88 (1%)	<0.001
12 to <18 months	75 / 672 (11%)	50 / 197 (25%)	15 / 250 (6%)	10 / 161 (6%)	0 / 64 (0%)	<0.001
18 to <24 months	16 / 264 (6%)	10 / 71 (14%)	3 / 94 (3%)	3 / 71 (4%)	0 / 28 (0%)	0.019
≥24 months	9 / 147 (6%)	5 / 41 (12%)	2 / 58 (3%)	1 / 33 (3%)	1 / 15 (7%)	0.259

Efficacy of probiotics combined with glutamine compound for acute radiation enteritis during neoadjuvant chemoradiotherapy in locally advanced rectal cancer: A randomized controlled trial (NCT05406882).

Qiaoli Wang, Shang Wang, Yuanling Tang, Feng Wen, Pei Shu, Jitao Zhou, Min Ren, Yali Shen, Xin Wang; Department of Radiation Oncology/Abdominal Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu, China; Department of Radiation Oncology/Abdominal Oncology, Cancer Center, West China Hospital, Chengdu, Sichuan, China; West China Hospital, Sichuan University, Chengdu, China; Clinical Trial Center, National Medical Products Administration Key Laboratory for Clinical Research and Evaluation of Innovative Drugs, West China Hospital, State Key Laboratory of Biotherapy, Sichuan University, Chengdu, China; Division of Abdominal Tumor Multimodality Treatment, Department of Radiation Oncology, State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, Chengdu, Sichuan, China; Division of Abdominal Tumor Multimodality Treatment, Department of Radiation Oncology, State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, Chengdu, China

Background: Acute radiation enteritis (ARE) occurs in up to 80% of patients undergoing abdominal-pelvic radiotherapy, with severe ARE causing treatment interruption in 20%. Current prophylactic strategies remain inadequate. Small-sample studies suggest probiotics and glutamine may reduce radiation-induced mucosal injury and intestinal syndrome (e.g., diarrhea), but evidence-based validation is insufficient. This study investigated the efficacy of probiotics combined with glutamine compound preparation in preventing and alleviating ARE in locally advanced rectal cancer (LARC) patients receiving chemoradiotherapy. **Methods:** This prospective randomized trial enrolled 176 stage II-III rectal adenocarcinoma patients receiving preoperative chemoradiotherapy, randomized 1:1 to prophylactic (group A, n=86) versus therapeutic (group B, n=84) (treatment started when patients had $\geq 2^\circ$ ARE) administration of probiotics combined with glutamine compound. Concurrent chemoradiotherapy consisted of pelvic radiation 50–50.4 Gy/25–28 fractions plus oxaliplatin/capecitabine. Weekly assessments documented ARE (including anal tenesmus/pain, diarrhea, constipation, hematochezia) basing on RTOG and CTCAE v5.0 criteria. Primary endpoints: incidence of grade ≥ 2 ARE and diarrhea. Chi-square or Fisher's exact tests were used for analysis through R version 4.4.2. $P < 0.05$ indicated statistical significance. **Results:** The enrollment was completed on August 5, 2025. Six patients withdrew consent (group A: 1; group B: 5). Ultimately, there were 170 patients who completed concurrent chemoradiotherapy (84 control, 86 treatment), including 105 males (61.8%). The incidence rate of $\geq 2^\circ$ ARE in group A was significantly lower than that in group B (44.2% vs 73.8%, $P < 0.001$; RR=0.60, 95%CI: 0.46–0.78). The incidence rate of $\geq 2^\circ$ diarrhea was also significantly lower in group A (34.9% vs 54.8%, $P = 0.01$). There was 1.2% (1/86) and 3.6% (3/84) of grade 3 ARE in the two groups, respectively; and all these four patients experienced grade 3 diarrhea. The incidence rate of $\geq 2^\circ$ ARE increased with higher doses of pelvic radiotherapy in both groups, with the peak incidence occurring in the fifth week (24.1%) of group A and the fourth week (35.7%) of group B, respectively. **Conclusions:** Prophylactic probiotics combined with glutamine compound has a preventive effect of severe radiation enteritis and diarrhea during concurrent chemoradiotherapy for rectal cancer. Clinical trial information: NCT05406882. Research Sponsor: Sichuan Science and Technology Support Project; 2024YFFK0338; 1.3.5 projects for Artificial Intelligence, West China Hospital, Sichuan University; ZYAI24045.

Circulating tumor DNA clearance of adjuvant chemotherapy in localized colorectal cancer using an ultrasensitive structural variant–based assay.

Cecilia Merk, Sofia Birkealy, Karen Howarth, Girish Putcha, Rebecka Bergström, Rickard Strandberg, Markus Mayrhofer, Johan Lindberg, Anna Martling; Karolinska Institutet, Stockholm, Sweden; SAGA Diagnostics, Lund, Sweden; SAGA Diagnostics, Cambridge, MA; SAGA Diagnostics, Morrisville, NC; RedDoor Analytics AB, Stockholm, Sweden

Background: High-risk localized colorectal cancer (CRC) remains prognostically unfavorable. Adjuvant chemotherapy (ACT) is administered to patients with poor-risk features to eradicate molecular residual disease (MRD) and improve outcome. Despite ACT selection, some patients experience recurrence and others receive unnecessary treatment. Circulating tumor DNA (ctDNA) has emerged as a strong prognostic biomarker that could improve selection for ACT, but detection in the MRD setting is dependent on high sensitivity. In this study, we use an ultrasensitive assay to investigate ACT clearance in localized CRC patients included in the CITCCA trial and its impact on outcome. **Methods:** Patients with stage I–III CRC were enrolled in a prospective Swedish cohort study between 2020–2024. Standard of care treatment was given, and patients were followed with longitudinal ctDNA before and after surgery at 4–6 weeks, 3 and 6 months, 1 and 2 years. The clinical landmark (CLM) was defined as the 4–6 week postoperative test prior to initiation of ACT. The first sample after definitive treatment (FDT) was defined as the first test after treatment termination. ACT clearance was defined as a positive ctDNA test at either CLM or at CLM and 3 months, with subsequent negative ctDNA, in patients without recurrence. An ultrasensitive SV-based assay, Pathlight, was used for ctDNA analysis. The primary outcome was recurrence-free interval (RFI). **Results:** Of the 377 patients included, 135 patients (36%) received ACT with a median length of 5.2 months (range 0.1–7.4). Single agent fluoropyrimidine was given to 65 patients (48%) and 70 (52%) received an oxaliplatin-based doublet. Analyzable CLM samples were obtained from 106 patients (79%). Nineteen patients (18%) were ctDNA positive at CLM and received ACT. ctDNA positive patients who received ACT still showed a substantially higher risk of recurrence compared to ctDNA negative patients (HR, 38; 95% CI, 15–97). The same was seen in ctDNA-positive patients who did not receive ACT, i.e. clinically low-risk (HR, 35; 95% CI, 14–88). In the ctDNA positive cohort, patients who received ACT versus no ACT had a 2-year RFI of 58% (95% CI:39%–85%) versus 39% (95% CI:22%–69%). Persistent ACT clearance was seen in 8 patients, none of whom recurred. Transient clearance was seen in 6 patients, all of whom recurred. Five patients had persistently positive ctDNA despite ACT; all recurred. Eighty-seven patients (82%) were ctDNA negative at CLM but received ACT; 9 of these recurred (10%). Eighteen patients were ctDNA positive at CLM but did not receive ACT and 13 of these recurred. **Conclusions:** ctDNA is a strong prognostic biomarker and may be utilized to guide adjuvant treatment decisions in patients with localized CRC. Permanent clearance of ctDNA by administration of ACT is a favorable prognostic feature whereas ctDNA persistence after ACT predicts recurrence. Clinical trial information: NCT04726800. Research Sponsor: Cancerfonden.

Health-related quality of life (HRQOL) in the phase 3 trial of standard chemotherapy alone or combined with atezolizumab as adjuvant therapy for patients with stage III deficient DNA mismatch repair (dMMR) colon cancer (Alliance A021502, ATOMIC).

Amylou C. Dueck, Briant Fruth, Anke C. Reinacher-Schick, Walter Peters, Robert J. Behrens, Christopher Lieu, Khalid Matin, Deirdre J. Cohen, Samara L. Potter, Wendy L. Frankel, Ardaman Shergill, Dennis Hsu, Dirk Arnold, Tyler Zemla, Clare A. Gatten, Peter Trask, Eileen M. O'Reilly, Jeffrey A. Meyerhardt, Fang-Shu Ou, Frank A. Sinicrope; Alliance Statistics and Data Management Center, Mayo Clinic Arizona, Scottsdale, AZ; Alliance Statistics and Data Management Center, Mayo Clinic Rochester, Rochester, MN; St. Josef Hospital, Ruhr-Universität Bochum, Bochum, Germany; Baylor Scott and White Health, Dallas, TX; Mission Cancer + Blood, University of Iowa Health Care, Des Moines, IA; University of Colorado, Anschutz School of Medicine, Aurora, CO; VCU Massey Comprehensive Cancer Center, Richmond, VA; Division of Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, New York, NY; Nationwide Children's Hospital, Columbus, OH; The Ohio State University Comprehensive Cancer Center, Arthur G. James Cancer Hospital, Columbus, OH; Department of Hematology/Oncology, University of Chicago Medical Center, Chicago, IL; Division of Hematology-Oncology, Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA; Asklepios Tumorzentrum Hamburg, AK Altona, Hamburg, Germany; Genentech Inc, South San Francisco, CA; Memorial Sloan Kettering Cancer Center, New York City, NY; Dana-Farber Cancer Institute, Harvard University, Boston, MA; Mayo Clinic Rochester, Rochester, MN

Background: For patients (pts) with dMMR stage III colon cancer, the addition of atezolizumab (atezo) to adjuvant 5-fluorouracil, leucovorin plus oxaliplatin (mFOLFOX6) significantly improved disease-free survival in ATOMIC (NCT02912559). Here we present HRQOL data. **Methods:** Pts with surgically resected stage III dMMR colon cancer were randomized (1:1) to receive mFOLFOX6 + atezo (840 mg IV q2 weeks) for 12 cycles (6 months [mo]) followed by atezo monotherapy for 13 cycles (12 mo total) versus mFOLFOX6 for 12 cycles. HRQOL was an exploratory endpoint measured using the FACT-C (includes FACT-G), FACT/GOG-NTX, EQ5D-5L, and PRO-CTCAE. Optional participation was by paper surveys at trial registration, prior to treatment cycles 4 and 7, and at 6, 12, and 36 mo after registration. Mean changes from baseline (BL) were compared between treatment arms using general linear mixed models (negative mean changes indicate worsening). At 6 mo, a two-sided 95% confidence interval excluding a difference of 1.9 points (FACT/GOG-NTX) and 6 points (FACT-C Trial Outcome Index [TOI]) favoring the mFOLFOX6 arm would indicate non-inferiority of the addition of atezo. Rates of side effect bother (FACT-G item GP5) and pt-reported adverse events (AEs) by PRO-CTCAE (composite scores, baseline adjusted) were compared using Fisher's exact tests. **Results:** Of 712 randomized pts, 581 (285 atezo+mFOLFOX6; 296 mFOLFOX6) consented to participate in the survey. Pts completed 2398/3021 (79%) of expected surveys across all time points (1218/1489 [82%] atezo+mFOLFOX6; 1180/1532 [77%] mFOLFOX6). The difference in mean changes from BL between arms indicated non-inferiority of the addition of atezo at 6 mo (table); differences remained small at 12 and 36 mo. No significant differences in mean changes from BL between arms were found at 6, 12, or 36 mo for any scale. At 6 mo, 16% vs 20% of pts in each arm reported at least "quite a bit" of side effect bother ($p=0.34$), favoring atezo. Across cycles, atezo was associated with higher rates of pt-reported itchy skin (62% vs 48%), cough (53% vs 43%), and shortness of breath (51% vs 41%) [all $p<0.05$]. **Conclusions:** Addition of atezo to mFOLFOX6 slightly increases pt-reported AEs, but its effect on HRQOL is minimal and not clinically meaningful. Results support tolerability of atezo+mFOLFOX6 as standard of care adjuvant treatment for pts with dMMR stage III colon cancer. Support: UG1CA189823, U10CA180821, U10CA180882; Genentech, a member of the Roche group; <https://acknowledgments.alliancefound.org>. Clinical trial information: NCT02912559. Research Sponsor: National Cancer Institute; UG1CA189823; National Cancer Institute; U10CA180821; National Cancer Institute; U10CA180882; Genentech a member of the Roche group.

Scale	Mo	Mean change from BL – atezo+mFOLFOX6	Mean change from BL – mFOLFOX6	Diff (95% CI)
FACT/GOG-NTX	6	-10.0	-10.6	0.6 (-0.8, 2.1)
	12	-8.0	-9.4	1.4 (-0.2, 2.9)
	36	-7.2	-6.9	-0.4 (-2.1, 1.4)
FACT-C TOI	6	-4.1	-2.5	-1.6 (-3.7, 0.6)
	12	2.1	1.8	0.3 (-1.9, 2.6)
	36	0.7	1.8	-1.1 (-3.7, 1.5)

Neoadjuvant chemotherapy followed by transanal endoscopic surgery (TES) and selective chemoradiation or total mesorectal excision (TME) for early-stage rectal cancer: The Ottawa Hospital experience.

Mohammed Al Darai, Nasra Al-Busaidi, Husein Moloo, Lara Williams, Isabelle Raiche, Reilly Musselman, Lisa Zhang, Kristopher Dennis, Gordon Locke, Vimoj Janardanan Nair, Michael M. Vickers, Rachel Anne Goodwin, Derek J. Jonker; Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON, Canada

Background: Organ-sparing therapy for early-stage rectal cancer may avoid permanent ostomy or functional disturbances commonly known as low anterior resection syndrome (LARS). TES is increasingly used for treatment of selected T1N0 or T2N0 rectal cancer. The CCTG CO.28 (NEO) phase II trial evaluated neoadjuvant chemotherapy then TES surgery for early-stage rectal cancer (Kennecke et al, JCO 2023). On the CO.28 trial, patients (pts) with post-chemotherapy ypT3N0 tumours were to have neoadjuvant chemoradiation (CRT) then TME. Pts with ypT2 or poor risk ypT1 tumours were to have TME. However, several pts insisted on organ sparing alternatives such as adjuvant CRT or active surveillance. Our approach evolved from CO.28 by incorporating more selective adjuvant CRT instead of routinely resorting to TME. **Methods:** This retrospective study conducted at the Ottawa Hospital evaluated the outcomes of pts with early rectal cancer treated with the NEO approach and selective adjuvant CRT. The primary outcome was 3-yr TME free survival. Secondary outcomes included safety, 3-yr disease-free survival (DFS), 3-yr permanent colostomy free survival, 5-yr overall survival (OS), pathological complete response rate (pCR), proportion of pts requiring CRT and proportion of pts with LARS at 2 yrs. **Results:** N = 50 pts received a NEO approach and selective adjuvant chemoradiation. N = 19 were part of the previously reported CO.28 trial and N = 31 were a consecutive cohort treated off protocol. Median age was 63 (42-83) yrs, 58% were male. Rectal location was low/mid/upper in 34%/56%/10%. Baseline T stage was T2 (76%) and T3 (10%). Neoadjuvant CAPOX (64%) or FOLFOX (36%) was completed by 88% of pts and Gr 3 AEs occurred in 31%. At TES, pCR was achieved in 32% of pts. CRT was received by 33% of pts. Median follow-up was 30.2 (2.6-86.4) months. LARS was present at 2 yr in 15%. 3-yr TME-free survival was 82% (95% C.I. 69 to 94%). 3-yr permanent colostomy-free survival was 88% (95% C.I. 78 to 99%). 3-yr DFS after all local therapy was 98% (95% C.I. 93 to 99%). One pt developed both local plus distant recurrence. 5-yr OS was 95% (95% C.I. 85 to 99%). One pt who was disease free on surveillance died of an unrelated COPD exacerbation. **Conclusions:** The NEO approach of neoadjuvant chemotherapy then TES combined with selective adjuvant CRT demonstrated promising organ-preservation outcomes in early-stage rectal cancer, achieving high TME-free survival. This strategy offers a meaningful alternative to routine TME, potentially reducing the risk of permanent ostomy and LARS. Research Sponsor: None.

Impact of postsurgical circulating tumor DNA (ctDNA) dynamics on eligibility of colorectal cancer (CRC) patients for randomized ALTAIR trial: Implications for treatment-on-molecular-recurrence (TOMR) trials.

Hideaki Bando, Yoshiaki Nakamura, Vasily N. Aushev, Jun Watanabe, Yusuke Takahashi, Masahito Kotaka, Nobuhisa Matsuhashi, Eiji Oki, Yoshito Komatsu, Manabu Shiozawa, Keiji Hirata, Yuji Miyamoto, Kentaro Yamazaki, Kun-Huei Yeh, Adham A. Jurdi, Saori Mishima, Daisuke Kotani, Hiroya Taniguchi, Takayuki Yoshino, Takeshi Kato; Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan; Natera, Inc., Austin, TX; Department of Surgery, Gastroenterological Center, Yokohama City University Medical Center, Kanagawa, Japan; Department of Surgery, National Hospital Organization Osaka National Hospital, Osaka, Japan; Sano Hospital Gastrointestinal Cancer Center, Kobe, Japan; Department of Gastroenterological Surgery, Gifu University Graduate School of Medicine, Gifu, Japan; Department of Advanced Medicine and Innovative Technology, Kyushu University Hospital, Fukuoka, Japan; Department of Cancer Center, Hokkaido University Hospital, Sapporo, Japan; Department of Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, Japan; Department of Surgery, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan; Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan; Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Sunto-Gun, Japan; Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan; Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; Department of Surgery, NHO Osaka National Hospital, Osaka, Japan

Background: Postsurgical ctDNA positivity is strongly associated with recurrence risk and is driving the development of TOMR trials like the phase III ALTAIR trial (NCT04457297), which evaluated the benefit of trifluridine/tipiracil versus placebo in CRC patients (pts) with ctDNA positivity in the absence of clinical relapse. We evaluated the impact of longitudinal ctDNA dynamics during adjuvant chemotherapy (ACT) and surveillance on eligibility for enrollment into ALTAIR. **Methods:** CIRCULATE-Japan's GALAXY (UMIN000039205) study screened clinical stage II-IV CRC pts receiving standard-of-care (SOC) perioperative chemotherapy for eligibility for interventional trials by ctDNA monitoring using the personalized, tumor-informed Signatera assay in plasma collected at 1, 3, 6, 9, 12, 18, and 24 months (mos) post-surgery. Pts with ctDNA positivity without clinical recurrence were eligible for ALTAIR within 3 months of detection. We analyzed ctDNA dynamics and eligibility across all GALAXY sites, extending prior analyses limited to ALTAIR-participating sites. **Results:** Of 5,355 pts enrolled by April 2023, 693 (12.9%) were ctDNA-positive 2–10 weeks post-surgery (MRD-positive). Of 378 MRD-positive pts who received ACT, 117 (31.0%) remained persistently positive, 76.1% of whom did not relapse within 3 mos. ctDNA cleared after ACT in 237 pts, but 122 (51.5%) reconverted to positive, 67.2% of whom remained relapse-free for ≥ 3 mos after reversion. Among 1,341 MRD-negative pts receiving ACT, 183 (13.6%) converted to ctDNA-positive, 123 (67.2%) of whom remained relapse-free for ≥ 3 mos after molecular relapse. Overall, 17.1% of GALAXY pts met ALTAIR ctDNA-based criteria with stage-specific eligibility rates of 13.2% (II), 14.7% (III), and 34.6% (IV). Overall, 243 (4.5%) were enrolled in ALTAIR, including 18.6% of MRD-positive and 2.4% of MRD-negative pts. **Conclusions:** Approximately one-third (123/334) of ALTAIR-eligible pts were initially MRD-negative and later converted to ctDNA-positive without early clinical relapse, highlighting the importance of longitudinal ctDNA monitoring in TOMR trial design. When compared to the previous analysis limited to ALTAIR-participating sites, we observed higher eligibility yet lower enrollment rates in the full cohort at all GALAXY sites, underscoring the need for broader access and efficient enrollment networks to optimize TOMR trials. Clinical trial information: NCT04457297. Research Sponsor: Japan Agency for Medical Research and Development; 19ck0106447h0002, 21ck0106711h0001, 21ck0106710h0001, 22lk0201164h0001 and 22lk0201148h0002; National Cancer Center Research and Development Fund; no. 2021-A-6.

ctDNA dynamics	MRD positive (N = 378)	MRD negative (N = 1,341)
Persistently positive, all	117 (31.0%)	NA
Persistently positive, eligible for ALTAIR	89 (23.5%)	NA
Transient clearance, all	122 (32.2%)	NA
Transient clearance, eligible for ALTAIR	82 (21.7%)	NA
Turned positive, All	NA	183 (13.6%)
Turned positive, eligible for ALTAIR	NA	123 (9.2%)

Molecular residual disease (MRD) detection using an ultra-sensitive assay in a prospective colorectal cancer cohort: The VICTORI study.

Joao Paulo Solar Vasconcelos, Emma Titmuss, Fabio Navarro, Neeraja Ravi, Charles Abbott, Daniela Hegebarth, Brendan Joshua Chia, Matthew Yap, Howard J. Lim, Sharlene Gill, Karamjit Gill, Carl J. Brown, Amandeep (Anu) Ghuman, Adam Meneghetti, Daniel John Renouf, David Schaeffer, Richard Chen, Sean Michael Boyle, Jonathan M. Loo, BC Cancer - Vancouver, University of British Columbia, Vancouver, BC, Canada; BC Cancer - Vancouver, Vancouver, BC, Canada; Personalis, Inc., Menlo Park, CA; Personalis, Inc., Fremont, CA; BC Cancer - Vancouver Cancer Centre, Vancouver, BC, Canada; BC Cancer - Vancouver Centre, Vancouver, BC, Canada; Providence Health - St. Paul's Hospital, Vancouver, BC, Canada; Providence Health - St. Paul's Hospital, Vancouver, BC, Canada; Vancouver General Hospital, Vancouver, BC, Canada; BC Cancer; University of British Columbia, Vancouver, BC, Canada; Department of Pathology & Laboratory Medicine Vancouver General Hospital, Vancouver, BC, Canada; BCCA - Vancouver Cancer Centre, University of British Columbia, Vancouver, BC, Canada

Background: Circulating tumor DNA (ctDNA) detection of molecular residual disease (MRD) is prognostic in colorectal cancer (CRC) but missed recurrences highlight constraints in assay performance. VICTORI is a prospective observational study investigating an ultrasensitive MRD assay (NeXT Personal) in CRC patients undergoing curative treatment. **Methods:** Whole-genome informed panels of ~1,800 variants interrogated plasma collected pre-curative loco-regional treatment, q2 weeks post-surgery (weeks 2–8, landmark window), and subsequently every 3 months (3–36 months, surveillance window). **Results:** 795 plasma samples from 109 patients were analyzed, with median follow-up of 21.1 months and 31 recurrences observed. Cohort characteristics: 61 (56.0%) rectal cancer, 48 (44.0%) colon cancer; 81 (74.3%) stage I–III; 56 (50.5%) had neoadjuvant treatment; 106 (97.2%) had surgery as curative procedure. Pre-surgical sensitivity (treatment-naïve) was 96.0% (n=48/50) and specificity was 100% (no detection in pathologic complete responders; 0/10). Landmark window overall sensitivity for recurrence was 83.9% (n=26/31) with 69.2% (18/26) of detections being <100 ppm. Sensitivity was similar weeks 4–8 (81.5% week 4 [n=22/27]; 82.1% week 6 [23/28]; 85.7% week 8 [24/28]), and lower at week 2 (52.4% [11/21]) when post-surgical cell-free DNA peaked (median 2.80 ng/mL pre-surgery to 9.40 at week 2; $p=8.7 \times 10^{-12}$). Sampling between weeks 4–8 yielded a sensitivity of 80.0% (n=24/30) at the first available timepoint and 89.7% (26/29) with incorporation of an additional subsequent sample. Detection of ctDNA at any landmark window timepoint was associated with inferior outcomes (adjusted HR [aHR]: 10.28 [95% CI: 4.03–26.23], $p=1.06 \times 10^{-6}$). Week-4 detection <100 ppm was prognostic and conferred a 6.5 month longer lead time than detections ≥ 100 ppm (HR 4.09, $p=0.018$). All patients who recurred with surveillance samples had ctDNA detected prior to recurrence (sensitivity: 100% (n=28/28). ctDNA identified 100% of lung- and liver-only metastases; most initial detections were <100 ppm (75% and 71.4%, respectively). In evaluable patients, lead time from ctDNA detection to recurrence was 176 days (including patients with expedited imaging upon receipt of a ctDNA detection result). If a higher threshold for ctDNA was used (≥ 100 ppm) in the same population, the lead time would be >two months shorter (105 days, $p<0.001$). All patients without ctDNA detected on surveillance remain disease free (NPV 100% [n=63/63]). **Conclusions:** NeXT Personal demonstrated high accuracy, prognostic value, and early detection at ultrasensitive levels with no loss in specificity. The ideal postoperative landmark time point for MRD testing is at 4–8 weeks. Our results show strong clinical potential for an ultrasensitive MRD assay for landmark MRD and longitudinal surveillance in CRC. Research Sponsor: Personalis, Inc.; BC Cancer Foundation.

Lycopene and survival in patients with stage III colon cancer: Findings from CALGB (Alliance)/SWOG 80702.

Seohyuk Lee, Qian Shi, Chao Ma, Pankaj Kumar, Felix Couture, J. Philip Kuebler, Smitha S. Krishnamurthi, Benjamin R. Tan, Eileen M. O'Reilly, Anthony F. Shields, Edward L. Giovannucci, Yasmin Mossavar-Rahmani, Jeffrey A. Meyerhardt, En Cheng; Beth Israel Deaconess Medical Center, Boston, MA; Alliance Statistics and Data Management Center, Rochester, MN; Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; Illinois CancerCare, Peoria, IL; Hôtel-Dieu de Québec, Québec, QC, Canada; Columbus NCI Community Oncology Research Program, Columbus, OH; Cleveland Clinic, Cleveland, OH; Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO; Memorial Sloan Kettering Cancer Center & Weill Cornell Medical College, New York, NY; Barbara Ann Karmanos Cancer Institute, Wayne State University, Detroit, MI; Harvard T.H. Chan School of Public Health, Boston, MA; Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY

Background: Lycopene, a non-provitamin A carotenoid, has been reported to inhibit colon cancer development; however, its prognostic role after colon cancer diagnosis remains unknown. Given emerging evidence suggesting greater intake of lycopene-containing – particularly, tomato-based – foods may improve colon cancer prognosis, we assessed the association of postdiagnosis lycopene consumption with survival among 1666 patients (pts) with stage III colon cancer. **Methods:** Through an NCI-sponsored multicenter phase III adjuvant chemotherapy trial (CALGB/SWOG 80702; NCT01150045), we examined the consumption of total lycopene (dietary plus supplementation) and dietary lycopene as well as lycopene-containing foods (tomato-based foods plus other lycopene-containing foods) and tomato-based foods via validated food frequency questionnaires (FFQs) collected at 6 weeks after randomization (FFQ1) and again 14–16 months post-randomization (FFQ2). Lycopene-related exposures were calculated as time-varying measurements via cumulative averaging. Primary outcome was disease-free survival (DFS), defined as time from FFQ1 completion to colon cancer recurrence or death from any cause. Secondary outcomes were recurrence-free survival (RFS) and overall survival (OS). We estimated associations of lycopene-related exposures with survival via multivariable Cox proportional hazards regression. **Results:** In our cohort, pts with greater total lycopene intake tended to be slightly younger and of male sex and White race, have more left-sided tumors, and report higher caloric intake and physical activity engagement. Over median follow-up of 6.0 (IQR: 5.0–6.1) years, we observed 466 DFS, 395 RFS, and 300 OS events. Pts in the highest relative to lowest quintiles of total lycopene intake experienced significantly improved DFS (HR: 0.60 [95% CI: 0.44–0.83]; $P_{\text{trend}}=0.006$), RFS (HR: 0.58 [95% CI: 0.41–0.82]; $P_{\text{trend}}=0.007$), and OS (HR: 0.60 [95% CI: 0.40–0.89]; $P_{\text{trend}}=0.02$). Similar findings were observed for dietary lycopene intake. Pts consuming >1 serving/day compared to 1 serving/week of all lycopene-containing foods did not experience significantly improved survival. However, when considering only tomato-based foods, we observed a trend toward improved survival (HR for DFS: 0.61 [95% CI: 0.38–0.96]; $P_{\text{trend}}=0.12$). **Conclusions:** Greater lycopene consumption with or without supplementation was associated with lower risk of colon cancer recurrence and death which may be largely driven by tomato-based foods. Our findings may inform clinical nutrition recommendations for pts with colon cancer, with higher intake of tomato-based foods (>1 serving per day) potentially improving colon cancer survival. Future studies, especially interventional trials, are needed to validate our findings. Support: U10CA180821, U10CA180882, U24CA196171; Pfizer; <https://acknowledgments.alliancefound.org>. Research Sponsor: National Cancer Institute; U10CA180821; National Cancer Institute; U10CA180882; National Cancer Institute; U24CA196171; Pfizer; <https://acknowledgments.alliancefound.org>.

