Advancements of immunotherapy in gastrointestinal cancers: a review of clinical evidence

Alexandra Pușcașu[1], Ioana Luca[1], Alexandru Grigorescu[2]

1. Medical Oncology Department, Fundeni Clinical Institute, Bucharest, Romania

2. "Dr. Carol Davila" Clinical Hospital of Nephrology, Bucharest, Romania

Corresponding author:
Alexandra Pușcașu
E-mail: puscasu.alexandra4@gmail.com

Abstract

Immunotherapy has transformed the treatment of gastrointestinal cancers, with immune checkpoint inhibitors (ICIs) playing a crucial role in improving survival across various malignancies. This review systematically analyzed phase II and III randomized clinical trials evaluating immune-based therapies in digestive cancers. A literature search was conducted in PubMed, focusing on randomized studies exploring these therapeutic approaches in gastric, esophageal, colorectal, hepatocellular, biliary tract and pancreatic cancers. The results highlight that ICIs provide significant survival benefits in MSI-H/dMMR colorectal cancer, PD-L1-positive gastroesophageal cancer and hepatocellular carcinoma, with key trials such as CheckMate 649, KEYNOTE-859, IMbrave150 and TOPAZ-1 establishing new standards of care. However, their efficacy remains limited in microsatellite-stable (MSS) colorectal and pancreatic cancers, necessitating combination strategies. Despite their success, immune-related adverse events, biomarker-driven patient selection, and resistance mechanisms remain major challenges. With recent regulatory approvals in Romania, the access to these therapies is expanding, underscoring their growing impact in clinical practice. Future directions should focus on optimizing combination regimens, refining predictive biomarkers and overcoming treatment resistance to further enhance patient outcomes in gastrointestinal oncology.

Keywords: *immunotherapy, gastrointestinal cancers, clinical evidence*

Rezumat

Imunoterapia a revoluționat tratamentul cancerelor gastrointestinale, inhibitorii punctelor de control imun (ICI) jucând un rol crucial în îmbunătățirea supraviețuirii în diverse malignități. Această lucrare a evaluat sistematic studiile clinice randomizate de fază II și III privind terapiile imunologice în cancerele digestive, în cadrul bazei de date PubMed. Rezultatele evidențiază faptul că ICI oferă beneficii semnificative de supraviețuire în cancerul colorectal MSI-H/dMMR, cancerul gastroesofagian PD-L1 pozitiv și în carcinomul hepatocelular, cu studii de referință precum CheckMate 649, KEYNOTE-859, IMbrave150 și TOPAZ-1 care au stabilit noi standarde de tratament. Totuși, eficacitatea acestora rămâne limitată în cancerul colorectal microsatelit-stabil (MSS) și în cel pancreatic, care necesită strategii combinate. În ciuda succesului, evenimentele adverse imune, selecția pacienților pe baza biomarkerilor și mecanismele de rezistență reprezintă provocări majore. Odată cu aprobările recente de rambursare în România, accesul la aceste terapii se extinde, subliniind impactul lor tot mai mare în practica clinică. Direcțiile viitoare ar trebui să se concentreze pe optimizarea combinațiilor terapeutice, perfecționarea biomarkerilor predictivi și pe depășirea rezistenței la tratament pentru a îmbunătăți în continuare rezultatele pacienților cu cancere gastrointestinale.

Cuvinte-cheie: *imunoterapie, cancere gastrointestinale, evidențe clinice*

Submission date: 11.02.2025
Acceptance date: 20.02.2025

Progrese ale imunoterapiei în cancerele gastrointestinale: un review al dovezilor clinice

Suggested citation for this article: Pușcașu A, Luca I, Grigorescu A. Advancements of immunotherapy in gastrointestinal cancers: a review of clinical evidence. Oncolog-Hematolog.ro. 2025;70(1):18-27.

Introduction

Over the past decades, immunotherapy has revolutionized oncology, with immune checkpoint inhibitors (ICIs) playing a pivotal role in transforming cancer treatment. Decades of research have revealed that some tumor cells evade immune detection by exploiting immune checkpoint proteins – natural brakes on T cells that prevent excessive immune activation. ICIs work by releasing these brakes, allowing the immune system to recognize and attack cancer cells more effectively.

The foundation of ICIs was laid in 1987 with the discovery of the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). Nearly a decade later, its immune checkpoint function was identified, leading to 16 years of preclinical and clinical research before the development of ipilimumab – the first CTLA-4 inhibitor[1]. Approved in 2011, ipilimumab has become the first therapy to improve survival in metastatic melanoma, marking the beginning of a new era in cancer immunotherapy[2]. Inspired by this success, researchers developed ICIs targeting the programmed

death-1/programmed death-ligand 1 (PD-1/PD-L1) pathway, with pembrolizumab becoming the first such agent approved in 2014[3]. Since then, the FDA has approved 11 ICIs targeting CTLA-4, PD-1/PD-L1 or lymphocyte activation gene-3 (LAG-3) across multiple cancer types[4]. Moreover, beyond ICIs, therapeutic cancer vaccines are also an area of active research, given their potential to enhance anti-tumor immunity. These breakthroughs have led to remarkable and durable responses in some patients, even in advanced disease stages.

