

Gastrointestinal Cancers: Updates in 2026

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Abstract

Gastrointestinal (GI) malignancies remain among the leading causes of cancer death worldwide. The therapeutic landscape has been reshaped over the past several years by the integration of immune checkpoint inhibition and biomarker-guided treatment. This review summarizes the practice-changing data across the major GI tumor sites. In advanced esophagogastric adenocarcinoma, first-line therapy is individualized based on PD-L1 combined positive score, mismatch repair/microsatellite instability status, HER2 status, and claudin 18.2 expression. In resectable disease, perioperative durvalumab plus FLOT (MATTERHORN) represents a new standard. In colorectal cancer, dual checkpoint blockade (CheckMate 8HW) has redefined first-line management of mismatch-repair-deficient (dMMR) metastatic disease, and adjuvant immunotherapy entered the curative setting (ATOMIC). Encorafenib-cetuximab plus chemotherapy is now the standard first-line treatment for BRAF V600E-mutated metastatic disease (BREAKWATER). Circulating tumor DNA (ctDNA) is validated as a prognostic biomarker after resection, though its role in guiding adjuvant treatment decisions remains under investigation. Retifanlimab plus carboplatin and paclitaxel (POD1UM-303) established the first chemoimmunotherapy standard for advanced anal cancer. In pancreatic cancer, the most transformative advance is daraxonrasib, a RAS(ON) multiselective inhibitor that doubled overall survival compared with chemotherapy in previously treated metastatic disease (RASolute 302). Tumor treating fields added to gemcitabine/nab-paclitaxel improved survival in locally advanced disease (PANOMA-3), and zenocutuzumab received FDA approval for NRG1 fusion-positive tumors; Comprehensive molecular profiling is now recommended for all treatment-eligible patients. In hepatocellular carcinoma, immunotherapy doublets (atezolizumab-bevacizumab; tremelimumab-durvalumab; nivolumab-ipilimumab) dominate first-line care, while adjuvant atezolizumab-bevacizumab after resection (IMbrave050) did not sustain its initial recurrence-free survival benefit on longer follow-up. In biliary tract cancer, the addition of durvalumab (TOPAZ-1) or pembrolizumab (KEYNOTE-966) to gemcitabine-cisplatin is the standard first-line regimen. Comprehensive molecular profiling is essential, as

therapies are now available for FGFR2 fusions, IDH1 mutations, HER2 overexpression, NRG1 fusions, RET fusions, and BRAF V600E mutations, among other actionable alterations. We summarize the pivotal trials, regulatory milestones, and the cross-cutting themes – biomarker-driven therapy, earlier use of immunotherapy, and molecular residual-disease monitoring – that define contemporary GI oncology, while noting important caveats regarding durability of benefit and appropriate patient selection.

Take Home Messages

1. First-line therapy for advanced esophagogastric adenocarcinoma is now biomarker-driven, integrating PD-L1 combined positive score, HER2 status, and claudin 18.2 expression, while perioperative durvalumab plus FLOT (MATTERHORN) has become a new standard for resectable disease.
2. Adjuvant immunotherapy plus chemotherapy via the ATOMIC trial has established a curative-intent option for stage III dMMR colon cancer. The combination of encorafenib-cetuximab plus chemotherapy (FOLFOX or FOLFIRI) is now the standard first-line treatment for metastatic cases with BRAF V600E based on BREAKWATER data.
3. In pancreatic cancer, daraxonrasib – a RAS (ON) multiselective inhibitor – doubled overall survival versus chemotherapy in previously treated metastatic disease (RASolute 302), while other RAS targeted agents are advancing rapidly.
4. Retifanlimab plus carboplatin and paclitaxel (PODIUM-303) is the first approved first-line chemoimmunotherapy for advanced anal cancer.