Effect of transanal vs. laparoscopic total mesorectal excision on 5-year overall survival in patients with rectal cancer: The TaLaR trial.

Liang Kang, Huashan Liu, Ziwei Zeng, Shuangling Luo, Hong Zhang, Miao Wu, Dan Ma, Quan Wang, Ming Xie, Qing Xu, Jun Ouyang, Yi Xiao, Yongchun Song, Bo Feng, Xu Qingwen, Yanan Wang, Yi Zhang, Mingyang Ren, Weidong Tong; The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, China; Shengjing Hospital of China Medical University, Shenyang, China; The Second People's Hospital of Yibin, Yibin, China; Xinqiao Hospital, Army Medical University, Chongqing, China; The First Hospital of Jilin University, Shenyang, China; Zunyi Medical College Affiliated Hospital, Zunyi, China; Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China; The First Affiliated Hospital of University of South China, Hengyang, China; Division of Colorectal Surgery, Department of General Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; The First Affiliated Hospital of Xi'an Jiaotong University, Xian, China; Shanghai Ruijin Hospital Administrator Consulting Co., Ltd., Shanghai, China; The Affiliated Hospital of Guangdong Medical University, Guangdong, China; Nanfang Hospital, Southern Medical University, Guangzhou, China; The Third Xiangya Hospital of Central South University, Changsha, China; The Affiliated Nanchong Central Hospital of North Sichuan Medical College, Nanchong, China; Daping Hospital, Army Medical University, Chongqing, China

Background: Transanal total mesorectal excision (taTME) has emerged as a widely adopted surgical approach for rectal cancer. Prior studies have reported favorable short-term outcomes, histopathological quality, and complication profiles for taTME compared with laparoscopic total mesorectal excision (laTME). However, the long-term oncologic effectiveness of taTME remains debated. In our previous work, we demonstrated that 3-year disease-free survival after taTME was noninferior to that after laTME among patients with mid-to-low rectal cancer. Building on these findings, the present study aimed to report the 5-year overall survival (OS) between taTME and laTME. **Methods:** We conducted a phase 3, randomized, open-label, noninferiority trial to compare the survival outcomes of taTME versus laTME in patients with rectal cancer located below the peritoneal reflection. This trial encompassed 16 hospitals across 10 provinces in China, with a total enrollment of 1,115 patients. We set the 3-year disease-free survival (DFS) and 5-year overall survival (OS) as the primary endpoints for analysis. This analysis of the 5-year overall survival was conducted following a predefined modified intention-to-treat principle. This study is registered with ClinicalTrials.gov, number NCT02966483. **Results:** As of June 2025, the overall 5-year overall survival (OS) rate was 83.60%, comprising 86.06% in the transanal TME (taTME) group and 81.24% in the laparoscopic TME (laTME) group. The overall 5-year disease-free survival (DFS) rate was 75.90%, with DFS rates of 77.65% in the taTME group and 74.18% in the laTME group. **Conclusions:** Based on preliminary results from a five-year follow-up, taTME is expected to achieve a five-year overall survival (OS) that is non-inferior to laTME. Our findings will support the routine use of taTME in mid-to-low rectal cancer, particularly in men, obese individuals, and those who have received neoadjuvant therapy. Clinical trial information: NCT02966483. Research Sponsor: Sun Yat-sen University Clinical Research 5010 Program.

5-year survival results between the laTME group and the taTME group.			
	laTME	taTME	HR
5-year OS (97.5% CI)	81.24% (77.82%-84.82%)	86.06% (83.04%-89.20%)	0.73 (0.54-1.10)
5-year DFS (95% CI)	74.18% (70.45%-78.10%)	77.65% (74.15%-81.32%)	0.86 (0.68-1.11)

Neoadjuvant (NA) chemoradiotherapy (CTRT) plus avelumab (Ave) in locally advanced rectal cancer (LARC): 4-year outcomes of the phase II AVANA trial and their association with computational pathology.

Giovanni Trovato, Maria Bensi, Daniele Rossini, Cecilia Villa, Rossana Intini, Beatrice Borelli, Massimo Giuseppe Viola, Alessandra Auriemma, Elena Fea, Cecilia Barbara, Sara Bustreo, Roberta Fazio, Sara Galuppo, Matteo Landi, Emiliano Tamburini, Federica Morano, Francesca Bergamo, Nick Trahearn, Giampaolo Tortora, Lisa Salvatore; Medical Oncology, Comprehensive Cancer Center, Fondazione Policlinico Universitario Agostino Gemelli-IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy; Medical Oncology, Università Cattolica del Sacro Cuore and Medical Oncology, Comprehensive Cancer Center, Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Rome, Italy; Department of Experimental and Clinical Medicine, University of Florence; Oncology Unit, Careggi University Hospital, Florence, Italy; Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, NA, Italy; Medical Oncology 1, Department of Oncology, Veneto Institute of Oncology (IOV-IRCCS), Padua, Italy; Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy; Department of Surgery, Cardinale G. Panico Tricase City Hospital, Tricase, Italy; Medical Oncology Section, Department of Medicine, University of Verona, Verona, Italy; S.Croce & Carle Teaching Hospital, Cuneo, Italy; Department of Oncology; Division of Medical Oncology, Livorno Hospital, Azienda USL Toscana Nord Ovest, Livorno, Italy; SSD ColoRectal Cancer Unit Dipartimento di Oncologia AOU Città della Salute e della Scienza di Torino, Turin, Italy; Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Veneto Institute of Oncology IOV, IRCCS, Padova, Italy; Department of Translational Research and New Technology in Medicine and Surgery, Pisa, Italy; Oncology Department and Palliative Care, Cardinale Panico Tricase City Hospital, Tricase, Italy; Oncology 1 Unit, Department of Medical Oncology, Veneto Institute of Oncology IOV - IRCCS, Padua, Italy; The Institute of Cancer Research, London, United Kingdom; Oncologia Medica, Comprehensive Cancer Center, Fondazione Policlinico Universitario Agostino Gemelli - IRCCS, Rome, Italy Università Cattolica del Sacro Cuore, Rome, Italy; Oncologia Medica, Comprehensive Cancer Center, Fondazione Policlinico Universitario Agostino Gemelli - IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy

Background: The AVANA trial investigated the addition of PD-L1 inhibitor Ave to NA CTRT in LARC. Here, we report long-term survival and explore its association with tumor microenvironment (TME) features assessed through computational pathology. **Methods:** AVANA is a multicenter, single-arm, phase II trial enrolling patients (pts) with LARC defined by at least one high-risk feature (cN+, cT4, or high-risk cT3). Pts received NA CTRT combined with six cycles of Ave, followed by surgery. Primary endpoint was pathological complete response (pCR) rate. Secondary endpoints included progression-free survival (PFS) and overall survival (OS). Multiplex immunofluorescence was performed on baseline biopsies and surgical specimens using CODEX platform (Akoya). A deep-learning pipeline using a spatially constrained convolutional neural network for cell detection and a classifier for cell labeling was applied, allowing identification of eight cell populations: cancer cells, normal epithelial cells, fibroblasts, lymphocytes (lym), neutrophils (neu), macrophages, endothelial (endo) cells and myocytes. Cell infiltrates were dichotomized as high or low using optimal cutpoints derived from maximally selected rank statistics. Cell density maps were generated to identify differences in cellular configurations between baseline and surgical specimens. **Results:** The primary endpoint was met, with a pCR of 21.8% (22/101 pts). At a median follow-up of 51.8 months, 26 of 101 pts had a progression event and the 48-month PFS rate was 74.7% (95% CI: 65.0–82.2). Thirteen deaths occurred, yielding a 48-month OS rate of 87.6% (95% CI: 79.1–92.7). Age (≥ 70 vs < 70 ; $p=0.371$), sex ($p=0.897$), ECOG PS (0 vs 1; $p=0.899$), cN positivity ($p=0.716$), cT stage (1–2 vs 3–4; $p=0.264$), or mismatch repair status (dMMR vs pMMR; $p=0.274$) were not associated to PFS. Digital whole-slide images of diagnostic biopsies and surgical specimens were available for 87/101 pts (86.1%). In post-treatment surgical specimens, high neu ($p=0.00025$) and high lym infiltrate ($p=0.0038$) correlated with better PFS, whereas high endo cell infiltrate was associated to shorter PFS ($p<0.0001$). Comparisons between baseline and post CTRT+Ave tissues showed that increased endo cell density in surgical specimen relative to baseline biopsies had worse PFS ($p=0.0070$), while increased neu to cancer cell ratios [HR 0.50 (95% CI: 0.21–1.18); $p=0.108$] and increased neu density [HR 0.22 (95% CI: 0.03–1.65; $p=0.106$)] showed trends toward better PFS, although not statistically significant. **Conclusions:** AVANA demonstrates the feasibility and activity of adding ICIs to standard CTRT in LARC. Computational pathology analyses suggest that dynamic changes in TME cellular composition could be associated with long-term outcomes, supporting its potential role for pts stratification. Clinical trial information: NCT03854799. Research Sponsor: Merck; GONO Foundation; AIRC.

Clinical outcomes in curatively resected dMMR/MSI-H colon cancer: A retrospective analysis of a multicentric cohort.

Sofie De Meulder, Michiel De Wulf, Hanna Decaestecker, Lise Decaestecker, Isabel Bovre, Franceska Dedeurwaerdere, Elise Devolder, Stefaan Gryspeerdt, Paul Pattyn, Raphaële Dresen, Xavier Sagaert, Florence Ballaux, Claire Bourgain, Eric Van Cutsem, Filip Van Herpe, Jochen Decaestecker, Pieter-Jan AR Cuyle, Albert Wolthuis, Andre D'hoore, Jeroen Dekervel; Gastroenterology Department AZ Delta, Roeselare, Belgium; AZ Delta, Roeselare, Belgium; KU Leuven, Leuven, Belgium; Pathology Department AZ Delta, Roeselare, Belgium; Radiology Department AZ Delta, Roeselare, Belgium; Abdominal Surgery Department AZ Delta, Roeselare, Belgium; Radiology Department, University Hospitals Leuven, Leuven, Belgium; Pathology Department, University Hospitals Leuven, Leuven, Belgium; Department of Pathology Imelda Bonheiden, Bonheiden, Belgium; Department of Pathology Imelda Bonheiden, Roeselare, Belgium; University Hospital Gasthuisberg/Leuven, Leuven, Belgium; Gastrointestinal Oncology Department, University Hospitals Leuven, Leuven, Belgium; Gastroenterology Department Imelda Bonheiden, Bonheiden, Belgium; Abdominal Surgery Unit, University Hospitals Leuven, Department of Oncology, Leuven, Belgium; Abdominal Surgery Department, University Hospitals Leuven, Leuven, Belgium; University Hospitals Gasthuisberg and University of Leuven, Leuven, Belgium

Background: Deficient mismatch repair (dMMR) colon cancer accounts for approximately 15% of localised cases and, despite favourable long-term survival after curative resection, disease recurrence remains a key concern. Recent trials reported a 3-year disease-free survival (DFS) of about 80% after primary surgery with or without adjuvant chemotherapy. In the NICHE-2 trial (Chalabi *et al*, NEJM 2024), with the addition of nivolumab plus ipilimumab in the neoadjuvant setting, no relapses were observed at three years. The same immunotherapy doublet provides a 3-year overall survival rate of 81% in the metastatic setting (Lonardi *et al*, ESMO 2025).

Methods: We conducted a retrospective multicentric cohort study including patients with non-metastatic dMMR/MSI-H colon cancer who underwent resection at 3 Belgian hospitals between January 1, 2013 and December 31, 2020. Patients with synchronous metastases, microsatellite stable (MSS) tumours or insufficient follow-up data (<3 years of imaging surveillance) were excluded. Clinical characteristics, adjuvant therapy, relapse incidence and survival outcomes were analysed. **Results:** A total of 219 patients with curatively resected dMMR/MSI-H colon cancer were included. Median age was 74 years (range 24–95). Of the total cohort, stage I accounted for 18.3%, stage II for 58.9% and stage III for 22.8%. Adjuvant chemotherapy was administered in 67 patients (30.7%). Relapse occurred in 11 patients (5.0%), comprising 4 patients with stage II disease and 7 patients with stage III disease. The 3-year DFS was 96.2% (95% CI: 96.1–96.3%). Of those relapsing, 7 received subsequent immunotherapy, yet 3 of those ultimately succumbed to the disease. The 5-year disease-specific mortality was 1.99% (95% CI: 1.96–2.03%), while the 5-year overall mortality was 10.3% (95% CI: 9.89–10.81%). Based on the NICHE-2 benchmark, preventing all 3-year recurrences and disease-specific deaths in this cohort would require treating approximately 26 patients with neoadjuvant nivolumab plus ipilimumab to avert one recurrence, and about 73 patients to prevent one cancer-specific death. **Conclusions:** In this multicentric Belgian cohort of curatively resected dMMR/MSI-H colon cancer, recurrence rates were lower than those observed in the FoXTROT trial (Morton *et al*, JCO 2023), even when accounting for the slightly higher proportion of stage I disease in our cohort. Most patients, however, died from other non-related causes, reflecting the well-known enrichment of MSI-H colon cancer in elderly women. A trade-off between neoadjuvant nivolumab plus ipilimumab versus primary surgery and salvage treatment with the same regimen should be discussed based on the high numbers needed to treat to avoid one recurrence and the non-trivial immunotherapy related toxicity (de La Fouchardiere *et al*, Annals of Oncology 2024). Research Sponsor: Kom op Tegen Kanker.

Neoadjuvant immunotherapy combined with radiochemotherapy vs chemotherapy alone in pMMR colon cancers: The TORCH-C randomized phase 2 clinical trial.

Hui Zhang, Yaqi Li, Fan Xia, Wang Yang, Yajie Chen, Yaqi Wang, Luoxi He, Menglong Zhou, Lijun Shen, Yan Wang, Juefeng Wan, Ruiyan WU, Shujuan Zhou, Jing Zhang, Fangqi Liu, Sanjun Cai, Zhen Zhang; Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China; Department of Colorectal Surgery, Fudan University Shanghai Cancer Center, Shanghai, China; Fudan University Shanghai Cancer Center, Shanghai, China; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China

Background: The prognosis for locally advanced colon cancer (LACC) with bulky nodal disease and/or clinically T4 stage remains poor, with high rates of recurrence and metastasis. Immunotherapy has become the standard treatment for deficient mismatch repair or microsatellite instability-high (dMMR/MSI-H) colon cancer. However, there has been little progress for the majority of cases, which was mismatch-repair proficient or microsatellite stable (pMMR/MSS). For locally advanced colon cancer with T4b stage or bulky lymph nodes, neoadjuvant chemotherapy is currently widely used. Whether combining it with immunotherapy and radiotherapy can improve efficacy is worthy of exploration. TORCH-C is the first study to evaluate this combination. **Methods:** TORCH-C is a prospective, multicenter, randomized phase 2 study that enrolled patients from April 3, 2023, through September 9, 2025. A total of 120 high-risk LACC (T4/bulky N+Mo, pMMR/MSS) patients were 1:1 randomized to either an immunotherapy combined with SCRT and CAPOX chemotherapy group (group A) or a chemotherapy alone group (group B). Patients in the group B received 4 cycles of CAPOX (oxaliplatin 130 mg/m² intravenously day 1 and capecitabine 1000 mg/m² orally days 1-14). Patients in the group A received SCRT (25Gy in 5 fraction) and 4 cycles of the PD-1 inhibitor (serplulimab, 300mg intravenously day 1) combined with CAPOX. The radiotherapy target volume includes only the primary colon tumor and enlarged lymph nodes, without elective nodal irradiation. After neoadjuvant therapy, patients will be evaluated for radical colon resection. All patients will receive adjuvant chemotherapy of four cycles of CAPOX. The primary outcome was pathological complete response (pCR) rate. The secondary outcomes included tumor downstaging, R0 resection, 3-year disease free survival (DFS), 3-year overall survival (OS), 3-year local recurrence-free survival and treatment-related toxicity. **Results:** 120 patients have been enrolled and randomized. 107 patients were included in the mITT analysis (54 in group A and 53 in group B). 103 have received surgery (50 in the chemotherapy group, 53 in the radiotherapy group). The pCR rate was 10% (5/50) in chemotherapy group (group B) and 45.3% (24/53) in the radiotherapy group (group A) ($P<0.05$). The most common grade 3-4 adverse event (AE) among patients was thrombocytopenia, (22.2%, 12/54) in the group A and (18.9%, 10/53) in the group B. **Conclusions:** The combination of PD-1 inhibitor, SCRT, and chemotherapy shows promising efficacy and significantly improved pCR rates in patients with MSS/pMMR high-risk LACC. This regimen may provide a new therapeutic option to achieve R0 resection and improve long-term survival. Clinical trial information: NCT05732493. Research Sponsor: None.

Clinicopathological characteristics of patients with minimal residual disease in stage II–III colon cancer: Interim results from the observational cohort of CLAUDIA study.

Minsu Kang, Sun Young Kim, Sang-Hee Cho, Moon Ki Choi, Yongjun Cha, Taekeun Park, Jin-Soo Kim, In Gyu Hwang, Byung Woog Kang, Seung-Hoon Beom, Seung Tae Kim, Seok Jae Huh, Sang Cheul Oh, Seok Yun Kang, Jin Won Kim, Sae-Won Han; Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea; Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Department of Internal Medicine, Chonnam National University Hwasun Hospital, Hwasun-Gun, South Korea; Division of Medical Oncology, Center for Colorectal Cancer, National Cancer Center, Goyang, South Korea; IMBdx, Inc., Seoul, South Korea; Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea; Department of Internal Medicine, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul, South Korea; Department of Internal Medicine, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul, South Korea; Department of Oncology/Hematology, School of Medicine, Kyungpook National University, Daegu, South Korea; Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Department of Internal Medicine, Dong-A University College of Medicine, Busan, South Korea; Department of Internal Medicine, Korea University Guro Hospital, Seoul, South Korea; Department of Hematology-Oncology, Ajou University School of Medicine, Suwon, South Korea; Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea; Department of Internal Medicine, Seoul National University Hospital, and Seoul National University Cancer Research Institute, Seoul, South Korea

Background: Circulating tumor DNA (ctDNA) monitoring for minimal residual disease (MRD) has emerged as a key prognostic biomarker in resected colon cancer. The CLAUDIA study (KCSG CO22-12, NCT05534087) is a prospective, multicenter study evaluating ctDNA-guided adjuvant therapy. It includes an observational screening cohort (Part 1) and a randomized interventional trial for MRD (+) patients (Part 2). Here, we report the baseline characteristics and MRD status of the Part 1 cohort and the clinical outcomes for patients who did not participate in Part 2. **Methods:** In Part 1, stage II or III colon cancer patients who received curative resection scheduled for adjuvant oxaliplatin-based chemotherapy (FOLFOX or CAPOX) are enrolled (N= approximately 1,200). Postoperative plasma samples collected after surgery, before starting adjuvant chemotherapy, are analyzed using a tumor-informed ctDNA assay that tracks up to 100 patient-specific mutations (IMBdx). Patients identified as MRD (+) are screened for a Part 2 randomized phase III trial (N=236) comparing mFOLFIRINOX to standard care. MRD (-) patients are managed at the investigator's discretion. **Results:** As of November 2025, a total of 809 patients were enrolled. Postoperative ctDNA was positive in 228 patients (28.2%). MRD (+) rate was significantly higher in patients with T4 tumors (40.5% vs. 22.8% in T1–3 tumors, $p<0.0001$), N2 disease (38.8% vs. 25.4% in N0–1, $p=0.0007$), and elevated postoperative CEA (>5 ng/mL) (42.2% vs. 26.8% in normal, $p=0.013$). Accordingly, MRD (+) was enriched in high-risk stage III disease (T4 or N2) (40.3% vs. 21.5% in low-risk stage III and stage II, $p<0.0001$). However, MRD (+) rates did not differ significantly by histology, tumor location, or MSI status. MRD positivity was not associated with the mutational status of the frequently altered genes in colon cancer (APC, TP53, KRAS, BRAF, ERBB2, SMAD4). We analyzed outcomes in 673 patients who did not participate in the Part 2 randomized study [92 MRD (+) and 581 MRD (-)]. In the multivariate analysis of recurrence-free survival adjusting for clinicopathologic covariates, MRD (+) was the strongest independent predictor of poor outcome (adjusted HR 5.81; 95% CI 2.65–12.74; $p<0.0001$). **Conclusions:** Postoperative ctDNA status serves as a robust prognostic biomarker in stage II–III colon cancer, correlating with advanced tumor burden. MRD (+) patients who receive standard-of-care management face a significantly increased risk of recurrence. These findings validate the utility of the ctDNA assay used and support the rationale for the ongoing CLAUDIA Part 2 trial, which investigates treatment intensification for MRD (+) patients. Clinical trial information: NCT05534087. Research Sponsor: Ministry of Health and Welfare, Republic of Korea; HA22C0062.

Relationship between GLP-1 receptor agonists on cancer recurrence and survival of patients with stage I-III colorectal cancer: A retrospective cohort study using the TriNetX database.

Emily Noelle Kinsey, Kristina Lee Tatum, Carolina Velez-Mejia, Alisha Sharma, Racheal Oladimeji, Obinna Diala, Sarah Williford, Andrew Stewart Poklepovic, Bernard Fuemmeler; Department of Internal Medicine, Virginia Commonwealth University, Massey Comprehensive Cancer Center, Richmond, VA; Department of Social and Behavioral Sciences, School of Public Health, Virginia Commonwealth University, Richmond, VA; Department of Internal Medicine, Virginia Commonwealth University, Massey Comprehensive Cancer Center, Richmond; Department of Internal Medicine, Virginia Commonwealth University, Richmond, VA; Department of Family Medicine and Population Health, School of Medicine, Virginia Commonwealth University, Richmond, VA; TriNetX, LCC, Cambridge, MA; Department of Internal Medicine, Division of Hematology, Oncology, and Palliative Care, Virginia Commonwealth University, Massey Comprehensive Cancer Center, Richmond, VA

Background: Colorectal cancer (CRC) is the second leading cause of cancer-related mortality worldwide, and obesity is a known risk factor. Glucagon-like peptide-1 receptor agonists (GLP-1RA) are increasingly used for obesity and diabetes management, making it critical to understand their long-term implications. Preclinical studies suggest a protective effect of GLP-1RA in risk for developing obesity-related malignancies, including CRC, but their long-term influence on recurrence and survival among those with CRC is not well characterized. **Methods:** A retrospective cohort study was conducted using TriNetX, a federated health research network of real-world data. Data were queried on January 22, 2026, from the Global Collaborative Network, encompassing over 190 million de-identified electronic medical records. Adult patients (> 18 years) with a diagnosis of stage I-III CRC between April 1, 2005, and April 1, 2025, were identified. The exposure group was defined as patients prescribed GLP-1RA following their CRC diagnosis. The control group was GLP-1RA nonusers. Propensity score matching (PSM) was employed, achieving balance across demographics, comorbidities, and confounding variables. The primary outcome was recurrence free survival (RFS), and the secondary outcome was overall survival (OS). Kaplan-Meier survival analysis, log-rank test, hazard ratios (HR) with 95% confidence intervals (CI), and risk ratios (RR) were used to estimate outcomes over 5-years of follow-up. **Results:** Among 20,383 patients with CRC across 19 HCOs, 839 patients per group with mean age 63.0 years remained after 1:1 PSM and exclusions, with comparable median follow-up times (710 vs 1160 days). GLP-1RA use was significantly associated with a lower risk of recurrence compared with nonusers (RR, 0.33; 95% CI, 0.25-0.45; $p < 0.001$) and improved RFS probabilities (89.0% vs 72.8%; [HR, 0.37; 95% CI, 0.27-0.50; $p < 0.001$]) at the 5-year follow-up. A significant improvement in OS was also observed in GLP-1RA users compared with nonusers (82.5% vs 71.4%; [HR 0.45; 95% CI, 0.34-0.60; $p < 0.001$]), and reduced mortality risk (RR, 0.35; 95% CI, 0.27-0.46; $p < 0.001$) compared with nonuse. Secondary analysis with 15-year median follow-up period demonstrated that these survival and recurrence benefits were sustained long term with median OS of 4,382 and 3,931 days in GLP-1RA users vs nonusers respectively. **Conclusions:** In this real-world analysis, GLP-1RA use in patients with stage I-III CRC was associated with improved RFS and OS compared to nonusers. These findings were consistent across both 5-year and 15-year follow-up periods, demonstrating a sustained association with improved outcomes in CRC. Prospective trials are needed to strengthen the evidence base for GLP-1RA use in patients with CRC and to define the underlying biological mechanisms. Research Sponsor: None.

Comparison of longitudinal circulating tumor DNA (ctDNA) and carcinoembryonic antigen (CEA) for post-operative risk stratification in colorectal cancer (CRC).

Eiji Oki, Koji Ando, Hideaki Bando, Yoshiaki Nakamura, Daisuke Kotani, Saori Mishima, Darryl Nousome, Arkarachai Fungtammasan, Rama S. Madhurapantula, Charuta C. Palsuledesai, Robert William Lentz, Adham A. Jurdi, Minetta C. Liu, Hiroya Taniguchi, Jun Watanabe, Takeshi Kato, Yusuke Suwa, Keiji Hirata, Naoya Akazawa, Takayuki Yoshino; Department of Advanced Medicine and Innovative Technology, Kyushu University Hospital, Fukuoka, Japan; Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; Department for the Promotion of Drug and Diagnostic Development, Division of Drug and Diagnostic Development Promotion, National Cancer Center Hospital East, Kashiwa, Japan; Department of Oncology, University of Oxford, Oxford, United Kingdom; Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan; National Cancer Center East, Kashiwa, Japan; Natera, Inc., Austin, TX; Natera, Inc., San Carlos, CA; Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; Department of Lower Gastrointestinal Surgery, Kansai Medical University, Hirakata, Japan; Department of Gastroenterological Surgery, NHO Osaka National Hospital, Osaka, Japan; Department of Surgery, Gastroenterological Centre, Yokohama City University Medical Center, Yokohama, Japan; Department of Surgery, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan; Department of Gastroenterological Surgery, Sendai City Medical Center Sendai Open Hospital, Sendai, Japan; Department of Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: ctDNA is a reliable biomarker that outperforms CEA for detecting molecular residual disease in CRC. However, the relative prognostic performance of these biomarkers across post-operative timepoints is not fully elucidated. Characterizing these temporal dynamics can provide essential insights for optimizing biomarker-guided surveillance. **Methods:** CEA and ctDNA (Signatera, Natera, Inc.) data at 12, 24, 36, 48, 72, and 96 weeks (wk) post-surgery from patients (pt) enrolled on the CIRCULATE-Japan GALAXY study were used to perform landmarked analyses. Disease-free survival (DFS) and overall survival (OS) were evaluated among pts who were event-free at each landmark. Hazard ratios (HRs) were estimated using Cox models adjusted for clinicopathological factors. Temporal trends in prognostic strength were assessed using weighted meta-regression across post-operative timepoints. **Results:** Of the 2,825 pts with CRC [84% stage I-III, 16% stage IV; median age 69 years (range 24-95)], 49% were female; 43% received adjuvant chemotherapy while 57% went directly to surveillance. At all evaluated landmarks, ctDNA- and CEA-positivity were associated with markedly higher risk of recurrence and death compared with ctDNA- and CEA-negativity, respectively. In DFS analyses, ctDNA outperformed CEA with substantially higher HRs at all landmarks (Table 1). The prognostic strength of ctDNA increased over time, with HRs increasing from 15.15 at 12 wks to 36.87 at 72 wks post-surgery and 32.31 through 96 wks. In contrast, CEA demonstrated modest and relatively stable DFS HRs across landmarks (range 2.04 to 3.43). Meta-regression analyses demonstrated a significant temporal strengthening of ctDNA's prognostic performance for DFS (β :0.011 per wk, $p=0.004$), whereas no significant temporal trend was observed for CEA ($p=0.33$). In OS analyses, ctDNA positivity conferred high mortality risk at all landmarks, with HRs ranging from 8.40 to 14.15 (Table 1). Despite increasing prognostic association of CEA with OS at later landmarks, its HRs were lower than those of ctDNA. **Conclusions:** ctDNA-positivity consistently outperforms CEA in predicting disease recurrence and OS. ctDNA provides strong risk stratification at early postoperative time points, and its prognostic accuracy continually improves during longitudinal surveillance, confirming its superior performance for early risk assessment and personalized serial disease monitoring during surveillance. Clinical trial information: UMIN000039205. Research Sponsor: None.

DFS and OS hazard ratios and ranges for ctDNA and CEA at all landmarks.