The effectiveness of ICIs is influenced by biomarkers such as PD-L1 expression, tumor mutation burden (TMB), and DNA repair deficiencies, including microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) status. Tumor-infiltrating lymphocytes (TILs) are also being explored as potential predictors of response. However, not all patients experience the same benefits, and ongoing research aims to refine patient selection criteria and optimize therapeutic strategies[5]. Additionally, ICIs can trigger immune-related adverse events (irAEs) due to immune system overstimulation, affecting organs such as the skin, colon, endocrine glands, liver, joints, and lungs. While most irAEs are manageable with corticosteroids and immunosuppressants, severe toxicities may necessitate treatment discontinuation. Identifying patients at higher risk for irAEs, particularly those with preexisting autoimmune conditions, remains a key area of investigation[6].

ICIs have rapidly expanded into gastrointestinal oncology, where they are beginning to reshape treatment paradigms. While traditional modalities such as chemotherapy, surgery, radiotherapy and targeted therapies remain essential, immunotherapy is now recognized as a promising addition to the therapeutic arsenal for certain digestive cancers. Ongoing research is refining our understanding of immune-modulating treatments, offering hope for more effective and personalized strategies. Notably, Romania has recently implemented new reimbursement policies to support access to innovative immunotherapies for digestive cancers, reflecting the growing importance of these treatments in clinical practice.

To explore the evolving role of immunotherapy, notably ICIs in digestive cancers, we conducted a systematic literature review of randomized phase II and III clinical trials published in the past eight years. This review aims to provide insights into the current landscape of immunotherapy in gastrointestinal malignancies, highlighting key advancements, challenges, and future directions.

Methodology

Search strategy

A systematic search was conducted on PubMed, on 1 February 2025, to identify randomized phase II and III clinical trials evaluating immunotherapy in gastrointestinal (GI) cancers. To ensure a comprehensive and structured approach, separate searches were performed for each cancer type, including gastric cancer, esophageal cancer, colorectal cancer, pancreatic cancer, biliary tract cancer and hepatocarcinoma.

For each search, a combination of MeSH terms and keywords was used to capture relevant studies. The primary search terms included: ("immune checkpoint inhibitors" OR "immunotherapy") AND ("[specific GI cancer]"). Additional filters included "randomized control trial" and "clinical trial".

To refine the results, specific filters were applied. Only randomized comparative phase II and III clinical trials published in the last seven years were included. Additional restrictions were applied to limit results to English-language publications and exclude nonrandomized studies such as single-arm trials, retrospective analyses, case reports, and preclinical research.

In addition to PubMed, references from relevant systematic reviews were screened to identify any additional studies that met the inclusion criteria. The focus of this review was on trials that contributed to the new regulatory approvals of ICIs in Romania.

Results and discussion

1. Gastric and gastroesophageal junction (GEJ) cancers

Table 1 summarizes our findings on phase II and III clinical trials evaluating ICIs in gastric and GEJ cancers. We identified 16 randomized clinical trials, including 10 phase III trials (six in the first-line metastatic setting, three in later-line treatment, and one in the adjuvant setting) and six phase II trials (two in the perioperative/neoadjuvant setting, two in the adjuvant setting, and two in metastatic disease). The ICIs studied included nivolumab alone or in combination (five trials), nivolumab plus ipilimumab (two trials), pembrolizumab (five trials), tislelizumab (one trial), sintilimab (one trial), toripalimab (two trials), and atezolizumab (one trial).

First-line immunotherapy strategies

The CheckMate 649 study provided pivotal insights into nivolumab plus chemotherapy as a first-line treatment for advanced or metastatic gastroesophageal adenocarcinoma. With a three-year follow-up, this regimen demonstrated substantial improvements in overall survival (OS), progression-free survival (PFS) and objective response rate (ORR), particularly in patients with a combined positive score (CPS) ≥5. These findings underscore the importance of PD-L1 expression as a key predictor of response. The addition of nivolumab not only conferred a meaningful survival advantage, but also maintained an acceptable safety profile[7]. Notably, this combination has recently become reimbursed in Romania, expanding access to an important treatment option.