1. Introduction

Gastrointestinal (GI) cancers, encompassing malignancies of the esophagus, stomach, colon and rectum, anus, pancreas, liver, and biliary tract, collectively account for approximately a quarter of global cancer incidence and a third of cancer-related deaths, representing one of the largest and most heterogeneous disease groups in oncology.^{1,2} For decades, cytotoxic chemotherapy formed the backbone of systemic treatment for most of these tumors. The last several years, however, have brought a period of rapid change, driven by the maturation of immune checkpoint inhibition across nearly every GI tumor type; the proliferation of molecularly targeted agents directed at actionable alterations such as HER2, BRAF, KRAS, FGFR2, IDH1, claudin 18.2, et al; and the emergence of circulating tumor DNA (ctDNA).

The GI cancers have grown in complexity; where chemotherapy doublet once sufficed as the default first-line option for advanced disease, clinicians must now navigate branching, biomarker-defined algorithms in which molecular testing precedes and dictates treatment selection.

The purpose of this review is to synthesize the pivotal trials and regulatory milestones into a coherent, clinically oriented update across the major GI tumor sites. Our scope is focused on systemic therapy for advanced disease and on perioperative strategies with recently reported, potentially practice-changing results. For each disease site we highlight the trials that have altered, or are poised to alter, the standard practice, place them in the context of prior standards of care, and note regulatory status where relevant. Our aim is to provide the practicing oncologist with a concise, evidence-anchored map of where the field stands in 2026 and where it is heading.

2. Methods

We identified the pivotal trials that led to practice-changing updates in the management of GI cancers by targeted searches of PubMed, the American Society of Clinical Oncology (ASCO) annual and gastrointestinal cancers symposia, the European Society for Medical Oncology (ESMO), and U.S. Food and Drug Administration (FDA) approval announcements. Priority was given to randomized phase 3 trials, landmark studies that established current standards of care, and the most recent regulatory decisions through mid-2026. Reported efficacy values, including median overall survival (OS), progression-free survival (PFS), hazard ratios (HR), confidence intervals (CI), and response rates were drawn from the primary publications and congress presentations of the respective trials. No formal quality-assessment instrument or meta-analytic synthesis was applied, consistent with the narrative scope of this review.

3. Findings

3.1 Esophageal, Gastroesophageal Junction, and Gastric Cancer

The management of advanced esophagogastric adenocarcinoma has become biomarker-driven. In CheckMate 649, nivolumab plus chemotherapy im-

proved median OS to 14.4 versus 11.1 months in patients with a PD-L1 combined positive score (CPS) of at least 5 (HR 0.7), with benefit sustained at five years.³ KEYNOTE-859 similarly demonstrated an OS advantage for pembrolizumab plus chemotherapy in HER2-negative disease (12.9 versus 11.5 months; HR 0.78), and tislelizumab plus chemotherapy showed OS benefit in RATIONALE-305 (15.0 versus 12.9 months in all randomized patients; HR 0.80).^{4,5} Critically, a 2024 FDA Oncologic Drugs Advisory Committee review found an unfavorable risk-benefit profile for PD-1 inhibitors in tumors with PD-L1 CPS below 1, reinforcing a CPS-based threshold – with NCCN and ASCO guidelines now recommending checkpoint inhibition for CPS ≥ 1 .⁶

For HER2-positive disease, KEYNOTE-811 established the addition of pembrolizumab to trastuzumab and chemotherapy as standard first-line therapy in tumors with PD-L1 CPS ≥ 1 , with final analyses confirming an OS benefit (20.1 versus 15.7 months; HR 0.79) and conversion to full FDA approval in 2025.⁷ The bispecific HER2-directed antibody zanidatamab may soon redefine this standard: in the phase 3 HERIZON-GEA-01 trial, zanidatamab plus tislelizumab and chemotherapy significantly improved both PFS (12.4 versus 8.1 months; HR 0.63) and OS (26.4 versus 19.2 months; HR 0.72) over trastuzumab plus chemotherapy, with benefit observed regardless of PD-L1 status.⁸ In later lines, the phase 3 DESTINY-Gastric04 trial confirmed trastuzumab deruxtecan as the new standard of care, with significantly longer OS than ramucirumab plus paclitaxel (14.7 versus 11.4 months; HR 0.70).⁹ Two additional biomarkers have entered routine testing. Zolbetuximab, a monoclonal antibody against claudin 18.2, added to first-line chemotherapy significantly improved PFS and OS in the SPOTLIGHT (with mFOLFOX6) and GLOW (with CAPOX) trials in claudin 18.2-positive (expression $>75\%$), HER2-negative disease, leading to FDA approval in October 2024.^{10,11} The next frontier is combining zolbetuximab with checkpoint inhibition: in the phase 2 ILUSTRO trial (Cohort 4), first-line zolbetuximab plus mFOLFOX6 and nivolumab achieved a median PFS of 14.8 months (18.0 months in CLDN18.2-high tumors) with an ORR of 62%, supporting the ongoing phase 3 LUCERNA trial of zolbetuximab plus