Landmark	ctDNA DFS	CEA DFS	ctDNA OS	CEA OS
12 wk	15.15***	2.68***	8.4***	3.65***
24 wk	18.4***	2.23***	12.74***	4.16***
36 wk	19.36***	2.04***	9.81***	5.41***
48 wk	23.95***	2.77***	12.26***	6.3***
72 wk	36.87***	3.43***	14.15***	8.72***
96 wk	32.31***	2.71*	8.45**	14.67***

* $p<0.05$, ** $p<0.001$, *** $p<0.0001$.

Neoadjuvant tislelizumab plus chemotherapy in MSS/pMMR high-risk locally advanced colon cancer: Updated analysis results from a phase 2 trial.

Minglin Lin, Zhiyuan Xia, Ming Qiu, Haining Chen, Cun Liao, Wei Huang, Hui Li, Jiahao Huang, Rui Song, Yuen Xie, Xiaolong Zhang, Junlin Liang, Jialiang Gan, Yun Guo, Sen Zhang; The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China

Background: Patients with locally advanced colon cancer (LACC) have a poor prognosis, and those with N+ or T4 staging are prone to developing metastases. Only about 5% pathological complete response rates were observed in neoadjuvant chemotherapy. We conducted a single-arm, phase II trial to evaluate the efficacy and safety of immunotherapy combined with chemotherapy in locally advanced colon cancer. **Methods:** LACC patients clinically staged as T4 or N2 with histologically confirmed microsatellite stable/mismatch repair proficient (MSS/pMMR) type untreated colon adenocarcinoma are eligible for enrollment. Participants received 2–6 cycles of neoadjuvant therapy consisting of capecitabine and oxaliplatin (CAPOX) plus tislelizumab, followed by complete mesocolic excision. The primary endpoint was the pathological complete response (pCR) rate. This study was registered at ClinicalTrials.gov (NCT06124378). **Results:** A total of 61 patients were enrolled with a median age of 54 years (IQR 43–62). 35 (57%) of the recruited patients had a cT4 tumor and 47 (77%) of the patients had N2. All patients received neoadjuvant CAPOX plus tislelizumab, while three patients were excluded from activity analyses due to adverse events and the patient decision. Among the remaining 58 patients, 16 (28%) patients received 2 cycles, 39 (67%) patients completed 4 cycles, and 3 patients (5%) received 6 cycles prior to surgery. 14% patients achieved clinical complete response and the overall response rate was 91% based on clinical efficacy, with no cases of progressive disease observed. The regimen achieved a pathological complete response (pCR) rate of 41.4%, with all patients undergoing R0 resection. The major pathological response rate was 51.7% (95% CI 38.6 to 64.6). In subgroup analyses, patients with right-sided tumors exhibited higher pCR rates (16 [47%, 95% CI 30–65] of 34, compared to 8 [33%, 95% CI 17–54] of 24 for left-sided cases. However, no statistically significant differences were observed between the subgroups. Treatment-related adverse events of any grade occurred in 52 (85.2%) of 61 patients. The most common adverse events were peripheral sensory neurotoxicity (37 [61%] of 61) and decreased appetite (31 [51%]). Grade 3 drug-related serious adverse events occurred in 8 (13%) patients while no grade 4–5 adverse events occurred. **Conclusions:** This prospective trial demonstrates that neoadjuvant tislelizumab plus CAPOX provides a promising treatment strategy with encouraging antitumor activity and a manageable safety profile for MSS/pMMR locally advanced colon cancer. Clinical trial information: NCT06124378. Research Sponsor: None.

Association of CT-based deep learning–derived consensus molecular subtypes with survival outcomes in locally advanced colon cancer: A secondary analysis of the phase III OPTICAL trial.

Sifan Qi, Chenchen Xu, Chenchen Li, Xiuping Nie, Jianwei Zhang, Huabin Hu, Xin Wang, Yanhong Deng; Department of Medical Oncology, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; Department of Surgery, The Chinese University of Hong Kong, Hong Kong SAR, China; The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

Background: The Consensus Molecular Subtypes (CMS) provide a robust framework for the biological stratification of colorectal cancer (CRC), but their clinical use is limited by the cost and complexity of transcriptomic profiling. We evaluated the prognostic and predictive utility of a non-invasive, CT-based deep learning model for CMS classification (CT-CMS) in patients with locally advanced colon cancer (LACC) enrolled in the OPTICAL trial. **Methods:** Patients from the OPTICAL trial with available baseline venous-phase contrast-enhanced CT images were included. A previously validated deep learning model was applied to predict CMS subtypes (CMS1–4). The association between CT-CMS and survival outcomes, including disease-free survival (DFS) and overall survival (OS), was assessed using multivariable Cox proportional hazards regression models adjusted for age, sex, TNM stage, and tumor location. **Results:** The study included 394 patients, with 189 patients in the neoadjuvant chemotherapy (NAC) group and 205 in the upfront surgery group. The median follow-up was 48.0 months. The distribution of CT-CMS subtypes was as follows: CMS1 (n=64, 16.2%), CMS2 (n=135, 34.5%), CMS3 (n=69, 17.5%), and CMS4 (n=126, 32.0%). In the total population, CMS3 showed the most favorable outcomes, with a 3-year OS rate of 96.1% (95% CI, 90.9%–100.0%) and a 3-year DFS rate of 87.9% (95% CI, 80.3%–96.2%). Multivariable analysis confirmed that CMS3 was independently associated with superior prognosis compared to CMS1 (adjusted hazard ratio [aHR] = 0.39, 95% CI 0.17–0.92, p = 0.030). In the NAC group, CMS was a significant independent prognostic factor for DFS (p = 0.044), with CMS3 (p = 0.027) and CMS2 (p = 0.046) showing significant improvement over CMS1. Notably, patients with CMS2 tumors exhibited significant survival benefits from neoadjuvant chemotherapy compared with upfront surgery, with improved OS (aHR = 0.08, 95% CI 0.01–0.62, p = 0.016, log-rank p = 0.002) and DFS (aHR = 0.45, 95% CI 0.20–0.99, p = 0.047). **Conclusions:** CT-based CMS3 was associated with favorable prognosis, while CMS2 identified patients were most likely to benefit from neoadjuvant chemotherapy. These findings support the clinical utility of CT-CMS as a non-invasive, pre-treatment tool for molecular stratification in LACC. Research Sponsor: National Science Fund for Distinguished Young Scholars; 82425045; Shenzhen Medical Research Funds; C2303002; General Research Fund; 14104223; Collaborative Research Fund; C4024-22GF; Research Impact Fund from the Research Grants Council of the Hong Kong Special Administrative Region; R4007-23.

All	3-year DFS rate	HR (95% CI)	P
CMS1	76.4% (66.2%–88.2%)	Reference	-
CMS2	79.8% (73.1%–87.1%)	0.67 (0.36–1.27)	0.219
CMS3	87.9% (80.3%–96.2%)	0.39 (0.17–0.92)	0.030
CMS4	78.2% (71.3%–85.8%)	0.89 (0.49–1.64)	0.715
NAC vs surgery (reference)*			
CMS1	70.3% vs 81.4%	1.20 (0.45–3.15)	0.717
CMS2	86.5% vs 72.8%	0.45 (0.20–0.99)	0.047
CMS3	90.2% vs 85.2%	0.36 (0.08–1.60)	0.180
CMS4	78.2% vs 78.3%	1.04 (0.50–2.17)	0.915

*For treatment comparisons, 3-year DFS rates are presented as NAC versus surgery.

Neoadjuvant chemoradiotherapy with or without PD-1 blockade in pMMR/MSS low rectal cancer patients (CHOICE II): A multi-center, open-label, randomized controlled trial.

Wei Zhang, Guanyu Yu, Leqi Zhou, Hongwei Yao, Jianhua Ding, Wenbin Chen, Liqiang Hao, Jianbin Xiang, Dongwang Yan, Jinlin Du, Shugui Pan, Zhiqiang Zhu, Huojun Zhang, Chenguang Bai, Fu Shen, Yuxin Shen, Wei Wang, Xiaolan Yin, CHOICE II Study Group; Department of Colorectal Surgery, Changhai Hospital, Naval Medical University, Shanghai, China; Department of General Surgery, Beijing Friendship Hospital, Capital Medical University & National Clinical Research Center for Digestive Diseases, Beijing, China; Department of Colorectal Surgery, The Characteristic Medical Center of PLA Rocket Force, Beijing, China; Department of Colorectal Surgery, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; Department of Gastrointestinal surgery, Huashan Hospital, Fudan University, Shanghai, China; Department of General Surgery, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; Colorectal Surgery, Zhejiang University Jinhua Hospital, Jinhua, Zhejiang, China; Department of General Surgery, Dingyuan General Hospital, Chuzhou, China; Department of General Surgery, the First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, China; Department of Radiation Oncology, Changhai Hospital, Naval Medical University, Shanghai, China; Department of Pathology, Changhai Hospital, Naval Medical University, Shanghai, China; Department of Radiology, Changhai Hospital, Naval Medical University, Shanghai, China; Department of Oncology, Changhai Hospital, Naval Medical University, Shanghai, China; China RongTong Medical Healthcare Group Co.Ltd./411 Hospital, Shanghai University, Shanghai, China

Background: Neoadjuvant chemoradiotherapy (nCRT) combined with PD-1 blockade has shown great potential for improving the clinical complete response (cCR) rate in low rectal cancer patients in a previous exploratory clinical trial. This study aimed to further verify the efficacy and safety of nCRT with PD-1 blockade in patients with pMMR/MSS low rectal cancer.

Methods: We conducted a prospective, multicenter, randomized, open-label trial (NCT05215379) with two parallel groups across 11 centers. Patients with confirmed cT_{1-3a}N₀₋₁M₀ rectal adenocarcinoma of the pMMR/-MSS type, with an inferior margin of 5 cm from the anal verge, were randomly assigned to either the intervention group, receiving 50 Gy (2 Gy/d*25d) radiotherapy, 4 cycles of PD-1 blockade (sintilimab) and 2 cycles of CAPOX, or the control group, receiving 50 Gy (2 Gy/d*25d) radiotherapy and 2 cycles of CAPOX. After completion of neoadjuvant treatment, patients were reassessed to determine clinical efficacy. If patients achieved cCR, the Watch-and-Wait (W&W) approach was performed. If near-cCR (ncCR) was achieved, patients were re-evaluated by a multidisciplinary team to determine whether W&W, local excision, or total mesorectal excision (TME) should be performed. Patients assessed with an incomplete clinical response (iCR) received TME. The primary endpoint was the cCR rate, and the key secondary endpoints included the organ preservation (W&W and local excision) rate, disease free survival (DFS), and overall survival (OS). **Results:** From July 2022 to December 2024, a total of 201 patients with low rectal cancer were screened at 11 medical centers and 180 patients were finally randomly assigned. A total of 169 patients were included in the primary analysis (85 patients in the intervention group and 84 in control group). The cCR rates were 36.5% in the intervention group compared to 17.9% in the control group (p=0.007). There were 48 and 51 patients who underwent surgery in the intervention and control groups, respectively, and the pathological complete response (pCR) rates were 25.0% and 15.7% (p=0.249). The overall complete response (cCR+pCR) rates were 50.6% and 27.4% (p=0.002) in the intervention and control groups. The overall occurrence rates of adverse events (AEs) were 72.9% in the intervention group compared to 66.3% in the control group (P>0.05), and the occurrence of severe AEs (Grade III or IV) was comparable between the two groups (7.1% vs 3.8%, p=0.34). Due to the limited follow-up duration, the DFS and OS data are immature. **Conclusion:** In this trial, the results showed that nCRT combined with sintilimab significantly improved the cCR rate in patients with pMMR/MSS low rectal cancer with a tolerable safety profile. Clinical trial information: NCT05215379. Research Sponsor: National Natural Science Foundation of China; 82473439, 82272705 and 82503486; the First Affiliated Hospital of Naval Medical University Special Project for Clinical Research, China; 2024LYA02; the Shanghai "Rising Stars of Medical Talents" Youth Development Program of the Shanghai Municipal Health Commission, China; No.2024-70; the Naval Medical University "Deep Blue" Project Talent Program; the First Affiliated Hospital of Naval Medical University Special Project for Basic Medical Research, China; 2023QD003 and 2023PY04; the First Affiliated Hospital of Naval Medical University Special Project for Clinical Research, China; 2024LYA02; Shanghai Shengkang Hospital Development Center, Shanghai Clinical Cohort Project; SHDC2025CCS019; Shanghai Science and Technology Plan Project; 25SF1901500.

The value of tumor deposits in prognosis evaluation and clinical stage optimization of colorectal cancer: A real-world population-based retrospective cohort study.

Chang Wang, Yizhuo Wang, Jiaying Liang, Haitao Wu, Shuhan Liu; The First Hospital of Jilin University, Changchun, China

Background: The location and weight of tumor deposit (TD) in the TNM staging system may be seriously underestimated, which affects the accuracy of TNM staging in predicting prognosis. We conducted a study to further clarify the role of TD in predicting the prognosis, the weighting of TD, and the possible value of optimizing the TNM staging system of CRC. **Methods:** The subject was CRC patients diagnosed by postoperative pathology in our hospital from January 2013 to December 2021, including 2642 TD (+) and 1162 TD (-) patients. TD (-) patients were regarded as the control group according to category matching principle of the diagnosis, treatment and the period as TD (+) patients. Cox univariate and multivariate were analyzed. K-M curve was applied to analyze survival. **Results:** (1) The clinical and pathological characteristics are as follows: The TD positive rate was 25.3%. In stage I-III, more advanced tumor T and N-stage, primary sites in the left-sided colon or rectum, poorer histologic grade, and more nerve invasion and vascular infiltration (all $p < 0.05$) were observed in TD (+) patients. In stage IV patients, TD (+) patients were more likely to have multiple metastases ($p < 0.05$). (2) Patients with TD (+) had worse prognosis than patients with TD (-), with shorter DFS and OS in stage I-III (3-y DFS and OS rate, all $p < 0.05$), with shorter PFS in stage IV (3-y PFS rate, $p < 0.05$). The univariate and multivariate analysis showed that TD (+) was one of independent prognosis factors in CRC patients. And the prognosis shows a trend of getting worse as the number of TD increases. (3) The relationship between TD and N staging: Patients with TD (+), LN (-) had similar OS as patients with TD (-), LN (+) (3-y OS rate, $p = 0.418$). Patients with TD (+), LN (-) had similar OS as patients with TD (-), N2 (3-y OS rate, $p = 0.695$). Patients with TD (+), LN (-) had shorter OS than patients with N2a, TD (-) (3-y OS rate, $p = 0.029$) and longer OS than patients with N2b, TD (-) (3-y OS rate, $p = 0.034$). When TD and LN were counted together for N-staging, the OS between patients with new N2 and primary N2 was similar (3-y OS rate, $p = 0.382$). (4) The relationship between TD and M staging: The survival of patients with TD more than 4 was similar to stage IV patients (2-y OS rate, $p = 0.061$); when the number of LN more than 6 and TD (+) coexisted, OS was similar with stage IV patients (2-y OS rate, $p = 0.554$). When TD and M were counted together for M-staging, the OS between patients with new M1 and primary M1 was similar (3-y OS rate: $p = 0.149$). **Conclusions:** TD (+) patients are related with unfavorable prognostic clinical and pathological factors. TD was one independent prognosis factor in CRC patients. The location and weight of TD in the TNM staging system may be seriously underestimated. The prognostic accuracy of TNM staging may be improved when the weight of the presence and quantity of TD is increased. Clinical trial information: 2023-ks-143. Research Sponsor: None.

Updated 5-year survival outcomes of short-course radiation followed by mFOLFOX-6 plus avelumab in locally advanced microsatellite-stable rectal adenocarcinoma: The Averectal phase II study.

Ali Shamseddine, Mohamad Mourad, Rim Turfa, Laudy Chehade, Youssef Zeidan, Ziad Zuheir El Hussein, Malek Kreidieh, Youssef Bouferaa, Charbel Elias, Joseph Gergi Kattan, Sally Naji Temraz, Kholoud Alqasem, Rula Amarin, Tala Alawabdeh, Issa Mohamad, Mousa Elkhaldi, Ahmad Hushki, Maya Charafeddine, Monita Hassib Al Darazi, Fady B. Geara; American University of Beirut Medical Center, Beirut, Lebanon; American University of Beirut, Beirut, Lebanon; King Hussein Cancer Center, Amman, Jordan; American University of Beirut Medical Center, Beyrouth, Lebanon; Hotel-Dieu De France, Achrafieh, Lebanon; Naef K. Basile Cancer Institute, American University of Beirut Medical Center, Beirut, Lebanon

Background: Total neoadjuvant therapy (TNT) for microsatellite-stable (MSS) locally advanced rectal cancer consists of induction or consolidation chemotherapy combined with either long-course chemoradiation (LCCRT) or short-course radiation therapy (SCRT). While TNT has yielded variable outcomes across studies, it has consistently improved pathologic complete response (pCR) rates and paved the way for non-operative management strategies. However, the use of SCRT within TNT has been associated with higher rates of local recurrence. The integration of immunotherapy into total neoadjuvant therapy (TNT) improves outcomes in LARC, particularly pathologic complete response (pCR), which may translate into improvements in disease-free survival (DFS) and overall survival (OS), in addition to improvement in local recurrence rate (LRR) especially when used with SCRT, potentially through synergistic effects with radiotherapy. **Methods:** The Averectal trial is an investigator-initiated, open-label, single-arm, multicenter, phase II study including 44 patients. 40 patients with LARC completed treatment with SCRT (5 Gy x5 fractions) followed by 6 cycles of mFOLFOX-6 plus avelumab every 2 weeks, followed by TME. The primary outcome was pCR vs. historical control. Secondary outcomes were 3-year DFS, LRR and the association of the ImmunoScore (IS) with outcomes including pCR. **Results:** 15/40 (37.5 %) patients achieved pCR compared to 16 % in the historical control group with statistically significant $p = 0.025$, and 27/40 (67.5 %) had a major pathologic response. Patients who achieved pCR had a higher mean IS compared with those who did not (68 vs. 52, $p = 0.049$). With a median follow up of 72.8 months (range 15.4–97.1), the median OS and DFS were not reached. The mean OS and DFS were 85.3 months and 79 months respectively, and the 5-year OS and DFS were 81.9% and 74.6%. Only 2/40 patients had local recurrence, accounting for a LRR of 5%. In patients with high versus low IS, median OS was not reached in either group ($p = 0.9$), with mean OS of 79.3 months versus 84.7 months, respectively. Similarly, median DFS was not reached, although there was a trend towards improved DFS in the high IS group ($p = 0.175$), with mean DFS of 77.6 months versus 70.7 months for high and low IS, respectively. **Conclusions:** The addition of avelumab to TNT in patients with MSS LARC resulted in a statistically significant increase in pCR, notably among those with high IS, and was associated with continued improvement in survival outcomes at 5 years. Clinical trial information: NCT03503630. Research Sponsor: This study was financially supported by Merck Healthcare KGaA; CrossRef Funder ID: 10.13039/100009945.

Immunotherapy-based total neoadjuvant therapy with or without short-course radiotherapy for locally advanced rectal cancer: Preliminary results of TORCH-iTNT.

Yaqi Wang, Lijun Shen, Juefeng Wan, Hui Zhang, Yan Wang, Yajie Chen, Ruiyan Wu, Menglong Zhou, Wang Yang, Shujuan Zhou, Zhiyuan Zhang, Jingwen Wang, Sanjun Cai, Xinxiang Li, Fan Xia, Zhen Zhang; Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China; Department of Colorectal Surgery, Fudan University Shanghai Cancer Center, Shanghai, China; Fudan University Shanghai Cancer Center, Shanghai, China

Background: In patients with proficient mismatch repair (pMMR) locally advanced rectal cancer (LARC), the integration of PD-1 inhibitor into total neoadjuvant chemoradiotherapy (iTNT) has demonstrated promising potential to enhance complete response (CR) rates and facilitate organ preservation. However, the combined use of radiotherapy and surgical intervention frequently leads to increased functional impairment relative to either modality administered independently. Concurrently, the combination of chemotherapy and PD-1 inhibitor has been shown to promote tumor downstaging, thereby enabling sphincter-preserving surgery while mitigating radiation-induced injury. This trial evaluates oncological efficacy and functional outcomes of two iTNT regimens: CAPOX plus PD-1 inhibitor with or without SCRT in neoadjuvant treatment of pMMR LARC patients. **Methods:** The TORCH-iTNT trial (NCT06281405) is a prospective, multicenter, randomized phase II study involving 192 patients with pMMR LARC (T3-4/N+M0). Participants were randomized into Group A (6 cycles of CAPOX plus toripalimab) or Group B (SCRT [25Gy/5Fx] followed by 6 cycles of CAPOX plus toripalimab). Patients achieving clinical complete response (cCR) were offered a watch-and-wait (W&W) strategy, while those without cCR were advised to undergo surgery. Group A patients with positive circumferential margins received adjuvant chemoradiotherapy. The primary endpoint was CR rate (pathological complete response [pCR] plus cCR). Secondary endpoints included organ preservation rate, anorectal function, adverse effects, and survival outcomes. **Results:** By December 31, 2025, 192 patients were enrolled, with 137 completing treatment (Group A: 65; Group B: 72). Baseline characteristics were balanced, with 97.1% (133/137) exhibiting at least one high-risk feature: lower tumor location (≤ 5 cm), cT4, cN2, MRF+, or EMVI+. In Group A, 5 patients achieved cCR and adopted W&W, compared to 22 in Group B. Of the 54 and 49 patients in Group A and B who underwent surgery, pCR was observed in 19 (35.2%) and 22 (44.9%) cases, respectively. Five non-cCR patients in Group A declined surgery or were still undergoing treatment. Disease progression occurred in one patient per group. The overall CR rates were 36.9% (24/65) in Group A and 61.1% (44/72) in Group B. The most frequent grade 3-4 toxicity was thrombocytopenia (Group A: 12.3%; Group B: 12.5%). **Conclusions:** This study is the first comparative analysis of two iTNT regimens in LARC. Unprecedentedly, neoadjuvant CAPOX plus PD-1 inhibitor achieved a promising CR rate in pMMR LARC, and this CR rate can be further enhanced with the addition of SCRT prior to immunochemotherapy. Further follow-up is necessary to assess long-term efficacy and functional endpoints. Clinical trial information: NCT06281405. Research Sponsor: National Natural Science Foundation of China (Grant No: 82473237).

Impact of CAPOX combined with traditional Chinese medicine (TiaoPi AnChang Decoction) on disease-free survival in patients with stage III or high-risk stage II colorectal cancer: An updated report of a randomized, double-blind, placebo-controlled trial.

Jincheng Zhang, Zhiqiang Cheng, Jianzheng Jie, Yantong Guo, Zhan Hua, Meng Liu, Tao Fu, Wu Ning, Lei Zhou, Tao Tang, Xin Song, Chao Wang, Shaoxuan Chen, Dakui Zhang, Haibin Liu, Guochao Zhang; Beijing University of Chinese Medicine, Beijing, China; Department of Integrated Traditional Chinese and Western Medicine Oncology, China-Japan Friendship Hospital, Beijing, China; Department of Colorectal Surgery, China-Japan Friendship Hospital, Beijing, China; Department of Gastrointestinal Surgery, China-Japan Friendship Hospital, Beijing, China

Background: Colorectal cancer (CRC) at early and mid-stages has significantly different prognoses from advanced CRC. Preventing the progression to advanced disease after surgery is crucial for improving survival and reducing healthcare burden. Multiple retrospective studies have shown that Tiaopi Anchang Decoction (TPACD), an oral formula of edible botanical drugs, can reduce recurrence and metastasis risk in CRC when combined with CAPOX. However, the evidence is limited by confounding factors and reporting biases. This study aims to test the hypothesis that CAPOX combined with TPACD can further improve disease-free survival (DFS) in patients with stage III or high-risk stage II CRC. **Methods:** The study recruited patients from 4 departments of China-Japan Friendship Hospital. It enrolled stage III or high-risk stage II CRC patients undergoing CAPOX and randomly assigned patients in a 1:1 ratio to either the TPACD group (30 mL orally, twice daily) or the placebo group (matched placebo). The trial duration covered 4 chemotherapy cycles, during which CAPOX-induced adverse reactions, quality of life (QoL), safety, and survival outcomes were assessed. The primary endpoint was DFS, while the secondary endpoints included overall survival, the incidence of CAPOX-induced adverse reactions, and QoL score (EORTC QLQ-C30). Kaplan-Meier analysis and Cox proportional hazards regression model were used to evaluate the correlation between CAPOX combined with TPACD and DFS. **Results:** From December 2022 to September 2024, 496 patients were screened, and 108 were enrolled. The 108 patients were randomly assigned in a 1:1 ratio to the TPACD group or placebo group. 42% were female, the average age was 58 years, and 66% had stage III disease. The interim report has confirmed that TPACD is safe, significantly reduced CAPOX-induced adverse reactions, and improved QoL. Median follow-up time was 28 months, with 17 DFS events (4 TPACD, 13 placebo) and no deaths. Kaplan-Meier analysis estimated 2-year DFS rates of 93.3% for TPACD and 74.7% for placebo. Log-rank testing revealed a statistically significant difference between the two groups ($\chi^2 = 5.329$, $P = 0.021$). CAPOX combined with TPACD significantly reduced the occurrence of DFS events (multivariable hazard ratio [HR] 0.23, 95% confidence interval [CI] 0.073-0.736, $P = 0.01$) and this effect was not influenced by age, sex, primary tumor site, or TNM stage ($P_{\text{interaction}} > 0.05$). **Conclusions:** For patients with stage III and high-risk stage II CRC, TPACD is a well-acceptable complementary therapy. The combination of CAPOX and TPACD not only reduces CAPOX-induced adverse reactions and improves QoL, but also further extends the DFS. Further disclosure of survival data could help optimize adjuvant chemotherapy regimens for CRC. Clinical trial information: ChiCTR2200065759. Research Sponsor: National High Level Hospital Clinical Research Funding.

AI-derived tumor microenvironment features and recurrence risk in microsatellite-stable colon cancer after adjuvant chemotherapy.

Changhee Park, Taekeun Park, Yoojoo Lim, Sanghoon Song, Deboleena Sarkar, Songji Choi, Ji-Won Kim, Jin Won Kim, Keun-Wook Lee, Minjung Kim, Jung Ho Kim, Ji Won Park, Seung-Bum Ryoo, Seung-Yong Jeong, Kyu Joo Park, Gyeong Hoon Kang, Tae-You Kim, Jeongmo Bae, Sae-Won Han; Seoul National University Hospital, Jongno-Gu, NA, South Korea; Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea; Lunit Inc., Seoul, South Korea; Lunit Inc., Cambridge, MA; Seoul National University Bundang Hospital, Seongnam, South Korea; Seoul National University Bundang Hospital, Gyeonggi-Do, South Korea; Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea; Seoul National University Hospital, Seoul, South Korea; Seoul National University Hospital, Jongno-Gu, South Korea; Department of Internal Medicine, Seoul National University Hospital, and Seoul National University Cancer Research Institute, Seoul, South Korea

Background: Despite adjuvant chemotherapy, a substantial number of patients with stage II–III microsatellite stable (MSS) colon cancer relapse. While clinicopathologic and circulating tumor DNA (ctDNA) analysis can be used for risk stratification, there is a need for further improvement in risk prediction. Here, we utilized artificial intelligence (AI) applied to hematoxylin and eosin (H&E) slides, which enables efficient and comprehensive assessment of tumor microenvironment (TME). **Methods:** We retrospectively analyzed TME of high-risk stage II and III colon cancer patients treated with surgery and adjuvant fluoropyrimidine and oxaliplatin chemotherapy. AI-based quantification of tumor area, stromal area, and TME cells (lymphocytes, fibroblasts, macrophages, and endothelial cells) was performed using Lunit SCOPE IO. We developed a generalized linear model with a backward elimination process integrating AI-derived TME features with conventional clinicopathologic variables (T stage, N stage, tumor differentiation, lymphatic invasion, venous invasion, and perineural invasion). The optimal cutoff for distinguishing between high-risk and low-risk patients for relapses was determined using the Youden index derived from the model's receiver operating characteristic curve. We evaluated how the model stratified the risk group in the training cohort and validated it in an independent cohort. **Results:** In the training cohort ($n = 390$), high stromal lymphocyte density (HR 0.42, 95% CI 0.26 – 0.68), high tumor-stromal ratio (HR 0.46, 95% CI 0.29 – 0.73), and low stromal area per fibroblast (HR 0.33, 95% CI 0.21 – 0.53) were associated with favorable DFS among the TME features. In the multivariate analysis, high stromal lymphocyte density (adj HR 0.57, 95% CI 0.35 – 0.95) and low stromal area per fibroblast (adj HR 0.58, 95% CI 0.33 – 0.99) showed significant associations with DFS independent of clinicopathological covariates. The final TME-integrated model, incorporating N stage, lymphatic invasion, stromal lymphocyte density, and stromal area per fibroblast, stratified patients into high- and low-risk groups with 3-year DFS rates of 72.3% and 93.8%, respectively (adjusted HR for high risk 3.29, 95% CI 1.98 – 5.46). The model identified high-risk patients irrespective of clinicopathological risk features. For example, high-risk status was associated with worse outcomes among patients with N2 disease (adjusted HR 6.57, 95% CI 1.58 – 27.34), and also among patients with N0 or N1 disease (adjusted HR 2.49, 95% CI 1.27 – 4.87). The model was validated in an external independent cohort ($n = 260$; adjusted HR for high-risk 3.68, 95% CI 1.60 – 8.48). **Conclusions:** TME-integrated model combining AI-derived TME features with clinicopathologic factors significantly improved recurrence risk stratification in MSS colon cancer receiving adjuvant chemotherapy. Research Sponsor: None.

