

MINI-REVIEW

Immunotherapy in esophageal, gastric/gastroesophageal junction, and colorectal cancers: Biomarker selection, current practice, and future directions

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Abstract

The management of advanced gastrointestinal malignancies now relies heavily on biomarker-driven immunotherapy. In esophageal, gastric/gastroesophageal junction (GEJ), and colorectal cancers, the clinical utility of immune checkpoint blockade is governed by tumor histology, mismatch repair status, and programmed death-ligand 1 (PD-L1) expression. Microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) status remains the most consistent predictor of durable immunotherapy benefit, enabling treatment de-escalation strategies in selected MSI-H/dMMR settings. Conversely, upper gastrointestinal adenocarcinomas require integration of overlapping biomarkers, including PD-L1 combined positive score, human epidermal growth factor receptor 2, and claudin 18.2, to guide immunotherapy-based and targeted treatment strategies. Major therapeutic gaps remain in microsatellite-stable colorectal cancer, where spatial heterogeneity, liver-mediated immune tolerance, and an immune-excluded microenvironment render tumors largely refractory to standard checkpoint inhibition. Accordingly, this narrative review focuses on practical biomarker selection, resistance mechanisms, and evidence-level distinctions across selected gastrointestinal cancers.

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1. Introduction

Gastrointestinal malignancies have highly variable immunologic profiles, requiring tailored treatment protocols. Collectively, colorectal, gastric, and esophageal cancers represent a significant global health burden, accounting for nearly 3.4 million new diagnoses annually.¹⁻³ Historically, the systemic management of these advanced cancers largely relied on cytotoxic chemotherapy.^{4,5} However, the integration of therapies targeting programmed death-1 (PD-1) and cytotoxic T lymphocyte-associated antigen 4

(CTLA-4) has significantly improved survival for selected patients.^{6,7}

The successful application of immune checkpoint blockade is guided by predictive biomarkers, most notably microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) status, and PD-L1 expression.^{1,8} Because the predictive value of these biomarkers varies significantly by tumor anatomy and histology, precise patient selection is critical. For instance, while MSI-H/dMMR metastatic colorectal tumors often exhibit marked sensitivity to checkpoint inhibitors, the vast majority of microsatellite-stable (MSS) tumors derive no meaningful benefit from these agents.^{7,9} Current therapeutic efforts focus on maximizing immunotherapy for responsive subgroups while mitigating resistance in immunologically “cold” tumors. Given the rapid expansion of biomarker-selected immunotherapy across gastrointestinal cancers, a practical challenge is determining which approaches are supported by routine clinical evidence, which are listed in guidelines only in selected contexts, and which remain investigational.

2. Methods

We conducted a narrative review of English-language literature published from January 2020 through April 2026 using PubMed/MEDLINE. Foundational phase 3 trials published before 2020 were included when needed to provide context for established standards of care. Search terms included combinations of “immune checkpoint inhibitor,” “immunotherapy,” “PD-1,” “PD-L1,” “CTLA-4,” “MSI-H,” “dMMR,” “MSS,” “HER2,” “CLDN18.2,” “ctDNA,” “esophageal cancer,” “gastric cancer,” “gastroesophageal junction cancer,” and “colorectal cancer.” Relevant American Society of Clinical Oncology guideline updates, National Comprehensive Cancer Network (NCCN) guidelines for esophageal and esophagogastric junction cancers, gastric cancer, colon cancer, and rectal cancer, and selected major oncology congress abstracts were also reviewed to provide clinical context and assess guideline alignment.

Studies were selected based on relevance to biomarker-guided immunotherapy, clinical applicability, trial phase, and disease site. Peer-reviewed guideline recommendations and phase 3 trials were prioritized. Prospective phase 2 studies, congress abstracts, and translational studies were included when they addressed emerging strategies or mechanisms of resistance, but these data are described as investigational when not incorporated into routine practice. Case reports, non-English articles, duplicate reports, and studies not directly

related to immunotherapy or biomarker-guided treatment in the selected gastrointestinal cancers were excluded. Because this was a narrative review, formal risk-of-bias assessment and meta-analysis were not performed. Our initial database search yielded approximately 2,150 results. The final synthesis incorporated 55 sources after relevance screening, including guideline documents, pivotal phase 3 trials, selected prospective phase 2 studies, translational studies, and major abstracts from oncology congresses.

