Midyear Highlights in Gastrointestinal Cancers

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A Review of Selected Presentations From the ASCO Gastrointestinal Cancers Symposium, ASCO Annual Meeting, and ESMO Gastrointestinal Cancers Congress

With Expert Perspectives by

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This year has marked a dynamic chapter in gastrointestinal cancer research, with both practice-informing and practice-changing data emerging from key international meetings, including the American Society of Clinical Oncology Gastrointestinal Cancers Symposium (January 23-25, San Francisco), the American Society of Clinical Oncology Annual Meeting (May 30-June 3, Chicago), and the European Society for Medical Oncology Gastrointestinal Cancers Congress (July 2-5, Barcelona).

In this supplement, we spotlight a series of pivotal studies presented at these meetings that are actively reshaping therapeutic strategies across disease stages, highlighting the expanding roles of targeted agents, immunotherapy, and circulating tumor DNA–guided treatment escalation. Featured trials include BREAKWATER (evaluating a triplet regimen in *BRAF* V600E-mutant metastatic colorectal cancer), MATTERHORN (investigating immunochemotherapy in resectable gastric and gastroesophageal junction cancers), DESTINY-Gastric04 (assessing second-line trastuzumab deruxtecan in human epidermal growth factor receptor 2–positive unresectable/metastatic gastric and gastroesophageal junction adenocarcinoma), ALTAIR (reporting on circulating tumor DNA–guided intervention in patients with molecular residual disease following curative resection of colorectal cancer), and CheckMate 8HW (health-related quality of life outcomes in microsatellite instability–high/deficient mismatch repair metastatic colorectal cancer). We also explore emerging data on the prognostic and predictive utility of circulating tumor DNA in stage III colon cancer, including its role in guiding adjuvant chemotherapy escalation.

Alongside concise summaries of these studies, Dr Ilson and I offer our perspectives on their potential impact on clinical practice and evolving standards of care.

—Tanios S. Bekaii-Saab, MD

Clinical Advances in
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Special Reporting on:

- Fruquintinib + Trifluridine/Tipiracil as Third-Line Treatment in Patients With mCRC
- BREAKWATER: First-Line Encorafenib + Cetuximab + mFOLFOX6 in *BRAF* V600E-Mutant mCRC
- MATTERHORN: Durvalumab + 5-Fluorouracil, Leucovorin, Oxaliplatin, and Docetaxel Chemotherapy in Resectable GC/GEJC
- Standard Chemotherapy Alone or Combined With Atezolizumab as Adjuvant Therapy for Patients With Stage III dMMR Colon Cancer (Alliance A021502; ATOMIC)
- DESTINY-Gastric04 Study: Trastuzumab Deruxtecan vs Ramucirumab + Paclitaxel in Second-Line Treatment of Patients with HER2+ Unresectable/Metastatic GC or GEJA
- ctDNA-Guided Adjuvant Chemotherapy Escalation in Stage III Cancer: Primary Analysis of the ctDNA-Positive Cohort From the Randomized AGITG DYNAMIC-III Trial (Intergroup Study of AGITG and CCTG)
- ALTAIR Study: Trifluridine/Tipiracil vs Placebo in Patients With Molecular Residual Disease Following Curative Resection of CRC
- CALGB (Alliance)/SWOG 80702: Prognostic and Predictive Role of ctDNA in Stage III Colon Cancer Treated With Celecoxib
- CAPRI-2 GOIM Study: Integrating Tissue and Liquid Biopsy Comprehensive Genomic Profiling to Predict Efficacy of Anti-EGFR Therapies in mCRC
- CheckMate 8HW: HRQoL With Nivolumab + Ipilimumab in MSI-H/dMMR mCRC

PLUS Meeting Abstract Summaries

Fruquintinib + Trifluridine/Tipiracil as Third-Line Treatment in Patients With mCRC

The anti–vascular endothelial growth factor receptor (VEGFR) therapy fruquintinib and the chemotherapy trifluridine plus tipiracil (TAS-102), in combination with bevacizumab, are both approved by the US Food and Drug Administration (FDA) for use in patients with metastatic colorectal cancer (mCRC) previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and anti–epidermal growth factor receptor (EGFR) therapy if *RAS* wild-type.[1,2]

A single-arm, open-label, phase 2 trial was undertaken to evaluate the combination of fruquintinib and TAS-102 as third-line treatment for patients with mCRC. The trial enrolled 50 patients with a median age of 60 years (range, 39-60 years), 42% with *RAS* mutations, 58% with liver metastases, and 18% with peritoneal metastases. In a preliminary analysis, fruquintinib plus TAS-102 demonstrated acceptable tolerability and clinical activity, with a partial response (PR) rate of 10.9% and a median progression-free survival (PFS) of 6.46 months.[3]

At the 2025 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium, investigators presented updated efficacy and safety data after a median follow-up of 17.6 months (Table 1).[4] The median PFS was 6.33 months and the median overall survival (OS) was 18.4 months. In subset analyses, PFS outcomes were comparable whether or not patients had liver metastases or peritoneal metastases. Moreover, Cox models found no significant association between PFS or OS and primary disease, number of prior lines of therapy (≥3 vs <3), age (≥65 vs <65 years), number of metastases (1 vs >1), or *KRAS* mutation status.

The most frequent grade 3 or 4 treatment-related adverse events (TRAEs) were decreased neutrophil count (54%), decreased white blood cell count (26%), anemia (20%), and increased blood bilirubin (12%). Investigators concluded that the analysis showed encouraging survival benefits and acceptable toxicity with fruquitinib plus TAS-102 as third-line treatment for patients with mCRC.

Also, at the 2025 ASCO Gastrointestinal Cancers Symposium, Niu and colleagues presented an exploratory study evaluating intermittent administration of TAS-102 combined with fruquintinib as third-line treatment for mCRC.[5] A total of 26 patients received fruquintinib (3 mg once daily on days 1-5 and 8-12) and TAS-102 (35 mg/m^2 twice daily on days 1-5) every 2 weeks. The median age of enrolled patients was 58 years (range, 19-77 years). Among 22 evaluable patients, the PR rate was 18.2%, the stable disease rate was 50%, and the median PFS was 135 days. The median PFS in patients with *RAS* mutations was 161 days (objective response rate [ORR], 25%), compared with 135 days in patients with *RAS* wild-type (ORR, 12.5%).

The most common grade 3 or higher TRAEs were leukopenia (11.5%), neutropenia (11.5%), and anemia (7.7%). The most common nonhematologic TRAEs of any grade were anorexia (46.2%) and fatigue (19.2%). Investigators concluded that intermittent TAS-102 administration plus fruquintinib reduces rates of hematologic toxicity and shows encouraging clinical activity.

