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REVIEW

New Targets, Novel Agents, and Radiotherapy in Gastrointestinal System Cancers

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SUMMARY

Gastrointestinal (GI) malignancies represent a major global health challenge, ranking among the most common cancers and leading causes of cancer-related mortality. Colorectal cancer is a principal contributor to cancer deaths, while gastric, esophageal, pancreatic, and hepatocellular carcinomas also exert a substantial burden on health care systems worldwide. Despite advances in multimodal treatment including surgery, chemotherapy, radiotherapy, and molecularly targeted agents therapeutic resistance remains a critical obstacle to durable disease control. Of particular concern are the persistently modest rates of pathological complete response following neoadjuvant chemoradiotherapy in rectal and esophageal adenocarcinomas, as well as the multifactorial resistance mechanisms observed in pancreatic cancer. These limitations highlight the urgent need to elucidate resistance biology and to develop innovative approaches that can enhance long-term outcomes. Recent research has explored radiosensitization strategies to overcome resistance. These include agents targeting DNA repair pathways, monoclonal antibodies against EGFR and VEGF signaling, immune checkpoint inhibitors, and drugs modulating tumor metabolism. Furthermore, the immunosuppressive role of the tumor immune microenvironment and cancer-associated fibroblasts has emerged as a key determinant of therapeutic response. Clinically, encouraging progress has been made: PD-1 inhibitors have achieved unexpectedly high complete response rates in rectal cancer, while the combination of radiotherapy and immunotherapy has shown significant improvements in pathological outcomes. In hepatocellular carcinoma, randomized data demonstrate a survival advantage when SBRT is combined with sorafenib compared with sorafenib alone. Collectively, current findings indicate that rational integration of radiotherapy with immunotherapy and targeted agents offers considerable promise in GI cancers, though further prospective studies are required to establish long-term survival benefits and inform clinical practice.

Keywords: Gastrointestinal system cancers; immunotherapy; radiotherapy.

INTRODUCTION

Gastrointestinal (GI) cancers, encompassing malignancies of the esophagus, stomach, liver, pancreas, small intestine, colon, rectum, and anus, represent one of the most prevalent groups of cancers worldwide. Colorectal cancer (CRC), one of the most frequently diagnosed malignancies, ranks among the top three leading causes of cancer-related mortality worldwide. Gastric and esophageal cancers are also major malignancies that contribute substantially to the global cancer burden and are recognized as the second and sixth leading causes of cancer-related mortality, respectively. Hepatocellular carcinoma (HCC), the most common primary liver malignancy, has shown a steadily increasing incidence worldwide. Pancreatic cancer is also recognized as the third leading cause of cancer-related mortality.[1]

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Surgery, chemotherapy, radiotherapy, anti-angiogenic therapy, and immunotherapy have constituted the main therapeutic approaches in the management of GI cancers. However, treatment resistance remains a significant clinical challenge; for instance, in esophageal adenocarcinoma and rectal adenocarcinoma, nearly 70% of patients fail to achieve a pathological complete response (pCR) following neoadjuvant chemoradiotherapy (CRT). Pancreatic cancers, by their very nature, are highly resistant to therapy, with five-year survival rates remaining below 5%. There is a critical need for novel targeted agents capable of enhancing the radiosensitivity of gastrointestinal cancers. Various strategies are being employed to develop radiosensitizers that are both highly effective and minimally toxic.[2]

Colorectal cancer (CRC) patients frequently develop resistance to chemotherapy, targeted therapies, and immunotherapies. Recent studies have shown that various immune cells may influence tumor progression in different cancer types. Certain intratumoral immune cell infiltrates can promote the proliferation of cancer cells through their ability to reverse adaptive immune responses, and may also support tumor angiogenesis, progression, and metastasis. In CRC, responses to chemotherapy, radiotherapy, targeted therapies, and immunotherapy are affected by the immune system. Moreover, the progression of CRC is also affected by the complex interactions between cancer cells and the tumor microenvironment (TME).[3]

Radiotherapy, while being a standard modality in the treatment of many cancers, achieves optimal outcomes by increasing radiation-induced damage in tumor tissues and simultaneously protecting normal tissues. Radioresistance is also multifactorial (polymodal) and arises from numerous biological and genetic alterations. These include alterations in cell cycle regulation, repopulation driven by cancer stem cells, hypoxia, evasion of apoptosis (inhibition of programmed cell death), modifications in DNA damage response and enhanced DNA repair, inflammation, altered regulation of oxidative stress, and changes in mitochondrial function and cellular energy metabolism.[4]