3. Core biomarkers guiding immunotherapy

Microsatellite instability-high or dMMR status represents a phenotype characterized by faulty DNA mismatch repair, yielding a hypermutated genome rich in neoantigens.^{7,10} This mutational landscape drives dense CD8⁺ T cell infiltration and upregulates PD-L1 expression within the tumor microenvironment, making it one of the most consistent predictors of immunotherapy response.¹⁰ In colorectal cancer, the 4–7% of metastatic cases harboring MSI-H/dMMR status experience durable benefits from checkpoint inhibitors, while MSS tumors remain largely refractory.^{9,11} Across esophagogastric cancers, the identification of MSI-H/dMMR status robustly predicts sensitivity to checkpoint blockade, establishing immunotherapy as a preferred frontline strategy.^{2,8,12}

Unlike MSI-H/dMMR, the predictive utility of PD-L1 expression is highly context-dependent.¹ In upper gastrointestinal cancers, PD-L1 expression is commonly reported using the combined positive score (CPS), which incorporates PD-L1 staining in tumor cells and immune cells relative to the total number of viable tumor cells.^{3,6,8,13} Tumor proportion score or tumor cell score (TPS/TC), in contrast, reflects PD-L1 staining in tumor cells only. These scoring systems are not interchangeable, and treatment thresholds may differ across trials and guideline recommendations.^{4,8,14} Therefore, PD-L1 results should be interpreted based on the assay, scoring method, tumor histology, and the treatment setting in which the therapy was studied. In colorectal cancer, PD-L1 testing has limited clinical utility, where mismatch repair status remains the dominant predictor of response.^{1,7,9}

Furthermore, while targets such as human epidermal growth factor receptor 2 (HER2) and claudin-18.2 (CLDN18.2) are traditionally addressed with directed monoclonal antibodies, they increasingly intersect with immunotherapy selection in upper gastrointestinal cancers.¹⁵ Evaluating these biomarkers is essential not only for selecting targeted therapies but for guiding complex multi-agent chemoimmunotherapy combinations in upper gastrointestinal cancers.^{16,17}

4. Disease-specific clinical application

4.1. Esophageal squamous cell carcinoma and localized esophageal cancers

The clinical management of localized, resectable esophageal cancer is stratified by histology. For esophageal squamous cell carcinoma (ESCC), a standard approach is chemoradiotherapy based on the CROSS regimen. However, for patients with resected disease harboring residual pathologic tumor after neoadjuvant chemoradiotherapy, adjuvant immunotherapy has shifted the standard of care. Adjuvant nivolumab significantly improves median disease-free survival compared to observation, establishing an NCCN Category 1 strategy to mitigate early systemic recurrence.^{8,18}

In the frontline metastatic setting, PD-L1 expression is an important but imperfect biomarker for selecting immunotherapy-based regimens in ESCC.^{4,8,14,19,20} Programmed cell death protein 1 (PD-1)-based combinations have improved outcomes compared with chemotherapy alone in selected patients. Nivolumab plus chemotherapy is guideline-supported for PD-L1 CPS ≥ 1 ESCC, while CheckMate 648 reported key efficacy outcomes using tumor cell PD-L1 expression/TPS $\geq 1\%$.^{4,8,19} Nivolumab plus ipilimumab provides a chemotherapy-free option for selected patients, although the pivotal CheckMate 648 efficacy subgroup was also reported using TPS/TC PD-L1 expression rather than CPS.^{4,19} Pembrolizumab plus chemotherapy has demonstrated