The KEYNOTE-062 trial initially explored pembrolizumab plus chemotherapy in the first-line setting, but it yielded mixed results. While the overall study was considered negative, subgroup analyses suggested greater benefit in patients with PD-L1 CPS ≥10. These findings were later confirmed by the KEYNOTE-859 trial, which demonstrated a significant overall survival improvement, ultimately leading to pembrolizumab's approval in combination with chemotherapy for metastatic gastric and GEJ cancers[8,9].

For HER2-positive unresectable or metastatic gastric/GEJ cancer, a phase III trial demonstrated that pembrolizumab plus trastuzumab and chemotherapy significantly improved OS compared to trastuzumab and chemotherapy alone (median OS: 20 versus 16.8 months; HR 0.80; 95% CI; 0.67-0.94; p=0.0040). The benefit was even more pronounced in patients with PD-L1 CPS ≥1 (OS: 20.1 versus 15.7 months; HR 0.79; 95% CI; 0.66-0.95). These findings support the approval of this combination as the new standard of care (SOC) for HER2-positive metastatic gastric/GEJ cancer[10].

Adjuvant immunotherapy strategies

In the adjuvant setting, a notable phase III trial evaluated nivolumab in patients with resected esophageal or gastroesophageal junction cancer who had previously undergone neoadjuvant chemoradiotherapy. The study found a significantly longer disease-free survival (DFS) with nivolumab compared to placebo (median DFS: 22.4 versus 11 months; HR 0.69; 95% CI; 0.56-0.86; p<0.001). These results highlight nivolumab's role in reducing recurrence risk and prolonging survival in high-risk patients post-surgery[11].

Perioperative/neoadjuvant strategies

In the perioperative and neoadjuvant setting, emerging evidence supports the role of ICIs in combination with chemotherapy to enhance tumor regression. A phase II trial evaluating toripalimab plus chemotherapy demonstrated a significantly higher tumor regression grade (TRG) 0/1 in the combination group compared to chemotherapy alone (44.4% versus 20.4%; risk difference: 22.7%; p=0.009), meeting its prespecified endpoint. Additionally, the pathological complete response rate (ypT0N0) was also improved in the toripalimab arm[12]. Similarly, in the DANTE trial, the addition of atezolizumab (ATZ) to perioperative FLOT chemotherapy was safe and improved postoperative staging and histopathologic regression. Histopathologic complete regression rates (pCR or TRG1a) were higher with FLOT + ATZ (24% versus 15%; p=0.032), with an even more pronounced benefit in patients with PD-L1 CPS ≥10 (33% versus 12%) and MSI tumors (63% versus 27%)[13]. These findings highlight the potential of ICI-based perioperative approaches in improving tumor response, particularly in biomarker-selected populations.

2. Esophageal cancers

Our review identified eight clinical trials evaluating ICIs in esophageal cancers, including seven phase III trials and one phase II trial. Among these, one trial investigated adjuvant therapy, four trials focused on first-line treatment, and three evaluated later-line therapies. The ICIs studied included nivolumab (three trials, one in combination), pembrolizumab (two trials), camrelizumab (one trial), sintilimab (one trial), and toripalimab (one trial). Three trials included adenocarcinoma (ADK), while the remaining focused exclusively on squamous cell carcinoma (SCC).

Advanced/metastatic setting

For esophageal squamous cell carcinoma (ESCC), ICIs have emerged as highly effective treatment options. The CheckMate 648 trial established nivolumab plus chemotherapy (NIVO + chemo) and nivolumab plus ipilimumab (NIVO + IPI) as first-line treatment options for advanced ESCC, leading to their approval in the US, EU, Japan and other countries. Recently, Romania has also included these therapies in its reimbursement list. With a minimum follow-up of 45 months, both regimens demonstrated sustained OS benefits and improved long-term survival rates in patients with PD-L1 tumor cell expression ≥1%, without new safety concerns[23].

Nivolumab as a second-line therapy also demonstrated clinically meaningful long-term improvement in overall survival compared with chemotherapy in previously treated patients with advanced ESCC. In this setting, median OS was longer with nivolumab than with chemotherapy (10.9 versus 8.5 months; HR 0.79; p=0.0264), with three-year OS rates of 15.3% versus 8.7%, respectively. The OS benefit was consistent across different best overall response (BOR) categories: complete/partial response (19.9 versus 15.4 months), stable disease (17.4 versus 8.8 months), and progressive disease (7.6 versus 4.2 months)[24].

Another promising ICI for esophageal and gastroesophageal junction (GEJ) cancers is pembrolizumab. The KEYNOTE-590 trial demonstrated that pembrolizumab plus chemotherapy was superior to chemotherapy alone in first-line treatment, particularly in patients with PD-L1 CPS ≥10[25].