Table 1. Fruquintinib + Trifluridine/Tipiracil as Third-Line Treatment in Patients With mCRC

PFS	
Median (95% CI), months	6.33 (4.20, 8.62)
6-month rate (95% CI), %	53.0 (40.2, 70.0)
9-month rate (95% CI), %	28.3 (17.4, 45.9)
12-month rate (95% CI), %	23.1 (13.2, 40.5)
OS	
Median (95% CI), months	18.4 (12.0, NA)
6-month rate (95% CI), %	87.0 (77.8, 97.3)
9-month rate (95% CI), %	66.9 (54.0, 82.9)
12-month rate (95% CI), %	64.3 (51.1, 80.8)

mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression-free survival.
Adapted from Peng J et al. Presented at: 2025 ASCO Gastrointestinal Cancers Symposium; January 23-25, 2025; San Francisco, California, USA. Abstract 145.[4]

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5. Niu J, Luo H, Chen W, et al. Exploratory study of TAS-102 combined with intermittent administration of fruquintinib in the treatment of third-line metastatic colorectal cancer. Presented at: 2025 ASCO Gastrointestinal Cancers Symposium; January 23-25, 2025; San Francisco, California, USA. Abstract 174.

Expert Perspective

Tanios S. Bekaii-Saab, MD: In refractory mCRC, options remain limited, especially for biomarker-negative patients. Current choices include fruquintinib, regorafenib, and TAS-102 with or without bevacizumab. Although TAS-102 plus bevacizumab is associated with improved outcomes over TAS-102 alone, the benefit diminishes in patients previously exposed to bevacizumab. With many patients expressing a preference for oral regimens, fruquintinib or regorafenib may be favored in this setting. Emerging exploratory data on fruquintinib plus TAS-102 suggest potential synergy, warranting further randomized trials. Although not yet practice-changing, this combination may expand future options in biomarker-negative refractory mCRC.

BREAKWATER: First-Line Encorafenib + Cetuximab + mFOLFOX6 in *BRAF* V600E-Mutant mCRC

BRAF V600E mutations are present in approximately 8% to 12% of mCRC and are associated with poor prognosis and resistance to chemotherapy.[1] The open-label, global, randomized, phase 3 BREAKWATER study compared the *BRAF* inhibitor encorafenib plus cetuximab (EC) with or without 5-fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) against standard of care (SOC; investigator's choice of mFOLFOX6, or 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan [FOLFOXIRI], or capecitabine and oxaliplatin [CAPOX], with or without bevacizumab) in patients with *BRAF* V600E-mutated mCRC. The trial initially randomly assigned patients 1:1:1 to EC (n=158), EC plus mFOLFOX6 (n=236), or SOC (n=243) but was amended to limit enrollment to the EC plus mFOLFOX6 and SOC arms.

In a prior analysis, the trial met its coprimary endpoint, demonstrating a significant improvement with EC plus mFOLFOX6 over SOC in ORR by blinded independent central review (BICR) (60.9% vs 40.0%; odds ratio [OR], 2.443; *P*=.0008).[2] Its initial activity and safety profile led to the accelerated approval of EC plus mFOLFOX6 for patients with mCRC with a *BRAF* V600E mutation.[3]

At the 2025 ASCO Annual Meeting, investigators presented additional results (Table 2). The trial met its coprimary endpoint, demonstrating a significant improvement in median PFS by BICR with EC plus mFOLFOX6 over SOC (12.8 vs 7.1 months; hazard ratio [HR], 0.53; *P*<.0001) and a significant improvement in median OS (30.3 vs 15.1 months; HR, 0.49; *P*<.0001).[4] The median PFS and OS in the EC arm were 6.8 months and 19.5 months, respectively, suggesting longer OS with EC vs SOC. In an updated response analysis, the best ORR was 45.6% with EC, 65.7% with EC plus mFOLFOX6, and 37.4% with SOC; median duration of response was 7.0 months, 13.9 months, and 10.8 months, respectively.

As reported at the European Society for Medical Oncology (ESMO) Gastrointestinal Cancers Congress, the control regimen associated with the highest ORR was FOLFOXIRI plus bevacizumab, at 55.9% (n=59), with a median duration of response (DOR) of 9.8 months.[5] Although this approach was numerically more effective than doublet chemotherapy regimens, it was numerically less effective than EC plus mFOLFOX6.

At the 2025 ASCO Annual Meeting, investigators reported that the safety profile of EC plus mFOLFOX6

Table 2. BREAKWATER: PFS by BICR and Second Interim Analysis of OS of First-Line EC + mFOLFOX6 vs SOC in *BRAF* V600E-Mutant mCRC

	EC + mFOLFOX6 (n=236)	SOC (n=243)
PFS		
n (%)	122 (51.7)	132 (54.3)
Median (95% CI), mo	12.8 (11.2, 15.9)	7.1 (6.8, 8.5)
HR (95% CI)	**0.53** (0.407, 0.677) *P*<.0001	
OS		
n (%)	94 (39.8)	148 (60.9)
Median (95% CI), mo	30.3 (21.7, NE)	15.1 (13.7, 17.7)
HR (95% CI)	**0.49** (0.375, 0.632) *P*<.0001[a]	

[a]Exceeding the threshold for statistical significance in this interim analysis.
BICR, blinded independent central review; mCRC, metastatic colorectal cancer; EC, encorafenib + cetuximab; HR, hazard ratio; mFOLFOX6, 5-fluorouracil, leucovorin, and oxaliplatin; mCRC, metastatic colorectal cancer; mo, months; NE, not evaluable; OS, overall survival; PFS, progression-free survival; SOC, standard of care.
Adapted from Elez E et al. Presented at: 2025 Annual Meeting of the American Society of Clinical Oncology; May 30-June 3, 2025; Chicago, Illinois, USA. Abstract LBA3500.[4]

was consistent with the safety of the individual components.[4] The rate of grade 3 or 4 TRAEs was 76.3% with EC plus mFOLFOX6, 58.5% with SOC, and 15.7% with EC. There were no increases in chemotherapy dose reduction or discontinuation.

Investigators concluded that EC plus mFOLFOX6 is a practice-changing new SOC for patients with *BRAF* V600E-mutated mCRC, and that EC may be considered for patients unable to tolerate chemotherapy.

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Expert Perspectives

Tanios S. Bekaii-Saab, MD: The BREAKWATER study marks a paradigm shift in the management of *BRAF* V600E-mutated mCRC. Historically associated with poor prognosis and limited treatment durability, this subgroup now benefits from first-line encorafenib plus cetuximab combined with chemotherapy (FOLFOX or FOLFOXIRI). The trial demonstrated significant improvements in PFS and OS, with striking response rates and curve separation. This regimen is now considered the SOC for *BRAF* V600E-mutated mCRC, with outcomes comparable to, if not surpassing, those in non-*BRAF* V600E-mutated mCRC. The findings underscore the critical importance of upfront molecular profiling (*BRAF*, *KRAS*, microsatellite instability [MSI] status, and human epidermal growth factor receptor 2 [HER2] amplification) to guide therapy selection and optimize outcomes.

David H. Ilson, MD, PhD: This practice-changing trial in mCRC with *BRAF* V600E mutations randomized patients to standard chemotherapy vs first-line FOLFOX plus encorafenib (BRAF inhibitor) and cetuximab (EGFR inhibitor). Although encorafenib–cetuximab is already approved in later-line settings, this study demonstrated striking first-line efficacy: PFS nearly doubled, response rates significantly improved, and OS increased from about 15 to 30 months. These results confirm the superiority of triplet therapy over chemotherapy alone. With regulatory approval already in place, this trial firmly establishes FOLFOX plus encorafenib–cetuximab as a new SOC in untreated *BRAF* V600E-mutated mCRC.