pembrolizumab and chemotherapy in CLDN18.2-positive, PD-L1 CPS ≥ 1 tumors.¹² Bemarituzumab, directed against FGFR2b, demonstrated a significant OS benefit in FGFR2b-overexpressing tumors ($\geq 10\%$ of tumor cells; HR 0.61) in the phase 3 FORTITUDE-101 trial, though full publication is awaited;¹³ However, FORTITUDE-102 trial (Bemarituzumab plus chemotherapy and Nivolumab) was terminated due to inadequate efficacy at an ad hoc analysis.

In the perioperative setting for potential resectable disease, MATTERHORN demonstrated that adding perioperative durvalumab to FLOT (fluoropyrimidine, leucovorin, oxaliplatin and docetaxel) chemotherapy significantly improved event-free survival (HR 0.71; $P < 0.001$) and pathological complete response (19.2% vs. 7.2%) in resectable stage II–IVA gastric and gastroesophageal junction adenocarcinoma, with an encouraging overall survival trend (HR 0.78; $P = 0.025$, not crossing the prespecified boundary), earning FDA approval and establishing a new standard of care.¹⁴ This contrasts with KEYNOTE-585, in which perioperative pembrolizumab increased pathologic complete response rates but narrowly missed its event-free survival boundary.¹⁵ For esophageal and junctional tumors with residual disease after neoadjuvant chemoradiotherapy (carboplatin + paclitaxel and concurrent radiation) and resection, adjuvant nivolumab doubled disease-free survival in CheckMate 577 (21.8 vs. 10.8 months; HR 0.76), though the final overall survival analysis did not reach statistical significance.¹⁶ In addition, for advanced esophageal squamous cell carcinoma, first-line pembrolizumab plus chemotherapy (KEYNOTE-590), nivolumab-based regimens (CheckMate 648) and tislelizumab plus chemotherapy (RATIONALE-306), all improved survival, with the greatest benefit in PD-L1-high tumors.^{17,18,19} Table 1 summarizes these pivotal esophagogastric trials.

3.2 Colorectal Cancer

Colorectal cancer (CRC) illustrates the maturation of biomarker-directed therapy perhaps better than any other GI malignancies. For mismatch-repair-deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic disease, first-line pembrolizumab established the value of checkpoint monotherapy over chemotherapy in KEYNOTE-177.²⁰ CheckMate 8HW has since gone

Table 1. Selected practice-changing trials in esophageal, gastroesophageal junction, and gastric cancer. 1L, first-line; CPS, combined positive score; DFS, disease-free survival; EFS, event-free survival; ESCC, esophageal squamous cell carcinoma, GEJ, gastroesophageal junction; OS, overall survival; PFS, progression-free survival.