Adjuvant setting

In the adjuvant setting, nivolumab has also shown benefit. Among patients with resected esophageal or GEJ cancer who had previously received neoadjuvant chemoradiotherapy, adjuvant nivolumab significantly prolonged disease-free survival (DFS) compared to placebo. However, grade 3 or 4 treatment-related adverse events occurred in 13% of nivolumab-treated patients versus 6% in the placebo group, leading to treatment discontinuation in 9% versus 3% of cases, respectively. These findings underscore the need to carefully balance efficacy and toxicity when considering adjuvant ICI therapy[26].

3. Hepatocellular carcinoma (HCC)

Our review identified nine clinical trials investigating ICIs in HCC, including eight phase III trials and one phase II trial. Among these, six trials focused on first-line therapy, two on second-line treatment, and one on the adjuvant setting. The ICIs evaluated were atezolizumab (two trials), camrelizumab (one trial), durvalumab (one trial), durvalumab + tremelimumab (one trial), pembrolizumab (three trials), nivolumab (one trial), and sintilimab (one trial).

First-line treatment

The IMbrave150 trial, a phase III study, enrolled 501 systemic treatment-naive patients with unresectable HCC, Child-Pugh class A liver function, and ECOG PS 0/1. The patients were randomized (2:1) to receive atezolizumab (1200 mg i.v. Q3W) + bevacizumab (15 mg/kg i.v. Q3W) versus sorafenib (400 mg b.i.d.) until unacceptable toxicity or loss of clinical benefit. Median OS was significantly improved with atezolizumab + bevacizumab (19.2 versus 13.4 months; HR 0.66; 95%

Table 1 ICI phase II/III clinical trials in gastric/gastroesophageal junction cancers

Trial	Type	Setting	CPS at inclusion	HER2 status	Year published	ICI arm/s	Comparator arm/s	Results
Janjigian et al. CheckMate 649[7]	Phase 3 trial	First-line advanced/ metastatic G/GEJ	any	neg	2021	Nivolumab alone Nivolumab Ipilimumab	CHT alone	OS benefit for Nivo +CHT PD-L1 CPS of 5 or more
Shitara et al. KEYNOTE-062[8]	Phase 3 trial	First-line advanced/ unresectable or metastatic G/GEJ	≥1	neg	2020	Pembrolizumab Pembrolizuamb with CHT	Placebo with CHT	No statistically significant survival benefit for ICI arm/s
Rha et al. KEYNOTE-859[9]	Phase 3 trial	First-line advanced or metastatic G/GEJ	any	neg	2023	Pembrolizumab with CHT	Placebo with CHT	OS benefit in ICI arm for PD-L1 CPS of 10 or higher
Janjigian et al. KEYNOTE-811[10]	Phase 3 trial	First-line advanced or metastatic G/GEJ	any	pos	2023	Pembrolizumab with CHT and trastuzumab	Placebo with CHT and trastuzumab	PFS benefit for ICI arm for CPS ≥1
Kang et al. ATTRACTION-4[14]	Phase 2-3 trial	First-line unresectable, advanced or recurrent G/GEJ	any	neg	2022	Nivolumab with CHT	Placebo with CHT	PFS benefit in ICI arm, no OS benefit
Yuan et al. Neosummit-01[12]	Phase 2 trial	Perioperative resectable gastric or EGJ cancer cT3-4aN + M0	any	neg	2024	Toripalimab plus SOX/XELOX followed by toripalimab	SOX/XELOX	Higher tumor regression grade (TRG) 0/1 in ICI arm
Lorenzen et al. DANTE/ IKF-s633 Trial[13]	Phase 2 trial	Perioperative resectable EGAJ (≥cT2 or cN+)	any	neg	2024	CHT (FLOT)+ Atezo followed by atezo maintenance	CHT	Improved postoperative stage and histopathologic regression in ICI arm
Shitara et al. KEYNOTE-061[15]	Phase 3 trial	Second-line advanced/ metastatic G	≥1	any	2018	Pembrolizumab	CHT (paclitaxel)	No Os benefit in ICI arm
Kang et al. ATTRACTION 2[16]	Phase 3 trial	(G/GEJ) cancer treated with ≥2 chemotherapy regimens	any	any	2020	Nivolumab	Placebo	OS benefit in ICI arm
Terashima et al. ATTRACTION 5[11]	Phase 3 trial	Adjuvant pStage III G/GEJ cancer	NS	NS	2023	Nivolumab with CHT	Placebo with CHT	No RFS benefit
Hegewisch-Becker et al. RELATIVITY-060[17]	Phase 2 trial	First-line advanced	NS	neg	2024	Nivolumab with relatlimab with CHT	Nivolumab with CHT	ORR not met
Lordick et al. 1707 VESTIGE study[18]	Phase 2 trial	Adjuvant resected G/GEJ following preoperative chemotherapy with high risk for recurrence (ypN+ and/or R1)	any	NS	2025	Nivolumab Ipilimunab	CHT alone	No DFS improvment
Shi et al.[19]	Phase 2 trial	Adjuvant N+ disease	NS	NS	2023	Tislelizumab with CHT (XELOX)	CHT alone (XELOX)	No DFS benefit
Wei et al.[20]	Phase 2 trial	Second-line advanced GC/EGJC	any	any	2024	Apatinib plus toripalimab	CHT alone	No survival benefit
Chung et al. KEYNOTE-063[21]	Phase 3 trial	Second-line advanced GC/EGJ (Asian patients)	≥1	any	2022	Pembrolizumab	Paclitaxel	No survival benefit
Xu et al. ORIENT-16[22]	Phase 3 trial	First-line advanced G/GEJ	any	neg	2023	Sintilimab with CHT	CHT alone	OS benefit in CPS >5