MATTERHORN: Durvalumab + 5-Fluorouracil, Leucovorin, Oxaliplatin, and Docetaxel Chemotherapy in Resectable GC/GEJC

In patients with locally advanced, resectable gastric or gastroesophageal junction adenocarcinoma (GEA), use of fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) provides an OS benefit over epirubicin, cisplatin, and fluorouracil or epirubicin, cisplatin, and capecitabine (ECF/ECX).[1] However, there remains a need for more effective regimens to reduce the risk of recurrence. Adding a programmed cell death protein 1 (PD-1) inhibitor to chemotherapy is associated with an OS benefit in patients with metastatic GEA.[2] However, its potential role in the early-stage disease setting had not been elucidated.

The global randomized, double-blind, phase 3 MATTERHORN trial was undertaken to evaluate the efficacy and safety of adding the programmed death ligand 1 (PD-L1) inhibitor durvalumab to FLOT chemotherapy in patients with resectable gastric or gastroesophageal junction cancer (GC/GEJC). The study enrolled 948 patients with stage II to IVa GEA who were randomly assigned to perioperative FLOT with or without durvalumab 1500 mg every 4 weeks. Patients received 2 cycles of neoadjuvant FLOT with or without durvalumab followed by surgery, then 2 cycles of adjuvant FLOT with or without durvalumab and 10 cycles of single-agent durvalumab or placebo.

At the 2025 ASCO Annual Meeting, investigators presented the primary endpoint of event-free survival (EFS) outcomes from MATTERHORN (Table 3).[3] Rates of treatment and surgery completion were similar between arms, with 84% to 87% of patients completing surgery, 92% of those patients attaining an R0 resection, and 52% completing adjuvant treatment. Durvalumab plus FLOT was associated with a significant improvement in EFS over placebo plus FLOT (median, not reached vs 32.8 months; HR, 0.71; 95% CI, 0.58-0.86; *P*<.001), with an EFS benefit that was consistent across key subgroups. There was no significant difference in OS between arms (median OS, not reached vs 47.2 months; HR, 0.78; 95% CI, 0.62-0.97; *P*=.025 [significance threshold *P*<.0001]). Rates of pathologic complete response (pCR) were also significantly higher in the durvalumab-containing arm than the control arm (19% vs 7%; OR, 3.08; 95% CI, 2.03-4.67; *P*<.001), as was disease-free survival (DFS) among patients with R0 resection (median, not reached vs 39.8 months; HR, 0.70; 95% CI, 0.53-0.93).

Table 3. MATTERHORN: EFS and OS of Durvalumab + FLOT in Resectable GC/GEJC

	Durvalumab + FLOT (n=474)[a]	Placebo + FLOT (n=474)[a]
EFS		
Median (95% CI), mo	NR (40.7, NR)	32.8 (27.9, NR)
HR (95% CI)	**0.71** (0.58, 0.86) Stratified log-rank *P*<.001[b]	
OS		
Median (95% CI), mo	NR (NR, NR)	47.2 (45.1, NR)
HR (95% CI)	**0.78** (0.62, 0.97) Stratified log-rank *P*=.025[c]	

[a]Full analysis set (all randomized patients, regardless of treatment received).
[b]Threshold for statistical significance *P*=.0239.
[c]Threshold for statistical significance *P*<.0001.
EFS, event-free survival; FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel; GC/GEJC, gastric or gastroesophageal junction cancer; HR, hazard ratio; mo, months; NR, not reached; OS, overall survival.
Adapted from Janjigian YY et al. Presented at: 2025 Annual Meeting of the American Society of Clinical Oncology; May 30-June 3, 2025; Chicago, Illinois, USA. Abstract LBA5.[3]

The safety analysis found no new toxicity concerns. The most common adverse events (AEs) of any grade were diarrhea, reported in 62% of patients receiving durvalumab plus FLOT vs 58% of patients receiving placebo plus FLOT, nausea (51% vs 51%), neutropenia (32% vs 33%), alopecia (31% vs 32%), and decreased appetite (31% vs 30%). The most common grade 3 or 4 AEs were neutropenia (21% vs 22%), and diarrhea (6% vs 6%). As reported at the 2025 ESMO Gastrointestinal Cancers Congress, there were no relevant differences between arms in the time to deterioration of quality of life as assessed by the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30.[4] Investigators concluded that perioperative durvalumab plus FLOT should be a new standard for patients with localized GC/GEJC.

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Expert Perspectives

Tanios S. Bekaii-Saab, MD: The MATTERHORN trial demonstrated a significant improvement in EFS with the addition of durvalumab to perioperative FLOT in resectable GC/GEJC, supporting a shift in standard practice. However, key uncertainties remain. The validity of EFS as a surrogate for OS is unproven and the benefit may be limited to patients with a Combined Positive Score (CPS) of at least 1. Although durvalumab is now a consideration in this setting, clinicians should weigh these caveats in shared decision-making with their patients.

David H. Ilson, MD, PhD: The global phase 3 MATTERHORN trial demonstrated that adding durvalumab to perioperative FLOT chemotherapy in resectable GC significantly improved EFS by about 10% at 2 years and tripled pCR rates (7% to 20%). The regimen was well tolerated across diverse populations, and benefit was observed regardless of PD-L1 status. Although OS data remain immature, trends favor the durvalumab arm. These findings establish FLOT plus durvalumab as a new global SOC in resectable GC.

Standard Chemotherapy Alone or Combined With Atezolizumab as Adjuvant Therapy for Patients With Stage III dMMR Colon Cancer (Alliance A021502; ATOMIC)

For patients with stage III colon cancer, the standard adjuvant therapy regardless of mismatch repair (MMR) status has been combination chemotherapy with a fluoropyrimidine plus oxaliplatin. However, deficiency in MMR (dMMR) may confer resistance to fluoropyrimidines.[1] Immune checkpoint inhibitors have an established role in the treatment of dMMR metastatic cancers.[2] However, their potential benefit in patients with dMMR stage III colon cancer has not been investigated.

The randomized, multicenter, open-label, phase 3 ATOMIC trial was undertaken to evaluate the addition of atezolizumab to adjuvant mFOLFOX6 in patients with resected stage III colon cancer with dMMR by immunohistochemistry (IHC). A total of 712 patients were randomly assigned to mFOLFOX6 plus atezolizumab for 6 months, followed by 6 months of single-agent atezolizumab (n=355) or 6 months of mFOLFOX6 alone (n=357).

At the 2025 ASCO Annual Meeting, investigators presented the primary analysis from the ATOMIC trial after a median follow-up of 37.2 months (Table 4).[3] Patient characteristics were well balanced between arms. Approximately 32% of patients had T4 disease, 37% had N2 disease, and 54% had high-risk disease (T4 and/or N2).