Trial	Regimen	Population	Key efficacy result	Status
CheckMate 649	Nivolumab + FOL-FOX/XELOX vs chemo	1L HER2-neg gastric/GEJ/esophageal adeno	OS 14.4 vs 11.1 mo (CPS ≥ 5 ; HR 0.71)	FDA approved 2021
KEYNOTE-859	Pembrolizumab + chemo vs chemo	1L HER2-negative gastric/GEJ	OS 12.9 vs 11.5 mo (HR 0.78)	FDA approved 2023
RATIONALE-305	Tislelizumab + chemo vs chemo	1L HER2-neg gastric/GEJ	OS 15.0 vs 12.9 mo (HR 0.80); TAP $\geq 5\%$: HR 0.74	FDA approved 2025
KEYNOTE-811	Pembrolizumab + trastuzumab + chemo	1L HER2-positive gastric/GEJ	OS 20.1 vs 15.7 mo (CPS ≥ 1 ; HR 0.79)	Full approval 2025
HERIZON-GEA-01	Zanidatamab $\pm$ tislelizumab + chemo vs trastuzumab + chemo	1L HER2-pos gastric/GEJ	PFS 12.4 vs 8.1 mo (HR 0.63); OS 26.4 vs 19.2 mo (HR 0.72) with tislelizumab	Not yet approved
SPOTLIGHT GLOW	Zolbetuximab + chemo vs chemo	1L CLDN18.2+, HER2-neg gastric/GEJ	PFS HR 0.75 / 0.69; OS benefit	FDA approved 2024
FORTITUDE-101	Bemarituzumab + mFOLFOX6 vs chemo	1L FGFR2b-overexpressing gastric/GEJ	OS 17.9 vs 12.5 mo (HR 0.61)	Not yet approved
CheckMate 577	Adjuvant nivolumab vs placebo	Resected esophageal/GEJ, residual disease	DFS 21.8 vs 10.8 mo (HR 0.69)	FDA approved 2021
MATTERHORN	Perioperative durvalumab + FLOT	Resectable stage II–IVA gastric/GEJ	EFS HR 0.71;	FDA approved 2025
Keynote-590	Pembrolizumab + chemo vs chemo	1L advanced esophageal (ESCC + adeno)/GEJ	OS 12.4 vs 9.8 mo (HR 0.73)	FDA approved 2021
Checkmate 648	Nivolumab + chemo vs Nivolumab + Ipilimumab vs chemo	1L advanced ESCC	Nivo + chemo OS 15.4 vs 9.1 mo (HR 0.54), nivo+ipi 13.7 vs 9.1 mo (HR 0.64) in PD-L1 ≥ 1	FDA approved 2022
Rationale-306	Tislelizumab + Chemo vs Chemo	1L advanced ESCC	OS 17.2 vs 10.6 mo (HR 0.66)	FDA approved 2025

further: first-line nivolumab plus ipilimumab produced a striking PFS benefit over chemotherapy (HR 0.21) and, across treatment lines, was superior to nivolumab monotherapy, making dual checkpoint blockade a preferred first-line option for dMMR/MSI-H disease.²¹ Immunotherapy has also entered the management of microscopic residual disease setting: in the ATOMIC trial, adding atezolizumab to adjuvant FOLFOX improved three-year disease-free survival from 76.2% to 86.3% (HR 0.50) in resected stage III dMMR colon cancer, the first demonstration of the benefit of immune

checkpoint inhibitor in this population.²² The neoadjuvant setting has proved equally striking: in the NICHE-2 study, short preoperative course of nivolumab plus ipilimumab in 111 patients with locally advanced dMMR colon cancer produced a major pathologic response in 95% and a pathologic complete response in 68%, with three-year disease-free survival of 100%.²³ In locally advanced dMMR rectal cancer, neoadjuvant dostarlimab has produced remarkable clinical complete response rates – 100% in all 49 patients completing treatment in

Table 2. Selected biomarker-targeted and immunotherapy trials in colorectal and anal cancer. CRC, colorectal cancer; ctDNA, circulating tumor DNA; DFS, disease-free survival; dMMR, mismatch-repair deficient; mCRC, metastatic CRC; MSI-H, microsatellite instability-high; ORR, objective response rate; RFS, recurrence-free survival; RAS-WT, RAS wild-type.