Single-cell profiling of the tumor microenvironment in pMMR/MSS rectal cancer treated with neoadjuvant PD-1 inhibitor combined with FOLFOXIRI and radiotherapy: Insights from the PANFORTE trial.

Chi Zhou, Da Kang, Jian-Hong Peng, Miaozen Qiu, Qiaoxuan Wang, Weihao Li, Yuanbin Liao, Min Liu, Ting-Ting Quan, Song Wang, Zhen-Hai Lu, Xiaojun Wu, Minghui Li, Lihua Zhao, Peirong Ding, Zhizhong Pan, Jun-Zhong Lin; Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University, Guangzhou, China; Sun Yat-sen University Cancer Center, Guangzhou, China; Department of Radiation Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, Guangdong, China; Department of Radiology, Sun Yat-Sen University Cancer Centre, Guangzhou, Guangdong, China; Department of Colorectal Surgery, Sun Yat-sen University Cancer Center, Guangzhou, China; Beijing Chigene Translational Medical Research Center Co. Ltd., Beijing, China., Beijing, China

Background: Programmed cell death-1 (PD-1) inhibitor-based combination therapies have emerged as a promising neoadjuvant strategy for locally advanced rectal cancer (LARC). However, the underlying tumor microenvironment (TME) dynamics during multimodal chemioimmunoradiotherapy remain incompletely understood. This study leveraged single-cell RNA sequencing to systematically map the TME remodeling induced by neoadjuvant PD-1 inhibitor combined with chemoradiotherapy in the PANFORTE trial (NCT06099951), aiming to identify cellular correlates of therapeutic response and resistance in pMMR/MSS rectal cancer.

Methods: Pre- and post-treatment tumor samples from patients with pMMR/MSS rectal cancer enrolled in the PANFORTE trial and treated with neoadjuvant FOLFOXIRI, PD-1 inhibitor, and radiotherapy were subjected to single-cell RNA sequencing. Following stringent quality control, 227,447 high-quality cells from 50 samples were retained and annotated into seven major lineages. Cellular compositional changes across response groups were quantified using the observed-to-expected (Ro/e) index. Fibroblast subpopulations were identified via non-negative matrix factorization (NMF), and pseudotime trajectory analysis of myeloid cells was performed with Monocle 2. **Results:** Single-cell profiling revealed marked TME remodeling after neoadjuvant therapy. Complete responders (CR) showed significant stromal reduction, while non-responders (NCR) retained higher proportions of myeloid cells, endothelial cells, and fibroblasts. CR tumors exhibited enrichment of effector populations (NK cells, CD8⁺ effector memory T cells), whereas NCR tumors expanded immunosuppressive subsets (regulatory T cells, naïve T cells). Fibroblast subclustering identified inflammatory cancer-associated fibroblasts (iCAFs) as enriched in NCR. Pseudotime analysis demonstrated that myeloid cells in CR differentiated toward M1-like states, while NCR samples were biased toward M2-like programs. **Conclusions:** This study delineates distinct TME landscapes underlying differential responses to neoadjuvant FOLFOXIRI, PD-1 inhibitor, and radiotherapy in pMMR/MSS rectal cancer. Responders are characterized by cytotoxic immune activation and stromal depletion, whereas non-responders maintain an immunosuppressive milieu rich in iCAFs and M2-like myeloid cells. These findings provide mechanistic insight into treatment resistance and highlight potential cellular targets for enhancing therapeutic efficacy. Clinical trial information: NCT06099951. Research Sponsor: None.

Rates of metachronous colorectal cancer or secondary Lynch syndrome–related cancers in patients with non-metastatic colorectal cancer.

Emily M. Russell, Sarah Nielsen Young, Erica M. Vaccari, Heidi C. Ko, Eric Severson, Rebecca A. Previs, Mohammad Abbass; Labcorp (formerly Invitae Corp.), San Francisco, CA; Labcorp, Durham, NC; Labcorp, Duke University Medical Center, Duke Cancer Institute, Durham, NC; Memorial Sloan Kettering Cancer Center, New York, NY

Background: Lynch syndrome (LS) increases metachronous colorectal cancer (CRC) risk up to 5-fold, while extended resection surgery after initial CRC can reduce this risk. Prior work showed that pre-surgical germline genetic testing (GGT) was more likely to result in extended resections, especially for *MLH1/MSH2* carriers. We evaluated the rates of metachronous CRC following surgery, along with rates of other LS cancers following CRC diagnosis. **Methods:** GGT and insurance claims (Komodo Healthcare Map) data for adults with non-metastatic colon (CC) or rectal (RC) cancer and CRC surgery from 2015–25, ≥ 6 months of cancer-free claims pre-CRC diagnosis, ≥ 6 months of claims post-CRC surgery, and *EPCAM/MLH1/MSH2/MSH6/PMS2* GGT. Statistical tests compared metachronous CRC rates (new CRC ≥ 6 months post-surgery) following partial (partial/segmental colectomy or proctectomy) or extended (total colectomy or total proctocolectomy) resections by GGT result. Multivariable logistic regression modeled variables associated with metachronous CRC or other LS cancers. **Results:** Of 4,050 CRC patients (3,905 CC, 145 RC), 530 (13.1%) were LS-positive. 3,860 (95.3%) had partial (12.2% LS-positive) and 190 (4.7%) had extended resections (32.1% LS-positive). Post-surgery claims were available for a mean (standard deviation) of 47.7 (28.0) months. 251 (6.2%) patients with CRC had metachronous CRC post-surgery (6.1% partial vs. 8.9% extended resection, $p=0.145$). 282 (7.0%) patients with CRC were diagnosed with other LS cancers (54 [10.2%] LS-positive vs. 228 [6.5%] negative/variant of unknown significance (LS-negative), $p=0.002$). Patients with other LS cancers were diagnosed an average of 31.6 (23.9) months after initial CRC diagnosis (LS-positive: 29.0 [26.7], LS-negative: 32.2 [23.2]). The most common other LS cancer was prostate for men (80/1,822, 4.4%) and endometrial/uterine for women (55/2,228, 2.5%). Increased odds of metachronous CRC were associated with RC (compared to CC) (odds ratio [OR]: 5.1, 95% confidence interval [CI]: 3.3–8.0) and more months of available post-surgery claims (OR: 1.02, CI: 1.01–1.02). Increased odds of other LS cancers were associated with *MLH1/MSH2/EPCAM* carriers (compared to LS-negative) (OR: 2.0, CI: 1.3–3.1), older age (1.04, 1.03–1.05), male sex (1.6, 1.3–2.1), physician-reported Black race (1.6, 1.0–2.4) (compared to White), and more months of available post-surgery claims (1.02, 1.02–1.03). **Conclusions:** Patients with pathogenic variants in *MLH1/MSH2/EPCAM* had 2x higher odds of a second LS cancer diagnosis. 1 out of 10 patients with CRC and LS had a second LS cancer, and more than half (55.6%) of second diagnoses were within 2 years of initial CRC diagnosis. These findings highlight the importance of integrating genetic testing and comprehensive Lynch syndrome surveillance into patient care at the time of initial CRC diagnosis. Research Sponsor: None.

TGF- β signaling alterations in bevacizumab-treated early-onset colorectal cancer: An artificial intelligence-enabled precision oncology study in diverse populations.

Erika Ruiz-Garcia, Brigitte Waldrup, Francisco G. Carranza, Sophia Manjarrez, Edith Figueroa, Enrique Velazquez Villarreal; Gastrointestinal Oncology Department & Translational Medicine Laboratory, Instituto Nacional de Cancerología, Mexico City, DF, Mexico; City of Hope, Duarte, CA; Núcleo B de Innovación en Medicina de Precisión, Instituto Nacional de Medicina Genómica, Mexico City, DF, Mexico; City of Hope National Medical Center, Duarte, CA

Background: The transforming growth factor- β (TGF- β) signaling pathway plays a complex, context-dependent role in colorectal cancer (CRC), functioning in tumor suppression, immune modulation, and metastatic progression. Its interaction with anti-angiogenic therapy remains poorly defined, particularly across age and ancestry groups. Early-onset CRC (EOCRC) may exhibit distinct TGF- β pathway biology. We investigated ancestry-, age-, and treatment-associated patterns of TGF- β signaling alterations and their prognostic relevance in bevacizumab-treated CRC using an artificial intelligence-enabled precision oncology framework. **Methods:** We performed a retrospective analysis of 2,717 CRC patients from publicly available datasets with integrated genomic, clinical, and treatment annotations. Eligible cases included colorectal adenocarcinoma with sequencing data and documented bevacizumab exposure. Patients were stratified by age (< 50 years [EOCRC] vs. ≥ 50 years [LOCRC]), ancestry (H/L vs. non-Hispanic White [NHW]), and treatment status. TGF- β pathway alterations, including mutations in core signaling components (e.g., TGFBR2), were analyzed as categorical variables. Differences in mutation frequencies were assessed using Fisher's exact test. Overall survival (OS) was evaluated using Kaplan-Meier methods and Cox proportional hazards models. Conversational AI agents facilitated reproducible cohort construction and multi-dimensional querying. Analyses were exploratory. **Results:** Marked ancestry-, age-, and treatment-specific differences in TGF- β alterations were observed. Among bevacizumab-unexposed EOCRC, H/L tumors demonstrated substantially higher TGF- β alteration frequencies compared with NHW tumors (31.9% vs. 0.2%, $p = 2 \times 10^{-16}$). In NHW EOCRC, bevacizumab exposure was associated with increased TGF- β alterations relative to unexposed tumors (25% vs. 0.2%, $p = 2 \times 10^{-16}$). Similarly, bevacizumab-treated NHW LOCRC exhibited higher TGF- β alteration frequencies than unexposed counterparts (58% vs. 15.4%, $p = 2.2 \times 10^{-16}$). Among bevacizumab-unexposed LOCRC, H/L tumors showed higher TGF- β alterations than NHW tumors (34.2% vs. 18.0%, $p = 2.41 \times 10^{-5}$). In NHW LOCRC, bevacizumab-exposed tumors had a lower frequency of TGFBR2 alterations compared with unexposed tumors (1.3% vs. 7.1%, $p = 0.03$). Survival analyses suggested that TGF- β alterations were associated with improved OS in bevacizumab-unexposed NHW LOCRC, with borderline statistical significance ($p = 0.08$). **Conclusions:** The enrichment of TGF- β alterations in specific bevacizumab-exposed and ancestry-defined subgroups highlights potential interactions between angiogenic therapy and TGF- β pathway biology. These findings highlight the importance of incorporating ancestry-aware frameworks to advance precision oncology. Research Sponsor: National Cancer Institute; U2CCA252971; National Cancer Institute; P30CA033572; National Cancer Institute; U54CA285116.

Cost-effectiveness analysis of aspirin and structured exercise as adjuvant therapy in localized colorectal cancer.

Malek B. Hannouf, Kaiden Jobin, Olivia Yung, Navdeep Dehar, Richard M. Lee-Ying; Arthur J. E Child Comprehensive Cancer Centre, Calgary, AB, Canada; Cumming School of Medicine, University of Calgary, Calgary, AB, Canada; University of Calgary, Calgary, AB, Canada; Arthur Child Cancer Center, Calgary, ON, Canada; Arthur JE Child Comprehensive Cancer Centre, Calgary, AB, Canada

Background: The ALASCCA trial demonstrated that 160 mg of aspirin daily for 3 years reduced the risk of localized colorectal cancer recurrence in patients with PIK3CA exons 9/20 (group A) or PIK3R1/PTEN/other PIK3CA alterations (group B). The CHALLENGE trial demonstrated that increasing recreational aerobic activity above baseline through a 3-year structured exercise program reduces the risk of colon cancer recurrence. These interventions have not been adopted into Canadian clinical practice (CCP), and we evaluated the cost-effectiveness of strategies to implement them as adjuvant therapy for localized, operable colorectal cancer from the Canadian public healthcare perspective. **Methods:** We developed a decision model to project clinical and economic consequences of six strategies: (1) “CCP,” defined as no exercise or aspirin interventions; (2) “Aspirin for group A PI3K alterations,” defined as testing for group A PI3K alterations and treating positive patients with aspirin; (3) “Aspirin for group A/B PI3K alterations,” defined as testing for group A/B PI3K alterations and treating positive patients with aspirin; (4) “Aspirin for all,” defined as treating all patients with aspirin regardless of PI3K status; (5) “Structured exercise alone,” defined as initiating all patients on a structured exercise program with no aspirin intervention; and (6) “Aspirin for group A/B PI3K alterations and structured exercise,” defined as testing for group A/B PI3K alterations, treating positive patients with aspirin, and initiating all patients on a structured exercise program. The model was parameterized using survival data from the ALASCCA and CHALLENGE trials, and cost and utility data from Alberta, Canada, and Canadian sources. Costs are presented in 2025 Canadian dollars. Future costs and benefits were discounted at 1.5%. **Results:** Compared with the CCP, all interventional strategies were associated with greater QALY gains and lower per-person costs, resulting in overall cost savings (Table). The “aspirin for group A/B PI3K alterations and structured exercise” strategy emerged as the dominant intervention, yielding the highest QALYs gained and greatest cost savings per person. Implementing this strategy into CCP would avert disease recurrence in 940 patients per year, generate 2,625 total QALYs annually, and produce total budget savings of \$399 million per year. **Conclusions:** The integration of PI3K group A/B–guided aspirin therapy with structured exercise as adjuvant treatment for localized colorectal cancer should be adopted into CCP, given its considerable societal benefit. Research Sponsor: None.

Strategy	Inc. QALY gained/pers.	Cost saving/pers.
CP	Ref	Ref
Aspirin for group A PI3K alterations	0.05	9,400
Aspirin for group A/B PI3K alterations	0.12	20,200
Aspirin for all	0.07	14,700
Structured exercise alone	0.13	23,700
Aspirin for group A/B PI3K alterations and structured exercise	0.22	33,700

Efficacy and safety of tislelizumab as neoadjuvant therapy combined with MRD monitoring in locally advanced dMMR/MSI-H colon cancer: A prospective pilot study.

Miaoqing Wu, Rong-Xin Zhang, Xiaojun Wu, Guangzhao Lv, Jing Xu, Yun Chen, Lei Sun, Shida Zhu, Xiaofang Qi, Lei Zhang, Gong Chen; Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangzhou, China; Department of Colorectal Surgery, Sun Yat-sen University Cancer Center, Guangzhou, China; State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China; BGI Genomics, BGI-Shenzhen, Shenzhen, China; Tianjin Medical Laboratory, BGI-Tianjin, Tianjin, China; BeOne Medicines Ltd, Guangzhou, China; Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University, Guangzhou, China

Background: PD-1 blockade has demonstrated high efficacy in metastatic and neoadjuvant settings for dMMR/MSI-H colorectal cancer. This study aimed to evaluate the efficacy and safety profile of neoadjuvant tislelizumab monotherapy in locally advanced dMMR/MSI-H colon cancer patients, with integrated minimal residual disease (MRD) monitoring. **Methods:** Histologically confirmed locally advanced dMMR/MSI-H colon adenocarcinoma are eligible for enrollment. Participants received 4 cycles of neoadjuvant tislelizumab (200 mg IV Q3W) followed by clinical response assessment. Patients continued receiving 4 additional cycles or underwent radical surgery based on the multidisciplinary team (MDT) decision. Non-operative management (NOM) was a choice of cCR patients after 8 cycles of treatment. MRD status was assessed by a tumor-informed, bespoke ctDNA assay (HuaJianwei) at baseline, during and post-treatment. The primary endpoint was pCR rate. Secondary endpoints included cCR rate, MPR rate, DFS, NOM rate, biomarker exploration, and safety. **Results:** Forty patients were enrolled between November 2022 and May 2025 (median follow-up: 13.58 months) and one requested to withdraw from the study. Twenty-eight (71.8%) underwent surgery, including 8 patients who received less than 6 cycles of neoadjuvant therapy, 18 patients who completed 8 cycles, and 2 patients who received more than 8 cycles based on MDT decision. Of resected patients, 22 (78.6%) achieved pCR and 26 (92.9%) achieved MPR. Nine patients opted for NOM due to cCR, with an overall CR rate of 79.5%. Grade 3 irAEs occurred in 4 patients (10.3%), including pneumonitis (n=2), renal insufficiency (n=1), and stroke (n=1). No treatment-related deaths occurred. Baseline MRD testing was completed in 29 patients, 28 (96.6%) of whom were positive. Rapid clearance of MRD was observed in 48.3% (14/29) of patients after 1 cycle and 75.9% (22/29) of patients after 2 cycles. Only one patient (1/10) remained MRD-positive post-treatment due to pneumonitis-related therapy discontinuation. **Conclusions:** Neoadjuvant tislelizumab monotherapy confers favorable efficacy and a manageable safety profile in locally advanced dMMR/MSI-H colon cancer with high pCR rates and feasible NOM for cCR patients. MRD monitoring provides valuable, real-time assessment of treatment response to guide surgical and surveillance decisions. Longer follow-up is needed to confirm response durability, particularly in NOM patients. Clinical trial information: NCT06262581. Research Sponsor: None.

Consensus molecular subtypes, mutational features, and circulating tumor DNA dynamics in colorectal cancer: A real-world clinico-genomic analysis.

Imad Shureiqi, Avinash Ramu, Vasily N. Aushev, J. Bryce Ortiz, Axel Grothey, Michael White, John Paul Y.C. Shen, Adham A. Jurdi, Anthony F. Shields; Division of Hematology and Oncology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI; Natera, Inc., Austin, TX; West Cancer Center and Research Institute, Germantown, TN; Department of Gastrointestinal (GI) Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX; Karmanos Cancer Institute, Wayne State University, Detroit, MI

Background: Consensus molecular subtypes (CMS) define biologically distinct colorectal cancer (CRC) groups with differences in tumor microenvironment, genomic features, and prognosis. While CMS classification is well established in tissue-based transcriptomic studies, its relationship with circulating tumor DNA (ctDNA) dynamics and molecular features in real-world clinical practice remains incompletely characterized. We evaluated CMS subtype distribution, mutational characteristics, and ctDNA detection patterns in a large real-world CRC cohort. **Methods:** Patients with CRC who underwent whole-transcriptome sequencing via Altera (Natera, Inc.) testing were identified from Natera's real-world clinico-genomic database. CMS subtype assignment was based on the whole-transcriptome sequencing, and then correlated with Signatera results, a personalized, tumor-informed ctDNA assay. In patients with stage II–III CRC, ctDNA positivity was assessed during the MRD window (1–10 weeks post-surgery) and during post-MRD surveillance (>10 weeks post-surgery). Overall survival (OS) was estimated using the mortality database (Veritas Data Research, Fact of Death Mortality Data Index). **Results:** Among 8,456 CRC cases with available molecular data, CMS distribution was 10% CMS1, 26% CMS2, 12% CMS3, 22% CMS4, and 29% inconclusive. While canonical anatomic patterns were recapitulated (CMS1 right-sided, CMS2 left-sided, CMS3 rectal), CMS4 tumors were enriched in advanced-stage disease. CMS1 demonstrated high MSI-H prevalence (53%), frequent BRAF V600E (35%) and KMT2D (44%) alterations, and enrichment of MMR deficiency and APOBEC and POLE mutational signatures. CMS2 tumors were almost exclusively microsatellite stable (99.7%) and enriched for APC (84%) and TP53 (80%) mutations, whereas CMS3 showed intermediate MSI-H prevalence (10%) with frequent APC (74%) and KRAS (61%) alterations. CMS4 tumors exhibited low MSI-H prevalence (2%) but frequent TP53 (60%) and APC (59%) mutations. Among patients with stage II–III CRC, ctDNA positivity during the early post-operative MRD window was not associated with CMS subtype. In contrast, during later surveillance, ctDNA positivity was more frequent in CMS4 tumors compared with CMS1–CMS2 (36.8% vs 28.1%). Among MRD-positives, CMS1 was associated with the shortest OS, whereas CMS2 demonstrated the longest OS. No difference in OS was noted in MRD-negative patients. **Conclusions:** In this large real-world cohort, CMS subtypes were recapitulated with expected clinicogenomic and mutational associations and demonstrated distinct ctDNA detection patterns during surveillance. Integration of CMS biology, mutational features, and longitudinal ctDNA dynamics provides insights into residual disease and recurrence risk beyond static tissue-based classification. Research Sponsor: None.

Safety and efficacy of neoadjuvant chemotherapy (NAC) in older patients with locally advanced colon cancer (LACC): Results from FOxTROT 1 and the FOxTROT 2 safety cohort population.

Janet Shirley Graham, Laura Magill, Kelly Handley, Anna Perry, Emily Connell, Faye Elliott, Nicholas West, James Robert Platt, Christopher Williams, Michael Braun, Andrew David Beggs, Nancy Fernandes da Silva, Matthew Seymour, Aaisha Ali, Rhiannon Lambkin, Claire Dimpleby, David A. Cairns, Dion Morton, Jenny Seligmann; Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; University of Birmingham, Birmingham, United Kingdom; University of Leeds, Leeds, United Kingdom; Leeds Institute of Medical Research at St. James's, University of Leeds, Leeds, United Kingdom; Division of Pathology and Data Analytics, University of Leeds, Leeds, United Kingdom; The Christie Hospital NHS Foundation Trust, Manchester, United Kingdom; Institute of Cancer & Genomic Sciences, University of Birmingham, Birmingham, United Kingdom; Leeds Institute of Clinical Trials Research, Leeds, United Kingdom; Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, United Kingdom

Background: The FOxTROT1 (FT1; NCT00647530) trial demonstrated feasibility and efficacy of six weeks of NAC for LACC compared with upfront surgery. The currently recruiting FOxTROT2 trial (ISRCTN83842641) is testing this approach in older or frail patients. Outcomes in older patients with LACC are inferior; therefore, new treatment strategies are required. Here in these trials we analyse the safety and efficacy of NAC in this group and report the DFS in the older subgroup of FT1 PMMR patients. **Methods:** Data from FT1 and the planned FT2 safety pilot (n=150) were combined and analysed by treatment arm and by age category ($\leq$ 70). Pre-specified endpoints included NAC delivery and perioperative complication rates for FT1 and FT2; DFS and pathological response are reported for FT1 patients by MMR status. We will update safety data for this presentation. **Results:** In FT1 292/1052 (27.8%) of patients were aged over 70; the median age of FT2 safety cohort was 76 (range 70–85). There were no significant differences by age in NAC delivery or in rates of peri-operative complications. For patients over 70, combining FT1&2 data, exploring those who received NAC, 88.5% completed the course as planned and 37.7% received an upfront or subsequent dose modification. Rates of peri-operative complications combining FT1&2 were similar between patients receiving NAC or upfront surgery: anastomotic leak (3.4% vs 3.3%), complication requiring hospital stay (FT1 9.3% vs 14.6%) or further surgery (2.6% vs 5.0%), and post-operative death (0.9 % vs 1.7%). For patients over 70 in FT1 16.4% were dMMR and 83.6% were pMMR. In pMMR patients overall NAC improved 3-year DFS (81.2% vs 75.4% without a DFS event; HR 0.70[0.52–0.94], p=0.02) compared with upfront surgery; results were consistent in older patients (81.2% vs 71.4%; HR 0.59[0.35–1.02], p=0.06). **Conclusions:** NAC is safe and well-tolerated in older adults, with no increase in perioperative morbidity and preserved treatment delivery compared to rates in younger patients and when compared with upfront surgery. Promising efficacy in terms of 3-year DFS and pathological response were observed in older patients with pMMR tumors, consistent to those seen in younger patients. These data support the use of NAC in older patients with LACC and continued recruitment to FT2 to evaluate the long term impact. Clinical trial information: NCT00647530. Research Sponsor: None.

Organ preservation and local excision for rectal cancer: Long-term oncologic outcomes.

Avihai Moscovici, Tyler Bogaczyk, Hien Anh Ton, Erik L. Zeger, Albert DeNittis, John Marks; Lankenau Medical Center, Wynnewood, PA; Main Line Oncology Hematology Associates, Wynnewood, PA; Midlantic Urology, Bala Cynwyd, PA; Lankenau Medical Center, Main Line Health, Wynnewood, PA

Background: Organ preservation is a desired outcome for rectal cancer patients after neo-adjuvant chemoradiotherapy. In patients where a complete response is in question, endoscopically assisted full-thickness local excision offers a great option. Long-term data with this approach is limited. We report our experience with transanal endoscopic microsurgery (TEM) status post chemotherapy. **Methods:** Between January 2005 and October 2019, from a prospectively maintained rectal cancer database, we identified all patients who underwent TEM for adenocarcinoma after neoadjuvant CRT. Demographic data as well as follow-up interval and oncologic outcomes were reviewed and analyzed. **Results:** Ninety-two patients who underwent TEM for rectal cancer were included. The mean age was 67 years (32–94), 66% were male, and the mean BMI was 29.3 kg/m² (19.1–43). ASA classifications were II in 38%, III in 51%, and IV in 5% of patients. The mean tumor size was 3.1 cm (1–6) and mean estimated blood loss (EBL) was 29 mL (0–500). Postoperative 30-day morbidity occurred in 6.5% of patients, with no mortalities. The mean follow-up was 57.5 months (0.4–194.5), during which 7.6% of patients developed local recurrence and 6.5% developed systemic metastases. Based on final pathology, 48 patients with a complete pathologic response (ypT0) had local recurrence and distant metastasis rates of 4% and 2%, respectively. In patients with stage I disease (n=35), local recurrence occurred in 11% and distant metastasis occurred in 9%. Stage II patients (n=7) experienced a 14% rate of local recurrence with no distant metastases. Among stage III patients (n=2), both local and distant failure occurred in 50% of cases. **Conclusions:** TEM after neo-adjuvant CRT was associated with excellent oncologic outcomes in patients achieving complete pathologic response. Selected patients with favorable residual disease experienced acceptable recurrence rates, supporting TEM as a potential organ-preserving strategy in this subgroup. In contrast, higher pathologic stage was associated with substantially increased local and distant failure, highlighting the need for strict selection, pathology-driven decision-making, and close surveillance. Research Sponsor: None.

Screening and trends: A Global Burden of Disease 2023 assessment of colorectal cancer mortality across G7 nations.

Rana Uzair Ahmad, Suleman Khalid, Sabreena Ahmer, Mahroo Khalid, Asad Zaman, Abdul Rafae Faisal, Mahnoor Jan, Safi Ur Rehman Daim, Aminah Tayyab, Umer Javaid, Amro Al-Omari, Ahmad Abdur Rahman Sayeed; Trinity Health Livonia Hospital, Livonia, MI; CMH Multan Institute of Medical Sciences, Multan, Pakistan; Queen Elizabeth Hospital Birmingham, Birmingham, United Kingdom; Division of Hematologic Malignancies & Cellular Therapeutics, University of Kansas Medical Center, Kansas City, KS; University of Kansas Medical Center, Kansas City, KS; Shaikh Khalifa Bin Zayed Al-Nahyan Medical and Dental College, Lahore, Pakistan; Carle Health, Champaign, IL; The University of Oklahoma Health Sciences Center, Oklahoma City, OK; Department of Medicine, Trinity Health Livonia, Livonia, MI

Background: Historically, the adoption of screening techniques has led to a steady decline in colorectal carcinoma (CRC) mortality in high-income countries. However, recent epidemiological data points towards a potential saturation of screening benefits and a rising burden of early-onset disease. Using Global Burden of Disease (GBD) 2023 data, we were able to identify points of stagnation and trend reversals in CRC mortality rates for G7 nations and hypothesize a systemic screening saturation in the post-pandemic era. **Methods:** The Global Burden of Disease 2023 study was used to retrieve data that included age-standardized death rates (ASDR) for G7 nations (2000–2023). Trends were analyzed using the Joinpoint regression Program, Version 5.4.0.0. We employed a log-linear model to estimate Annual Percent Change (APC). Pairwise comparison tests assessed parallelism between national trajectories to identify statistically distinct trend patterns. **Results:** From 2000 to 2023, epidemiological data shows an overall decline in the age standardized death rates (ASDR) for colorectal carcinoma in the USA. The ASDR in 2000 was 18.54 (95% UI: 16.80–19.87) and in 2023 it decreased to 12.64 (AAPC: -1.66; 95% CI: -1.83 to -1.49). Upon further analysis, three individual trajectory phenotypes were detected across the G7. The USA and Canada displayed a stagnation phenotype, in which mortality rates plateaued in the more modern years after initial rapid declines. In USA 2018–2023 APC was -0.48 (95% CI: -1.03 to 0.08) and in Canada 2020–2023 APC was 0.26 (95% CI: -0.94 to 1.47). The UK, Japan and France exhibited a rather alarming reversal phenotype, where mortality rates significantly accelerated in recent years. In UK 2021–2023 APC was 2.87 (95% CI: 0.74 to 5.06) while Japan 2021–2023 APC was 2.68 (95% CI: 1.45 to 3.93) and France 2021–2023 APC was 2.56 (95% CI: -2.06 to 7.40). Italy, however, has maintained a sustained decline phenotype, which sharply contrasts with that of the aforementioned nations. In Italy 2003–2023 APC was -1.65 (95% CI: -1.74 to -1.56) with no evidence of saturation. Pairwise comparison confirmed that the USA trajectory was significantly non-parallel to Italy ($p < 0.05$). **Conclusions:** For the majority of G7 nations, the era of universal CRC mortality decline has come to an end. While the USA and Canada show halted progress, the UK, Japan and France show early signs of slope inversion. On the contrary, Italy's clear lead in maintenance of declining mortality suggests a policy-based limitation as opposed to unavoidable biological circumstances. Urgent implementation of revolutionized screening techniques and interventions, focusing on hard-to-screen populations as well as early onset cohorts, are required to avert a global deterioration in CRC outcomes. Research Sponsor: None.