The trial met its primary endpoint, demonstrating a significant improvement in DFS with mFOLFOX6 plus atezolizumab vs mFOLFOX alone (36-month DFS, 86.4% vs 76.6%; HR, 0.50; 95% CI, 0.34-0.72; $P<.0001$). The DFS benefit was similar among the 88% of patients testing dMMR by central laboratory (36-month

Table 4. DFS With Standard Chemotherapy Alone or Combined With Atezolizumab as Adjuvant Therapy for Patients With Stage III dMMR Colon Cancer (Alliance A021502; ATOMIC)

	mFOLFOX6 + Atezolizumab	mFOLFOX6
Events/Total	45/355	80/357
DFS (95% CI), %	86.4 (81.8, 89.9)	76.6 (71.3, 81.0)
HR (95% CI)	**0.50** (0.34, 0.72) Log-rank *P*<.0001	

DFS, disease-free survival; HR, hazard ratio; mFOLFOX6, 5-fluorouracil, leucovorin, and oxaliplatin.
Adapted from Sinicrope FA et al. Presented at: 2025 Annual Meeting of the American Society of Clinical Oncology; May 30-June 3, 2025; Chicago, Illinois, USA. Abstract LBA1.[3]

DFS, 86.6% vs 77.1%; HR, 0.53; 95% CI, 0.36-0.79; *P*<.0007). OS data were not mature at the time of analysis.

The rate of grade 3 or 4 TRAEs was 72.3% with mFOLFOX plus atezolizumab vs 59.2% with mFOLFOX6 alone; there were 2 fatal TRAEs in the atezolizumab arm (1 sudden death and 1 sepsis, each possibly treatment-related) and none in the control arm. The most common AEs of any grade reported in the mFOLFOX6 plus atezolizumab and mFOLFOX arms, respectively, were fatigue (93% vs 88%), nausea (77% vs 69%), peripheral sensory neuropathy (76% vs 70%), neutrophil count decreased (74% vs 68%), platelet count decreased (68% vs 66%), and diarrhea (72% vs 62%). The most common grade 3 or 4 AEs were neutrophil count decreased (43% vs 36%), peripheral sensory neuropathy (19% vs 15%), diarrhea (12% vs 8%), and fatigue (10% vs 4%).

Investigators noted that the safety profile of mFOLFOX6 plus atezolizumab was consistent with the known safety profile of each agent. They concluded that atezolizumab plus mFOLFOX6 provides a clinically meaningful reduction in the risk of recurrence or death over mFOLFOX6 alone and is a practice-changing treatment for patients with dMMR stage III colon cancer.

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Expert Perspectives

Tanios S. Bekaii-Saab, MD: The ATOMIC trial introduces adjuvant atezolizumab plus FOLFOX for stage III dMMR/microsatellite instability–high (MSI-H) colon cancer, showing improved DFS. However, several limitations temper its immediate clinical impact. The absence of an immunotherapy-only arm limits conclusions about chemotherapy necessity, especially given emerging data suggesting limited benefit in this subgroup. Additionally, the use of 6-month FOLFOX diverges from current standards favoring 3-month CAPOX, and the 1-year atezolizumab duration may be excessive. Furthermore, with the survival data pending, the DFS–OS correlation specifically in MSI-H disease remains uncertain. If the addition of atezolizumab only delays progression but does not impact survival outcomes, then the value of this combination can come into question. Therefore, although the ATOMIC trial is practice-informing, it is not fully practice-defining. For now, clinicians should weigh efficacy against toxicity, cost, and evolving evidence favoring immunotherapy-only strategies, including in the neoadjuvant setting or potentially nonoperative management approaches.

David H. Ilson, MD, PhD: The ATOMIC trial was the first to evaluate adjuvant chemotherapy plus atezolizumab in MSI-H stage III colon cancer, demonstrating a 10% improvement in EFS and confirming the benefit of immunotherapy in this setting. However, the regimen, which is 6 months of chemotherapy and 1 year of atezolizumab, may be unnecessarily intensive. Emerging data suggest neoadjuvant immunotherapy may offer superior efficacy with less treatment burden. The NICHE trial from the Netherlands showed that just 2 doses of ipilimumab and nivolumab prior to surgery yielded a 60% pCR rate, 80% near-CR, and 100% 3-year DFS. Given these results, neoadjuvant checkpoint blockade is likely to become the preferred strategy for MSI-H stage II or III colon cancer, reserving approaches like those used in ATOMIC for patients undergoing upfront surgery. The paradigm shift already underway in MSI-H rectal cancer further supports this trajectory.

DESTINY-Gastric04 Study: Trastuzumab Deruxtecan vs Ramucirumab + Paclitaxel in Second-Line Treatment of Patients with HER2+ Unresectable/Metastatic GC or GEJA

For the subset of patients with HER2+ GC/GEJA, the current first-line therapy is chemotherapy plus trastuzumab, plus pembrolizumab in patients testing PD-L1 positive.[1] The HER2-targeted antibody-drug conjugate trastuzumab deruxtecan (T-DXd) is FDA-approved for use in patients with locally advanced or metastatic HER2+ GC/GEJA who have received a prior trastuzumab-based regimen.[2] However, T-DXd had not been compared with the standard second-line regimen of ramucirumab plus paclitaxel in a phase 3 trial.

At the 2025 ASCO Annual Meeting, and with a concurrent publication, Shitara and colleagues reported primary results from DESTINY-Gastric04, a global, randomized, multicenter, open-label phase 3 trial comparing T-DXd vs ramucirumab plus paclitaxel as second-line treatment in patients with HER2+ metastatic GC/GEJA.[3,4] The trial enrolled 494 patients with HER2+ (IHC 3+ or IHC 2+/ISH+) GC/GEJA without clinically active central nervous system metastases. Patients were assigned to T-DXd 6.4 mg/kg every 3 weeks (n=246) or ramucirumab plus paclitaxel (n=248).

The trial met its primary endpoint, demonstrating a significant improvement in OS with T-DXd vs ramucirumab plus paclitaxel (median, 14.7 vs 11.4 months; HR, 0.70; 95% CI, 0.55-0.90; *P*=.0044; Table 5). The OS benefit with T-DXd was consistent in a sensitivity analysis accounting for subsequent therapies. T-DXd was also associated with a significant PFS benefit over ramucirumab plus paclitaxel (median PFS, 6.7 vs 5.6 months; HR, 0.74; 95% CI, 0.59-0.92; *P*=.0074) and a significant improvement in confirmed ORR (44.3% vs 29.1%; *P*=.0006).

Safety analyses showed a similar incidence between T-DXd and ramucirumab plus paclitaxel in rates of drug-related grade 3 or higher treatment-emergent adverse events (TEAEs) (50.5% vs 54.1%), serious TEAEs (18.4% vs 17.6%), treatment discontinuations (11.5% vs 13.3%), and deaths (1.6% vs 0.9%). The most frequent drug-related TEAEs were fatigue (48.0% vs 37.8%), neutropenia (48.0% vs 48.9%), nausea (44.3% vs 14.2%), and anemia (31.1% vs 33.0%). The most frequent drug-related grade 3 or higher TEAEs were neutropenia (28.7% vs 35.6%), anemia (13.9% vs 13.7%), thrombocytopenia (8.6% vs 3.0%), and hypertension (0% vs 8.2%). Drug-related interstitial lung disease/pneumonitis occurred in 34 patients (13.9%) receiving T-DXd vs 3 patients (1.3%) receiving ramucirumab plus paclitaxel. Left ventricular dysfunction occurred in 2.5% and 1.7% of patients, respectively. Patient-reported outcomes showed a maintenance of patient health-related quality of life (HRQoL) during T-DXd treatment. No clinically meaningful changes were noted on the EQ-5D-5L visual analogue scale (VAS) and Functional Assessment of Cancer Therapy–Gastric subscales.