benefit, particularly in CPS ≥ 10 disease, and tislelizumab plus chemotherapy improved survival in the broader intent-to-treat ESCC population.^{14,20,21} RATIONALE-306 should be interpreted separately because it used tumor area positivity (TAP) rather than CPS or TPS as its PD-L1 scoring framework.^{20,21} Concordance analyses have shown significant agreement between TAP and CPS at analogous cutoffs (Cohen's κ , 0.64–0.85), supporting their clinical comparability for tislelizumab-treated patients.²² NCCN also notes that TAP and CPS scores have high concordance and may be interchangeable for tislelizumab.⁸ However, CPS and TPS/TC should not be considered interchangeable. CPS includes PD-L1 staining of tumor and immune cells, whereas TPS/TC reflects staining of tumor cells only. Therefore, TPS-based trial subgroup results should not be directly converted into CPS thresholds; PD-L1 results should be interpreted according to the assay, scoring method, and treatment context used in the relevant trial or guideline recommendation.^{4,8,14,19} Key frontline immunotherapy strategies for ESCC are summarized in Table 1.

Esophageal squamous cell carcinoma has a distinct immunotherapy profile compared with many other gastrointestinal tumors, although PD-L1 remains an imperfect selection marker. Emerging ESCC strategies are evaluating approaches to overcome PD-1 resistance, including dual checkpoint inhibition, T cell immunoreceptor with Ig and ITIM domains/PD-L1 combinations, and bispecific PD-1/CTLA-4 blockade.

Table 1. Frontline immunotherapy strategies in esophageal squamous cell carcinoma

Biomarker	Key trial	Regimen	Key efficacy data	NCCN category
ESCC, PD-L1 CPS ≥ 1 ; trial efficacy reported by TPS/TC $\geq 1\%$	CheckMate 648 ^{4,19}	Nivolumab + FP/platinum	mOS 15.4 vs. 9.1 months in PD-L1 TPS $\geq 1\%$ subgroup; HR: 0.54 (13-month primary analysis)	Category 1
ESCC, PD-L1 CPS ≥ 10	KEYNOTE-590 ¹⁴	Pembrolizumab + FP/cisplatin	mOS 13.9 vs. 8.8 months in CPS ≥ 10 ESCC subgroup; HR: 0.57	Category 1
ESCC, ITT benefit reported; TAP/CPS concordance noted for tislelizumab	RATIONALE-306 ^{20–22}	Tislelizumab + FP/platinum or paclitaxel	mOS 17.2 vs. 10.6 months in ITT population; HR 0.66 (primary); HR: 0.70 (3-year follow-up)	Category 1
ESCC, PD-L1 CPS ≥ 1 ; trial efficacy reported by TPS/TC $\geq 1\%$	CheckMate 648 ^{4,19}	Nivolumab + ipilimumab	mOS 13.7 vs. 9.1 months in PD-L1 TPS $\geq 1\%$ subgroup; HR: 0.64 (13-month primary analysis)	Preferred

Notes: For CheckMate 648, key PD-L1 subgroup efficacy outcomes were reported using tumor cell PD-L1 expression/TPS $\geq 1\%$. CPS-based wording reflects guideline or clinical selection context. RATIONALE-306 used TAP rather than CPS or TPS as its PD-L1 scoring framework. CPS and TPS/TC are not interchangeable.

Abbreviations: CPS: Combined positive score; ESCC: Esophageal squamous cell carcinoma; FP: Fluorouracil plus platinum; HR: Hazard ratio; ITT: Intention-to-treat; mOS: Median overall survival; NCCN: National Comprehensive Cancer Network; PD-L1: Programmed death-ligand 1; TAP: Tumor area positivity; TC: Tumor cell; TPS: Tumor proportion score.

These approaches remain investigational unless supported by guideline-listed indications.