Trial	Regimen	Population	Key efficacy result	Status
CheckMate 8HW	Nivolumab + ipilimumab vs chemo	1L MSI-H/dMMR metastatic CRC	PFS not reached vs 5.9 mo (HR 0.21)	FDA approved 2025
BREAKWATER	Encorafenib + cetuximab + FOLFOX	1L BRAF V600E metastatic CRC	OS 30.3 vs 15.1 mo (HR 0.49)	Full approval 2026
POD1UM-303	Retifanlimab + carboplatin/paclitaxel	1L advanced anal squamous cell	PFS 9.3 vs 7.4 mo (HR 0.63), OS 32.8 vs 22.2 mo (HR 0.75)	FDA approved 2025
CodeBreaK 300	Sotorasib + panitumumab	Refractory KRAS G12C mCRC	PFS 5.6 vs 2.0 mo (HR 0.49)	FDA approved 2025
MOUNTAINEER	Tucatinib + trastuzumab	Refractory HER2+, RAS-WT mCRC	ORR 39.3%; OS 23.9 mo	FDA approved 2023
ATOMIC	Atezolizumab + FOLFOX (adjuvant)	Resected stage III dMMR colon	3-yr DFS 86.3% vs 76.2% (HR 0.50)	Practice-changing
DYNAMIC	ctDNA-guided adjuvant therapy	Stage II colon cancer	Chemo use 15% vs 28%; RFS non-inferior	Practice-informing

the rectal cohort – raising the prospect of organ preservation and nonoperative management.^{24,25}

For the much larger population of microsatellite-stable (MSS, pMMR) tumors, progress has come through targeting specific molecular alterations. In BRAF V600E–mutant metastatic CRC, the BREAKWATER trial showed that adding encorafenib and cetuximab to first-line FOLFOX markedly improved response (approximately 61% versus 40%), PFS (12.8 versus 7.1 months), and OS (30.3 versus 15.1 months; HR 0.49), leading to full FDA approval in 2026 and superseding the previous post-progression BEACON doublet standard, and recent updated data showed similar benefit in the combination of FOLFIRI with encorafenib and cetuximab.^{26,27,28}

The KRAS-inhibitor + anti-EGFR pairing has emerged as the backbone for KRAS G12C–mutant disease: sotorasib plus panitumumab (CodeBreaK 300) improved outcomes over standard later-line options; Adagrasib plus cetuximab showed promising activity in KRYSTAL-1, however, confirmatory phase 3 KRYSTAL-10 study missed its dual primary endpoints (PFS and OS), despite markedly higher objective response rate (47% vs 16%) as reported at ESMO GI 2026.^{29,30,31} HER2-amplified, RAS wild-type tumors respond to dual HER2 blockade with tucatinib plus trastuzumab (MOUN-

TAINEER) and to trastuzumab deruxtecan (DESTINY-CRC02).^{32,33} Sidedness and RAS status continue to guide first-line biologic selection, with anti-EGFR therapy preferred over bevacizumab in left-sided RAS wild-type disease (PARADIGM).³⁴

Finally, ctDNA has emerged as a powerful tool for detecting molecular residual disease. The DYNAMIC trial showed that a ctDNA-guided approach in stage II colon cancer roughly halved adjuvant chemotherapy use without compromising recurrence-free survival, while observational data from GALAXY/CIRCULATE demonstrated the profound prognostic impact of postoperative ctDNA positivity.^{35,36} Interventional escalation and de-escalation strategies, however, have yielded mixed results to date, and ctDNA-guided management remains an area of active investigation rather than an established standard. Table 2 summarizes selected colorectal and anal cancer advances.

3.3 Anal Cancer

Advanced squamous cell carcinoma of the anal canal, long treated with platinum-based chemotherapy extrapolated from other squamous malignancies, gained its first modern standard with POD1UM-303 (InterAACT-2). The addition of the PD-1 inhibitor retifanlimab to carboplatin and paclitaxel improved PFS (9.3 versus 7.4 months; HR 0.63) and on final analysis, OS (32.8 vs 22.2 months,

HR 0.75); It was FDA approved for first-line therapy specifically for advanced anal cancer in 2025.³⁷ This built upon the earlier InterAACT study, which had established carboplatin–paclitaxel as the preferred chemotherapy backbone over cisplatin–5-fluorouracil.³⁸ Chemoimmunotherapy is now the standard first-line approach for this uncommon but rising malignancy.