Investigators concluded that in the second-line treatment of patients with HER2+ metastatic GC/GEJA, T-DXd was associated with significant improvements over ramucirumab plus paclitaxel in OS, PFS, and confirmed ORR, while demonstrating a toxicity profile that was generally manageable and consistent with its established safety profile. They added that the findings confirm T-DXd as the global SOC for second-line therapy in patients with HER2+ metastatic GC/GEJA.

Table 5. DESTINY-Gastric04 Study: T-DXd vs Ramucirumab + Paclitaxel in Second-Line Treatment of Patients with HER2+ Unresectable/Metastatic GC/GEJA

	T-DXd	Ramucirumab + Paclitaxel
PFS		
Median (95% CI), mo	6.7	5.6
HR (95% CI)	**0.74** (0.59, 0.92) *P*=.0074	
OS		
Median (95% CI), mo	14.7	11.4
HR (95% CI)	**0.70** (0.55, 0.90) *P*=.0044	

GC/GEJA, gastric cancer or gastroesophageal junction adenocarcinoma; HR, hazard ratio; mo, months; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan.
Adapted from Shitara K et al. Presented at: 2025 Annual Meeting of the American Society of Clinical Oncology; May 30-June 3, 2025; Chicago, Illinois, USA. Abstract LBA4002.[3]

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Expert Perspectives

Tanios S. Bekaii-Saab, MD: The DESTINY-Gastric04 trial reinforces T-DXd as a second-line therapy for HER2+ gastric and gastroesophageal cancers. Although not practice-changing in the United States, where the National Comprehensive Cancer Network guidelines already support T-DXd post-trastuzumab, this study supports current clinical practice. Globally, the impact of DESTINY-Gastric04 is more pronounced, as it provides evidence supporting T-DXd over paclitaxel-based regimens in regions where paclitaxel is the second-line standard, making ramucirumab-paclitaxel a viable later-line option.

David H. Ilson, MD, PhD: The DESTINY-Gastric04 trial establishes T-DXd as a new global second-line standard for HER2+ GC following progression on trastuzumab-based first-line therapy. Compared with paclitaxel plus ramucirumab, T-DXd significantly improved OS, PFS, and response rates. HER2 status was confirmed prior to enrollment, and benefit was consistent across HER2 subgroups. Previously approved in later-line settings, this marks a practice-changing shift toward earlier use of T-DXd in HER2+ GC.

ctDNA-Guided Adjuvant Chemotherapy Escalation in Stage III Colon Cancer: Primary Analysis of the ctDNA-Positive Cohort From the Randomized AGITG DYNAMIC-III Trial (Intergroup Study of AGITG and CCTG)

Nearly one-third of patients with stage III colon cancer develop recurrence after adjuvant oxaliplatin-based chemotherapy, highlighting a need for a different approach for some patients.[1] In patients with high-risk stage III colon cancer, 6 months of adjuvant oxaliplatin-based chemotherapy has demonstrated a lower risk of recurrence than 3 months of this treatment, suggesting a potential role for escalating therapy in some patients.[1] Given the prognostic value of postoperative circulating tumor DNA (ctDNA), postoperative ctDNA levels could identify patients who would benefit from a more intense adjuvant therapy.[2]

The randomized phase 2/3 DYNAMIC-III trial evaluated this strategy of ctDNA-guided adjuvant chemotherapy escalation in patients with stage III colon cancer.[3] A total of 1002 patients with R0-resected stage III colon cancer underwent tumor-informed ctDNA analysis, then were randomly assigned to ctDNA-informed management, in which patients testing ctDNA-positive received therapy escalation from the preplanned SOC, or standard management, consisting of treatment per clinician's choice.

The intention-to-treat population included 482 patients assigned to ctDNA-guided treatment and 479 patients assigned to standard management; 27% of patients in each arm tested ctDNA-positive. Patients with clinical high-risk disease (T4 or N2) accounted for 60% of the ctDNA-informed group and 53% of the standard management group. Extramural tumor deposits were present in 39% and 31%, respectively.

The most common chemotherapy regimens in the ctDNA-informed group were FOLFOXIRI administered for at least 3 months (50%) and an oxaliplatin doublet administered for 6 months (44%); the most common

regimens in the standard management arm were 3 months of an oxaliplatin doublet (45%) and 6 months of an oxaliplatin doublet (41%).

After a median follow-up of 42.2 months, there was no significant difference in recurrence-free survival (RFS) between arms; median RFS was 29.24 months with ctDNA-guided therapy and 36.80 months with SOC (HR, 1.11; *P*=.57). The 3-year RFS rates were 48% and 52%, respectively. A post hoc analysis showed no significant improvement with FOLFOXIRI vs doublet therapy in RFS (HR, 1.09; *P*=.662) or ctDNA clearance rates (60% vs 62%). In subgroup analyses, the only factor that showed a trend toward a significant treatment interaction with RFS was T-stage (*P*=.0627).

End of treatment ctDNA clearance was significantly associated with risk of recurrence: 3-year RFS rates were 84% in patients with ctDNA clearance and 12% in patients with ctDNA persistence (HR, 11.1; *P*<.0001). The extent of ctDNA burden was significantly associated with RFS; 3-year RFS rates ranged from 78% for patients in the lowest quartile of ctDNA burden to 22% for patients in the highest quartile.

Safety outcomes were similar between arms; the rate of treatment-related hospitalization was 16% with ctDNA-informed escalation and 13% with standard therapy. Grade 3 or 4 TRAEs occurred in 18.6% and 16.9% of patients, respectively.

Investigators concluded that the recurrence risk for patients with stage III colon cancer and detectable ctDNA postsurgery remains high and rises with increasing ctDNA burden. Treatment escalation based on ctDNA, including switching from an oxaliplatin doublet to FOLFOXIRI, did not affect ctDNA clearance or reduce the risk of recurrence. However, outcomes were favorable among patients attaining ctDNA clearance. They noted that novel adjuvant strategies should be evaluated and ctDNA clearance could be an indicator of efficacy.

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Expert Perspective

David H. Ilson, MD, PhD: The Australian DYNAMIC-III trial evaluated ctDNA-guided escalation of adjuvant therapy in stage III colon cancer. Among patients with postoperative ctDNA positivity (15%-20%), escalation to 6 months of FOLFOX, CAPOX, or FOLFOXIRI was permitted. The trial showed no survival benefit for escalation, with only one-half of patients in the intensified arm receiving FOLFOXIRI. Lack of treatment standardization and underpowered design limit interpretability. Importantly, ctDNA positivity correlated with poor prognosis, and failure to clear ctDNA predicted high recurrence risk. Although ctDNA remains a strong prognostic marker, the role of irinotecan-based escalation requires validation in better-designed trials.