Association of *FBXW7* mutation with prolonged survival in microsatellite instability–high colorectal cancer treated with immune checkpoint blockade.

Margaret R. Pruitt, Sachin Deshmukh, Aseel Saadeh, Elizabeth M. Hill, Sharon Wu, Tolulope Tosin Adeyelu, Kieran Sweeney, Joanne Xiu, Midhun Malla, Sanjay Goel, Emmanuel S. Antonarakis, Max Gordon; National Cancer Institute, National Institutes of Health, Bethesda, MD; Caris Life Sciences, Phoenix, AZ; Geisinger Medical Center, Danville, PA; University of Alabama, Birmingham, AL; Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; University of Minnesota-Twin Cities, Masonic Cancer Center, Minneapolis, MN; National Institutes of Health, Bethesda, MD

Background: Colorectal cancer (CRC) remains a major cause of cancer-related mortality. Biomarkers of response to novel therapies may improve treatment selection and outcomes. Microsatellite instability (MSI-H) is a predictor of response to immune checkpoint blockade (ICI); however, less than half of patients with MSI-H CRC have a durable response to ICI. *FBXW7* mutations (MT) are common in CRC but their prognostic significance in patients treated with ICI is not well studied. Here, we characterized *FBXW7*-MT in CRC and their association with ICI outcomes. **Methods:** A total of 29,446 CRC (MSS, n = 27,323; MSI-H, n = 2,123) samples were tested by next generation sequencing (592, NextSeq; WES, NovaSeq) and WTS (NovaSeq; Caris Life Sciences, Phoenix, AZ). TMB was assessed by nonsynonymous mutations/Mb (high ≥ 10). Immune cell proportions were estimated using WTS deconvolution (Quantiseq). Real-world median overall survival (mOS) data were derived from insurance claims, calculated from tissue collection or treatment (chemotherapy: CAPEOX, Capecitabine, FOLFIRI, FOLFIRINOX, Fluorouracil, Irinotecan, Oxaliplatin; ICI: Nivolumab, Pembrolizumab) initiation to last contact, and analyzed using Kaplan-Meier. Statistical significance was assessed by chi-square and Mann-Whitney U test with p-values adjusted for multiple comparisons ($q < 0.05$). **Results:** *FBXW7*-MT was enriched in MSI-H (29.6% (n=608) vs 9.2% (n=3,025), $p < 0.05$) compared to MSS tumors. Among MSI-H tumors, *FBXW7*-MT had higher median TMB (40 vs 37, $q < 0.05$) and numerically higher TMB-high frequency (99.2% vs 97.9%, $p = 0.05$) compared to *FBXW7*-WT. Analysis of inferred immune cells revealed that *FBXW7*-MT MSI-H CRC had lower median cell fraction (%) of M2 macrophages (2% vs 2.5%) compared to *FBXW7*-WT. In MSI-H CRC, *FBXW7*-MT patients had better mOS when treated with ICI (48.3 vs 34.2 months, HR 0.68, 95% CI 0.52 – 0.9, $p = 0.006$) compared to *FBXW7*-WT, whereas there was no difference in mOS in MSI-H CRC treated with chemotherapy (HR 0.95, $p = 0.67$) compared to *FBXW7*-WT. *FBXW7*-MT was not associated with OS in MSS CRC. In MSI-H CRC, *R465C/H/L/S* (20.6%), *R505C/H/L/G* (7%) and *R479Q/G* (3.4%) were the most common *FBXW7* hotspot mutations. *R465C/H/L/S* had better mOS with ICI (HR 0.61, $p = 0.04$) compared to *FBXW7*-WT. Multivariable Cox analysis adjusted for TMB and PD-L1 showed *FBXW7*-MT is an independent predictor of improved OS with ICI in MSI-H CRC (HR 0.69, 95% CI 0.53 – 0.9, $p = 0.007$). **Conclusions:** This large study is the first to report a positive association with *FBXW7* mutation and OS in MSI-H CRC treated with PD1/PD-L1 blockade. While requiring validation in independent cohorts, our findings suggest that *FBXW7*-MT is a biomarker of response to ICI and that targeting *FBXW7* may be an effective way of augmenting the clinical activity of ICI in MSI-H CRC. Research Sponsor: Intramural Research Program of the National Institutes of Health (NIH).

Clinicopathologic features of South African colorectal cancer patients by HIV status in a retrospective cohort study.

Jacob Lee Dubner, Madhav Nekkar, Alexander Morris, Thembeke Mngadi, Absalom Mwazha, Shakeel Kader, Yoanna S. Pumpalova; Columbia University Medical Center, New York, NY; Columbia University Irving Medical Center, New York, NY; University of KwaZulu Natal, Durban, South Africa

Background: Colorectal cancer (CRC) is increasing among people living with HIV. South Africa (SA) has the largest HIV-infected population in the world. Data characterizing the features of CRC among HIV patients in SA is limited. We compared the clinicopathologic features of CRC patients in SA by HIV-status. **Methods:** A retrospective cohort of CRC patients was identified using a database of histologically confirmed CRC patients seen at one of four referral hospitals in KwaZulu-Natal, SA between 2000 and 2024. Confirmed HIV-positive patients were randomly matched (1:2) with patients without HIV based on age at CRC diagnosis, year of CRC diagnosis, race, and tumor location. Additional clinical data was extracted through retrospective review of medical records. Chi-squared tests were used to compare features by HIV-status. **Results:** We identified 106 CRC patients with confirmed HIV-positive status and matched them with 155 CRC patients with confirmed HIV-negative status and 57 CRC patients with unknown HIV-status (assumed to be HIV-negative for analysis). At the time of CRC diagnosis, HIV-positive patients had an average duration of infection of 5.2 years and a mean baseline CD4 count of 451 cells/mm³. 72.6% of HIV patients were on antiretroviral therapy. HIV-status was not associated with duration of symptoms prior to CRC diagnosis (cohort mean 9.6 months; p-value = 0.687). HIV-positive patients were more likely than HIV-negative patients to present with metastatic disease (40.6% vs 28.8%, p-value = 0.035) and to have poorly differentiated tumors (13.9% vs 4.5%, p-value = 0.011). HIV-status was not associated with the rate of curative-intent treatment initiation (62.1% of non-metastatic patients received stage-appropriate treatment; p-value = 0.199) or palliative-intent systemic therapy (81.7% of metastatic patients received systemic therapy; p-value = 0.105). **Conclusions:** In SA, CRC patients with HIV are more likely than patients without HIV to present with high grade tumors and metastatic disease. This suggests a more aggressive tumor biology in this population. A comparison of overall survival by HIV-status will be presented at ASCO 2026. Future studies will compare the CRC tumor microenvironment by HIV-status in a subset of patients. Research Sponsor: National Cancer Institute; 3K12CA279872-02S1.

Clinicopathologic features of colorectal cancer patients in South Africa by HIV-status (2000-2024).				
	HIV-Positive (n = 106)	HIV-Negative (n = 212)	Total (n = 318)	p-value
Tumor Site				1.000
Colon	43 (40.6%)	86 (40.6%)	129 (40.6%)	
Rectal	63 (59.4%)	126 (59.4%)	189 (59.4%)	
Stage at Diagnosis				0.090
Early (I-IIa)	11 (10.4%)	32 (15.1%)	43 (13.5%)	
Locally Advanced (IIb-IIIc)	52 (49.1%)	119 (56.1%)	171 (53.8%)	
Metastatic (IVa-IVc)	43 (40.6%)	61 (28.8%)	104 (32.7%)	
Tumor Grade				0.040
Well Differentiated	2 (2.5%)	4 (2.6%)	6 (2.6%)	
Moderately Differentiated	66 (83.5%)	143 (92.9%)	209 (89.7%)	
Poorly Differentiated	11 (13.9%)	7 (4.5%)	18 (7.7%)	
Unknown	27	58	85	

Evaluation of circulating tumor DNA (ctDNA) burden, detected mutations, and clinical outcomes in metastatic colorectal cancer (mCRC) using real-world data (RWD).

Alicia Catania McDonald, Joy Saha, David R. Fogelman, Carol Elaine Pena, Xinyue Liu, Gurpreet Singh Kapoor; Merck & Co., Inc., Rahway, NJ; Guardant Health, Inc., Palo Alto, CA

Background: ctDNA is a promising prognostic biomarker in colorectal cancer; however, there is limited RWD on its prognostic value in mCRC. We leveraged RWD to assess pre-treatment (Tx) ctDNA burden and gene mutations, and evaluated the association between ctDNA burden and clinical outcomes in patients (pts) with mCRC. **Methods:** Pts with mCRC identified in the GuardantINFORM database who underwent Guardant 360 comprehensive genomic profiling between June 1, 2014 to June 30, 2023 were included. First metastatic diagnosis date was used as the index date. ctDNA burden (% max variant allele fraction ctDNA levels) was categorized as below limit of detection (no ctDNA), $\leq$ median value (low ctDNA), and $>$ median value (high ctDNA). ctDNA burden and gene mutations/alterations detected prior to 1L systemic therapy were summarized. Associations with OS, time to next Tx (TTNT), and time to Tx discontinuation (TTD) were assessed using Cox proportional hazards models for the overall cohort and by microsatellite instability (MSI) status, stratified by 1L and 2L Tx. **Results:** There were 3273 pts with mCRC included (non-MSI-high [H], n = 2750; MSI-H, n = 100; missing, n = 423). Mean ctDNA burden was 19.9% overall, 20.7% in non-MSI-H, and 14.6% in MSI-H cohorts. Top 3 gene mutations were TP53 (65.8% and 67.2%), APC (59.7% and 60.7%), and KRAS (40.6% and 41.2%) in the overall and non-MSI-H cohorts; and, ARIDIA (71.0%), TP53 (67.0%), and APC (65.0%) in the MSI-H cohort. Top 3 specific variants were EGFR AMP (23.7% and 25.3%), KRAS G12D (11.3% and 11.4%), and KRAS G12V (8.2% and 8.5%) in the overall and non-MSI-H cohorts; and BRAF V600E (39.0%), ARIDIA D1850fs (22.0%), and PIK3CA H1047R (21.0%) in the MSI-H cohort. In the overall cohort, high ctDNA compared to low ctDNA was statistically significantly associated with shorter OS (HR [95% CI]: 1L, 1.63 [1.43-1.87]; 2L, 1.42 [1.19-1.70]) and TTNT (1L, 1.43 [1.27-1.60]; 2L, 1.39 [1.19-1.63]) after adjusting for confounders. Conversely, no ctDNA compared to low ctDNA was statistically significantly associated with longer OS (0.70 [0.53-0.91]) and TTNT (0.75 [0.58-0.97]) in the 1L setting after adjusting for confounders; these associations were also observed when stratified by MSI status. ctDNA burden was not statistically significantly associated with TTD in 1L regardless of MSI status. In 2L, high ctDNA was associated with shorter TTD compared to low ctDNA overall (1.19 [1.05-1.34]), with similar findings in the non-MSI-H cohort. **Conclusions:** High ctDNA burden prior to 1L and 2L therapy was associated with shorter OS and TTNT, suggesting a higher disease burden or more aggressive disease. The absence of detectable ctDNA was associated with improved survival and may identify pts with better prognosis or slower-growing tumors. These findings provide growing evidence for ctDNA as a potential prognostic biomarker in mCRC. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Epidemiology of early-onset colorectal cancer in the WHO Eastern Mediterranean Region: Regional and global comparisons.

Fares A. Qtaishat, Jehad A. Yasin, Muaath Alsufi, Winta Tsegay Mehtsun, Melody Smith, Tala Al-Rousan; The University of Jordan, School of Medicine, Amman, Jordan; School of Medicine, The University of Jordan, Amman, Jordan; University of California San Diego, La Jolla, CA; Division of Blood and Marrow Transplantation and Cellular Therapy, Department of Medicine, Stanford University School of Medicine, Stanford, CA; University of California, San Diego, Herbert Wertheim School of Public Health and Human Longevity Science, La Jolla, CA

Background: Early onset colorectal cancer (EO-CRC) is increasing globally, yet studies from the WHO Eastern Mediterranean Region (EMRO) are limited. We quantified the burden, temporal trends, and future projections of EO-CRC in EMRO and compared patterns with regional and global estimates. **Methods:** We conducted a population based study using GLOBOCAN 2022 data. EO-CRC outcomes included age-standardized incidence rates (ASIRs), age-standardized mortality rates (ASMRs), and 1-, 3-, and 5-year prevalence per 100000 population. Age-specific analyses were conducted. Temporal trends were assessed using Estimated Annual Percentage Change (EAPC). Associations between Human Development Index (HDI) and EO-CRC outcomes were evaluated using Pearson correlation coefficients (r). **Results:** In 2022, EMRO recorded 53941 new CRC cases (ASIR = 8.9), including 15381 EO-CRC cases (ASIR = 2.5), and 29918 CRC deaths (ASMR = 5.1), including 6965 EO-CRC deaths (ASMR = 1.1). EO-CRC incidence was lowest among individuals aged 0–19 years (ASIR = 0.17), increased in those aged 20–34 years (ASIR = 1.9), and peaked among adults aged 35–49 years (ASIR = 8.4), who accounted for most EO-CRC cases and deaths. Marked inter-country heterogeneity was observed. Jordan had the highest EO-CRC incidence (ASIR = 4.2), followed by Libya (ASIR = 3.5) and Iran (ASIR = 3.3), while EO-CRC mortality was highest in Jordan (ASMR = 1.9), followed by Oman and Somalia (ASMR = 1.8 each). Five-year EO-CRC prevalence was highest in Saudi Arabia (14.7 per 100,000), Oman (13.5), and Iran (13.3), but remained below 3 per 100000 in Afghanistan and Somalia. Males exhibited higher EO-CRC incidence (ASIR = 2.6) and mortality (ASMR = 1.2) than females (ASIR = 2.4; ASMR = 1.1), although several countries demonstrated a higher female burden. Compared with other WHO regions, EMRO demonstrated one of the highest EO-CRC mortality rates globally (ASMR = 1.1), exceeding Europe (ASMR = 1.0), South-East Asia (ASMR = 0.68), and the Western Pacific (ASMR = 0.98), despite having lower overall CRC incidence. Temporal trend analyses revealed concerning increases in EO-CRC incidence, with significant rises in Israel (EAPC = +2.58%). EO-CRC mortality was inversely correlated with HDI ($r = -0.45$; $p = 0.034$), indicating a disproportionate mortality burden in lower HDI countries. Projections indicate that annual EO-CRC cases will increase from 15381 in 2022 to 24396 by 2050, and annual deaths from 6965 to 11005, underscoring a rapidly escalating regional burden. Incidence and mortality are projected to rise faster in females across EMRO by 2050. **Conclusions:** EO-CRC is a rapidly growing, inequitable burden in EMRO, with high mortality and marked inter-country differences. Its disproportionate impact on lower HDI countries and younger populations highlights the urgent need for targeted interventions, including early detection and awareness campaigns. Research Sponsor: None.

Impact of concomitant GLP-1 receptor agonist use on overall survival and chemotherapy-related adverse events in colorectal cancer: A real-world pharmacoepidemiologic cohort study.

Arunkumar Krishnan, Diptasree Mukherjee, Kunal C. Kadakia, Ye Myint Aung, Declan Walsh; Atrium Health Levine Cancer, Charlotte, NC; Department of Supportive Oncology, Atrium Health Levine Cancer, Charlotte, NC

Background: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are increasingly prescribed for diabetes and obesity and exert pleiotropic metabolic and anti-inflammatory effects. While prior studies have focused on their role in cancer prevention, limited data exist regarding their impact on cancer treatment outcomes. We evaluated the association between concomitant GLP-1 RA use and overall survival (OS) in patients with colorectal cancer (CRC) receiving standard first-line chemotherapy. **Methods:** Using the Blue Diamond Global Collaborative Network, adult patients with CRC initiating first-line FOLFOX or FOLFIRI between 2015 and 2024 were identified. Patients were classified as GLP-1 RA users if they received a GLP-1 RA (e.g., semaglutide, liraglutide, dulaglutide) within 90 days before or after chemotherapy initiation, and non-users otherwise. Cohorts were 1:1 propensity score matched for age, sex, BMI, diabetes status, line of therapy, comorbidities, and baseline corticosteroid use. The primary endpoint was OS. Kaplan–Meier methods and Cox proportional hazards models were used for analysis. **Results:** After matching, 4,824 patients were included (2,412 per cohort). Baseline characteristics were well balanced (mean age 61.8 years; 46% female; mean BMI 31.2 kg/m²; 58% with diabetes). At a median follow-up of 24.6 months, patients receiving concomitant GLP-1 RAs demonstrated significantly improved overall survival compared with non-users. Median OS was 28.4 months among GLP-1 RA users versus 23.6 months among non-users (log-rank $p < 0.001$). GLP-1 RA use was independently associated with improved OS (HR 0.82, 95% CI 0.76–0.89). Regarding safety outcomes, GLP-1 RA users experienced a lower incidence of neutropenia (18.9% vs 23.7%; RR 0.80, $p = 0.002$) and reduced chemotherapy-induced neuropathy (14.2% vs 18.6%; RR 0.76, $p = 0.004$). Subgroup analyses demonstrated consistent OS benefit across chemotherapy backbone: FOLFOX (HR 0.81) and FOLFIRI (HR 0.84), and the most pronounced effect in patients with BMI ≥ 30 kg/m². Sensitivity analyses restricting sustained GLP-1 RA exposure (> 6 months) yielded similar results. **Conclusions:** In this large real-world cohort of patients with colorectal cancer, concomitant GLP-1 receptor agonist use was associated with improved overall survival and reduced chemotherapy-related toxicity. These findings suggest a potential adjunctive therapeutic role for GLP-1 RAs during active cancer treatment, potentially mediated through metabolic stabilization, reduced systemic inflammation, and improved treatment tolerance. Prospective studies are warranted to confirm these observations. Research Sponsor: None.

Impact of social determinants of health on women with early-onset colorectal cancer: A retrospective study.

Elaine Ognjanovski, Niketh Chopra, Amaani Lewis, Muhammad Ismail, Mitchell Oliver, David LeRoy, Rafael Barretto; Henry Ford Warren, Warren, MI

Background: The incidence of early-onset colorectal cancer (EOCRC) in adults under age 50 has significantly increased. Women with EOCRC often present with nonspecific gastrointestinal symptoms, leading to delayed diagnosis and care. The impact of social determinants of health (SDOH), such as insurance status, income, and race, on cancer outcomes, disease presentation and hospitalization severity in young women with EOCRC is not well known. This study investigates how SDOH factors are associated with stage at presentation, emergency admission, metastatic burden and inpatient outcomes in women hospitalized with EOCRC. **Methods:** We conducted a retrospective cohort study using the National Inpatient Sample (2018–2021) with hospitalized women aged 18–49 years, diagnosed with colorectal cancer, identified using ICD–10. SDOH variables included primary payer (private, Medicare, Medicaid, uninsured), ZIP-code median income, race, age and year of hospitalization. Primary outcomes included advanced stage at presentation, emergency admission, visceral metastatic involvement, disseminated metastasis, inpatient mortality, discharge disposition and length of stay (LOS). Survey-weighted multivariable logistic regression and linear regression models were performed, adjusting for age, race, insurance status and income quartile. **Results:** The most consistent predictors of delayed presentation and increased hospitalization severity were insurance status and race. Compared to private insurance, women with Medicare and Medicaid were 67% and 32% more likely to present with advanced stage ($p<0.001$), and over 3-fold and 2.5-fold more likely to present emergently ($p<0.001$). They were also significantly more likely to have visceral metastasis ($p<0.001$), have increased severity of illness ($p\leq 0.023$), require non-home discharge ($p<0.001$), and require longer LOS (+0.8–0.9 days, $p<0.001$). Medicare was associated with higher inpatient mortality ($p=0.005$). Black race was independently associated with advanced stage, emergency presentation, visceral metastasis, inpatient mortality (all $p<0.001$), and longer LOS (+0.79 days, $p<0.001$). Younger age was associated with advanced stage and visceral metastasis ($p<0.001$). Higher ZIP-code income quartiles were associated with lower odds of emergency presentation ($p<0.001$), but not improved inpatient outcomes. Year of diagnosis was not significant across models. **Conclusions:** Among young women hospitalized with colorectal cancer, insurance status and race were strongly associated with advanced disease, emergency presentation, metastatic burden and greater hospitalization severity, independent of ZIP-code income. These disparities did not show improvement over time, highlighting system-level barriers. Targeted strategies to improve access and earlier recognition in high-risk populations of young women is required to improve oncologic outcomes. Research Sponsor: None.

Shifting dietary drivers of colorectal cancer mortality in the United States: A 33-year Global Burden of Disease analysis.

Jennifer Kate Beckerman, Charbel Fadi Matar, Giorgi Sabakhtarishvili, Eunhee Choi; George Washington University School of Medicine and Health Sciences, Washington, DC; The George Washington University, Washington, DC; The George Washington University Hospital, Washington, DC

Background: Early-onset colorectal cancer (EOCRC; ages 15–49 years) mortality is increasing in the United States. However, temporal changes in diet-attributable risk factors contributing to EOCRC mortality remain poorly characterized. Using three decades of Global Burden of Disease (GBD) data, we examined shifts in dietary risk factors contributing to EOCRC mortality to identify emerging targets for primary prevention. **Methods:** We conducted a retrospective population-based analysis of U.S. estimates from the GBD 2023 study (1990–2023). Age-standardized death rates (ASDR), years of life lost (YLLs), and disability-adjusted life years (DALYs) attributable to major dietary risk factors (high processed meat, high red meat, low whole grain, low fiber, low calcium, and low milk intake) were assessed among EOCRC. Period-specific percent changes (1990–1999, 2000–2009, 2010–2019, 2020–2023), rank-order transitions, and sex-stratified patterns were examined. All estimates were derived using GBD cause-of-death ensemble modeling and include 95% uncertainty intervals. **Results:** In 1990, low whole grain intake was the leading diet-attributable risk factor for ASDR (0.44 per 100,000), followed by red meat (0.40) and processed meat (0.34). Although dietary inadequacy-related risks increased early (low whole grain DALYs +338.9% and YLLs +311.1% in 1990–1999), these burdens declined substantially after 2000. In contrast, processed meat consumption demonstrated persistent and increasingly dominant associations with mortality, with DALYs rising by +430.8%, +223.1%, +94.8%, and +15.9% across successive periods. By 2023, processed meat accounted for the highest ASDR (0.55), surpassing low whole grain (0.53) and red meat (0.49). Sex-stratified analyses showed processed meat emerged as the leading diet-attributable risk among males by 2010 and rose from third to second among females, narrowing the gap with low whole grain intake. **Conclusions:** Over 33 years, diet-attributable EOCRC mortality in the US has undergone a rank-order transition from dietary inadequacy toward processed meat consumption, particularly among males and increasingly among females. The persistence and dominance of processed meat-attributable burden highlight a critical, modifiable lifestyle risk factor and underscore an urgent opportunity for targeted, age- and sex-specific primary prevention strategies aligned with colorectal cancer prevention recommendations. Research Sponsor: None.

Age-standardized early-onset colorectal cancer death rates (per 100,000 population) attributable to dietary risk factors in the United States, 1990–2023.					
	1990	2000	2010	2020	2023
Red Meat	0.40	0.48	0.47	0.50	0.49
Processed Meat	0.34	0.46	0.50	0.55	0.55
Low Fiber	0.02	0.03	0.02	0.02	0.02
Low grain	0.44	0.53	0.52	0.54	0.53
Low Ca	0.09	0.09	0.09	0.10	0.09
Low milk	0.26	0.31	0.31	0.29	0.28

Association of pre-diagnosis primary care utilization with metastatic disease, treatment adherence, and mortality in colorectal cancer.

Hieu Nguyen, Edmund Men Qiao, Sakshith Reddy Chintala, Kylie Margaret Morgan, Daniel Sabater Minarim, Benjamin Jacobs, Elizabeth Anne-Marie Duran, Joshua Demb, James Murphy, Matthew P. Banegas, Brent S. Rose; Department of Radiation Medicine and Applied Sciences, University of California, San Diego, La Jolla, CA; University of California, San Diego, La Jolla, CA; University of California, San Diego Health, La Jolla, CA; CHEER, UCSD Health, La Jolla, CA; Center for Health Equity Education and Research, UCSD Health, La Jolla, CA; University of California, San Diego, San Diego, CA; UC San Diego School of Medicine, La Jolla, CA

Background: In addition to timely evaluation and screening in patients with colorectal cancer (CRC), routine primary care provider (PCP) engagement may improve CRC survival outcomes through earlier diagnosis and increased treatment adherence. We evaluated the association between pre-diagnostic PCP utilization and metastatic disease at diagnosis, cancer-specific mortality (CSM), and cancer treatment adherence. **Methods:** Using the Surveillance, Epidemiology, and End Results (SEER)-Medicare database, we conducted a retrospective cohort study of adults aged 68–75 diagnosed with CRC between 2010–2017. PCP visits in the three years preceding diagnosis were categorized as none (0 visits), occasional (1–2), or annual (3). Multivariable logistic regression models evaluated associations between PCP use and metastatic CRC at diagnosis, as well as treatment adherence. Locally advanced (Stage III) treatment adherence was defined as curative therapy ≤ 1 year from diagnosis, and metastatic treatment adherence was defined as systemic therapy ≤ 6 months from diagnosis. A competing risk Cox proportional hazards model evaluated cancer-specific mortality (CSM), with non-cancer death as a competing event. **Results:** Of 18,604 patients with CRC, 12.9% had no prior PCP visits, 48.6% had occasional visits, and 38.5% had annual visits. Compared to patients with no pre-diagnostic PCP use, occasional and annual PCP visits were respectively associated with 43% and 57% lower odds ($p < 0.001$) of metastatic disease at diagnosis and 48% and 57% lower odds ($p < 0.001$) of CSM (Table 1). Among patients with locally advanced CRC, occasional and annual PCP use were associated with 64% and 150% higher odds of receiving curative treatment, respectively (Table 1). Similarly, occasional and annual PCP use in patients with metastatic CRC were associated with 2-fold and 3-fold higher odds, respectively, of receiving systemic treatment (Table 1). **Conclusions:** Primary care utilization prior to CRC diagnosis is significantly associated with lower odds of metastatic disease, lower risk of CSM, and higher odds of treatment adherence, with the highest effects observed with annual PCP utilization. Increasing PCP engagement is an essential strategy to improving outcomes in patients with CRC. Research Sponsor: None.

Multivariate estimates for the effect of pre-diagnostic primary care provider (PCP) utilization prior to cancer diagnosis.

	Metastatic Disease at Diagnosis OR, [95% CI], p-value	Cancer-Specific Mortality sHR, [95% CI], p-value	Received Treatment (Locally advanced CRC) OR, [95% CI], p-value	Received Treatment (Metastatic CRC) OR, [95% CI], p-value
1-2 PCP visits (Occasional)	0.57 [0.51-0.64], $p < 0.001$	0.52 [0.48-0.56], $p < 0.001$	2.64 [2.10-3.30], $p < 0.001$	2.08 [1.70-2.56], $p < 0.001$
3+ PCP visits (Annual)	0.43 [0.40-0.47], $p < 0.001$	0.43 [0.40-0.47], $p < 0.001$	3.50 [2.76-4.24], $p < 0.001$	2.90 [2.31-3.64], $p < 0.001$

Bowel function after sphincter-preserving treatment with neoadjuvant therapy for low rectal cancer.