CI; 0.52-0.85; p=0.0009)[31]. As a result, atezolizumab + bevacizumab is now established as a standard of care for previously untreated, unresectable HCC.

Other frontline options include camrelizumab plus rivoceranib, which significantly extended OS to 22.1 months versus 15.2 months with sorafenib (HR 0.62; p<0.0001)[32], and durvalumab plus tremelimumab, which showed a median OS of 16.43 months compared to 13.77 months with sorafenib[33]. However, pembrolizumab and lenvatinib combination and nivolumab monotherapy did not demonstrate a survival benefit in this setting[34,35].

4. Colorectal cancer (CRC)

A total of 13 clinical trials (five phase III trials and seven phase II trials) evaluated immunotherapy in CRC.

Table 2 ICI phase 2/3 clinical trials in esophageal cancer

Trial	Type	Setting	Year of publishing	Histopathological type	CPS/TPS at inclusion	ICI arm/s	Comparative arm/s	Results
Kelly et al. Checkmate 577[26]	Phase 3 trial	Adjuvant for resected (R0) stage II or III E/GEJ ≥ypN1 or ypN0 following CRT and surgery	2021	Squamous or ADK	any	Nivolumab	Placebo	Prolonged PFS in ICI arm
Sun et al. KEYNOTE-590[25]	Phase 3 trial	First-line advanced, unresectable or metastatic E or Siewert type 1 GEJ cancer	2021	Squamous or ADK	any	Pembrolizumab with CHT (5fu and cisplatin)	Placebo with CHT (5fu and cisplatin)	Prolonged OS in esophageal squamous cell carcinoma and PD-L1 CPS of 10 or more
Doki et al. Checkmate 648[23]	Phase 3 trial	First-line unresectable advanced, recurrent, or metastatic	2022	Squamous	any	Nivolumab with CHT Nivolumab with ipilimumab	CHT alone	Longer OS in both ICI arms
Luo et al. ESCORT-1st[27]	Phase 3 trial	First-line advanced or metastatic	2021	Squamous	any	Camrelizumab with CHT (cisplatin paclitaxel)	Placebo with CHT (cisplatin paclitaxel)	PFS and OS benefit in ICI arm
Kojima et al. KEYNOTE-181[28]	Phase 3 trial	Second-line advanced/ metastatic	2020	Squamous or ADK	any	Pembrolizumab	CHT (investigator's choice of paclitaxel, docetaxel, or irinotecan)	OS benefit in ICI arm
Wang et al. JUPITER-06[29]	Phase 3 trial	First-line advanced/ metastatic	2022	Squamous	any	CHT paclitaxel plus cisplatin followed by toripalimab maintenance	Paclitaxel plus cisplatin (TP) followed by placebo maintenance	PFS and OS benefit in ICI arm
Kato et al. ATTRACTION-3[24]	Phase 3 trial	Second-line unresectable advanced/ recurrent disease	2019	Squamous	any	Nivolumab	Investigator's choice of chemotherapy (paclitaxel or docetaxel)	OS benefit in ICI arm
Xu et al. ORIENT-2[30]	Phase 2 study	Second-line advanced/ metastatic	2022	Squamous	any	Sintilimab	CHT	OS benefit in ICI arm