ALTAIR Study: Trifluridine/Tipiracil vs Placebo in Patients With Molecular Residual Disease Following Curative Resection of CRC

Use of tumor-informed ctDNA testing to guide adjuvant therapy was also explored in the randomized, double-blind, placebo-controlled, phase 3 ALTAIR study, which evaluated trifluridine/tipiracil (FTD/TPI) as adjuvant therapy in patients with CRC with molecular residual disease (MRD) as assessed by ctDNA positivity after curative resection.[1,2]

The trial enrolled patients with CRC testing ctDNA-positive after curative resection who had received standard perioperative therapy. A total of 243 patients were randomly assigned to FTD/TPI (n=122) or placebo (n=121), each for 6 cycles. The study arms were balanced for key demographic, disease-related, and treatment-related factors. More than one-third of patients (36%) were older than 70 years; 27% of patients had stage IV disease and 36% had received neoadjuvant treatment.

As reported at the 2025 ASCO Gastrointestinal Cancers Symposium, investigators found no significant improvement with FTD/TPI in the primary endpoint of DFS; median DFS was 9.30 months with FTD/TPI and 5.55 months with placebo (HR, 0.79; 95% CI, 0.60-1.05; *P*=.107) and 24-month DFS rates were 16.9% and 14.5%, respectively.[1] DFS was significantly improved with FTD/TPI vs placebo in the subset of patients with stage IV disease, in whom the median DFS was 9.76 and 3.96 months, respectively (HR, 0.53; 95% CI, 0.32-0.87; *P*=.012).

Grade 3 or higher AEs occurred in 73% of patients in the FTD/TPI arm and 3.3% in the placebo arm. Grade 3 or higher AEs reported in the FTD/TPI arm included neutropenia (56.6%) and leukopenia (17.2%).[2] Dose reductions owing to AEs were required in 37.7% of patients receiving FTD/TPI compared with 0.8% in the placebo arm. Investigators noted that no new safety signals were identified.

FTD/TPI was associated with significantly greater reductions in QoL than placebo as assessed by the EORTC QLQ-C30 Global Health Status at week 8 (*P*=.028); no significant differences in QoL between arms were reported after the completion of treatment. There was also no significant difference in ctDNA clearance rate with FTD/TPI vs placebo (17.2% vs 12.4%; *P*=.367).[2]

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Expert Perspectives

Tanios S. Bekaii-Saab, MD: The ALTAIR trial evaluated trifluridine/tipiracil in patients with resected stage II-IV colorectal cancer who remained ctDNA-positive following standard adjuvant therapy. Despite its promise, the study was negative, underscoring that switching to another fluoropyrimidine may not meaningfully alter outcomes in patients with MRD. This reinforces a broader insight that MRD positivity likely reflects biologically persistent disease requiring more than cytotoxic escalation. Emerging data from trials like BREAKWATER and CheckMate 8HW suggest that early integration of targeted therapy or immunotherapy yields superior outcomes. ALTAIR highlights the need to study matching MRD-positive patients to biologic therapies rather than relying on chemotherapy substitution alone.

David H. Ilson, MD, PhD: The ALTAIR trial was a randomized, double-blind, placebo-controlled phase 3 study evaluating trifluridine/tipiracil in patients with positive ctDNA following adjuvant therapy or metastatic resection. Despite ctDNA positivity being strongly prognostic for recurrence, early intervention with trifluridine/tipiracil did not significantly improve outcomes. A nonsignificant trend toward improved PFS was observed, but the study was overall negative. These findings suggest that trifluridine/tipiracil should not be adopted as a post-treatment strategy in ctDNA-positive patients, underscoring the need for more effective interventions in this high-risk population.

CALGB (Alliance)/SWOG 80702: Prognostic and Predictive Role of ctDNA in Stage III Colon Cancer Treated With Celecoxib

In the randomized, phase 3 CALGB (Alliance)/SWOG 80702 trial, the addition of the cyclooxygenase 2 inhibitor celecoxib to standard adjuvant chemotherapy was not associated with a significant improvement in DFS in patients with stage III colon cancer.[1] Moreover, there was no improvement in DFS based on duration of adjuvant chemotherapy. However, the separation of the DFS curves with celecoxib vs placebo suggested a benefit with celecoxib in a subgroup of patients.

At the 2025 ASCO Gastrointestinal Cancers Symposium, Nowak and colleagues presented results of an analysis evaluating the prognostic and predictive role of

postoperative ctDNA in patients randomized in CALGB/SWOG 80702 (Table 6).[2] Postsurgical ctDNA analysis was evaluable for 940 of the 2526 randomized patients; 18.4% tested ctDNA-positive and 81.6% tested ctDNA-negative. Baseline factors associated with a higher likelihood of testing ctDNA-positive included male sex (*P*=.003), higher T-stage (*P*=.001), N2 vs N1 (*P*<.0001), and assignment to celecoxib (*P*=.048).

Regardless of treatment arm, ctDNA status was highly prognostic for DFS and OS. The estimated 3-year DFS rate was 86.5% in patients testing ctDNA-negative vs 33.7% in patients testing ctDNA-positive, and estimated 5-year OS rates were 91.5% and 52.6%, respectively (*P*<.0001).

Among patients testing ctDNA-negative, DFS was not significantly longer with celecoxib vs placebo; estimated 3-year DFS rates were 87.4% and 85.6%, respectively (HR, 0.76; 95% CI, 0.54-1.08; *P*=.1293). However, among patients testing ctDNA-positive, DFS was significantly longer with celecoxib vs placebo, with 3-year DFS rates of 41.0% and 22.6%, respectively (HR, 0.55; 95% CI, 0.39-0.80; *P*=.0013). Similar trends were seen for OS. The 5-year OS rates with celecoxib and placebo were 91.8% and 91.3%, respectively (HR, 0.86; 95% CI, 0.55-1.35), in ctDNA-negative patients, and 61.6% and 39.9%, respectively, in ctDNA-positive patients (HR, 0.58; 95% CI, 0.38-0.90; *P*=.0135).

After adjusting for demographic, tumor-related, and clinical factors, the DFS and OS differences with celecoxib over placebo in patients testing ctDNA-positive yielded an HR of 0.63 (95% CI, 0.43-0.92; *P*=.0167) for DFS and 0.63 (95% CI, 0.40-0.98; *P*=.0419) for OS. Additional subset analyses suggested an OS benefit with celecoxib over placebo among ctDNA-positive patients with microsatellite-stable tumors and *PIK3CA*-wild type tumors. Investigators concluded that ctDNA status was highly prognostic and appeared to predict a benefit with adjuvant celecoxib. Additional studies are ongoing, including an evaluation of the benefit of 3 vs 6 months of adjuvant FOLFOX based on ctDNA status.

Table 6. CALGB (Alliance)/SWOG 80702: Prognostic and Predictive Role of ctDNA in Stage III Colon Cancer Treated With Celecoxib

	ctDNA status	
	Negative	**Positive**
DFS		
Events/Total	131/767	118/173
3-year survival estimate (95% CI), %	86.5 (84.0, 89.1)	33.7 (27.1, 41.8)
OS		
Events/Total	77/767	85/173
5-year survival estimate (95% CI), %	91.5 (89.5, 93.6)	52.6 (45.3, 61.0)

ctDNA, circulating tumor DNA; DFS, disease-free survival; OS, overall survival.