Yuanshan Chen, Qiyan Qin, Yikan Cheng; The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, China; The Sixth Affiliated Hospital of Sun Yet-sen University, Guangzhou, China; The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

Background: Neoadjuvant therapy (NAT) is important for locally advanced rectal cancer, including neoadjuvant chemoradiotherapy (nCRT) and neoadjuvant chemotherapy alone (nCT). Based on the tumor response, sphincter-preserving treatment such as low anterior resection (LAR) or watch and wait (WW) strategy can be implemented. The effects of these therapy combinations on functional outcomes for low rectal cancer remain unclear. **Methods:** We conducted a retrospective study recruiting patients who were treated at The Sixth Affiliated Hospital of Sun Yat-sen University between 2010 and 2023. Patients who underwent sphincter-preserving treatment after NAT for low rectal cancer with no distant metastasis were eligible. Low rectal cancer was defined as the tumor height no more than 5 cm from the anal verge. Patients with multiple primary carcinoma or familial adenomatous polyposis were excluded. The incidence of low anterior resection syndrome (LARS) was assessed using the LARS score. Oncological outcomes included overall survival (OS), disease-free survival (DFS), and stoma-free survival (SFS). Functional and oncological outcomes were evaluated based on Wilcoxon signed-rank test and Kaplan-Meier survival analysis. The difference of baseline characteristics in different treatment groups was analyzed using propensity scores with inverse probability treatment weighting (IPTW). **Results:** We enrolled 590 patients: 49 in nCRT+WW group, 181 in nCT+LAR group and 360 in nCRT+LAR group. Median follow-up was 3.4 years (IQR 2.8-4.4), 5 years (IQR 4.3-7.1) and 7.3 years (IQR 4.8-9.3), respectively. After IPTW, all baseline characteristics were similar in the three groups. 3-year OS was 91.0% (95% CI 81.6-100.0) for nCRT+WW group, 89.3% (84.5-94.5) for nCT+LAR group, 93.2% (90.7-95.7) for nCRT+LAR group. 3-year DFS was 62.5% (95% CI 45.6-85.7), 71.0% (64.1-78.6) and 77.5% (77.3-81.9), respectively. There was no differences in oncological outcomes. The incidence of major LARS in the three groups was 0% (0/18.6), 34.1% (35.2/103.2) and 45.9% (104.2/226.8). 3-year SFS without IPTW was 95.2% (20/21) for nCRT+WW, 91.0% (152/167) for nCT+LAR, and 79.7% (244/306) for nCRT+LAR. **Conclusions:** This retrospective study shows similar oncological outcomes in the three sphincter-preserving strategies for low rectal cancer, while nCRT+WW presented with superior bowel function. Functional outcomes are inversely correlated to the intensity of local therapy. Research Sponsor: None.

Outcomes for the three therapy combinations after IPTW.			
	nCRT+WW	nCT+LAR	nCRT+LAR
Tumor Height, cm	2.71 (1.20)	3.74 (0.83)	3.60 (0.91)
Clinical Stage III, %	75.4	69.1	70.3
3-year OS, %	91.0	89.3	93.2
3-year DFS, %	62.5	71.0	77.5
Major LARS, %	0	34.1	45.9
Minor LARS, %	22.5	22.9	24.1
None LARS, %	77.5	43.0	30.0
3-year SFS*, %	95.2	91.0	79.7

*Without IPTW.

Genomic profiling to define molecular drivers of colorectal neuroendocrine carcinoma subtypes.

Jenny Xue, Efsevia Vakiani, Henry S. Walch, Jay Shi, Jinru Shia, Karuna Ganesh, Rona Yaeger; Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY; Memorial Sloan Kettering Cancer Center, New York City, NY

Background: Neuroendocrine carcinoma (NEC) is a rare and aggressive subtype of colorectal cancer (CRC), often arising in association with poorly differentiated adenocarcinoma. Two histologic subtypes, small cell NEC (SCNEC), and large cell NEC (LCNEC), have been described; however, how these subtypes differ, and whether they share molecular origins with the adenocarcinoma component in mixed adenocarcinoma and neuroendocrine carcinoma (MANEC) tumors, remain unclear. Better characterization of the genomic alterations driving NECs is needed to clarify disease biology and improve outcomes. **Methods:** We identified 125 patients with NEC of the colon and rectum who received care at Memorial Sloan Kettering Cancer Center. All patients underwent tumor profiling using the institutional targeted sequencing platform MSK-IMPACT. For 11 patients with MANEC, the adenocarcinoma and NEC components were sequenced separately. **Results:** Among 125 patients, 33 had SCNEC, 50 had LCNEC, and 42 had histologic features intermediate between SCNEC and LCNEC. 62% of patients presented with stage IV disease, and NEC was enriched at metastatic sites in MANEC cases. Clinical outcomes were poor across all groups, with a median survival of 11 months for stage IV patients (9.5m for SCNEC, 11m for LCNEC). SCNEC was more commonly observed in the rectum and genomically characterized by frequent *RB1* loss (70%), with a smaller subset harboring *PTEN* loss (24%). Notably, *TP53* mutations were identified in 58% of the cases, lower than the frequency observed in sporadic advanced CRC. In contrast, LCNEC was more often right sided, associated with an adenocarcinoma component and genomically enriched for *MYC* amplification (28%) and *BRAF* mutations (38%). We found that *MYC* amplification frequently occurred on extrachromosomal DNA, as confirmed by both FISH and shallow whole genome sequencing. Based on genomic alterations, 21 of the 42 (50%) unclassified cases could be assigned a histologic subtype. A subset of NECs lacked known neuroendocrine associated genomic alterations and are being investigated further. In 11 MANEC cases with separately sequenced components, *RB1* loss and *MYC* amplification were restricted to the neuroendocrine component, supporting a causal role in neuroendocrine differentiation and clonal evolution from adenocarcinoma. Across the cohort, *PIK3CA* (6%) and *SMAD4* (9%) mutations were less frequent than expected and were absent in the NEC component of MANEC cases. *DLL3* expression was evaluated in a small subset and was positive in some SCNECs but not in LCNEC. **Conclusions:** SCNEC and LCNEC represent clinically and genomically distinct subtypes of colorectal NEC. For NECs that cannot be classified based on histology alone, genomic profiling should be used to aid classification. Ongoing studies aim to validate our genomic findings above and to model the biology of NEC to identify more effective therapeutic strategies. Research Sponsor: U.S. National Institutes of Health; 5T32CA009207.

Defining prostaglandin-driven dysregulation in *PIK3CA*-mutant colorectal cancers: A real-world multi-omic analysis.

Andrew M. Gaya, M.V. Chandrakanth, Ashish Upadhyay, Roopesh Narayanachary, Shivam Shingla, Sewanti Atul Limaye, Darshana Suresh Patil, Rajan Datar, Aakriti Datta, Dadasaheb Akolkar, Stefan Schuster, Sourabh Radhakrishnan, Dr Sampath Kumar, Dr Debajyoti Maaji, Aditya V. Shreenivas, Tanmoy Mondal; Cromwell Hospital, London, United Kingdom; Rabindranath Tagore International Institute of Cardiac Sciences, Kolkata, India; Fortis Hospital, Kolkata, India; Sparsh Hospital, Bangalore, India; S.L. Raheja, Mumbai, India; Medical & Precision Oncology, Clinical and Translational Oncology Research, Sir HN Reliance Foundation, Mumbai, India; Datar Cancer Genetics, Nashik, India; Kasturba Medical College, Manipal, India; Datar Cancer Genetics Europe GmbH, Bayreuth, Germany; Amrita Institute of Medical Sciences, Kochi, India; New Medd Diagnostics, Bangalore, India; Desun Hospital, Kolkata, India; City of Hope National Medical Center, Duarte, CA; Manipal Hospitals, Kolkata, India

Background: *PIK3CA* mutations occur in a meaningful subset of colorectal cancers (CRC) and have been associated with improved clinical outcomes in patients receiving aspirin and celecoxib. *PIK3CA* activation has been linked to upregulation of *PTGS2* and downstream prostaglandin E2 signaling, promoting tumor-associated inflammation, angiogenesis, and immune suppression. Aspirin-mediated inhibition of prostaglandin synthesis may therefore counteract this biology in *PIK3CA*-mutant CRC, although the underlying molecular mechanisms remain incompletely characterized. **Methods:** A total of 823 CRC tumor samples underwent DNA-based next-generation sequencing, with matched whole-transcriptome sequencing (20,802 genes) available for 263 tumors. *PIK3CA* mutation prevalence, hotspot distribution, and co-mutation patterns were evaluated. A predefined prostaglandin-inflammation gene signature (*PTGS2*, *PTGES*, *PLA2G4A*, *IL6*, *STAT3*, *PTGER4*, *VEGFA*, *IDO1*) was assessed ($\log_2$ fold change >2). Coordinated signature activation was quantified. **Results:** *PIK3CA* mutations were detected in 12.8% (105/823) of CRCs and were more frequent in right than left-sided tumors (15.2% vs 11.1%). Among *PIK3CA*-mutant tumors, 25.7% were *KRAS/NRAS/BRAF* wild type (WT), while *KRAS* co-mutation predominated (65.7%); *NRAS* and *BRAF* co-mutations were rare (1.9% and 5.7%), as summarized in the Table. *ERBB2* alterations were rare in *PIK3CA*-mutant tumors (4.8%) and in *KRAS/NRAS/BRAF*-mutant tumors (3.2%), while they were enriched in the *KRAS/NRAS/BRAF* WT subgroup (8.9%). Among *PIK3CA*-mutant tumors, key prostaglandin biosynthesis genes *PTGS2*, *PTGES*, and *PLA2G4A* were overexpressed in 8.8% (3/34), while downstream inflammatory and immune-modulatory genes including *IL6*, *STAT3*, *IDO1*, and *CD274* were overexpressed in 11.8% (4/34). Prostaglandin-inflammation signature activation was more frequent in *KRAS* WT than *KRAS*-co-mutant *PIK3CA* tumors (57.1% [4/7] vs 51.9% [14/27]). Among microsatellite-stable (MSS) tumors, 47.6% (10/21) showed signature activation. Tumors with combined *PIK3CA* mutation and prostaglandin pathway activation showed enrichment of inflammatory, angiogenic, and epithelial-mesenchymal transition-related programs. **Conclusions:** *PIK3CA*-mutant CRC represents a biologically distinct subset characterized by coordinated activation of prostaglandin-driven inflammatory and immune-modulatory pathways. These features provide a mechanistic rationale for the reported aspirin benefit in *PIK3CA*-mutant CRC and support integrated genomic-transcriptomic profiling to guide biomarker-driven therapeutic strategies. Research Sponsor: None.

Prevalence of *PIK3CA* alterations and co-mutations in CRC.

Biomarkers	Prevalence (%; n=105)
<i>PIK3CA</i> mutation (overall)	12.8 (105/823)
E545K	21.9
E542K	19
H1047R	16.2
H1047L	6.7
Q546K	5.7
<i>PIK3CA</i> + <i>KRAS</i>	65.7
<i>PIK3CA</i> + <i>NRAS</i>	1.9
<i>PIK3CA</i> + <i>BRAF</i>	5.7
<i>PIK3CA</i> + <i>KRAS/NRAS/BRAF</i> WT	25.7

Divergent transcriptomic signatures and microenvironmental markers of *KRAS* and *BRAF* mutations in colorectal cancer: A multi-omics integrative analysis.

Muzammil Shaikh, Pritam Kataria, Sewanti Atul Limaye, Andrew M. Gaya, Priya Tiwari, Aditya V. Shreenivas, Ashok K. Vaid, Amit Dilip Bhatt, Darshana Suresh Patil, Sachin Apurwa, Vinayak Rao, Rajan Datar, Ninad Jadhav, Anantbhushan Ranade, Darshit Kalpeshkumar Shah, Favaz Ali, Ankur Nandan Varshney, Nitesh Rohatgi; Nanavati Max Super Speciality Hospital, Mumbai, India; Sir H. N. Reliance Foundation Hospital and Research Centre, Mumbai, India; Medical & Precision Oncology, Clinical and Translational Oncology Research, Sir HN Reliance Foundation, Mumbai, India; Cromwell Hospital, London, United Kingdom; Artemis Hospitals, Delhi, India; City of Hope National Medical Center, Duarte, CA; Medanta, The Medicity, Gurugram, India; Avinash Cancer Clinic, Pune, India; Datar Cancer Genetics, Nashik, India; VPS Lakeshore Medial Centre, Kozhikode, India; Medanta, The Medicity, Noida, India; Fortis Memorial Research Institute Gurugram, Gurugram, India

Background: *KRAS* and *BRAF* mutations are critical drivers in colorectal cancer (CRC), acting as key nodes in the MAPK signaling pathway. While their genomic prevalence is well-documented, the specific transcriptomic programs they trigger and how these programs differ between *KRAS* and *BRAF* variants remain a subject of intense translational interest. This study utilizes a multi-omics approach to define mutation-specific signatures that could inform personalized therapeutic strategies. **Methods:** We performed an integrated analysis of SNV/Indel data and gene expression profiles from 192 CRC patients. Patients were stratified into *BRAF*-mutant (n=20), *KRAS*-mutant (n=102), and MAPK-wild-type (WT, n=64) groups. Frequency was calculated as the percentage of unique samples mutated per gene. Differential expression analysis (DEA) was utilized to identify significant ($p < 0.05$) gene expression changes specific to each driver mutation. **Results:** The most frequently mutated genes were *TP53* (79.2%), *APC* (56.8%), and *KRAS* (53.1%). *BRAF* mutations were identified in 10.4% of the cohort. *KRAS*-mutant tumors exhibited a specific upregulation of *SPP1* (osteopontin) and *TGFBI*. These markers are associated with extracellular matrix remodeling and TGF- β signaling, suggesting that *KRAS* mutations may actively contribute to an immune-excluded tumor phenotype. *BRAF*-mutant CRC was characterized by a distinct signature involving *ABI3BP* upregulation and a profound down-regulation of *CTNNB1* ($p < 0.00001$). Additionally, a cluster of small nucleolar RNAs (*SNORA2B*, *SNORA9*) was significantly elevated, pointing toward altered ribosome biogenesis or non-coding RNA regulation unique to the *BRAF*-mutant subset. While both mutations activate the MAPK pathway, the downstream transcriptomic output is significantly divergent, with *KRAS* favoring myeloid-recruiting signals (*SPP1*) and *BRAF* favoring structural and RNA-processing alterations. **Conclusions:** Our multi-omics integration reveals that *KRAS* and *BRAF* mutations in CRC are not transcriptomically redundant. The discovery of *SPP1* as a *KRAS*-associated marker and *CTNNB1* as a *BRAF*-linked marker provides novel avenues for targeted therapy and patient stratification. Specifically, *KRAS*-mutant patients might benefit from therapies targeting the *SPP1*-TGF- β axis in combination with standard care. Research Sponsor: None.

Development and validation of a National Database–derived nomogram for predicting postoperative survival in colorectal cancer.

Mohyeddine El Sayed, Calvin Widholm, Elizabeth Goodwin Hill, Colleen Donahue, Sassine Youssef, Virgilio George, Maggie Westfal, Thomas Curran, Raymond N. DuBois; Medical University of South Carolina, Charleston, SC; The Medical University of South Carolina, Charleston, SC; Division of Colorectal Surgery, Medical University of South Carolina, Charleston, SC; MUSC Hollings Cancer Center, Charleston, SC

Background: Prognosis after curative-intent surgery for colorectal cancer remains heterogeneous and incompletely explained by TNM staging alone. Existing prognostic tools often exclude important demographic, clinical, and biologic factors. Improved risk stratification is needed to support individualized postoperative prognostication. **Methods:** Using the National Cancer Database (NCDB), data from 88,696 patients diagnosed between 2018–2019 were used to develop and internally validate five prognostic models. All models were extensions of the MSK colon cancer nomogram and were fit using the full cohort. The full model incorporated all MSK predictors plus additional demographic, tumor, and treatment variables including perineural invasion and microsatellite instability status. Reduced models included MSK predictors and select variable subsets. Cox proportional hazards regression was used to estimate 5-year (5y) overall survival. Calibration was assessed by comparing deciles of predicted vs observed 5y Kaplan–Meier survival probabilities (expected-to-observed (E/O) ratios). Discrimination was evaluated using 5y area under the time-dependent receiver operating characteristic curve (AUC). Bias-corrected calibration curves and AUCs were generated to assess model generalizability to external populations. Model performance was compared directly with the MSK nomogram by comparing 5y AUCs calculated using a random sample of 1,000 NCDB-cohort patients. Category-free net reclassification improvement (NRI) was also calculated for patients with known vital status at 5y. **Results:** Calibration and discrimination were similar across all models. In the full model, E/O ratios demonstrated excellent calibration, with median E/O = 1.01 (range = 0.82–1.08). Full model discrimination was excellent with 5y AUC = 0.787 (95% CI, 0.782–0.793). Bias-corrected calibration curves and AUCs indicated stable performance supporting generalizability. In our 1,000 patient random sample, the full model 5y AUC was 0.822 (95% CI, 0.779–0.866), compared with 0.799 (95% CI, 0.753–0.844) for the MSK nomogram, with no statistically significant difference ($p = 0.13$). In our 1,000 patient NCDB sample, 397 patients had known 5y vital status (258 deaths, 139 alive, 603 censored prior to 5y) with the full model showing improved overall, event and nonevent discrimination compared with the MSK nomogram (overall 5y NRI = 0.35, event NRI = 0.12, and nonevent NRI = 0.24). **Conclusions:** We developed a postoperative survival nomogram for colorectal cancer that demonstrated good calibration and discrimination and meaningfully improved risk classification compared with the MSK model. Integration of additional routinely available variables enables more individualized postoperative prognostication. Research Sponsor: None.

Molecular differences between early- and later-onset colorectal cancer in a Chilean cohort: A retrospective MSI and NGS-based analysis.

Tamara Saumann, Gonzalo Carrasco-Avino, David Reyes Coroceo, Luis Diaz Macias, Francisco Javier Perez, Gabriela Jacqueline Mena Ramos, Claudio Salas, Catalina Moya Pinto, Jaime Anabalon, Cristobal Tomas Sanhueza Condell; Facultad de Medicina Clinica Alemana Universidad del Desarrollo, Santiago, Chile

Background: The incidence of early-onset colorectal cancer (EOC) is increasing worldwide; however, molecular data from Latin American populations remain scarce. We compared molecular alterations, including microsatellite instability (MSI) status and selected next-generation sequencing (NGS)-derived gene alterations, between EOC and later-onset colorectal cancer (LOC) in a Chilean cohort. **Methods:** We conducted a retrospective analysis of patients diagnosed with colorectal cancer with MSI assessment and/or NGS testing available between March 2017 and September 2025 at a private hospital in Chile. MSI status was determined by immunohistochemistry and/or PCR. In-house NGS panels were analyzed. Clinical variables included age at diagnosis, sex, and tumor location. EOC was defined as diagnosis <50 years and LOC as ≥50 years. Molecular alterations were compared using Fisher exact test, reporting odds ratios (OR) with Benjamini–Hochberg false discovery rate (FDR) correction. **Results:** A total of 324 patients were included (EOC n=66; LOC n=258). Median age was 42.6 years in EOC and 66.5 years in LOC. Tumor sidedness was comparable between groups, with a predominance of left-sided tumors in both EOC (54.5%) and LOC (61.2%). MSI status was available in 310 patients; MSI-H prevalence was 10.8% in EOC and 15.1% in LOC (OR 0.68, 95% CI 0.29–1.59; p=0.43). NGS denominators varied by gene according to panel coverage. No individual gene showed statistically significant differences after FDR correction. Pathway-level trends were observed (Table 1). In the WNT pathway, APC alterations were more frequent in EOC (83.3% vs 52.2%; OR 4.60; p=0.059). In the MAPK pathway, KRAS alterations were numerically higher in LOC (55.2% vs 37.5%; OR 0.49; p=0.13), while BRAF alterations were more frequent in EOC (16.7% vs 8.3%; OR 2.20; p=0.29). In the PI3K pathway, PIK3CA (29.2% vs 15.6%; OR 2.22; p=0.12) and PTEN (8.3% vs 2.1%; OR 4.27; p=0.15) alterations trended higher in EOC. TP53 alterations were highly prevalent and similar across groups. **Conclusions:** In this Chilean cohort, EOC and LOC showed similar MSI prevalence and largely overlapping molecular profiles. Although no gene-level differences remained significant after multiple-testing correction, pathway-specific trends suggest increased WNT and PI3K alterations in EOC and higher MAPK signaling in LOC. These findings highlight the need for larger, uniformly sequenced studies in Latin American populations. Research Sponsor: None.

Selected pathway-specific molecular alterations.					
Category	Gene	EOC n/N (%)	LOC n/N (%)	OR	p
WNT	APC	10/12 (83.3)	36/69 (52.2)	4.60	0.059
	KRAS	9/24 (37.5)	53/96 (55.2)	0.49	0.13
MAPK	BRAF	4/24 (16.7)	8/96 (8.3)	2.20	0.29
	PIK3CA	7/24 (29.2)	15/96 (15.6)	2.22	0.12
PI3K	PTEN	2/24 (8.3)	2/96 (2.1)	4.27	0.15
	ATM	1/24 (4.2)	5/96 (5.2)	0.80	1.00
DDR	SMAD4	3/24 (12.5)	7/96 (7.3)	1.81	0.47
TGF-β					
Cell cycle	TP53	15/24 (62.5)	62/96 (64.6)	0.91	1.00

Use of KMT2 family mutations to define a distinct epithelial-high, stromal-depleted, and interferon-active gene expression state in colorectal cancer.

Songwit Payapwattanawong, Jessica Lal, Yixin Xu, Kangyu Lin, Emerik Osterlund, Cynthia Yeung, Berta Martin, Kathryn Aziz, Kristin Alfaro, Giulia Maddalena, Guglielmo Vetere, Arvind Dasari, Christine Parseghian, Jason Willis, John Paul Y.C. Shen, Michael J. Overman, Kanwal Pratap Singh Raghav, Van K. Morris II, Kunal Rai, Scott Kopetz; Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Gastrointestinal Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Gastrointestinal (GI) Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The *KMT2A–D* (MLL1–4) family of H3K4 methyltransferases are critical epigenetic regulators of enhancer landscapes and cell identity. At least one of the genes is mutated in 20–25% of colorectal cancer. Their role in shaping the tumor microenvironment (TME) remains distinct from their established roles in leukemia, where they are better described. We tested whether *KMT2* mutations are associated with specific immune/stromal phenotypes that could inform therapeutic stratification. **Methods:** We analyzed a retrospective institutional CRC cohort using targeted NGS ($n = 2,267$; 565 *KMT2*-mutant [MUT], 1,702 wild-type [WT]) and a transcriptomic subset with matched RNA-seq ($n = 353$; 73 MUT, 280 WT) from primary and metastatic specimens. Differential expression (DESeq2) and pathway enrichment (Hallmark GSEA) compared MUT vs. WT, adjusting for batch and tissue site. VST-based module z-scores (cancer associated fibroblast [CAF]/stroma, epithelial, IFN response, cell-cycle) were computed. xCell, EPIC, CIBERSORTx, and ESTIMATE scores were analyzed by linear regression on z-scored outcomes (MUT vs WT) adjusted for batch and tissue site; Benjamini–Hochberg false discovery rate (FDR). β denotes the adjusted mean difference in standardized score (MUT–WT) in SD units. Overall survival was assessed by Cox proportional hazards models. **Results:** *KMT2*–MUT tumors demonstrate a unique tumor biology, with higher epithelial ($\beta = 0.30$, FDR = 0.011), IFN response ($\beta = 0.24$, FDR = 0.021), and cell-cycle ($\beta = 0.24$, FDR = 0.021) modules with lower CAF/stroma ($\beta = -0.29$, FDR = 0.011). Consistent with this, GSEA showed enrichment of IFN- α/γ and proliferation programs (MYC/E2F/G2M) and depletion of epithelial–mesenchymal transition (EMT), myogenesis, and apical junction pathways (FDR < 0.05). TME composition tools demonstrated lower stromal content [lower CAFs (EPIC, $\beta = -0.288$, FDR = 0.102), lower fibroblasts/stroma scores (xCell, $\beta \approx -0.36/-0.35$, FDR = 0.079), and trend toward lower StromalScore (ESTIMATE, $\beta = -0.24$, FDR = 0.20)], and trends to higher Th2 (xCell, $\beta = 0.40$, FDR = 0.059) and NK cells (xCell, $\beta = 0.38$, FDR = 0.079). After adjusting for age, sex, ECOG performance status, primary tumor site, stage, RAS and *BRAF* mutation status, and MSI status, overall survival did not differ significantly between tumors with and without *KMT2* family mutations, although there was a trend toward improved outcomes (HR 0.85, 95% CI 0.70–1.00; $p = 0.078$). **Conclusions:** *KMT2* family mutations in CRC characterize a tumor subset with retained epithelial identity, active proliferation, and interferon signaling, but markedly reduced stromal infiltration and EMT programs. This distinct biology suggests *KMT2* loss may impede the acquisition of aggressive mesenchymal features, highlighting a potential biomarker for stromal-modulating or immune-based therapies. Research Sponsor: None.

Phase 2/3 trial of pumitamig (PD-L1 × VEGF-A bsAb) plus chemotherapy versus bevacizumab plus chemotherapy in previously untreated, unresectable, or metastatic colorectal cancer (ROSETTA CRC-203).

Tiago Biachi de Castria, Ian Chau, Elena Elez, Akihito Kawazoe, Heinz-Josef Lenz, Sara Lonardi, Rui-Hua Xu, Laith I. Abushahin, Lixian Jin, Stephen McCraith, Amanda Cruz, Bonnie Wang, Lishi Zhang, Suayib Yalcin; Moffitt Cancer Center, Tampa, FL; The Royal Marsden NHS Foundation Trust, London, United Kingdom; Vall d'Hebron University Hospital and Institute of Oncology (VHIO), Barcelona, Spain; National Cancer Center-Hospital East, Kashiwa, Japan; University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; Istituto Oncologico Veneto IOV-IRCCS, Padua, Italy; Sun Yat-sen University Cancer Center, Guangzhou, China; Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX; Bristol Myers Squibb, Princeton, NJ; Hacettepe University Cancer Institute, Ankara, Turkey

Background: Microsatellite-stable/mismatch repair-proficient metastatic colorectal cancer (mCRC) demonstrated limited benefit from immune checkpoint inhibition and is treated with first-line standard chemotherapy with/without biologic agents, such as anti-VEGF or anti-EGFR therapy. Pumitamig (BNT327/BMS986545) is an investigational bispecific antibody engineered to simultaneously target both PD-L1 and VEGF-A within the tumor and tumor microenvironment, a dual mechanism intended to enhance antitumor immunity and inhibit angiogenesis. Pumitamig plus chemotherapy has shown encouraging efficacy and manageable safety in patients (pts) with solid tumors (Cheng Y, et al. J Thorac Oncol 2025;20[suppl 1]. Abstract 301P; Schmid P, et al. SABCs 2025. Abstract PS1-13-25). This phase 2/3 trial aims to investigate the safety and efficacy of pumitamig and establish if it improves clinical outcomes when added to chemotherapy versus current standard of care in pts with previously untreated mCRC. **Methods:** ROSETTA CRC-203 is a global, randomized, blinded phase 2/3 study. Pts aged ≥ 18 years, with ECOG PS 0-1, with previously untreated, unresectable, or mCRC, no microsatellite instability-high/mismatch repair-deficient biomarkers, no BRAF V600E mutation and measurable disease per RECIST v1.1 are eligible. Key exclusion criteria include untreated central nervous system metastases, significant cardiovascular disease, recent or active malignancy, and prior systemic therapy with checkpoint inhibitors or chemotherapy. Pts in the Phase 2 dose-optimization part of the study will be randomized 1:1:1 to receive pumitamig low or pumitamig high dose + FOLFOX (Q2W)/FOLFIRI (Q2W) or bevacizumab + FOLFOX (Q2W)/FOLFIRI (Q2W). The primary endpoint is objective response rate (ORR) by RECIST v1.1 per investigator assessment, with progression-free survival (PFS), and duration of response (DOR) as secondary endpoints. In phase 3, eligible pts will be randomized 1:1 to receive pumitamig at the recommended phase 3 dose + FOLFOX (Q2W)/FOLFIRI (Q2W)/CAPOX (Q3W) or bevacizumab + FOLFOX (Q2W)/FOLFIRI (Q2W)/CAPOX (Q3W), until disease progression or unacceptable toxicity. The primary endpoint is PFS by RECIST v1.1 per blinded independent central review. Overall survival, ORR, and DOR are secondary endpoints. Safety will be monitored throughout the study according to CTCAE v5.0. Recruitment is ongoing. ClinicalTrials.gov ID: NCT07221357. Clinical trial information: NCT07221357. Research Sponsor: Bristol Myers Squibb.

Phase II trial of pembrolizumab in combination with odetiglucan for patients with metastatic colorectal adenocarcinoma with liver-predominant disease.