4.2. Advanced gastric, gastroesophageal junction, and esophageal adenocarcinoma

Because advanced esophageal adenocarcinoma, gastroesophageal junction (GEJ) adenocarcinoma, and gastric adenocarcinoma share a unified biological and biomarker landscape, their systemic management is directed under a shared therapeutic framework (Table 2).⁶ Upfront molecular profiling is required to navigate a hierarchical biomarker evaluation, prioritizing mismatch repair (MSI-H/dMMR) status, HER2, and PD-L1 (CPS).^{3,6,13}

In the metastatic setting, biomarker assessment helps guide the use of immunotherapy and targeted therapy in upper gastrointestinal adenocarcinoma.^{3,6,13} For MSI-H/dMMR tumors, immune checkpoint blockade is a preferred option in selected settings.^{8,13,23} For HER2-positive disease with PD-L1 CPS ≥ 1 , pembrolizumab plus trastuzumab and chemotherapy is guideline-supported based on KEYNOTE-811.^{13,24,25} For HER2-negative tumors with PD-L1 CPS ≥ 5 , nivolumab plus chemotherapy is a Category 1 guideline-supported regimen based on CheckMate 649.^{13,26,27} CLDN18.2-directed therapy should be distinguished from immunotherapy, because zolbetuximab plus chemotherapy is a biomarker-directed targeted strategy rather than an immune checkpoint inhibitor regimen. Zolbetuximab plus chemotherapy is guideline-supported for appropriately selected CLDN18.2-

positive gastric/GEJ adenocarcinoma^{13,28}, whereas combinations adding immune checkpoint blockade to CLDN18.2-directed therapy should be regarded as investigational and hypothesis-generating until supported by mature randomized data.¹⁶

Perioperative immunotherapy strategies for upper gastrointestinal adenocarcinoma should be interpreted in light of the level of evidence and clinical context (Table 3). Fluorouracil, leucovorin, oxaliplatin, and docetaxel plus durvalumab are guideline-listed for selected patients, with category strength varying by tumor location, PD-L1 CPS/TAP status, nodal status, and histologic subtype.^{8,13,29} For MSI-H/dMMR gastric, GEJ, and esophageal adenocarcinomas, neoadjuvant or perioperative immunotherapy may also be considered in selected circumstances.^{8,13} Other perioperative or neoadjuvant approaches, including TERRIFIC, NEOSUMMIT-01, and conversion strategies, remain investigational and require further validation before routine use.^{30–32} Emerging upper GI strategies will likely focus less on single-agent checkpoint escalation and more on rational integration of PD-1 blockade with biomarker-selected targeted platforms, particularly HER2- and CLDN18.2-directed combinations.

In upper gastrointestinal adenocarcinomas, treatment selection increasingly depends on the integration of multiple biomarkers, including MSI-H/dMMR status, HER2, PD-L1 CPS, and CLDN18.2. Because these biomarkers may overlap, clinicians must distinguish established guideline-supported regimens from investigational combinations. A

Table 2. Biomarker-guided strategies relevant to immunotherapy selection in advanced gastric, gastroesophageal junction, and esophageal adenocarcinoma

Biomarker	Key trial	Regimen	Key efficacy data	NCCN/clinical status
MSI-H/dMMR (Any histology)	Multiple (e.g., CheckMate 649, KEYNOTE-158) ^{23,27}	PD-1 inhibitor + chemotherapy	Clinically meaningful benefit reported in MSI-H/dMMR subsets	Preferred / guideline-supported in selected settings
PD-L1 CPS ≥ 5	CheckMate 649 ^{26,27}	Nivolumab + chemotherapy	mOS: 14.4 vs. 11.1 months; 5-year OS: 16% vs. 6%; ORR: 58% vs. 46%	Category 1
HER2-positive/ PD-L1 CPS ≥ 1	KEYNOTE-811 ^{13,24,25}	Pembrolizumab + trastuzumab + chemo	mOS: 20.1 vs. 15.7 months; OS HR: 0.79. mPFS: 10.9 vs. 7.3 months; PFS HR: 0.72. ORR: 73% vs. 58%	Category 1
CLDN18.2+/CPS ≥ 1	ILUSTRO (Cohort 4B) ¹⁶	Zolbetuximab + mFOLFOX6 + nivolumab	mPFS: 23.6 months in the CLDN18.2-high/PD-L1 ⁺ subgroup	Investigational; hypothesis-generating early-phase combination