In order to improve the response of gastrointestinal cancers to radiotherapy, approaches that target the fundamental biological hallmarks of cancer are being investigated. These mechanisms include sustaining proliferative signaling, evading growth suppressors, escaping immune surveillance, enabling replicative immortality, inducing tumor-promoting inflammation, enhancing invasion and metastasis, inducing angiogenesis, generating genomic instability and mutations, resisting cell death, and deregulating cellular energy metabolism. Given the heterogeneous nature of tumors, targeting a single hallmark may not be sufficient to enhance the efficacy of radiotherapy. Simultaneous targeting of multiple cancer hallmarks could provide greater advantages in improving radiosensitivity; however, further research is required to determine which combinations are most effective.[2]

In recent years, numerous studies have demonstrated that the tumor immune microenvironment (TIME) is the most critical factor determining tumor progression, the development of treatment resistance, and the clinical course of gastrointestinal cancers. Among the various immune cell populations interacting with the tumor are tumor-associated macrophages (TAMs), regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), dendritic cells (DCs), B lymphocytes, and natural killer (NK) cells.

Upon recognition of tumor antigens, NK cells and dendritic cells (DCs) can become activated. While NK cells exert direct cytotoxic effects against tumors, DCs may activate regulatory T cells (Tregs) and stimulate T helper (Th)17 cells through the secretion of interleukin (IL)-10, IL-35, and transforming growth factor-beta (TGF-β). Th17 cells, in turn, can suppress the functions of effector T cells by secreting IL-17A, IL-21, IL-22, and IL-26.

In addition, Tregs can activate B cells and weaken antitumor effects by promoting the infiltration of $CD8^+$ T cells and $CD39^+$ T cells into the tumor. Moreover, cancer cells can produce large amounts of fibrinogen-like protein 1 (FGL1), which suppresses effective T-cell activation and thereby inhibits antitumor immune responses.

Cancer-associated fibroblasts (CAFs) can suppress the activity of NK cells and effector T cells through the secretion of prostaglandin E2 (PGE-2), fibroblast activation protein (FAP), transforming growth factor-beta (TGF-β), epidermal growth factor (EGF), and vascular endothelial growth factor (VEGF). M1 macrophages are activated by interferon-gamma (IFN-γ) and provide resistance against cancer cells by producing pro-inflammatory cytokines such as IL-1, IL-6, IL-12, and tumor necrosis factor (TNF). In contrast, M2 macrophages, under the influence of TGF-β and IL-10, secrete growth factors (EGF, TGF-β, and VEGF) and suppress the activity of NK cells and effector T cells.[3]

COLORECTAL CANCERS

All patients with colorectal cancer should undergo mismatch repair (MMR) or microsatellite instability (MSI-H) testing. The purpose of this testing is to screen for Lynch syndrome and to identify patients who may be eligible for immunotherapy.[5]

Rectal Cancer: Agents Targeting DNA Repair Mechanisms

In rectal cancer, clinical trials have investigated agents targeting DNA repair mechanisms in order to enhance radiosensitivity.

Bortezomib (a proteasome inhibitor) was assessed in a 2010 phase I trial in colorectal cancer, and when combined with chemoradiotherapy, the maximum tolerated dose was reported to be of limited clinical relevance.[6]

CRLX101, a topoisomerase I inhibitor, is being investigated in an ongoing phase Ib/II trial for rectal cancer. When administered biweekly in combination with standard chemoradiotherapy, no severe adverse events were observed; however, toxicities were reported in the cohort receiving weekly dosing.[7]

Trametinib, a MEK1/2 inhibitor, is under evaluation in an ongoing phase I trial as a neoadjuvant treatment for rectal cancer, with no published results available to date.[8]

Enhancing Radiosensitivity with Monoclonal Antibodies Targeting the EGFR Pathway

In a 2008 phase I/II trial involving 60 patients with rectal cancer in the neoadjuvant setting, the combination of cetuximab with capecitabine, oxaliplatin, and radiotherapy was shown to be safe. However, it was emphasized that the optimal treatment sequence needs to be determined in order to achieve the best efficacy.[9]

In a 2013 phase II trial involving 68 patients with rectal cancer in the neoadjuvant setting, the combination of panitumumab with chemoradiotherapy resulted in a high pathological complete response (pCR) rate; however, this regimen was associated with increased toxicity.[10]