Table 3 ICI phase 2/3 trials in hepatocellular carcinoma

Yau et al. COSMIC-312[36]	Phase 3 trial	First-line advanced hepatocellular carcinoma	Atezolizumab with cabizantinib	Sorafenib	2024	PFS but no OS benefit in ICI arm
Finn et al. Imbrave 150[31]	Phase 3 trial	First-line advanced hepatocellular carcinoma	Atezolizumab with beva	Sorafenib	2020	OS and PFS benefit in ICI arm
Qin et al. CARES-310[32]	Phase 3 trial	First-line advanced hepatocellular carcinoma	Camrelizumab with rivoceranib	Sorafenib	2023	OS and PFS benefit in ICI arm
Llovet et al. LEAP-002[35]	Phase 3 trial	First-line advanced hepatocellular carcinoma	Pembrolizumab with lenvatinib	Placebo woth lenvatinib	2023	No OS but PFS benefit in ICI arm
Yau et al. CheckMate 459[34]	Phase 3 trial	First-line advanced hepatocellular carcinoma	Nivolumab	Sorafenib	2021	No OS benefit in ICI arm
Qin et al.[37]	Phase 3 trial	Second-line advanced hepatocellular carcinoma	Pembrolizumab	Placebo	2023	PFS benefit in ICI arm
Finn et al. KEYNOTE-240[38]	Phase 3 trial	Second-line advanced hepatocellular carcinoma	Pembrolizumab	Placebo	2020	No OS but PFS benefit in ICI arm
Wang et al.[39]	Phase 2 trial	Adjuvant for resected HCC with MVI	Sintilimab	Active surveillance	2024	RFS benefit in ICI arm
Abou-Alfa et al. HYMALAYA trial[33]	Phase 3 trial	First-line advanced hepatocellular carcinoma	Durvalumab with tremelimumab Durvalumab alone	Sorafenib	2022	OS benefit for ICI combination

These included two first-line studies for MSI-H/dMMR CRC, three studies in MSS CRC (two first-line, one later-line), and two neoadjuvant trials in rectal cancer. The ICIs assessed were pembrolizumab (three trials), atezolizumab (two), durvalumab-tremelimumab (one), nivolumab-ipilimumab (one), nivolumab (three), avelumab (one), toripalimab (one), and one phase III trial evaluating autologous PD-1 T-cell immunotherapy.

First-line MSI-H/dMMR

In the first-line treatment of MSI-H/dMMR metastatic colorectal cancer (mCRC), immunotherapy has shown significant efficacy over chemotherapy. Data from CheckMate 8HW confirmed that this combination improves progression-free survival (PFS) in the first-line setting for MSI-H/dMMR mCRC, offering a meaningful and statistically significant advantage over chemotherapy. With a median follow-up of 31.5 months (range: 6.1 to 48.4), progression-free survival was significantly improved in the nivolumab plus ipilimumab group compared to chemotherapy ($p<0.001$; two-sided stratified log-rank test). At 24 months, the PFS rate was 72% (95% CI; 64-79) with nivolumab plus ipilimumab, whereas it was only 14% (95% CI; 6-25) with chemotherapy[40]. Similarly, the KEYNOTE-177 trial established pembrolizumab as a superior first-line option, showing a significantly longer PFS compared to chemotherapy (median 16.5 versus 8.2 months; HR 0.60; 95% CI; 0.45-0.80; p=0.0002), with the added benefit of fewer treatment-related adverse events[41].

First-line MSS/pMMR

In the first-line treatment of MSS mCRC, the results with immune checkpoint inhibitors have been less promising. Two phase II trials evaluating avelumab with chemotherapy and nivolumab failed to demonstrate a significant PFS improvement in MSS CRC[42,43]. However, the AtezoTRIBE trial provided promising results, showing that the addition of atezolizumab to FOLFOXIRI plus bevacizumab led to a significant improvement in both PFS and overall survival (OS) in metastatic CRC, including patients with proficient mismatch repair (pMMR). In the pMMR cohort of 202 patients, the median overall survival was 30.8 months in the FOLFOXIRI plus bevacizumab and atezolizumab group, compared to 29.2 months in the FOLFOXIRI plus bevacizumab group (HR 0.80; 80% CI; 0.63-1.02; p=0.117). Additionally, a notable interaction between treatment group, tumor mutational burden (TMB), and Immunoscore IC was observed (pint = 0.043 and 0.092, respectively), suggesting that patients with TMB-high and Immunoscore IC-high tumors derived greater benefit from the addition of atezolizumab[44].

Neoadjuvant setting

In the neoadjuvant setting for rectal cancer, the TORCH trial evaluated immunotherapy in combination with chemoradiotherapy. Patients with clinical T3-4 and/or N+ rectal adenocarcinoma were randomized to receive either short-course radiotherapy (SCRT) followed by six cycles of consolidation immunochemotherapy with toripalimab or an alternative sequencing with two cycles of induction immunochemotherapy followed by SCRT. The SCRT-first group had higher complete response rates (cCR: 43.5% versus 35.6%) and lower grade 3-4 thrombocytopenia (24.2% versus 33.9%), making it the preferred strategy for future trials[45]. Additionally,

pembrolizumab added to chemoradiotherapy as part of total neoadjuvant therapy was found to be safe, but the NAR score difference did not support further investigation of this approach[46].