3.4 Pancreatic Cancer

Pancreatic ductal adenocarcinoma (PDAC) remains among the most lethal solid tumors, and progress has been hard-won. In the first-line metastatic setting, NAPOLI-3 demonstrated that NALIRIFOX (liposomal irinotecan, oxaliplatin, and 5-fluorouracil/leucovorin) modestly improved OS over gemcitabine plus nab-paclitaxel (11.1 versus 9.2 months; HR 0.83), providing a new triplet option and receiving FDA approval in 2024.³⁹ These outcomes remain broadly consistent with historical benchmarks set by FOLFIRINOX (PRODIGE 4) and gemcitabine–nab-paclitaxel (MPACT), though cross-trial comparisons must be interpreted cautiously given differing eras and populations.^{40,41} In the adjuvant setting, modified FOLFIRINOX remains as the commonly accepted regimen for fit patients following the PRODIGE 24 trial, which reported a median OS exceeding four years.⁴²

The most exciting recent developments target the KRAS oncogene, mutated in more than 90% of pancreatic cancers and historically considered undruggable. Selective inhibitors of KRAS G12C, such as sotorasib, produced modest activity (ORR 21%; median OS 6.9 months) in the small subset (1–2%) of patients with this mutation.⁴³ More consequentially, daraxonasib, an oral RAS(ON) multiselective inhibitor, doubled median overall survival compared with chemotherapy in the phase 3 RASolute 302 trial (13.2 versus 6.6 months; HR 0.40; $P < 0.001$) among previously treated patients with metastatic disease, the vast majority harboring RAS G12 mutations, and is pending FDA approval.⁴⁴ Broad RAS inhibition represents the most important therapeutic advance in pancreatic cancer in a generation, and first-line trials are eagerly awaited.

3.5 Hepatocellular Carcinoma

First-line systemic therapy for advanced hepatocellular carcinoma (HCC) has shifted decisively

from tyrosine kinase inhibitor monotherapy to immunotherapy-based combinations. IMbrave150 established atezolizumab plus bevacizumab as a new standard, improving OS over sorafenib (updated median 19.2 versus 13.4 months; HR 0.66).⁴⁵ The dual immune checkpoint inhibitor regimen of tremelimumab plus durvalumab (the STRIDE regimen) in HIMALAYA offered a chemotherapy- and antiangiogenic-free alternative with durable long-term survival, an option particularly suited to patients at higher risk of bleeding.⁴⁶ More recently, CheckMate 9DW showed that nivolumab plus ipilimumab improved OS over lenvatinib or sorafenib (23.7 versus 20.6 months; HR 0.79) with high response rates, earning FDA approval in 2025 and adding a further first-line immunotherapy doublet. Notably, early Kaplan-Meier curve crossing reflected higher early mortality with the immunotherapy doublet (HR 1.65 in the first six months), followed by sustained separation thereafter (HR 0.61), and treatment-related deaths were more frequent (12 versus 3), underscoring the importance of patient selection and close early monitoring.⁴⁷

Immune checkpoint inhibition is also moving into earlier disease stages. In intermediate-stage HCC, EMERALD-1 showed that adding durvalumab and bevacizumab to transarterial chemoembolization (TACE) improved PFS (15.0 versus 8.2 months; HR 0.77); however, the final analysis reported at the ESMO Gastrointestinal Cancers Congress 2026 showed no significant overall survival benefit. LEAP-012, which combines TACE with Lenvatinib and pembrolizumab, similarly improved PFS but did not meet its overall survival endpoint and was closed early on the basis of prespecified interim analysis indicating a low likelihood of achieving OS significance.^{48,49} Together these results indicate that adding systemic therapy to TACE delays progression but has not yet translated into a survival advantage. EMERALD-3 added durvalumab, tremelimumab, and Lenvatinib to TACE and met its primary endpoint with statistically significant and clinically meaningful PFS improvement over TACE alone; overall survival showed a favorable trend but had not reached statistical significance at the reported interim analysis, with follow up ongoing.⁵⁰ In the adjuvant setting, IMbrave050 initially reported improved recurrence-free survival with atezolizumab plus bevacizumab after resection

or ablation, but this early benefit was not maintained on longer follow-up (updated RFS HR 0.90; OS HR 1.26), prompting the AASLD to formally revise its guidance, concluding that the benefit-risk ratio does not support adjuvant atezolizumab plus bevacizumab – a cautionary example of the importance of mature data before adopting adjuvant immunotherapy.⁵¹