Adapted from Nowak JA et al. Presented at: 2025 ASCO Gastrointestinal Cancers Symposium; January 23-25, 2025; San Francisco, California, USA. Abstract LBA14.[2]

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2. Nowak JA, Shi Q, Twombly T, et al. Prognostic and predictive role of ctDNA in stage III colon cancer treated with celecoxib: findings from CALGB (Alliance)/SWOG 80702. Presented at: 2025 ASCO Gastrointestinal Cancers Symposium; January 23-25, 2025; San Francisco, California, USA. Abstract LBA14.

Expert Perspectives

Tanios S. Bekaii-Saab, MD: CALGB/SWOG 80702 evaluated celecoxib in stage III colorectal cancer following adjuvant chemotherapy. The overall trial confirmed the noninferiority of 3 vs 6 months of adjuvant therapy, and a secondary randomization assessed celecoxib vs placebo over 3 years. Although no benefit was observed in the unselected population, in MRD-positive patients, celecoxib significantly improved DFS and OS, independent of *PIK3CA* mutation status. However, only about 40% of patients had evaluable MRD data, and the analysis was retrospective. Because of these limitations, the potential for celecoxib in MRD-positive CRC is compelling but not practice-changing.

David H. Ilson, MD, PhD: As part of the IDEA trial, patients were randomized to receive 3 or 6 months of adjuvant chemotherapy, with an additional arm evaluating celecoxib for up to 2 years. Although the overall trial was negative for celecoxib benefit, exploratory analysis revealed that in the 15% to 20% of the patients who were ctDNA positive post-operatively, DFS rates were significantly improved from 22% to 41% with celecoxib, suggesting a potential benefit in high-risk ctDNA-positive patients. Additional compelling biomarker-driven data come from a European study showing that aspirin significantly improved outcomes in about 30% of patients with *PI3K* mutations, whereas no benefit was seen in wild-type cases. Together, these studies highlight emerging opportunities to personalize adjuvant strategies using ctDNA and molecular profiling.

CAPRI-2 GOIM Study: Integrating Tissue and Liquid Biopsy Comprehensive Genomic Profiling to Predict Efficacy of Anti-EGFR Therapies in mCRC

The prospective, single-arm, phase 2 CAPRI-2 GOIM trial is evaluating the efficacy of biomarker-driven anti-EGFR therapy over 3 lines of therapy in patients with *RAS/BRAF* V600E wild-type mCRC. Comprehensive genomic profiling was performed on tissue and plasma samples before initiating first-line therapy. At the 2025 ESMO Gastrointestinal Cancers Congress, Cioli and colleagues presented results of an analysis evaluating the ability of tissue biopsy-based and liquid biopsy-based molecular profiling to predict the efficacy of FOLFIRI plus cetuximab in this population.[1]

Tissue and plasma samples were evaluated from 156 patients and outcomes were compared for patients who were negatively hyperselected, defined as lacking mutations in genes associated with anti-EGFR drug resistance, vs those with these mutations.[2] The negatively hyperselected patients had significantly better outcomes than those with mutations, including higher ORR (79.6% vs 44.2%; *P*<.001) and longer median PFS (12.4 vs 7.4 months; *P*<.001). The molecular profile was concordant between tissue and liquid biopsy in 23 patients and was discordant in 20 cases. Compared with discordant cases, concordant cases were associated with a trend toward worse ORR outcomes (39.1% vs 50.5%; *P*=.5) and a significantly worse median PFS (3.94 vs 11.50 months; *P*=.02).

The ctDNA tumor fraction was significantly lower in patients with alterations detected only in tissue than in patients with concordant alterations (1.7% vs 23.0%; *P*=.01). Moreover, pathogenic variants that were only detected by one method or another yielded a lower mean clonality than concordant alterations, whether detected by liquid biopsy only (1.5% vs 95.2%; *P*<.001) or by tissue biopsy only (5.6% vs 81.9%; *P*=.04). Using a ctDNA tumor fraction threshold of greater than 10% allowed nearly all pathogenic variants detectable by tissue biopsy to also be detected by liquid biopsy. In 8 cases, variants were only detected by liquid biopsy and the median PFS for these patients was 8.24 months.

Investigators concluded that integrating both tissue and liquid biopsy for comprehensive genomic profiling may better reflect the molecular landscape and allow for better patient selection. Liquid biopsy appears to be reliable for predicting the efficacy of anti-EGFR therapy for patients with a high tumor frequency, whereas tissue biopsy provides additional information about pathogenic variants for patients with a tumor fraction less than 10%.

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Expert Perspective

Tanios S. Bekaii-Saab, MD: The CAPRI-2 GOIM study reinforces the clinical relevance of anti-EGFR rechallenge in mCRC, demonstrating that patients previously treated with EGFR inhibitors (cetuximab or panitumumab) may benefit from re-exposure in later lines if *RAS* and *BRAF* mutations are absent on ctDNA. Key insights are: (1) *RAS/BRAF* mutations are key drivers of resistance to EGFR-targeted therapy; (2) ctDNA-guided selection enables identification of patients with molecular regression of resistant clones; and (3) rechallenge in selected patients yields 20% to 30% response rates in later lines. This study underscores the importance of dynamic molecular profiling to guide personalized rechallenge strategies.

CheckMate 8HW: HRQoL With Nivolumab + Ipilimumab in MSI-H/dMMR mCRC

At the 2025 ESMO Gastrointestinal Cancers Congress, several abstracts reported HRQoL outcomes with nivolumab plus ipilimumab in patients with gastrointestinal malignancies. Fernandez and colleagues presented an HRQoL analysis from the open-label phase 3 CheckMate 8HW trial, which compared nivolumab plus ipilimumab against nivolumab alone or chemotherapy with or without targeted therapy chemotherapy in patients with unresectable or metastatic CRC with MSI-H/dMMR status.[1] As reported previously, the trial met its dual primary endpoints, demonstrating significant improvements in PFS with nivolumab plus ipilimumab compared with chemotherapy as first-line therapy (HR, 0.21; *P*<.001) and with nivolumab plus ipilimumab compared with nivolumab alone across all lines of therapy (HR, 0.62; *P*=.0003).[2,3]

Among 582 patients with MSI-H/dMMR mCRC who received nivolumab plus ipilimumab (n=296) or nivolumab alone (n=286), both nivolumab plus ipilimumab and nivolumab were associated with improvements in HRQoL, including mean improvements from baseline in global health status (GHS), physical functioning, fatigue, diarrhea, and pain. Changes in GHS and fatigue crossed the threshold for minimally important change (MIC) in the nivolumab plus ipilimumab arm starting at week 21, and the change in pain exceeded the MIC in both groups starting at week 7. Nivolumab plus ipilimumab was also associated with improvements in the EQ-5D-3L VAS that exceeded the MIC starting at week 21. Investigators concluded that nivolumab plus ipilimumab was associated with improved HRQoL and reduced symptoms from baseline, and that adding ipilimumab to nivolumab was associated with improvements in PFS without reducing HRQoL.

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Expert Perspective

Tanios S. Bekaii-Saab, MD: CheckMate 8HW demonstrated that nivolumab plus ipilimumab improves PFS over chemotherapy and single-agent nivolumab in MSI-H/dMMR mCRC. However, interpretation is limited by pooled data across all therapy lines, without a dedicated first-line nivolumab plus ipilimumab vs nivolumab comparison. Key concerns include (1) potential differential benefit of dual immunotherapy in later lines owing to altered tumor immune milieu; (2) toxicity and cost of ipilimumab in first-line without clear survival advantage; and (3) unclear need for dual immunotherapy in Lynch syndrome patients, who respond well to PD-1 monotherapy. Until first-line head-to-head data are available, pembrolizumab remains the preferred standard, with nivolumab plus ipilimumab an alternative standard perhaps best reserved for select cases requiring deeper responses.