Abbreviations: CLDN18.2: Claudin-18.2; CPS: Combined positive score; dMMR: Mismatch repair-deficient; HER2: Human epidermal growth factor receptor 2; HR: Hazard ratio; mFOLFOX6: Modified fluorouracil, leucovorin, and oxaliplatin; MSI-H: Microsatellite instability-high; mOS: Median overall survival; mPFS: Median progression-free survival; NCCN: National Comprehensive Cancer Network; ORR: Objective response rate; PD-1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1.

Table 3. Perioperative immunotherapy strategies in upper gastrointestinal adenocarcinoma: Guideline-supported and emerging approaches

Setting	Key trial	Regimen	Key clinical status/outcome
Selected resectable gastric/GEJ adenocarcinoma	MATTERHORN (phase 3) ²⁹	FLOT + durvalumab	Guideline-listed option for selected patients; category and applicability vary by tumor location, biomarker status, and histology
Neoadjuvant	TERRIFIC (phase 2b) ³⁰	Tislelizumab + chemoradiotherapy	Phase 2b; investigational. pCR 25.7% vs. 5.3% with chemoradiotherapy alone; requires validation before routine use
Perioperative	NEOSUMMIT-01 (phase 2) ^{31,32}	Toripalimab + chemotherapy	Phase 2; investigational. 3-year EFS 74.7% vs. 56.2% and pCR 25.0% vs. 8.3%; requires further validation

Abbreviations: EFS: Event-free survival; FLOT: Fluorouracil, leucovorin, oxaliplatin, and docetaxel; GEJ: Gastroesophageal junction; pCR: Pathological complete response.

major practical challenge is obtaining timely and adequate tissue for molecular profiling before clinical status declines.

4.3. Colorectal cancer

In colorectal cancer, a patient's mismatch repair profile is the dominant predictor of immunotherapeutic efficacy. For the 4–7% of patients with metastatic MSI-H/dMMR disease—as well as those with ultra-hypermutated *POLE/POLD1* mutations—immune checkpoint blockade is the NCCN-preferred first-line strategy.^{7,33,34} The KEYNOTE-177 trial established pembrolizumab monotherapy as a Category 1 standard of care, demonstrating a median progression-free survival of 16.5 months and a median duration of response exceeding six years^{7,35} (Table 4). Dual immune checkpoint blockade has further optimized these outcomes; CheckMate 8HW established nivolumab plus ipilimumab as a Category 1, preferred strategy in this population, significantly extending progression-free survival compared to monotherapy.^{9,33} In nonmetastatic colon cancer, NCCN now recognizes neoadjuvant checkpoint inhibitor immunotherapy for selected MSI-H/dMMR or *POLE/POLD1*-mutated tumors, particularly T4 or bulky primary tumors.³⁴

Immunotherapy is also being studied in early-stage MSI-H/dMMR colorectal cancer, particularly in locally advanced dMMR rectal cancer. In a single-arm phase 2 study, neoadjuvant dostarlimab achieved high rates of clinical complete response and supported a nonoperative management approach in a highly selected population. However, these findings should be interpreted in the context of modest cohort size, specialized multidisciplinary assessment, intensive surveillance, and still-maturing long-term follow-up. A clinical complete response requires careful endoscopic, radiographic, and clinical confirmation, and uncertainty remains regarding late local regrowth, distant relapse, and reproducibility in centers

without experience. Therefore, dostarlimab-based organ preservation is an important strategy for selected patients with dMMR rectal cancer, but it requires careful patient selection and close follow-up.^{36,37}

Recent translational studies further support the biologic complexity of MSS/mismatch repair-proficient (pMMR) colorectal cancer resistance, implicating epigenetic immune-evasion pathways and microbiome–tumor microenvironment interactions.^{38,39}