5. Biliary tract cancer (BTC) and pancreatic cancer

A total of nine clinical trials have evaluated immune checkpoint inhibitors (ICIs) in BTC and pancreatic cancer, comprising three phase III and six phase II trials. Of these, five trials focused on BTC and four on pancreatic cancer. The ICIs assessed included pembrolizumab (n=2), durvalumab (n=1), atezolizumab (n=2), nivolumab (n=2), and ipilimumab (n=1). Additionally, three trials incorporated cancer vaccines (GVAX and Hep A).

Treatment in BTC

Two notable phase III trials, KEYNOTE-966 and TOPAZ-1, have evaluated the role of ICIs in BTC. In TOPAZ-1, durvalumab plus chemotherapy significantly improved overall survival (OS) and progression-free survival (PFS)

Table 4 ICI Phase 2/3 trials in CRC

Trial	Type of trial	Setting	Year of publication	ICI arm/s	Comparative	Results
André et al. KEYNOTE 177[41]	Phase 3 trial	First-line dMMR/MSI-h mCRC	2020	Pembrolizumab	5-fluorouracil-based therapy with or without bevacizumab or cetuximab	PFS benefit in ICI arm
Chen et al. The Canadian Cancer Trials Group CO.26 Study[47]	Phase 2 trial	Metastatic refractory CRC	2020	Tremelimumab with durvalumab	BSC	OS benefit in ICI arm
Pan et al.[48]	Phase 3 trial	First-line mCRC	2024	XELOX with bevacizumab with autologous PD1-T cell immunotherapy	XELOX with bevacizumab	PFS and OS benefit in ICI arm
Antoniotti et al. AtezoTRIBE[44]	Phase 2 study	First-line mCRC	2022	Atezolizumab with CHT (FOLFOXIRI) and bevacizumab	CHT (FOLFOXIRI) with bevacizumab	PFS and OS benefit in the later analysis
Andre et al. Checkmate 8hw[40]	Phase 3 trial	First-line mCRC d MMR/MSI H	2024	Nivolumab with ipilimumab Nivolumab alone	CHT with or without targeted therapy	PFS benefit in combo arm
Lenz et al. CheckMate 9X8[49]	Phase 2/3 trial	First-line mCRC	2024	Nivolumab with CHT(FOLFOX) with bevacizumab	CHT (FOLFOX) with bevacizumab	No PFS benefit in ICI arm
Xia et al. (TORCH)[45]	Phase 2 trial	Neoadjuvant cT3-4 and/or N+ LARC MSI-H/dMMR	2024	SCRT followed by 6 cycles of CHT (CAPOX) and toripalimab (TNT Arm)	2 cycles of CHT with toripalimab and CAPOX followed by SCRT and the rest 4 doses	Improved CR in TNT arm
Eng et al. IMblaze370[50]	Phase 3 trial	mCRC >2 lines	2019	Atezolizumab with cobimetinib Atezolizumab alone	Regorafenib	No OS benefit in ICI arms
Rahma et al.[46]	Phase 2	Neoadjuvant – stage II/III LARC with distal location	2021	CHT (FOLFOX) followed by CRT (capecitabine with 50.4 Gy) and with pembrolizumab	CHT (FOLFOX) followed by CRT (capecitabine with 50.4 Gy)	No improvement in NAR
Mettu et al.[51]	Phase 2 trial	Refractory mCRC	2022	Atezolizumab with CHT (capecitabine) and bevacizuamb	Capecitabine with bevacizumab	No survival benefit
Kawazoe et al. LEAP-017 Study[52]	Phase 3 trial	Previously treated pMMR or MSS mCRC	2021	Pembrolizumab with lenvatinib	Regorafenib or lonsurf	No survival benefit
Redman et al.[42]	Phase 2 trial	First-line MSS mCRC	2022	Avelumab plus CEA-targeted vaccine with CHT (FOLFOX) with bevacizumab	CHT (FOLFOX) with bevacizumab	No PFS benefit
Ree et al. METIMMOX trial[43]	Phase 2 trial	First-line MSS mCRC	2024	Nivolumab with CHT (FLOX)	FLOX	No PFS benefit

compared to placebo plus chemotherapy. The hazard ratio (HR) for OS was 0.80 (95% CI; 0.66-0.97; p=0.021), with an estimated 24-month OS rate of 24.9% (95% CI; 17.9-32.5) for durvalumab versus 10.4% (95% CI; 4.7-18.8) for placebo. The HR for PFS was 0.75 (95% CI; 0.63-0.89; p=0.001)[53]. In KEYNOTE-966, pembrolizumab plus chemotherapy demonstrated a median OS of 12.7 months (95% CI; 11.5-13.6) compared to 10.9 months (95% CI; 9.9-11.6) in the placebo group (HR 0.83; 95% CI; 0.72-0.95]; one-sided p=0.0034, significance threshold p=0.0200)[54].