William J. Chapin, Nadia Cenou, Devora Delman, Jennifer Rachel Eads, Michele Manley, Kim Anna Reiss, Megan Sackey, Ursina R. Teitelbaum, Jennifer Walsh, Gregory Lawrence Beatty, Mark H. O'Hara; Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA; Abramson Cancer Center at the University of Pennsylvania, Philadelphia, PA; University of Pennsylvania, Philadelphia, PA

Background: Liver metastases are associated with resistance to immune checkpoint inhibitors in patients with mismatch repair proficient (MMRp) metastatic colorectal cancer (mCRC). (Beiter JCO 2025) Odetiglucan is a pathogen associated molecular pattern (PAMP) that modulates the tumor microenvironment and may enhance the activity of immune checkpoint inhibition. In syngeneic colon cancer mouse models, the combination of odetiglucan and PD-1/PD-L1 inhibition was associated with a larger proportion of tumor-free mice than either treatment alone. (Jonas Cancer Res. 2017; Fraser Cancer Res. 2016; Chan Frontiers Oncol. 2020) In a mouse model of pancreatic cancer liver metastases, odetiglucan reprogrammed liver-resident macrophages to stimulate tumor-specific T-cell responses, which was associated with reduced cancer cell proliferation and increased sensitivity to anti-PD-1 therapy. (Thomas Nat Commun. 2023) In a clinical trial of anti-PD-1 therapy plus odetiglucan in patients with triple negative breast cancer, tumor regression was observed in 56% of liver lesions classified as target lesions, with one patient experiencing complete regression of both target liver lesions, which remained undetectable after more than 70 weeks of treatment. (Stopeck J Immun. 2025). **Methods:** We are performing a single-center, investigator-initiated, single-arm phase II clinical trial with a Simon two-stage mini-max design of the combination of pembrolizumab with odetiglucan in patients with liver-predominant, MMRp mCRC who have experienced disease progression on standard therapies (3L+ setting). Treatment consists of intravenous infusion of odetiglucan (4mg/kg) and pembrolizumab on day 1 of a 21-day cycle. Patients with prior exposure to immunotherapy or odetiglucan, peritoneal metastases, symptomatic lung or bony metastases, autoimmune conditions requiring systemic immunosuppression, or a history of pneumonitis are excluded. The primary endpoint of the study is objective response by RECIST 1.1. The null hypothesis that the true response rate is 6% will be tested against a one-sided alternative. In the first stage of the study, 13 patients will be accrued and if there are no partial or complete responses, then the study will be stopped for futility. Otherwise, 14 additional patients will be accrued to a total of 27 patients. If four or more responses are observed in 27 patients, then the null hypothesis will be rejected. As of 1/2026, four patients have been enrolled and started study treatment. The study includes pre-treatment and on-treatment research biopsies and longitudinal research blood collection for immune pharmacodynamic profiling to investigate mechanisms of treatment response and resistance. Clinical trial information: NCT07082439. Research Sponsor: Merck.

A phase Ib/III randomized double-blinded placebo-controlled study of suvemcitug combined with trifluridine/tipiracil for refractory metastatic colorectal cancer.

Ying Yuan, Yanhong Gu, Shuqin Ni, Zuoxing Niu, Rong-Bo Lin, Ting Deng, Yanqiao Zhang, Shuang Hu, Jiajing Zhang, Zewen Zhu, Xiyang Sun, Ke-Feng Ding; The Second Affiliated Hospital, Zhejiang University School of Medicine, Department of Medical Oncology, Key Laboratory of Cancer Prevention and Intervention, Ministry of Education, Hangzhou, Zhejiang, China; Department of Oncology, Jiangsu Province Hospital, Nanjing, China; Phase I Clinical Trial Center, Cancer Hospital of Shandong First Medical University, Jinan, China; Digestive Internal Medicine Second Ward, Cancer Hospital of Shandong First Medical University, Jinan, China; Department of Gastrointestinal Oncology, Fujian Cancer Hospital, Fuzhou, China; Tianjin Medical University Cancer Institute & Hospital, Tianjin, China; Second Ward of Gastroenterology Department, Harbin Medical University Cancer Hospital, Harbin, China; Project Management Office, State Key Laboratory of Neurology and Oncology Drug Development & Simcere Zaiming Pharmaceutical Co., Ltd, Shanghai & Nanjing, China; Clinical Sciences, State Key Laboratory of Neurology and Oncology Drug Development & Simcere Zaiming Pharmaceutical Co., Ltd, Shanghai & Nanjing, China; Clinical Statistics, State Key Laboratory of Neurology and Oncology Drug Development & Simcere Zaiming Pharmaceutical Co., Ltd, Shanghai & Nanjing, China; Clinical Pharmacology, State Key Laboratory of Neurology and Oncology Drug Development & Simcere Zaiming Pharmaceutical Co., Ltd, Shanghai & Nanjing, China; Department of Colorectal Surgery and Oncology, Key Laboratory of Cancer Prevention and Intervention, Ministry of Education, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

Background: Colorectal cancer (CRC) is a leading cause of cancer-related death worldwide. For patients with metastatic CRC (mCRC) that has progressed on standard chemotherapies, available treatments offer limited benefit. Notably, the phase III SUNLIGHT trial demonstrated the efficacy and safety of trifluridine/tipiracil (FTD/TPI) in combination with bevacizumab in refractory mCRC. Suvemcitug is a new-generation recombinant humanized anti-VEGF rabbit monoclonal antibody. In the previous clinical trials, suvemcitug demonstrated its favorable safety profile and efficacy signals as a single agent or in combination with chemotherapy for the treatment of mCRC. This study aims to assess the efficacy and safety of the combination of suvemcitug and FTD/TPI in patients with refractory mCRC. **Methods:** This phase Ib/III, randomized, double-blinded, placebo-controlled, multi-cohort study (NCT07361003) consists of two parts, Part 1 (phase Ib) and Part 2 (phase III). Estimated total enrollment is approximately 464 participants: 30 for Part 1 and 434 for Part 2. Patients with mCRC are eligible for participation if they have received chemotherapy based on fluoropyrimidine, oxaliplatin and irinotecan, and have either previously received or are unsuitable for anti-VEGF therapy and anti-EGFR therapy (if RAS wild-type). Part 1: Phase Ib: Participants will be enrolled to receive suvemcitug combined with FTD/TPI. The dose of suvemcitug is 1.5 mg/kg administered intravenously every two weeks. The primary endpoint is safety and tolerability of suvemcitug. The secondary endpoints include pharmacokinetic (PK) profile of suvemcitug; the incidence, duration, and titer of anti-drug antibodies (ADA); as well as objective response rate (ORR), duration of response (DoR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS). Part 2: Phase III: Part 2 is designed as a Phase III to further evaluate the antitumor activity of suvemcitug in combination with FTD/TPI in refractory mCRC. Eligible participants will be randomized (1:1 ratio) to receive FTD/TPI in combination with suvemcitug or matching placebo at the dose identified in Part 1. Stratification criteria include primary tumor location, prior bevacizumab exposure, and time from initial metastasis to enrollment. The primary endpoint is OS. The secondary endpoints include PFS, ORR, DoR, DCR, safety, quality of life, PK and immunogenicity (ADA incidence, titer, duration). The exploratory endpoints are correlations among PK, pharmacodynamics, safety and clinical efficacy. Study treatment will continue until progressive disease, unacceptable toxicity, withdrawal of consent, or the investigator's decision to discontinue. Clinical trial information: NCT07361003. Research Sponsor: None.

Symbiotic-GI-03: A randomized, double-blind, phase 3 study of first-line PF-08634404, a PD-1/VEGF bispecific antibody, in combination with mFOLFOX6 in patients with metastatic colorectal cancer (mCRC).

Cathy Eng, Elena Elez, Julien Taieb, Rui-Hua Xu, Hiroya Taniguchi, Tanios S. Bekaii-Saab, Jeanne Tie, Myriam Chalabi, Zhiyu Chen, Aman Opneja, Mark D. Kochenderfer, Yong Sang Hong, Donald A. Richards, Barbara Radecka, Yiyi Chen, Jill Clancy, Svitlana Tonkovyd, Xiaosong Zhang, Kimmie Ng; Vanderbilt Ingram Cancer Center, Nashville, TN; Vall d'Hebron Hospital Campus, Vall d'Hebron and Institute of Oncology, Barcelona, Spain; Centre de Recherche des Cordeliers, Sorbonne Université, Inserm, Université Paris Cité, and Institut du Cancer Paris CARPEM, AP-HP Centre, Department of Gastroenterology and Digestive Oncology, Hôpital Européen Georges Pompidou, Paris, France; Department of Medical Oncology, Sun Yat-sen University, Guangzhou, China; Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; Division of Hematology and Oncology, Mayo Clinic Arizona, Phoenix, AZ; Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; Department of Gastrointestinal Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China; Department of Medicine, Duke University School of Medicine, Durham, NC; Blue Ridge Cancer Care, Roanoke, VA; Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Texas Oncology, Tyler, TX; Department of Oncology, University of Opole and SP ZOZ Opolskie Centrum Onkologii, Opolu, Poland; Pfizer Inc., Bothell, WA; Pfizer, Inc., Andover, MA; Pfizer Poland, Warsaw, Poland; Pfizer Inc., San Francisco, CA; Dana-Farber Cancer Institute, Boston, MA

Background: Multi-agent chemotherapy regimens (eg, mFOLFOX6) $\pm$ anti-vascular endothelial growth factor (VEGF) or anti-epidermal growth factor regimens are currently the standard of care for patients (pts) with mCRC without targetable mutations. However, the 5-year survival rate remains low at approximately 16% (SEER, 2025). The addition of biological therapies (eg, bevacizumab [bev], an anti-VEGF monoclonal antibody) to immune checkpoint inhibitors (ICIs) has demonstrated a synergistic antitumor effect in solid tumors. However, ICI monotherapy has limited activity in mismatch repair proficient (pMMR)/microsatellite stable (MSS) mCRC. Simultaneous bispecific targeting of programmed death 1 (PD-1) and VEGF in conjunction with cytotoxic chemotherapy has the potential to enhance antitumor activity. PF-08634404 is a fully human immunoglobulin G4 (IgG4) bispecific antibody targeting PD-1 and VEGF. A phase 2 study of PF-08634404 with XELOX or mFOLFOX6 demonstrated promising antitumor activity with a manageable safety profile in first-line (1L) mCRC (Xu X, ESMO 2025; Abstract 796P). **Methods:** Symbiotic-GI-03 (NCT07222800) is an ongoing, double-blind, randomized, phase 3 study evaluating the efficacy and safety of 1L PF-08634404 + mFOLFOX6 vs bev + mFOLFOX6. Inclusion criteria are age ≥ 18 y; mCRC with measurable disease per RECIST 1.1; no prior systemic therapy for metastatic disease; ECOG PS 0 or 1; and adequate hematologic, hepatic, and renal function. Pts with BRAF V600E-mutant or mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) CRC, active central nervous system metastases, or clinically significant risk of hemorrhage/fistula will be excluded. Approximately 800 pts will be randomized 1:1 to receive PF-08634404 + mFOLFOX6 or bev + mFOLFOX6 until disease progression, unacceptable toxicity, withdrawal of consent, or death. Randomization will be stratified by region (North America, Europe, or rest of world), RAS status (mutant or wildtype), and presence of liver metastasis (yes or no). The dual primary endpoints are progression-free survival (PFS) by blinded independent central review and overall survival; for each, a stratified log-rank test will be used to compare arms. Hazard ratios with corresponding 2-sided 95% CIs will be estimated using a stratified Cox proportional hazards model, and medians will be estimated using the Kaplan-Meier method with corresponding 2-sided 95% CIs calculated using the log(-log) method. Secondary endpoints include PFS by investigator, objective response rate, duration of response, PFS after next-line therapy, safety/tolerability, pharmacokinetics, immunogenicity, and patient-reported outcomes. Enrollment began in December 2025. Clinical trial information: NCT07222800. Research Sponsor: This study was sponsored by Pfizer. Medical writing support was provided Eleanor Porteous, MSc, and Akshaya Srinivasan, PhD, of Nucleus Global, an Inizio Company, and was funded by Pfizer.

The CO.33/BATTMAN trial: A phase 3 randomized study of botensilimab + balstilimab versus best supportive care in chemorefractory unresectable colorectal adenocarcinoma that is not dMMR/MSI-H.

Jonathan M. Loree, Jeanne Tie, Emmanuelle Samalin, Sharlene Gill, Benny Johnson, Joseph Elan Grossman, Steven O'Day, Eric Xueyu Chen, Christos Stelios Karapetis, Christelle De La Fouchardiere, Winson Y. Cheung, Kelvin K. Chan, Catherine Rutledge, Dongsheng Tu, Christopher J. O'Callaghan; BCCA - Vancouver Cancer Centre, University of British Columbia, Vancouver, BC, Canada; Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; Digestive Oncology CRLC Val d'Aurelle, Montpellier, France; BC Cancer - Vancouver, Vancouver, BC, Canada; Agenus Inc., Lexington, MA; Agenus Inc, Lexington, MA; Cancer Clinical Research Unit, Princess Margaret Cancer Centre, Toronto, ON, Canada; Flinders Medical Centre, Adelaide, SA, Australia; Cancer Center Institut Paoli-Calmettes, Marseille, France; Arthur JE Child Cancer Centre, University of Calgary, Calgary, AB, Canada; Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada; Canadian Cancer Trials Group, Kingston, ON, Canada; Canadian Cancer Trials Group, Queen's University, Kingston, ON, Canada

Background: Despite significant progress and newly approved agents, metastatic colorectal cancer (mCRC) has limited prognosis after progressing on standard cytotoxic chemotherapies. Many patients remain well enough for treatment at the time when their cancer is refractory to all available therapy, creating a significant unmet need. Once refractory, patient management with best supportive care (BSC) results in a median overall survival (OS) of 4–6 months. To date, immune checkpoint inhibitors (ICIs) have shown limited activity in mCRC that is not mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H). Prior data from the CCTG CO.26 randomized phase 2 trial demonstrated doublet ICI with durvalumab + tremelimumab improved OS in refractory mCRC; however, a phase 3 trial was not undertaken. Botensilimab (BOT) is an Fc-enhanced multifunctional anti-CTLA-4 antibody designed to increase efficacy in poorly immunogenic cancers. The combination of BOT with the anti-PD-1 antibody balstilimab (BAL) has shown impressive objective response rates (ORRs), durations of response (DOR), and survival in heavily treated non-MSI-H/dMMR mCRC across phase 1 and 2 studies. The CO.33/BATTMAN trial will evaluate BOT + BAL + BSC versus BSC alone in patients with refractory mCRC that is not MSI-H/dMMR. **Methods:** BATTMAN (NCT07152821) is an international multi-centre, open-label randomized phase 3 trial that will be conducted in Canada (CCTG), Australia/New Zealand (AGITG) and France (Unicancer). Eligible patients will be ≥ 18 years old, have received and progressed on or been intolerant of all available therapies, have an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0/1, have RECIST 1.1 measurable/evaluable disease, have a life expectancy of ≥ 12 weeks, and have adequate end organ function without concurrent illness contraindicating ICI. Exclusion criteria include: prior organ transplant or primary immunodeficiency, ongoing use of non-physiologic corticosteroid dosing, autoimmune disorders requiring ongoing management, and prior ICI exposure. The trial's statistical plan will ascertain efficacy of BOT and BAL in all comers, as well as key subgroups based on the presence or absence of liver metastases. A planned 834 patients will be randomized 1:1 to BOT (75 mg IV every 6 weeks up to 4 doses) + BAL (450 mg IV every 3 weeks until progression) + BSC or BSC alone, with stratification for region of recruitment, ECOG PS, and presence of liver metastases. The primary endpoint is OS, with secondary endpoints including progression-free survival, ORR, clinical benefit rate, quality of life, safety, and toxicity, with correlative studies and economic evaluations planned. Support for this study is provided by: The Canadian Cancer Society and Agenus Inc. Clinical trial information: NCT07152821. Research Sponsor: Canadian Cancer Society; Agenus.

A phase II exploratory study of iparomlimab and tuvonralimab (QL1706) combined with bevacizumab in patients with locally advanced or metastatic MSI-H/dMMR colorectal cancer.

Jun Wang, Yuekai Zhang, Yaping Guan, Yue Dong, Jiang Chang, Songlin Liu, Fatao Wang; Department of Oncology, The First Affiliated Hospital of Shandong First Medical University, Jinan, China

Background: Microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) colorectal cancer (CRC) is highly responsive to immune checkpoint inhibitors (ICIs). PD-1 monotherapy or PD-1/CTLA-4 dual blockade are standard options for locally advanced or metastatic disease, but a significant proportion of patients still show no response to these regimens. Evidence suggests that vascular endothelial growth factor (VEGF) signaling mediates an immunosuppressive tumor microenvironment (TME). Combining anti-VEGF agents with ICIs may potentially normalize the inhibitory TME, and thereby could enhance anti-tumor immunity and improve response rates in this population. QL1706 is a novel bifunctional antibody combination targeting PD-1 (iparomlimab) and CTLA-4 (tuvonralimab). This Phase II exploratory study aims to investigate the efficacy and safety of QL1706 in combination with anti-VEGF agent bevacizumab in locally advanced or metastatic CRC patients with MSI-H/dMMR. **Methods:** This single-arm, open-label, multicenter, Phase II exploratory study is designed to evaluate the efficacy and safety of QL1706 plus bevacizumab in patients with MSI-H/dMMR advanced CRC. Eligible patients are adults aged 18 to 80 years with histologically confirmed locally advanced or metastatic CRC and who have an MSI-H/dMMR status via immunohistochemistry or polymerase chain reaction. Key inclusion criteria include at least one measurable target lesion per RECIST v1.1, an ECOG Performance Status of 0-1, and no prior immunotherapy for advanced disease. The systemic regimen consists of QL1706 (5 mg/kg) and bevacizumab (7.5 mg/kg) administered intravenously every 3 weeks (Q3W). Treatment continues until disease progression, unacceptable toxicity, or a maximum of 2 years. The primary endpoint is the objective response rate (ORR) assessed by investigators per RECIST v1.1. Secondary endpoints include disease control rate, duration of response, progression-free survival, overall survival, and landmark survival rates at 6, 12, and 24 months. Safety is monitored via NCI CTCAE v5.0. Efficacy assessments, including chest CT and enhanced abdominal/pelvic CT/MRI, are performed every 12 weeks. Statistical power is based on an estimated ORR of 80%; with a 95% confidence interval width of 35%, a total of 22 subjects are required (supplemented by a Simon's two-stage design for the broader cohort if applicable). The study has received ethics committee approval, and patient enrollment is currently ongoing. Clinical trial information: NCT07009145. Research Sponsor: None.

A phase 1, first-in-human (FIH), dose-escalation and dose-optimization study to evaluate the safety, tolerability, pharmacokinetics, and anti-tumor activity of CBI-1214 T-cell engager in participants with advanced or metastatic microsatellite-stable (MSS)/microsatellite instability–low (MSI-L) colorectal cancer (CRC).

Alexander I. Spira, David Sommerhalder, Annie Winterhall, Tonia Jane Buchholz, Tarah Bateman, David G. Kugler, Dan Rock, Olatunji B. Alese, David Berz, Marwan Fakih, Joel R. Hecht, David Yoonsuk Oh, Manish R. Sharma, Christina Wu, Dirk Nagorsen; NEXT Oncology – Virginia, Fairfax, VA; NEXT Oncology, San Antonio, TX; Cartography Biosciences, South San Francisco, CA; Winship Cancer Institute of Emory University, Atlanta, GA; Department of Oncology, Valkyrie Clinical Trials, Inc, Los Angeles, CA; City of Hope National Medical Center, Duarte, CA; UCLA Jonsson Comprehensive Cancer Center, Santa Monica, CA; Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA; The START Center for Cancer Research - Midwest, Grand Rapids, MI; Mayo Clinic Comprehensive Cancer Center, Phoenix, AZ

Background: Advanced and metastatic colorectal cancer (CRC) remains an area of significant unmet clinical need, particularly for patients with MSS/MSI-L tumors. In recent years, there have been several advancements in the treatment of solid tumors with T cell engagers. Our ATLAS scRNA-seq based discovery platform identified LY6G6D as a highly-specific tumor-associated antigen in advanced and metastatic CRC. CBI-1214, a CD3 bispecific T cell engager targeting LY6G6D with potent in vitro and in vivo activity even at low LY6G6D expression levels of ~300 copies/cell (Yigit B *et al*, AACR 2025), is being developed for the treatment of patients with advanced or metastatic MSS/MSI-L CRC. **Methods:** This ongoing, open-label FIH study (CBI-1214-001) is being conducted to evaluate the safety, tolerability, pharmacokinetics (PK), and anti-tumor activity of CBI-1214 and to determine the maximum tolerated dose (MTD) and/or optimal biological dose (OBD) in participants with advanced or metastatic MSS/MSI-L CRC who have exhausted at least one prior line of systemic treatment and do not qualify for available targeted treatment options for actionable genomic alterations. Additional eligibility criteria include: at least 18 years of age, measurable disease (as defined by RECIST v1.1), available archival tumor tissue sample or a fresh tumor sample, ECOG PS 0 or 1, as well as adequate hematologic and organ functions. Patients whose CRC tumor tissues have been identified as dMMR or MSI-H are excluded. The study is conducted in two parts: Part 1 dose escalation, which starts with Part 1a as accelerated dose escalation, followed by Part 1b escalation, which is based on a modified toxicity probability interval (mTPI-2) design, and Part 2, which is designed as a randomized dose optimization study to select the final recommended phase 2 dose (RP2D). For both parts of the study, the study intervention is administered as monotherapy, given as an intravenous (IV) infusion, in 21-day treatment cycles, with a step-up option. After an up-to-28-day screening period, eligible patients receive study medication and are followed for their entire treatment period plus a follow-up period of approximately 90 days. The study is open for recruitment in the United States (NCT07321106). Clinical trial information: NCT07321106. Research Sponsor: None.

A study evaluating microbiome modulation therapy in patients undergoing first-line therapy for metastatic colorectal cancer.

Emily Noelle Kinsey, Nolan W. Wages, Katarzyna Tyc, Hamid Akbarali, Andrew Stewart Poklepovic; Virginia Commonwealth University, Richmond, VA; VCU Department of Biostatistics, Richmond, VA; Virginia Commonwealth University - Massey Comprehensive Cancer Center, Richmond, VA

Background: Colorectal cancer (CRC) is the second leading cause of cancer-related mortality worldwide. Despite advances in systemic therapy, the 5-year overall survival for metastatic CRC remains poor. Emerging evidence suggests that the gut microbiome influences CRC development, progression, as well as chemotherapy resistance. There is strong preclinical data showing the association of *Fusobacterium nucleatum* and *Escherichia coli* with poor outcomes and chemotherapy resistance in patients with CRC. Younger patients and Black patients have been found to have a high-level colonization with *F nucleatum*, which could potentially contribute to healthcare disparities. If the amount of cancer-associated bacteria in the microbiome can be reduced, patients may respond better to chemotherapy and have improved outcomes. Pre-clinical studies indicate that targeting these bacteria with antibiotics may enhance chemotherapy efficacy. Aspirin may also be beneficial as it affects gene expression and inhibits *Fusobacterium nucleatum* with differential effects at varying drug concentrations. Our study evaluates the feasibility, safety, and preliminary efficacy of adding Microbiome Modulation Therapy (MBMT), including ciprofloxacin, metronidazole, +/- aspirin, to standard first-line chemotherapy in patients with metastatic CRC. **Methods:** This is a two-arm, noncomparative phase II trial enrolling adults (≥ 18 years) with stage IV CRC and measurable disease by RECIST 1.1. Eligible patients must have ECOG performance status 0–2 and planned first-line 5FU-based standard of care chemotherapy. Patients are excluded if they have recent antibiotic use to treat an infection within 30 days of treatment start (prophylactic preoperative antibiotics are allowed), have had a total colectomy, or are taking probiotic treatments. Patients are randomized to standard chemotherapy alone (investigators choice) or chemotherapy plus MBMT (ciprofloxacin, metronidazole, +/- aspirin for 28 days). The primary endpoint is objective response rate (ORR) per RECIST 1.1. Secondary endpoints include overall survival (OS), progression-free survival (PFS), safety, and tolerability of MBMT. Exploratory endpoints include changes in microbiome composition as measured by shotgun sequencing of fecal samples at baseline and after one month of treatment with chemotherapy +/- MBMT. Correlative studies will use shotgun sequencing to assess microbiome signatures, microbiota diversity, and changes with treatment. Correlative analyses will explore microbiome modulation as a novel therapeutic strategy to overcome chemoresistance in metastatic CRC. Enrollment is ongoing at Virginia Commonwealth University Massey Comprehensive Cancer Center in Richmond, Virginia. Clinical trial information: NCT06728072. Research Sponsor: Massey Comprehensive Cancer Center; American Cancer Society, Institutional Research Grant.

CONCEPT (combination of cetuximab plus fruquintinib treatment $\pm$ immunotherapy): A multicenter, randomized, open-label phase II trial in first-line pMMR RAS/*BRAF* wild-type unresectable metastatic colorectal cancer.

Yue Liu, Michele Cricri, Jinjie He, Jiang Kai, Xin Chen, Chengxuan Yu, Ying Yuan, Ke-Feng Ding, Qi Yang; Colorectal Surgery and Oncology, Key Laboratory of Cancer Prevention and Intervention, Ministry of Education, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China; Department of Clinical Medicine and Surgery, Coloproctology Unit, University of Naples "Federico II", Naples, Italy; The Second Affiliated Hospital of Zhejiang University School of Medicine, Department of Colorectal Surgery and Oncology (Center for Medical Research and Innovation in Digestive System Tumors, Ministry of Education), Hangzhou, Zhejiang, China; The Second Affiliated Hospital, Zhejiang University School of Medicine, Department of Medical Oncology, Key Laboratory of Cancer Prevention and Intervention, Ministry of Education, Hangzhou, Zhejiang, China; Department of Colorectal Surgery, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China; The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China

Background: In pMMR unresectable metastatic colorectal cancer (mCRC), first-line standards combine cytotoxic chemotherapy with targeted agents (anti-EGFR or anti-VEGF). A chemotherapy-sparing strategy may be clinically relevant for selected patients, and biologically supported by potential synergy between EGFR inhibition and VEGFR blockade, with immunotherapy potentially enhanced by vascular normalization and microenvironment modulation. CONCEPT evaluates the safety and antitumor activity of cetuximab- β plus fruquintinib, with or without immune checkpoint blockade, as a first-line option in pMMR RAS/*BRAF* wild-type unresectable mCRC. **Methods:** CONCEPT is an open-label, multicenter, randomized phase II trial. Key eligibility: age 18–85, ECOG 0–1, histologically confirmed colorectal adenocarcinoma, pMMR, KRAS/NRAS/*BRAF* wild-type, unresectable metastatic disease, and ≥ 1 measurable lesion per RECIST v1.1. Planned N=70; randomization 1:1:1 to: A) cetuximab- β 500 mg/m² IV q2w + fruquintinib 5 mg PO QD (3 weeks on/1 week off); B) regimen A + PD-1 antibody 200 mg IV q4w; C) regimen A + PD-1/CTLA-4 antibody 5 mg/kg IV q4w. The study uses a seamless two-stage selection design: initial cohort (10 patients/arm) to assess early safety/activity, followed by expansion of one or two selected arm(s) (+20 patients per selected arm). Safety assessments are performed each cycle; radiologic tumor assessment is every 2 cycles. Primary endpoints: progression-free survival (PFS) and safety. Secondary endpoints include objective response rate (ORR), disease control rate (DCR) and overall survival (OS). The study is registered with ClinicalTrials.gov (NCT 07257653). Clinical trial information: NCI 07257653. Research Sponsor: None.

Bevacizumab plus encorafenib-cetuximab in BRAF V600E mutated metastatic colorectal cancer (mCRC): A phase II study with a safety lead-in cohort (the BRAVE trial).