In another 2015 phase II trial involving 19 patients with rectal cancer in the neoadjuvant setting, moderate tumor regression was observed when panitumumab was administered in combination with preoperative radiotherapy. However, as the primary endpoint of achieving a complete response was not met, it was concluded that this combination cannot be recommended outside of a research setting.[11]

In another 2017 phase II Panitumab trial involving 54 patients with rectal cancer in the neoadjuvant setting, tumor regression was observed; however, no statistically significant improvement was achieved. Nonetheless, the drug exhibited a tolerable safety profile.[12]

The RaP/STAR-03 trial aimed to evaluate the activity and safety of panitumumab alone, without chemotherapy, as a preoperative treatment in low-risk, locally advanced rectal cancer (LARC). In patients with KRAS wild-type and low-risk LARC, the addition of panitumumab to preoperative radiotherapy yielded a pCR rate of 10.9%; however, the primary endpoint of achieving a pathological complete response was not met. The study demonstrated a favorable toxicity profile and good compliance with the combination therapy. Further analyses of NRAS and BRAF status, as well as tissue and circulating levels of EGFR ligands and vascular factors (including soluble vascular endothelial growth factor and E-selectin), were suggested to provide insights into potential molecular pathways involved in the anti-EGFR response.[13]

Anti-VEGF/VEGFR Antibodies

Bevacizumab, an anti-angiogenic antibody, has been demonstrated to be more effective than chemotherapy when combined with irinotecan (IRI), 5-fluorouracil (5-FU), and leucovorin (LV) with placebo in the phase II and III AVF2107 trials based on anti-angiogenic therapy for CRC. The AVF2107 study showed that bevacizumab, a humanized IgG monoclonal antibody targeting VEGF-A, improved both progression-free survival (PFS) and overall survival (OS) in metastatic CRC (mCRC) (RR: 44.0% vs. 34.8%; OS: 20.3 vs. 15.6 months; HR: 0.66, p=0.001; PFS: 10.6 vs. 6.2 months; HR: 0.54, p=0.001).[14] In the E3200 trial, patients with CRC who had progressed after treatment with folinic acid (LV) + 5-FU + oxaliplatin (FOLFOX) achieved superior PFS (7.3 vs. 4.7 months, HR: 0.61, p=0.001) and OS (12.9 vs. 10.8 months, HR: 0.75, p=0.0011) with the combination of FOLFOX and bevacizumab compared to FOLFOX alone.[15]

Bevacizumab was identified as the only antibody approved by the FDA as a first- and second-line VEGF-targeted therapy for CRC.[16]

Another drug approved by the FDA for second-line treatment of mCRC is ramucirumab, a fully humanized monoclonal IgG antibody targeting VEGFR-2. According to the phase III RAISE trial, the combination of ramucirumab with FOLFIRI significantly improved PFS (5.7 vs. 4.5 months; HR: 0.79, p=0.0005) and OS (13.3 vs. 11.7 months; HR: 0.84, p=0.022) compared with FOLFIRI plus placebo.[17]

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Targeting Cellular Bioenergetics

Targeting cellular energy metabolism is an increasingly investigated approach to enhance radiosensitivity when combined with radiotherapy. Metformin inhibits mitochondrial respiration by targeting Complex I of the mitochondrial electron transport chain. Growing scientific evidence indicates that metformin exerts anticancer effects.[18] Along with its favorable safety profile, the potential repurposing of metformin in cancer therapy has attracted considerable attention. Delayed DNA damage repair, cell cycle arrest at the G2/M phase, and increased apoptosis have been observed. Interestingly, these effects were more pronounced in p53-deficient cells, suggesting that metformin may serve as a potential radiosensitizer in tumors harboring p53 mutations.[19]

Hypoxia-targeting Drugs and Strategies

Nitroimidazole compounds bind to the free radicals generated by radiation on DNA, thereby inducing DNA strand breaks and exerting a radiosensitizing effect similar to oxygen. In both *in vitro* and *in vivo* models of colorectal cancer, these compounds have been shown to enhance radiosensitivity.[20] Nimorazole is currently being tested in a phase III randomized controlled trial in combination with chemoradiotherapy for HPV-negative head and neck cancers. If successful, the evaluation of these agents in gastrointestinal cancers may also become a subject of investigation.[21]

Immune Checkpoint Receptor–Ligand Complexes

The immune system has developed checkpoints to prevent damage to self-cells. The most widely used immunomodulatory antibodies are immune checkpoint inhibitors (ICIs). ICIs act as immune brakes by blocking the interaction of checkpoint proteins with their corresponding ligands. The combination of ipilimumab with radiotherapy has demonstrated the most favorable clinical responses, warranting further investigation. Immunotherapeutic approaches such as pembrolizumab, durvalumab, and DC-CIK are still being evaluated at early stages.[2]

PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

The standard treatment for locally advanced rectal cancer is neoadjuvant chemotherapy and radiotherapy followed by surgical resection. However, this approach is associated with significant complications and toxic effects. Research has demonstrated that immune checkpoint blockade is highly effective in patients with mismatch repair–deficient metastatic colorectal cancer. Nevertheless, it remains unknown whether this strategy is effective in mismatch repair–deficient, locally advanced rectal cancer.