Abstract Summaries

ANCHOR Trial: Anlotinib vs Bevacizumab Added to Standard First-Line Chemotherapy Among Patients With *RAS/BRAF* Wild-Type, Unresectable mCRC

At the 2025 ASCO Annual Meeting, Ding and colleagues presented results of the randomized, phase 3, noninferiority ANCHOR trial comparing the multitargeted tyrosine kinase inhibitor anlotinib plus oxaliplatin and capecitabine (CapeOX) against bevacizumab plus CapeOX in 748 patients with previously untreated *RAS/BRAF* wild-type mCRC (Abstract LBA3502). Patients received 4 to 8 cycles of induction therapy followed by maintenance therapy with either anlotinib or bevacizumab, each with capecitabine. Anlotinib plus CapeOX was noninferior to bevacizumab plus CapeOX, with a median PFS of 11.04 months in each arm (HR, 1.00; *P*=.8740), and demonstrated similar ORR (61.93% vs 62.13%). The safety profile was considered manageable; grade 3 or higher TRAEs occurred in 64.88% of patients in the anlotinib group and 44.80% in the bevacizumab group during induction, and 26.57% and 26.77%, respectively, in the maintenance period. HRQoL was comparable. The results suggest the feasibility of an intravenous-free maintenance strategy with anlotinib plus CapeOX.

KEYFORM-007 Study: Co-Formulated Favezelimab + Pembrolizumab vs SOC in Previously Treated, PD-L1-Positive mCRC

At the 2025 ASCO Gastrointestinal Cancers Symposium, Segal and colleagues presented results of the KEYFORM-007 trial comparing a coformulation of the anti-lymphocyte activation gene-3 antibody favezelimab and pembrolizumab against SOC (regorafenib or TAS-102) in 441 patients with PD-L1-positive microsatellite stable/mismatch repair proficient mCRC (Abstract LBA248). After a median follow-up of 28.2 months, favezelimab plus pembrolizumab was not associated with improvements over SOC in median OS (7.3 vs 8.5 months; HR, 0.98; 95% CI, 0.80-1.20; *P*=.418) or median PFS (2.1 vs 2.6 months; HR, 1.34; 95% CI, 1.09-1.64). The rate of grade 3 or greater TRAEs was 20% and 32%, respectively.

SCIENCE Trial: Comparing Chemotherapy + Sintilimab and Chemoradiotherapy + Sintilimab vs Chemoradiotherapy for Neoadjuvant Treatment in Resectable Locally Advanced Esophageal Squamous Cell Carcinoma

At the 2025 ASCO Gastrointestinal Cancers Symposium, Leng and colleagues reported preliminary results from the randomized, phase 3 SCIENCE trial comparing 3 approaches to neoadjuvant therapy in patients with resectable locally advanced esophageal squamous cell carcinoma: sintilimab plus nab-paclitaxel (n=46), nab-paclitaxel plus radiation therapy (RT) (n=55), or sintilimab plus nab-paclitaxel plus RT (n=45) (Abstract LBA329). The pCR rate was significantly higher with nab-paclitaxel plus RT vs sintilimab plus nab-paclitaxel (47.3% vs 13%; OR, 6; *P*=.0005) and was also significantly higher with sintilimab plus nab-paclitaxel plus RT vs sintilimab plus nab-paclitaxel (60% vs 13%; OR, 10; *P*<.0001). Rates of surgical complications in the sintilimab plus nab-paclitaxel-RT and nab-paclitaxel-RT arms were 46.7% and 49.1%, respectively; rates of lymphopenia were 11.1% and 30.9%, respectively; and rates of leukopenia were 24.4% and 29.1%, respectively. Investigators concluded that the addition of sintilimab to neoadjuvant chemoradiotherapy improved pathologic outcomes without increasing surgical risks.

EORTC-1203 GITC "INNOVATION": OS Results of Integration of Trastuzumab, With or Without Pertuzumab, Into Perioperative Chemotherapy of HER2+ Stomach Cancer

At the 2025 ASCO Gastrointestinal Cancers Symposium, Wagner and colleagues presented OS results from the randomized, open-label, phase 2 INNOVATION trial evaluating the addition of trastuzumab or trastuzumab plus pertuzumab to perioperative chemotherapy in 172 patients with HER2+ resectable gastric cancer (Abstract LBA331). As reported previously, the trial did not meet its primary endpoint, showing no significant increase in major pathologic response rate (mpRR) with chemotherapy plus trastuzumab (37.0%) or chemotherapy plus trastuzumab and pertuzumab (26.4%) vs chemotherapy alone (23.3%) (Wagner ASCO 2023 Abstract 4057). Adding both trastuzumab and pertuzumab to chemotherapy demonstrated higher toxicity and no efficacy benefit. Although the addition of trastuzumab to chemotherapy was associated with numerical increases in PFS (HR, 0.84; 95% CI, 0.43-1.63) and OS (HR, 0.89; 95% CI, 0.42-1.88), this benefit was not sustained after the trial was amended to the use of FLOT chemotherapy. OS outcomes are not yet mature. Investigators concluded that addition of trastuzumab to chemotherapy could be considered particularly when tumor downsizing is needed to attain curative resection, given the high mpRR rate with this approach.

FRESCO-2 Subgroup Analysis: Efficacy and Safety of Fruquintinib vs Placebo by Metastatic Site in mCRC

At the 2025 ESMO Gastrointestinal Cancers Congress, Garcia-Carbonero and colleagues presented a subgroup analysis from the FRESCO-2 trial (Abstract 37P). The trial had previously demonstrated a significant improvement in median OS with fruquintinib over placebo in patients with refractory mCRC (7.4 vs 4.8 months; HR, 0.66; 95% CI, 0.55-0.80; *P*<.0001) (Dasari *Lancet* 2023). The subgroup analysis evaluated outcomes based on site of metastasis. Fruquintinib demonstrated a significant improvement in median OS over placebo in the 4% of patients with liver metastases (8.5 vs 3.1 months; HR, 0.26; 95% CI, 0.08-0.82) and the 11% to 12% with bone metastases (7.6 vs 3.4 months; HR, 0.40; 95% CI, 0.22-0.74), and trended longer in the 15% to 17% with peritoneal metastases (5.4 vs 4.2 months; 95% CI, 0.40-1.13). In the 5% to 7% of patients with lung metastases only, median OS was 14.1 months with fruquintinib and not evaluable with placebo (HR, 1.00; 95% CI, 0.21-4.79). The rate of grade 3 or higher TEAEs with fruquitinib and placebo was 53% and 40%, respectively, in patients with liver metastases only; 64% and 70%, respectively, in patients with bone metastases only; 70% and 49%, respectively, in patients with peritoneal metastases; and 56% and 31%, respectively, in patients with lung metastases only. Investigators concluded that fruquintinib may be effective and tolerable for patients with liver-only, bone, or peritoneal metastases.