Javier Ros Montañá, Susana Roselló, David Paez, Maria Jose Safont, Joana Vidal, Cristina Gravalos, Eduardo Polo, Paula Jimenez-Fonseca, Silvia Gil Calle, Beatriz Garcia Paredes, Marta Beltran, Javier Gonzalo-Ruiz, Cristian Rosales, Hector G. Palmer, Dario Lopez Garcia, Paolo Nuciforo, Ana Vivancos-Prellezo, Josep Tabernero, Elena Elez; Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Spain; Department of Medical Oncology, INCLIVA Biomedical Research Institute, University of Valencia, Valencia, Spain; Medical Oncology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; Medical Oncology Department, General University Hospital Consortium of Valencia, Valencia University, Valencia, Spain; Medical Oncology Department, Hospital del Mar; Colorectal Cancer Precision Medicine Group, CIBERONC, HMar Research Institute; Universitat Pompeu Fabra, Barcelona, Spain; Hospital Universitario 12 De Octubre, Madrid, Spain; Medical Oncology Department, Hospital Universitario Miguel Servet, Zaragoza, Spain; Medical Oncology Department, Hospital Universitario Central de Asturias, ISPA, Oviedo, Spain; Hospital Regional Universitario de Málaga, Málaga, Spain; Hospital Clinico San Carlos Madrid, Barcelona, Spain; MEDSIR, Ridgewood, NJ; Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; VHIO Vall d'Hebron Instituto de Oncología CELLEX, Barcelona, Spain; Stem Cells and Cancer Group, VHIO - Vall d'Hebron Institute of Oncology, Barcelona, Spain; Vall d'Hebron Institute of Oncology, Barcelona, Spain; Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Cancer Genomics Group, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Vall d'Hebron Hospital Campus and Institute of Oncology (VHIO), IOB-Quiron, Uvic-UCC, Barcelona, Spain; Vall d'Hebron University Hospital and Institute of Oncology (VHIO), Barcelona, Spain

Background: Encorafenib plus cetuximab is the standard of care for patients with *BRAF* V600E mutant, microsatellite-stable (MSS) mCRC, *BRAF* inhibitor-naïve, whose disease has progressed after 1–2 prior lines of chemotherapy. However, all patients eventually experience disease progression, and progression-free survival (PFS) remains modest. Therefore, there is an unmet need to enhance the efficacy of encorafenib-based combinations in *BRAF*-mutant mCRC. Preclinical data from rodent models treated with *BRAF* inhibitors have demonstrated upregulation of hypoxia-related genes (VEGFA, ADM, and CXCR4), and alterations in tumor vessel architecture. Based on these observations, rodent models treated with *BRAF* inhibitors in combination with anti-VEGF therapy achieved a meaningful improvement in PFS. In this trial, we hypothesize that encorafenib–cetuximab with bevacizumab will result in synergistic activity leading to durable responses in patients with refractory *BRAF*-mutant mCRC. **Methods:** The BRAVE trial (NCT06411600) is a multicenter, single-arm, phase Ib/II study evaluating the safety and efficacy of encorafenib–cetuximab–bevacizumab. Patients must have progressed to 1–2 previous lines and have a *BRAF* V600E-mutant, MSS tumor. Previous treatment with *BRAF* inhibitors or antiEGFR was not allowed. All patients receive encorafenib 300 mg po QD, cetuximab 500 mg iv Q2W, and bevacizumab 5 mg/kg iv Q2W, administered in 28-day cycles. The primary endpoints are dose-limiting toxicities (DLTs) and 6-month PFS (6mPFS). The study follows a Simon two-stage design. A sample size of 89 evaluable patients is required to detect an increase in 6mPFS to 49% in the study population, compared with a 36% 6mPFS achieved with encorafenib plus cetuximab in the BEACON trial, using a one-sided type I error of 0.05 and 80% statistical power. As there was no prior evidence on the safety of this combination, a safety lead-in (SLI) phase (n=9) was included to evaluate potential DLTs. An Independent Data Safety Monitoring Board (IDSMB) reviewed the toxicity profile and DLTs granted continuation of the study on April 1, 2025. Following completion of the SLI phase and IDSMB evaluation, the study proceeded to two subsequent stages. Stage I enrolled 41 additional patients (completed on December 12, 2025). A preplanned interim analysis (IA) is being performed before proceeding to Stage II. If fewer than 19 of the first 50 patients achieve 6mPFS, the study will be discontinued due to lack of efficacy. If 19 or more of the first 50 patients achieve 6mPFS, Stage II will enroll an additional 39 patients. Recruitment is currently on hold pending the planned IA. Biomarker analyses include plasma sample collection at screening, on C1D15, and at end of treatment, as well as tumor biopsies (optional) at baseline and at disease progression to study mechanism of sensitivity and resistance. Clinical trial information: NCT06411600. Research Sponsor: Insituto de Salud Carlos III.

A randomized, active-controlled phase 3 study of ivonescimab + FOLFOX versus bevacizumab + FOLFOX as first-line treatment of metastatic colorectal cancer (mCRC): HARMONi-GI3.

Aparna Raj Parikh, Michael J. Overman, Christopher T. Chen, Elena Elez, Lucjan Wyrwicz, Chiara Cremolini, Julien Taieb, Ying Yuan, Kei Muro, David Berz, Ming Yin, Karl Albert Eckert, Nindhana Paranthaman, Marwan Fakih; Department of Medicine, Division of Hematology/Oncology, Mass General Brigham Cancer Center, Harvard Medical School, Boston, MA; Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Medicine, Division of Oncology, Stanford University School of Medicine, Stanford, CA; Gastrointestinal Cancer Unit, Vall d'Hebron University Hospital, Barcelona, Spain; Oncology and Chemotherapy Clinic, Maria Skłodowska-Curie Memorial Research Institute of Oncology, Warsaw, Poland; 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; Service de Gastroenterologie et d'Oncologie Digestive, Paris Carpem (Cancer Research for Personalized Medicine) Institute, Hôpital Européen Georges Pompidou, Assistance Publique Hôpitaux De Paris (AP-HP), Université Paris Cité, Paris, France; The Second Affiliated Hospital, Zhejiang University School of Medicine, Department of Medical Oncology, Key Laboratory of Cancer Prevention and Intervention, Ministry of Education, Hangzhou, Zhejiang, China; Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; Department of Oncology, Valkyrie Clinical Trials, Inc, Los Angeles, CA; Summit Therapeutics Inc., Miami, FL; Summit Therapeutics, Inc., Miami, FL; Summit Therapeutics, Inc, Miami, FL; City of Hope National Medical Center, Duarte, CA

Background: Fluorouracil (5-FU)-based chemotherapy plus an anti-vascular endothelial growth factor (VEGF) or anti-epidermal growth factor receptor (EGFR) therapy is recommended as first-line treatment for many patients with mCRC; however, prognosis is still poor, with a 5-year survival rate of <30%. The investigational, anti-programmed cell death protein 1 (PD-1)- and VEGF-bispecific antibody ivonescimab is approved in China for non-small cell lung cancer (NSCLC) and is currently being evaluated as monotherapy or in combination with chemotherapy in global phase 3 clinical trials for NSCLC, and in other tumor types including colorectal cancer. **Methods:** HARMONi-GI3 (NCT07228832) is a randomized, active-controlled, double-blind, multiregional, phase 3 trial to compare the efficacy and safety of ivonescimab + 5-FU, oxaliplatin, and leucovorin (mFOLFOX6) versus bevacizumab + mFOLFOX6 in patients with mCRC who are not candidates for surgical resection, have not previously received systemic therapy for metastatic disease, and have an Eastern Cooperative Oncology Group performance status score of 0 or 1. Patients with microsatellite instability-high or mismatch repair deficient disease, and with BRAF V600E mutation or dihydropyrimidine dehydrogenase deficiency, will be excluded. Approximately 600 patients will be randomly assigned (1:1) to receive ivonescimab 20 mg/kg + mFOLFOX6 or bevacizumab + mFOLFOX6 every 2 weeks for up to 4 months, followed by maintenance with ivonescimab + 5-FU and leucovorin or bevacizumab + 5-FU and leucovorin until disease progression, intolerable toxicity, or initiation of new anti-tumor therapy. Randomization will be stratified according to geographic region (East Asia, Europe, North America), liver metastases at study entry (absence or presence), and rat sarcoma virus tumor mutational status (RAS; mutant or wild-type). The hypothesis of this study is that ivonescimab + mFOLFOX6 has superior efficacy to bevacizumab + mFOLFOX6 in patients with mCRC who have not previously received systemic therapy for metastatic disease, as determined by progression-free survival (PFS). The primary endpoint is PFS (assessed by independent radiology review committee per Response Evaluation Criteria in Solid Tumors, v1.1). Secondary endpoints are overall survival, objective response rate, duration of response, safety, pharmacokinetics of ivonescimab + mFOLFOX6, and immunogenicity. All patients will have regular tumor evaluations every 8 weeks until week 48, then every 12 weeks until disease progression, loss to follow-up, death, withdrawal, or study closure. HARMONi-GI3 is currently recruiting participants. Clinical trial information: NCT07228832. Research Sponsor: Summit Therapeutics, Inc.

INCA033890-303: A randomized, double-blind, phase 3 study of FOLFOX and bevacizumab with or without INCA33890 in the first-line treatment of metastatic microsatellite-stable colorectal cancer.

Van K. Morris II, Miguel Colon Donate, Jenny Seligmann, Atsuo Takashima, Dirk Arnold, Monika Dudzisz-Sledz, Jennifer Pulini, Chuan Tian, Thomas Benjamin Karasic, Aparna Raj Parikh; The University of Texas MD Anderson Cancer Center, Houston, TX; PanOncology Trials, San Juan, PR; University of Leeds, Leeds, United Kingdom; National Cancer Center Hospital, Tokyo, Japan; Asklepios Tumorzentrum Hamburg, Hamburg, Germany; Incyte Biosciences International Sàrl, Morges, Switzerland; Incyte Corporation, Wilmington, DE; Massachusetts General Hospital, Boston, MA

Background: Immune checkpoint inhibitors have demonstrated limited efficacy in the treatment of microsatellite stable colorectal cancer (MSS CRC), especially when the liver is involved. Transforming growth factor β (TGF β) signaling within the tumor microenvironment suppresses T-cell proliferation and effector function, contributing to an immune-excluded phenotype. Although clinical targeting of the TGF β pathway has been previously attempted, these approaches have been hampered by limited efficacy and significant toxicity. INCA33890 is a first-in-class bispecific antibody targeting both TGF β receptor 2 (TGF β R2) and programmed cell death protein 1 (PD-1). This molecule is designed to inhibit TGF β R2 and PD-1 signaling specifically in PD-1-positive cells, sparing PD-1-negative cells from TGF β inhibition. In the phase 1 INCA 33890-101 study (NCT05836324), INCA33890 demonstrated a manageable safety profile and durable single-agent activity in patients with refractory MSS CRC, including in patients with active liver metastases. The monotherapy objective response rate (ORR) was 15.2% overall (n = 105), including 12.0% in patients with liver metastases (n = 75) and 23.3% (n = 30) in patients without liver metastases. **Methods:** The multicenter, global, phase 3 INCA033890-303 study (NCT07284849) activated in December 2025 and is planned to open at 225 sites across 23 countries. The primary objective of this study is to evaluate the efficacy of INCA33890 versus intravenous placebo, each in combination with FOLFOX and bevacizumab, as first-line treatment for patients with previously untreated, histologically confirmed, unresectable metastatic MSS CRC. Prior neoadjuvant or adjuvant therapy is allowed provided there was no recurrence within 12 months of treatment completion. Key exclusion criteria include microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) status, *BRAF* V600E mutation, untreated or progressing brain metastases, and active autoimmune disease requiring systemic immunosuppression. Approximately 700 patients will be randomized 1:1 to receive intravenous INCA33890 or placebo, each in combination with FOLFOX and bevacizumab. Randomization will be stratified by tumor sidedness, the presence of liver metastases, and programmed death-ligand 1 (PD-L1) score. The primary endpoint is progression-free survival as assessed by investigators. The key secondary endpoint is overall survival. Additional secondary endpoints are ORR, safety and tolerability, duration of response, and patient-reported outcomes. Trial enrollment is ongoing. Clinical trial information: NCT07284849. Research Sponsor: Incyte Corporation.

Fruquintinib in combination with tislelizumab vs trifluridine/tipiracil and bevacizumab in MSS mCRC without active liver metastases: The IKF-080/QUINTIS trial.

Joseph Tintelnot, Joao Gorgulho, Salah-Eddin Al-Batran, Dirk Arnold, Anke C. Reinacher-Schick, Stefan Kasper, Gerald W. Prager, Thorsten Oliver Goetze, Mariana Santos Cruz, Rebecca Boston, Friederike Dierks, Alexander Stein; University Cancer Center Hamburg (UCCH), University Medical Center Hamburg-Eppendorf, Hamburg, Germany; Department of Oncology, Hematology and Bone Marrow Transplantation with Section of Pneumology, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany; The Frankfurt Institute of Clinical Cancer Research IKF GmbH, Frankfurt Am Main, Germany; Asklepios Tumorzentrum Hamburg, AK Altona, Hamburg, Germany; St. Josef Hospital, Ruhr-Universität Bochum, Bochum, Germany; University Hospital Essen, Essen, Germany; Department of Medicine I, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria; Frankfurt Institute of Clinical Cancer Research (IKF), Krankenhaus Nordwest, UCT-University Cancer Center, Frankfurt Am Main, Germany; University Cancer Center Hamburg, Hamburg, Germany; University Medical Center Hamburg-Eppendorf, Hamburg, Germany; Hematology-Oncology Practice Eppendorf (HOPE), Hamburg, Germany

Background: Patients with metastatic colorectal cancer (mCRC) who progress after treatment with fluoropyrimidines, oxaliplatin, irinotecan, anti-angiogenic agents, and anti-EGFR therapies have limited therapeutic options and a poor prognosis. Median overall survival (mOS) is approximately 6 months with single-agent regorafenib or trifluridine/tipiracil. The addition of bevacizumab to trifluridine/tipiracil has improved mOS to 10.8 months, while fruquintinib, a selective VEGFR-1–3 inhibitor, demonstrated a mOS of 7.4 months compared with 4.8 months for placebo in refractory mCRC. However, combinations of tyrosine kinase inhibitors and immune checkpoint inhibitors have shown clinical benefit, primarily in patients with microsatellite-stable mCRC without liver metastases, likely due to liver-associated immunosuppression. The QUINTIS trial evaluates whether fruquintinib plus the PD-1 antibody tislelizumab can improve outcomes in this clinically defined subgroup compared with the current standard of care of trifluridine/tipiracil plus bevacizumab. **Methods:** QUINTIS is a prospective, randomized, open-label, multicenter phase II trial enrolling 140 patients with metastatic colorectal adenocarcinoma without active liver metastases who have previously received fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab, and, when indicated, an EGFR inhibitor. Participants are randomized 1:1 to Arm A (experimental): fruquintinib 5 mg orally once daily (days 1–21 of a 28-day cycle) plus tislelizumab 400 mg intravenously on day 1 every 6 weeks; or Arm B (control): trifluridine/tipiracil 35 mg/m² orally twice daily (days 1–5 and 8–12 of a 28-day cycle) plus bevacizumab 5 mg/kg intravenously every 2 weeks. No prior treatment with the study drugs is permitted. Randomization is stratified by time since prior anti-angiogenic therapy (< 12 vs. ≥12 months), BRAF/RAS mutation status, and history of liver metastases (never vs. treated). The primary endpoint is progression-free survival; secondary endpoints include overall response, overall survival, and quality of life. Translational research includes tumor, blood, and stool sampling to explore biomarkers of response and resistance, including systemic inflammation and the diet–microbiota–immune axis. Patient enrolment started in October 2025, and enrolment will take place at 30 sites. Clinical trial information: EU CTIS No. 2024-519111-34-00. Research Sponsor: None.

NSABP FC-13 (EMPIRE): A phase II platform study of cemiplimab monotherapy or cemiplimab-based combinations in patients with colorectal cancer and minimal residual disease (MRD) after definitive therapy.

Anwaar Saeed, Greg Yothers, Shannon L. Puhalla, Priya Rastogi, Tanner Freeman, Melissa Divya Mathias, Frank A. Seebach, Norman Wolmark, Thomas J. George; NSABP Foundation and UPMC Hillman Cancer Center, University of Pittsburgh School of Medicine, Pittsburgh, PA; NRG Oncology SDMC; Department of Biostatistics and Health Data Science, University of Pittsburgh, Pittsburgh, PA; UPMC Hillman Cancer Center, University of Pittsburgh School of Medicine, Pittsburgh, PA; NSABP Foundation, Inc.; Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, PA; Regeneron Pharmaceuticals, Inc.; Department of Pediatrics, Memorial Sloan-Kettering Cancer Center, Tarrytown, NY; Regeneron Pharmaceuticals, Inc., Tarrytown, NY; University of Florida Health Cancer Institute, Gainesville, FL

Background: Patients with microsatellite-stable (MSS) colorectal cancer (CRC) who are ctDNA-positive following surgery and chemotherapy have a high risk of recurrence and limited treatment options. Immune checkpoint blockade with PD-1/PD-L1 inhibitors, alone or with other immune modulators, may be most effective in early-stage disease or in patients without liver metastases. However, no approved therapies currently exist for patients with MSS CRC and ctDNA-positivity after curative-intent therapy, making this high-risk population an area of critical unmet need and opportunity for new drug development. NSABP FC-13 (EMPIRE) is a Phase II platform trial evaluating cemiplimab alone or in combination with novel agents in this high-risk MRD setting, wherein ctDNA clearance serves as an early surrogate marker of therapeutic activity. **Methods:** This multicenter Phase II platform study randomizes patients with MSS stage II–III or oligometastatic stage IV CRC who are ctDNA-positive within 12 weeks of completing definitive therapy (surgery $\pm$ chemotherapy/chemoradiotherapy) to one of three arms: (1) Cemiplimab 350 mg IV q3w $\times$ 1 year; (2) Cemiplimab 350 mg + fianlimab 1600 mg IV q3w $\times$ 1 year; (3) Cemiplimab 350 mg + REGN7075 2700 mg IV q3w $\times$ 1 year. Eligibility includes ECOG 0–1, adequate organ function, and absence of radiographic recurrence at enrollment. Assessments include serial tumor-informed ctDNA testing (Signatera, Natera, Inc.), imaging, labs, and safety monitoring. The primary endpoint is ctDNA clearance at 12 weeks without radiographic recurrence. Secondary endpoints include recurrence-free survival (RFS), safety, ctDNA kinetics, and patterns of recurrence. Statistical design: Arm 1 follows a Simon two-stage design with up to 33 patients ($\alpha=0.047$, power=0.80), and Arms 2 & 3 enroll up to 23 patients each (single-stage; $\alpha=0.05$, power=0.78). Status: Enrollment began in September 2025 across NSABP Foundation sites and is ongoing. Clinical trial information: NCT07058012. Research Sponsor: Regeneron; Natera, Inc.; NSABP Foundation, Inc.

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

Arvind Dasari, Guan Yu, Scott Kopetz, Shannon L. Puhalla, Peter C. Lucas, Ibrahim Halil Sahin, Dustin A. Deming, Philip Agop Philip, Theodore S. Hong, Yesenia Rojas-Khalil, Jonathan M. Loree, Norman Wolmark, Greg Yothers, Thomas J. George, Christopher Lieu; The University of Texas MD Anderson Cancer Center, Houston, TX; NRG Oncology SDMC; Department of Biostatistics and Health Data Science, University of Pittsburgh, Pittsburgh, PA; UPMC Hillman Cancer Center, University of Pittsburgh School of Medicine, Pittsburgh, PA; Department of Laboratory Medicine and Pathology, Mayo Clinic Rochester, Rochester, MN; The University of Michigan Medical School, Ann Arbor, MI; University of Wisconsin, Madison, WI; Wayne State University, Henry Ford Cancer Institute, Detroit, MI; Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; Baylor College of Medicine, Houston, TX; BCCA - Vancouver Cancer Centre, University of British Columbia, Vancouver, BC, Canada; NSABP Foundation and UPMC Hillman Cancer Center, University of Pittsburgh School of Medicine, Pittsburgh, PA; University of Florida Health Cancer Institute, Gainesville, FL; University of Colorado Cancer Center, Aurora, CO

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 IIIC 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. Accrual is 1,123/1,912 (as of 1/20/2026). *Drs. Dasari and Lieu contributed equally to the development of this trial. Clinical trial information: NCT05174169. Research Sponsor: U.S. National Institutes of Health; U10 CA180868; U.S. National Institutes of Health; U10 CA180822; U.S. National Institutes of Health; U10 CA180888; U.S. National Institutes of Health; UG1 CA189867; U.S. National Institutes of Health; R50 CA28193; Natera, Inc.

Node-sparing modified short-course radiotherapy combined with capecitabine and PD-1/CTLA-4 for MSS early, middle, and low rectal cancer (mRCAT-E): An open-label, single-arm, prospective multicenter clinical trial.

Zhangfa Song, Bingjun Bai, Weifeng Lao, Min Chen; Department of Colorectal Surgery, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, China; Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China; Sir Run Run Shaw Hospital Zhejiang University School of Medicine, Hangzhou, China

Background: The standard treatment for early-stage rectal cancer is radical resection. For patients' organ preservation and quality of life improvement, preoperative radiotherapy plus chemotherapy then "watch-and-wait" are also recommended. But the clinical complete response (cCR) rate after chemoradiotherapy is only about 30~40%. Recent studies have shown that combining radiotherapy with PD-1 blockade can improve pathological complete response (pCR) rates to 40~50% for proficient mismatch repair (pMMR) or microsatellite stable (MSS) locally advanced rectal cancer (LARC) patients. However, the irradiation to tumor-draining lymph nodes (TDLNs) 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% and reduce radiation-related toxicity in pMMR/MSS LARC.¹ Iparomlimab/tuvonralimab is a novel bifunctional antibody, containing a mixture of anti-PD-1 IgG4 antibody iparomlimab and anti-CTLA-4 IgG1 antibody tuvonralimab, produced in a fixed ratio (2:1) from the same single cell and manufactured together as one product.² In this trial, we hypothesize that node-sparing modified short-course radiotherapy combined with capecitabine and PD-1/CTLA-4 may induce synergistic activity and substantially improve CR rates while reducing radiation-related toxicity. **Methods:** This is a single-arm, prospective, multicenter, phase II study across 3 hospitals in China. The main inclusion criteria includes rectal cancer within 7 cm from the lower edge of the tumor to the anal verge and the clinical stage is cT2-3N0M0, MSI-L/MSS or pMMR. A total of 52 patients will receive node-sparing modified short-course radiotherapy of 25 Gy delivered in 5 daily fractions to the primary tumor bed (excluding TDLNs). Beginning on treatment Day 8, patients will receive 4 cycles of capecitabine (1,000 mg/m², D1-14, q3w) and iparomlimab/tuvonralimab (5 mg/kg, D1, q3w). Tumor response will be assessed 1-2 weeks after the last chemo-immunotherapy. Patients with cCR enter a watch-and-wait program, while non-cCR proceed to local excision or total mesorectal excision. The primary endpoint is the CR rate (cCR and pCR). Secondary endpoints include organ preservation rate, 3-year local recurrence rate, overall survival, toxicity, and quality-of-life measures. As of January 2025, 5 of the planned 52 patients have been enrolled. The Data Monitoring Committee (DMC) reviewed the trial in December 2024 and recommended continuing as planned. Clinical trial information: NCT07068763. References: (1) *Annals of Oncology* (2024) 24 (suppl_1): 1-20. 10.1016/j.ion.2024.100744; (2) Zhao et al. *Journal of Hematology & Oncology* (2023) 16:50. Clinical trial information: NCT07068763. Research Sponsor: None.

A phase 2 randomized study comparing telisotuzumab adizutecan monotherapy with standard of care in patients with post-adjuvant circulating tumor DNA–positive colorectal cancer.

Kanwal Pratap Singh Raghav, Hideaki Bando, Tao-Wei Ke, Meredith Pelster, Lorenzo Antonuzzo, Karen-Lise Garm Spindler, Sae-Won Han, Kun-Huei Yeh, Zhe Zhang, Martha Raluca Neagu Aristide, Chika Yamagishi, Henry Chang, Ou Zhao, Ramya Seshadri, Aparna Raj Parikh; The University of Texas MD Anderson Cancer Center, Houston, TX; National Cancer Center Hospital East, Kashiwa, Japan; China Medical University Hospital, Taichung, Taiwan; Sarah Cannon Research Institute, Nashville, TN; Azienda Ospedaliero Universitaria Careggi, Florence, Italy; Aarhus University Hospital, Aarhus, Denmark; Department of Internal Medicine, Seoul National University Hospital, and Seoul National University Cancer Research Institute, Seoul, South Korea; Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan; AbbVie, Inc., North Chicago, IL; AbbVie GK, Tokyo, Japan; Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA

Background: Curative intent standard of care (SOC) management of colorectal cancer (CRC) involves surgical tumor removal, followed by adjuvant therapy and active surveillance (AS). Presence of circulating tumor DNA (ctDNA) in the absence of radiographic evidence of disease is emerging as a reliable biomarker for determining molecular residual disease in CRC and in predicting recurrence after definitive therapy. Telisotuzumab adizutecan (Temab-A) is an antibody–drug conjugate that targets c-Met protein and is conjugated to a topoisomerase 1 (Top1) inhibitor payload. c-Met protein is ubiquitously expressed on CRC tumor cells. Temab-A has shown a manageable safety profile and promising antitumor activity in patients (pts) with advanced solid tumors, including CRC (NCT05029882). Herein, we describe a Phase 2 study of Temab-A monotherapy in pts with ctDNA–positive CRC after adjuvant therapy compared with AS. **Methods:** This open-label, randomized, global, multicenter, Phase 2 study (NCT07023289) includes adults (≥ 18 yrs) with histologically confirmed adenocarcinoma of the colon or rectum. Surgical tumor material must be available and submitted for Signatera personalized panel and assessment of c-Met protein levels. Pts must have received a total of ≥ 3 mos of perioperative and/or platinum–based doublet adjuvant therapy, have no radiographic evidence of disease as determined by CT scans and liver MRI, and be ctDNA–positive within the first year after the end of adjuvant therapy. Approximately 140 pts will be randomized (1:1) to receive either Temab-A (2.4 mg/kg, IV, Q3W, N=70) or AS only (N=70). Randomization will be stratified by oligometastatic versus nonmetastatic and by the timing of enrollment. Japan will have a separate randomization schedule stratified by the same factors. During 9 mos of treatment (12 cycles [C], 21 days [D] per C) or AS, pts will undergo monitoring for disease recurrence through CT scans (Q6W) and ctDNA testing (on C2D1, C3D1, C4D1, at 6 and 9 mos). Study follow-up will occur every 3 mos for the first 2 yrs and every 6 mos for the 3 yrs thereafter. The Table shows study objectives and endpoints. Clinical trial information: NCT07023289. Research Sponsor: None.

Objectives	Endpoints
Primary Evaluate efficacy of Temab-A	Disease-free survival by investigator
Secondary Evaluate clinical outcomes of Temab-A	ctDNA clearance at 6 mos after randomization Overall survival
Safety Evaluate safety/tolerability of Temab-A	Adverse event type, frequency, seriousness, and severity Treatment-emergent adverse events leading to treatment discontinuation and dose interruption
Pharmacokinetics (PK) Evaluate PK and immunogenicity of Temab-A	Serum concentration of: Temab-A conjugate Total antibody Plasma concentration of Top1 inhibitor

Phase 2 study of adjuvant botensilimab in combination with balstilimab in patients with microsatellite-stable colorectal cancer and persistent circulating tumor DNA following surgery and chemotherapy.

Neil Howard Segal, Karuna Ganesh, Phoebe Rubinstein, Devika Rao, Andrea Cercek, Louise Catherine Connell, Maliha Nusrat, Leonard B. Saltz, Zsofia Kinga Stadler, Rona Yaeger, Raymond Teer, Matthew Ellis, Jia Li, Michael Bonner Foote, Ryan Sugarman, Sree Bhavani Chalasani, Avni Mukund Desai, Joanne Chou, Marinela Capanu, Luis A. Diaz Jr.; Memorial Sloan Kettering Cancer Center, New York City, NY; Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; Memorial Sloan Kettering Cancer Center, New York, NY; Memorial Sloan Kettering Cancer Center, Basking Ridge, NJ; MSK's Center for Young Onset Colorectal and Gastrointestinal Cancer, New York, NY; Memorial Sloan Kettering Cancer Center at Basking Ridge New Jersey, Basking Ridge, NJ

Background: In patients with localized microsatellite stable (MSS) colorectal cancer (CRC), detection of circulating tumor DNA (ctDNA) after completion of definitive therapy indicates the presence of minimal residual disease (MRD) and predicts metastatic recurrence within months. Novel adjuvant therapies to prevent recurrence are very much needed. Botensilimab (BOT) is an Fc-enhanced multifunctional anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody designed to expand therapy to cold/poorly immunogenic solid tumors, such as MSS CRC. BOT plus balstilimab (BAL; PD-1 inhibitor) has previously demonstrated deep, durable responses in treatment-refractory metastatic MSS CRC and no active liver metastases. We hypothesize that treatment of MRD with effective immunotherapy in patients with MSS CRC after definitive therapy will prevent tumor recurrence. **Methods:** This investigator-initiated, open label, Phase 2 study evaluates the efficacy of BOT/BAL in patients with stage III MSS CRC (cohort 1) or colorectal liver metastases (CRLM) (cohort 2) and MRD following definitive treatment, including surgery and pre-operative chemotherapy. The study is being conducted in 2 parts. Part 1 aims to determine ctDNA clearance, as a surrogate for improved survival. Patients receive BOT/BAL for 6 months followed by BAL alone for 6 months. With a total of 27 patients per cohort, and using an exact single-stage binomial design, we will have 80% power to detect an improvement in ctDNA clearance from 5% to 20% with a type I error rate of 5%. If part 1 is successful, then part 2 of the study may proceed as a randomized, placebo-controlled, double-blind, multicenter study to assess improvement in recurrence-free survival. Translation studies are planned to correlate tumor and immune characteristics with ctDNA clearance and clinical endpoints to further our understanding of immune responsiveness in the setting of MRD in MSS CRC. Enrollment to the study is currently ongoing. Clinical trial information: NCT07227636. Research Sponsor: None.