Conversely, checkpoint inhibitors are not standard practice for the approximately 95% of patients with MSS/pMMR colorectal cancer outside of clinical trials.^{10,40} Because these immune-excluded tumors are largely refractory to standard PD-1 blockade, clinical progress in this majority population relies heavily on cytotoxic regimens and biomarker-selected targeted therapies for actionable alterations. Although *BRAF* V600E and *KRAS* G12C subsets have biomarker-selected targeted options, these therapies are not primary immunotherapies and should be distinguished from checkpoint inhibitor-based strategies.¹ To bridge this immunotherapy gap, early studies are evaluating aggressive immune-modulating combinations, including Fc-enhanced CTLA-4 blockade with botensilimab plus PD-1 blockade with balstilimab, to bypass MSS immune resistance.⁴¹

Colorectal cancer represents a major efficacy gap in gastrointestinal immuno-oncology. While mismatch repair deficiency allows meaningful treatment de-escalation, including organ-preservation strategies, in selected localized disease, these successes are confined to a small subset of patients. For most MSS tumors, standard checkpoint blockade remains largely ineffective. Overcoming this innate resistance will likely require rational immune-modulating strategies beyond PD-1 monotherapy, including Fc-enhanced CTLA-4/PD-1

Table 4. Immunotherapy strategies in colorectal cancer

Biomarker	Key trial	Regimen	Key efficacy data	NCCN/clinical status
Advanced MSI-H/dMMR	KEYNOTE-177 ^{7,35}	Pembrolizumab	mPFS: 16.5 vs. 8.2 months; median DOR exceeding six years	Category 1, Preferred
Advanced MSI-H/dMMR	CheckMate 8HW ^{9,33}	Nivolumab + ipilimumab	mPFS: not reached vs. 39.3 months vs. nivolumab alone	Category 1, Preferred
Localized dMMR rectal	MSK Phase II ^{36,37} (NCT04165772)	Dostarlimab (Neoadjuvant)	High clinical complete response rate in a single-arm phase 2 study; nonoperative management under intensive surveillance in selected patients	Guideline-incorporated for selected dMMR rectal cancer; requires close surveillance
MSS/pMMR (Resectable)	NEST-1 & NEST-2 ⁴¹	Botensilimab + balstilimab (Neoadjuvant)	Major pathologic response of ≥90% observed in up to 47% of MSS patients	Investigational

Abbreviations: dMMR: Mismatch repair-deficient; DOR: Duration of response; mPFS: Median progression-free survival; MSI-H: Microsatellite instability-high; MSS: Microsatellite stable; NCCN: National Comprehensive Cancer Network; pMMR: Mismatch repair-proficient.

approaches, innate immune activation, microbiome modulation, bispecific constructs, and cellular therapies designed to improve T cell priming and overcome immune exclusion.

5. Mechanisms of immunotherapy resistance

The marked immunotherapy resistance observed in MSS colorectal cancer is largely driven by a low tumor mutational burden, limited neoantigen generation, and insufficient T cell priming.^{10,42} Tumor-intrinsic signaling pathways, including WNT/β-catenin and transforming growth factor beta, may further promote immune exclusion and suppress cytotoxic T cell infiltration, explaining why checkpoint blockade alone rarely produces meaningful responses in MSS disease.⁴⁰

Beyond classical immune exclusion, emerging translational data suggest that epigenetic regulation and microbiome–tumor microenvironment interactions may contribute to colorectal cancer immune evasion. Protein arginine methyltransferase 5-mediated AlkB homolog 5 methylation has been linked to increased CD276/B7-H3 expression and impaired cytotoxic T cell activity, suggesting a potential epigenetic immune-evasion axis.³⁹ Separately, microbiome-directed approaches, including an orally administered inulin-based hydrogel strategy in colorectal cancer models, have been investigated as a way to modify local immune responses.³⁸ These findings remain translational rather than practice-changing, but they provide biologic rationale for ongoing efforts to sensitize MSS/pMMR colorectal cancer to immune-based approaches.