3.6 Biliary Tract Cancer

Biliary tract cancers—including intrahepatic and extrahepatic cholangiocarcinoma and gallbladder cancer—have benefited from both immunotherapy and an unusually rich array of targetable alterations. The addition of a PD-L1 or PD-1 inhibitor to first-line gemcitabine and cisplatin is now standard: TOPAZ-1 (durvalumab) and KEYNOTE-966 (pembrolizumab) each demonstrated a modest but reproducible OS benefit over chemotherapy alone, with four-year TOPAZ-1 data confirming durable benefit (OS HR 0.75; 48-month OS 11.8% versus 4.3%).^{52,53} Molecular profiling is essential, because intrahepatic cholangiocarcinoma in particular harbors a high frequency of actionable alterations. FGFR2 fusions or rearrangements are targeted by pemigatinib and futibatinib, with high response rates in the second-line setting.^{54,55} Notably, the first-line phase 3 FIGHT-302 trial reported in 2026 that pemigatinib improved PFS over gemcitabine–cisplatin (8.3 vs. 6.8 months; HR 0.58) with a markedly higher response rate (47% vs. 15%), though the trial closed early due to change in standard of care.⁵⁶ IDH1-mutant disease responds to ivosidenib (ClarIDHy), which improved PFS and, after adjustment for crossover, OS.⁵⁷

HER2-positive biliary tract cancer represents another important actionable subset: the bispecific antibody zanidatamab (HERIZON-BTC-01) and the antibody–drug conjugate trastuzumab deruxtecan (via the tumor-agnostic DESTINY-PanTumor02 program) both produced meaningful response rates and gained accelerated approval.^{58,59} Finally, BRAF V600E–mutant biliary cancers respond to dabrafenib plus trametinib, approved under a tumor-agnostic indication (ROAR).⁶⁰ The practical implication is clear: comprehensive molecular profiling should be performed for all patients with advanced biliary tract cancer, as it frequently identifies a therapy with activity superior to further chemotherapy. Table 3 summarizes key trials

across pancreatic, hepatocellular, and biliary tract cancers.

4. Discussion

Viewed collectively, the advances highlighted in this review reflect several unifying themes that now define GI oncology. The first and most pervasive is the transition to biomarker-driven treatment selection. Across multiple GI cancers the choice of first-line therapy increasingly depends on the results of molecular and immunohistochemical testing performed at diagnosis. PD-L1 CPS, HER2 status, claudin 18.2, mismatch-repair status, BRAF, KRAS, FGFR2, IDH1 et al, have all become decision points, and the failure to perform comprehensive profiling now risks withholding therapies with substantial and sometimes categorical advantages over chemotherapy. This reality argues for reflex, broad molecular testing, ideally including next-generation sequencing (NGS), at the time of diagnosis of advanced GI malignancy, rather than sequential single-gene testing that delays treatment.

A second theme is the steady migration of immunotherapy from later to earlier lines and from advanced to curative-intent settings. Immune checkpoint inhibition is now embedded in first-line therapy for advanced esophagogastric, colorectal (dMMR), hepatocellular, biliary, and anal cancers, and has crossed into the perioperative and adjuvant space. The dMMR/MSI-H phenotype has become a setting where immunotherapy can produce deep and durable responses; and, in localized rectal cancer, prospect of cure without surgery or radiation.

A third theme is the growing role of ctDNA and molecular residual-disease detection. The prognostic power of postoperative ctDNA is now firmly established, yet the translation of ctDNA detection into treatment decisions that improve outcomes remains incomplete: several interventional escalation and de-escalation trials have failed to meet their endpoints, underscoring that a prognostic biomarker is not automatically a useful predictive or actionable one. ctDNA should therefore be applied thoughtfully and, where possible, within clinical trials until its role is better defined.