In a prospective, phase 2, single-group study conducted by Cercek et al.,[22] the efficacy and safety of the programmed death-1 (PD-1) inhibitor dostarlimab were evaluated in patients with mismatch repair–deficient stage II or III rectal adenocarcinoma. Adult patients received intravenous dostarlimab every 3 weeks for a total of 6 months. Normally, this would have been followed by chemoradiotherapy and total mesorectal excision; however, patients who achieved a complete response to dostarlimab were exempted from chemoradiotherapy and surgery. The primary endpoint was a complete clinical response to dostarlimab, determined by magnetic resonance imaging, endoscopy, and rectal examination.

Of the sixteen patients enrolled, twelve completed 6 months of dostarlimab therapy. All twelve achieved a complete clinical response (no evidence of tumor detected by any imaging or test). At 12 months of follow-up, no patients exhibited progression or recurrence, and none required additional chemoradiotherapy or surgery. No grade 3 or higher adverse events were observed. The trial was limited by its small sample size and single-center design, with most participants being of White ethnicity. Longer follow-up was required to assess the durability of response.

In conclusion, all patients with mismatch repair–deficient, locally advanced rectal cancer achieved a complete clinical response after 6 months of treatment with the PD-1 inhibitor dostarlimab alone; however, long-term follow-up is needed to determine sustained outcomes.[22]

In the UNION trial, irrespective of MSI status (i.e., applicable to both MSI-high and microsatellite stable [MSS] patients), short-course radiotherapy (SCRT) combined with camrelizumab (immunotherapy) and capecitabine plus oxaliplatin (CAPOX) chemotherapy was compared with CAPOX chemotherapy alone (control group). Patients included in the study were those with locally advanced rectal adenocarcinoma (T3–4 or N+), treatment-naïve and eligible for surgery, with the inferior border of the tumor located ≤10 cm from the anal verge, and an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1 (indicating good overall condition). A total of 231 patients were enrolled (experimental arm: 113; control arm: 118).

In the experimental arm (113 patients), the treatment regimen consisted of SCRT followed by camrelizumab plus CAPOX (2 cycles), total mesorectal excision (TME), then 6 cycles of camrelizumab plus CAPOX, and subsequently camrelizumab monotherapy (up to 9 cycles). In the control arm (118 patients), patients received long-course radiotherapy (LCRT), CAPOX chemotherapy (2 cycles), TME, and then an additional 6 cycles of CAPOX. The primary endpoint was the pathological complete response (pCR=ypT0N0), while secondary endpoints included 3-year disease-free survival (DFS) and OS.

The findings demonstrated a pCR rate of 39.8% (45/113) in the camrelizumab plus CAPOX group compared with 15.3% (18/118) in the CAPOX-only group, representing an absolute difference of 24.6% ($p<0.001$, statistically significant) and an odds ratio of 3.7, indicating that patients in the experimental arm were 3.7 times more likely to achieve pCR. The rates of surgical complications were comparable between the two groups. Results for DFS and OS were reported as not yet mature.

In conclusion, the combination of camrelizumab (immunotherapy) with short-course radiotherapy and CAPOX achieved a substantially higher rate of complete tumor eradication compared with chemotherapy alone.[23] This suggests that, irrespective of MSI status, immunotherapy may potentially become an integral component of standard treatment for locally advanced rectal cancer in the future. However, long-term survival data (DFS and OS) are still awaited. The summary of major clinical trials concerning targeted agents and immune checkpoint inhibitors in colorectal cancer is presented in Table 1.