Beyond tumor mutational burden, immunotherapy

resistance is heavily driven by complex microenvironmental dynamics. The presence of immunosuppressive cell populations—such as regulatory T cells, myeloid-derived suppressor cells, and M2-polarized macrophages—establishes an immunologically adverse niche.^{12,42,43} In ESCC, spatial transcriptomic analyses reveal immune-exclusion signatures characterized by intratumoral CD8⁺ T cell depletion mediated by cancer-associated fibroblasts.⁴⁴ Additionally, chronic antigenic stimulation drives T cell exhaustion and the compensatory upregulation of secondary inhibitory receptors, including T cell immunoreceptor with Ig and ITIM domains, lymphocyte activation gene-3, and T cell immunoglobulin and mucin-domain containing-3.^{45,46}

The anatomic site of metastatic spread may also influence systemic immune responses. Hepatic dissemination is a clinically relevant barrier to immunotherapy efficacy across gastrointestinal malignancies, partly through liver-associated immune tolerance and reduced responsiveness to checkpoint blockade.^{11,47} In early-phase combination studies, responses have often appeared more favorable in patients without active liver metastases, although this observation requires cautious interpretation because of small sample sizes and heterogeneous study populations.⁴⁷ Intratumoral heterogeneity and clonal evolution further complicate treatment sequencing and provide a rationale for dynamic monitoring approaches, including circulating tumor DNA (ctDNA), to capture molecular changes over time.^{48,49} Dynamic ctDNA monitoring may complement baseline tissue biomarkers by assessing molecular residual disease, treatment response, and clonal evolution over time. In colorectal cancer, ctDNA-guided postoperative management reduced adjuvant chemotherapy use without compromising recurrence-free survival in stage

II colon cancer, supporting its role in risk stratification and clinical trial design.⁵⁰ In advanced gastrointestinal cancers, serial ctDNA may be useful when repeat tissue biopsy is limited by tissue availability, anatomic access, or declining performance status. However, ctDNA-guided immunotherapy escalation or de-escalation remains investigational in most gastrointestinal cancer settings, and broader implementation will require assay standardization, clearer clinical actionability, and improved access.⁵⁰

6. Emerging immunotherapy strategies

Emerging immunotherapy strategies in gastrointestinal cancers largely focus on overcoming immune exclusion, impaired T cell priming, and adaptive checkpoint resistance. These approaches include dual checkpoint blockade, innate immune activation, microbiome modulation, bispecific antibodies, and cellular therapies. Most remain early-phase or investigational, and their role in routine practice will depend on validation in larger controlled studies. Beyond standard PD-1/PD-L1 and CTLA-4 blockade, several studies are evaluating secondary inhibitory receptors and dual-checkpoint strategies. For example, T-cell immunoreceptor with Ig and ITIM domains/PD-L1 combinations and bispecific PD-1/CTLA-4 blockade have shown early clinical activity in selected upper gastrointestinal cancer settings, but these approaches require further validation before routine clinical adoption.^{51,52} Other early-phase strategies, including STING agonists, oncolytic viruses, and microbiome-directed approaches, aim to increase immune infiltration or modify the tumor microenvironment in otherwise immune-refractory tumors.⁵³

Cellular therapies are also being evaluated in solid gastrointestinal tumors, although their development remains limited by challenges in antigen selection, T cell trafficking and persistence, and toxicity. In refractory metastatic colorectal cancer, early-phase chimeric antigen receptor T cell studies targeting mucosal or tumor-associated markers have reported preliminary clinical activity, but these findings require confirmation in larger controlled studies before integration into routine practice.⁵⁴

Allogeneic natural killer (NK) cell therapies are another area of active investigation. Because some gastrointestinal tumors downregulate major histocompatibility complex class I molecules to evade immunity, NK cells may provide a major histocompatibility complex-independent approach to immune recognition.⁵⁵ Unlike chimeric antigen receptor T cell platforms, allogeneic NK cells may carry lower risks of cytokine release syndrome and graft-versus-host disease, enabling scalable, “off-the-shelf” cellular products.⁵⁵ Early-phase trials are evaluating CLDN18.2- and NK group 2, member D-targeted chimeric antigen receptor–NK constructs, including platforms designed to improve in vivo persistence through interleukin-15 armoring or gene-editing strategies.⁵⁵ At present, these approaches remain investigational.⁵⁵

7. Clinical algorithm and practical takeaways

Frontline systemic immunotherapy selection for advanced and metastatic disease is dictated by histology-specific biomarker testing algorithms. Table 5 summarizes the essential biomarkers, therapeutic relevance, and primary immunological limitations for each major gastrointestinal cancer subtype in the metastatic setting.