Additionally, the IMbrave-151 trial evaluated the combination of atezolizumab and bevacizumab with cisplatin/gemcitabine in the first-line setting, showing modest improvements in PFS and a higher six-month PFS rate compared to atezolizumab/placebo/cisplatin/gemcitabine[55]. In the second-line setting, a combination of atezolizumab with cobimetinib demonstrated some PFS benefit, though the results were not practice-changing[56].

Pancreatic cancer

In pancreatic ductal adenocarcinoma (PDAC), the impact of immune checkpoint inhibitors remains limited, with most patients deriving minimal or no clinical benefit. Trials evaluating cancer vaccines such as GVAX and HAPa failed to meet overall survival (OS) endpoints.

Overall, while immunotherapy has shown promising results in BTC, particularly in the first-line setting, its role in pancreatic cancer remains modest, necessitating further research to identify effective combinations and predictive biomarkers.

Conclusions

The integration of immune checkpoint inhibitors (ICIs) into the treatment landscape of gastrointestinal cancers has led to significant advancements, particularly in gastric, esophageal, colorectal, hepatocellular and biliary tract cancers. The efficacy of ICIs is largely biomarker-dependent, with PD-L1 expression, microsatellite instability (MSI), and tumor mutation burden (TMB) serving as key predictors of response. Notably, MSI-high/dMMR colorectal cancer and PD-L1-positive gastroesophageal cancers have shown the most benefit, while microsatellite-stable (MSS) colorectal and pancreatic cancers remain resistant, necessitating alternative therapeutic strategies. Landmark trials such

Table 5 ICI phase 2/3 trials for pancreatic and biliary tract cancers

Trial	Type of trial	Setting	Year of publication	ICI arm/s	Comparative	Results
Kelley et al. KEYNOTE-966[54]	Phase 3 trial	First-line la/mBTC	2023	Pembrolizumab with gemcitabine and cisplatin	Placebo with gemcitabine and cisplatin	OS benefit in ICI arm
Hewitt et al.[57]	Phase 3 trial	Borderline resectable or la PDAC	2022	CHT (FOLFIRINOX or gemcitabine/nab-paclitaxel) followed by CRT combined with HAPa immunotherapy	CHT (FOLFIRINOX or gemcitabine/nab-paclitaxel) followed by CRT	No OS benefit in imuno arm
Oh et al. TOPAZ 1[53]	Phase 3 trail	First-line la/m BTC	2022	Durvalumab with CHT (gemcitabine and cisplatin)	CHT (gemcitabine with cisplatin)	OS and PFS benefit in ICI arm
Tsujikawa et al.[58]	Phase 2 trial	≥Second-line mPDAC	2020	Cy/GVAX followed by CRS-207 (Listeria-Mesothelin) with nivolumab	Cy/GVAX followed by CRS-207	No OS benefit in ICI arm
Overman et al.[59]	Phase 2 trial	≥Second-line la/mPDAC	2020	Pembrolizumab with acalabrutinib	Acalabrutinib alone	No survival benefit in ICI arm
Wu et al.[60]	Phase 2 trial	Maintenance after first line mPDAC	2020	CHT (FOLFIRINOX) followed by GVAX and ipilimumab	FOLFIRINOX	NO survival benefit in ICI arm
Yarchoan et al.[56]	Phase 2 trial	≥Second-line la/mBTC	2021	Atezolizumab with cobimetinib	Atezolizumab alone	PFS benefit in ICI arm
El-Khoueiry et al. IMbrave 151[55]	Phase 2 trial	First-line la/mBTC	2023	Atezolizumab with bevacizumab and gemcitabine/cisplatin	Atezolizumab with placebo and gemcitabine/cisplatin	PFS benefit in combination arm
Sahai et al. BilT-01[61]	Phase 2 trial	First-line la/m BTC	2022	Nivolumab with gemcitabine/cisplatin	Nivolumab with ipilimumab	No survival difference

as CheckMate 649 and KEYNOTE-859 in gastric cancer, IMbrave150 in hepatocellular carcinoma and TOPAZ-1 in biliary tract cancer have established ICIs as essential components of treatment. Despite these successes, challenges remain, including immune-related toxicities, resistance mechanisms, and the need for combination approaches to improve efficacy in MSS tumors. With recent regulatory approvals expanding access in Romania, ongoing research is focused on refining patient selection, optimizing treatment combinations, and exploring novel immunotherapies to further improve outcomes in gastrointestinal malignancies. ■

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CONFLICT OF INTERESTS: none declared.

FINANCIAL SUPPORT: none declared.