These advances must be tempered by important caveats. Several of the newest results derive

Table 3. Key trials in pancreatic, hepatocellular, and biliary tract cancers. gem/cis, gemcitabine–cisplatin; HCC, hepatocellular carcinoma; OS, overall survival; PFS, progression-free survival; TACE, transarterial chemoembolization; TKI, tyrosine kinase inhibitor, DOR, duration of response.

Tumor	Trial	Regimen	Key efficacy result	Status
Pancreatic	NAPOLI-3	NALIRIFOX vs gemcitabine/nab-paclitaxel	OS 11.1 vs 9.2 mo (HR 0.83)	FDA approved 2024
Pancreatic	RASolute 302	Daraxonrasib vs chemo	OS 13.2 vs 6.6 mo (HR 0.4)	Not yet FDA approved
HCC	IMbrave150	Atezolizumab + bevacizumab vs sorafenib	OS 19.2 vs 13.4 mo (HR 0.66)	FDA approved 2020
HCC	CheckMate 9DW	Nivolumab + ipilimumab vs TKI	OS 23.7 vs 20.6 mo (HR 0.79)	FDA approved 2025
HCC	HIMALAYA	Tremelimumab + durvalumab vs sorafenib	OS 19.6% vs 9.4% (HR 0.76)	FDA approved 2022
Biliary	TOPAZ-1	Durvalumab + gem/cis	OS HR 0.75	FDA approved 2022
Biliary	Keynote 966	Pembrolizumab + gem/cis	OS HR 0.86	FDA approved 2023
Biliary	FIGHT-302	Pemigatinib vs gem/cis (FGFR2 fusion)	PFS 8.3 vs 6.8 mo (HR 0.58)	Reported 2026
Biliary	ClarIDHy	Ivosidenib vs placebo (IDH1-mutant)	PFS 2.7 vs 1.4 mo (HR 0.37)	FDA approved 2021
Biliary	HERIZON-BTC-01	Zanidatamab (HER2 IHC 3+ subset)	ORR 52%; DOR 14.9 mo; OS 18.1 mo	FDA approved 2024

from interim analyses, conference presentations, or topline press disclosures that await full peer-reviewed publication. The experience with adjuvant atezolizumab–bevacizumab in HCC (IMbrave050), where an early RFS advantage was not sustained, and the failure of demonstration of an OS benefit, illustrate the hazards of adopting therapies on the surrogate endpoints prematurely. Many of the survival gains in the most lethal GI cancers, particularly pancreatic and biliary tract cancer, remain measured in months, and the absolute benefit for individual patients must be weighed against toxicity, financial cost, and quality of life.

The principal limitation of this review is its narrative and selective nature: it distills conference-highlighted, practice-changing studies rather than performing an exhaustive systematic synthesis, and it necessarily omits many valuable trials and ongoing studies. Efficacy figures reported here should be confirmed against the primary publications, particularly for results not yet published in full. Looking forward, the field is likely to see continued expansion

of antibody-drug conjugates (ADC), further maturation of RAS-directed therapy, more sophisticated use of ctDNA for adaptive treatment, and increasingly rational combinations of immunotherapy with targeted and locoregional approaches.

5. Conclusions

The systemic therapy for gastrointestinal malignancies has become firmly biomarker-driven and immunotherapy-inclusive. First-line chemioimmunotherapy is now standard across esophagogastric, hepatocellular, biliary, and anal cancers; dual checkpoint blockade and adjuvant immunotherapy have redefined the management of dMMR/MSI-H colorectal cancer; perioperative immunochemotherapy has entered curative-intent care for resectable gastroesophageal cancer. ctDNA is poised to further personalize adjuvant decision-making as its predictive role is clarified. For the practicing oncologist, the central practical message is that comprehensive molecular and biomarker profiling at diagnosis is now indispensable to delivering optimal,

individualized care. At the same time, clinicians should interpret the newest and least mature data with appropriate caution, recognizing that durability of benefit and real-world applicability must be confirmed. Continued progress will depend on rigorous trials, thoughtful patient selection, and the ongoing translation of molecular insight into meaningful improvements in survival and quality of life.

Conflict(s) of Interest

WS: Ipsen, Revolution Medicines, BeOne

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