Table 5. Practical biomarker-driven immunotherapy algorithm for advanced/metastatic disease

Tumor type	Required biomarkers	First-line immunotherapy relevance	Key immunological limitation
ESCC	PD-L1 CPS ^a ; MSI-H/dMMR	Guideline-supported PD-1–based options depend on histology, PD-L1 framework, and treatment context	PD-L1 assay and threshold variability; distinct spatial exclusion ^{8,44}
EAC, GEJ, and gastric adenocarcinoma	MSI-H/dMMR, PD-L1 CPS, HER2, CLDN18.2	Biomarker-guided chemoimmunotherapy; integration of PD-1 with targeted agents	Overlapping biomarker complexity; spatial heterogeneity ^{12,48,49}
CRC	MSI-H/dMMR; POLE/POLD1 where available	Established benefit in MSI-H/dMMR disease; MSS/pMMR immunotherapy strategies remain investigational outside selected clinical-trial settings	Substantial innate MSS resistance and hepatic immune tolerance ^{11,47}

Note: ^aCheckMate 648 efficacy outcomes are commonly reported by the PD-L1 TPS subgroup.

Abbreviations: CLDN18.2: Claudin-18.2; CPS: Combined positive score; CRC: Colorectal cancer; dMMR: Mismatch repair-deficient; EAC: Esophageal adenocarcinoma; ESCC: Esophageal squamous cell carcinoma; GEJ: Gastroesophageal junction; HER2: Human epidermal growth factor receptor 2; MSI-H: Microsatellite instability-high; MSS: Microsatellite stable; PD-1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; pMMR: Mismatch repair-proficient; POLE: DNA polymerase epsilon catalytic subunit; POLD1: DNA polymerase delta 1 catalytic subunit.

8. Conclusion

While the integration of immune checkpoint blockade has changed treatment options for selected patients with esophageal, gastric, and colorectal cancers, translating these advances into routine clinical practice remains challenging. For the practicing oncologist, a major hurdle is tissue stewardship. As the required panel of predictive biomarkers expands to include mismatch repair, PD-L1, HER2, and emerging targets such as CLDN18.2, physicians must extract increasingly large amounts of molecular data from limited endoscopic biopsy samples. This tissue scarcity is compounded by an ongoing lack of assay harmonization; differing PD-L1 antibodies and scoring thresholds often complicate therapeutic selection and clinical decision-making.³

Furthermore, there is a recognized efficacy gap between highly selected clinical trial cohorts and real-world patient populations. Patients with gastrointestinal malignancies frequently experience physiological challenges such as cachexia, biliary obstruction, and hepatic dysfunction that may diminish immunologic responses. The complex interplay between the gut microbiome, chronic mucosal inflammation, and liver-mediated immune tolerance creates an immunosuppressive environment that preclinical models and early-phase trials struggle to accurately replicate.^{11,48}

Moving forward, progress in gastrointestinal immunology will depend on more than identifying new checkpoint targets. Meaningful advances will also require addressing practical barriers, including limited tissue availability, assay standardization, and the need for pragmatic clinical trials that better reflect real-world patients with gastrointestinal cancers. Access to molecular profiling, PD-L1 assay standardization, CLDN18.2 testing, clinical trials, and multidisciplinary organ-preservation programs may vary substantially across regions and practice settings. Reducing these gaps will be essential for extending biomarker-selected immunotherapy beyond specialized centers and achieving broader clinical benefit.

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