ESOPHAGEAL CANCER

EGFR is overexpressed in approximately 30–90% of patients with esophageal cancer, and this finding is associated with poor prognosis. The rate of EGFR positivity is higher in esophageal squamous cell carcinoma (ESCC) compared with esophageal adenocarcinoma (EAC); therefore, EGFR-targeted therapies have been primarily focused on ESCC. HER2, a member of the EGFR family, plays a critical role in cell survival and proliferation. Unlike EGFR, the tyrosine kinase activity of HER2 is not dependent on ligand binding. HER2 is recognized as an important therapeutic target, particularly in EAC.[24]

Drugs Targeting the EGFR Pathway (Primarily Used in ESCC)

Nimotuzumab: Nimotuzumab is a fully recombinant humanized IgG1 monoclonal antibody. Phase II studies have demonstrated that, when combined with chemotherapy and radiotherapy in patients with locally advanced esophageal cancer (EC), it increased the rate of complete endoscopic response. It is considered a safe and effective option, particularly in elderly patients.[25]

Cetuximab: Cetuximab binds to EGFR, thereby inhibiting phosphorylation and the associated signaling pathways. In the phase III SAKK75/08 trial, the addition of cetuximab to neoadjuvant chemoradiotherapy reduced local recurrence rates and improved survival compared with chemoradiotherapy alone. A more pronounced survival benefit was observed in patients with ESCC.[26]

Icotinib: Icotinib is an EGFR tyrosine kinase inhibitor approved in China. Phase II studies have shown its efficacy in previously treated EGFR-positive ESCC patients. When combined with radiotherapy, it has been demonstrated to prolong survival.[27]

Gefitinib: Gefitinib is an EGFR tyrosine kinase inhibitor effective in patients harboring EGFR mutations. The COG trial did not demonstrate an improvement in survival in the overall population; however, potential benefit was observed in patients with EGFR amplification.[28]

HER2 Pathway–Targeted Agents (Primarily Used in EAC)

Trastuzumab (Herceptin) is a monoclonal antibody targeting HER2. The ToGA Phase III trial demonstrated that, when combined with chemotherapy, trastuzumab significantly prolonged survival. However, in the RTOG-1010 trial, the addition of trastuzumab to neoadjuvant chemoradiotherapy did not improve survival.[29,30]

VEGF/VEGFR Pathway–Targeted Therapies (Particularly for EAC)

Bevacizumab is a humanized monoclonal antibody that targets VEGF-A and inhibits tumor angiogenesis. Findings from this large, multicentre, randomized, open-label phase II–III trial demonstrated that the addition of bevacizumab to perioperative chemotherapy failed to improve overall survival in patients with resectable gastric, esophagogastric junction, or distal esophageal adenocarcinoma, while significantly increasing the incidence of wound-healing complications. Consequently, bevacizumab is not recommended for the routine management of EAC, as it confers no therapeutic benefit and is associated with higher rates of adverse events.[31]

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Table 1 Summary of key clinical trials for targeted agents and ICI in coloectal cancer

Target/pathway	Drug/study	Phase	Year	Clinical findings	OS/PFS	Ref. no
DNA repair/ radiosensitization	Bortezomib+standard 5-FU + EBRT (rectal cancer)	Phase I	2010	Evaluated with combined CRT; maximum tolerated dose had limited clinical significance	Not reported	[6]
DNA repair/ radiosensitization	CRLX101 (topo I inhibitor)+ nCRT (rectal cancer)	Phase I/II	2019	Biweekly administration was safe; weekly arm showed increased toxicity	Not reported	[7]
DNA repair/ radiosensitization	Trametinib (MEK1/2 inhibitor, neoadjuvant)	Phase I	2017	Ongoing study; no published results yet	Not reported	[8]
EGFR pathway	Cetuximab+capecitabine/ oxaliplatin + RT (neoadjuvant)	Phase I/II	2008	Safe; emphasized the need to determine optimal sequence for best efficacy	Not reported	[9]
EGFR pathway	Panitumumab+CRT (LARC, KRAS WT) – SAKK 41/07	Phase II	2013	High pCR; increased toxicity	Not reported	[10]
EGFR pathway	Panitumumab+preop RT (KRAS WT, 19 patients)	Phase II	2015	Moderate tumor regression: complete response not achieved	Not reported	[11]
EGFR pathway	Panitumumab+preop RT – NEORIT (RAS WT, 54 patients)	Phase II	2017	Tumor regression observed; no statistically significant improvement; tolerable	Not reported	[12]
EGFR pathway	Panitumumab+preop RT– RaP/STAR-03 (low-risk LARC, KRAS WT)	Phase II	2018	pCR 10.9%; primary endpoint (complete response) not achieved; good compliance/tolerance	Not reported	[13]
VEGF/VEGFR pathway	Bevacizumab + IRI/5-FU/LV vs placebo (AVF2107, 1st-line mCRC)	Phase II/III	2004/ 2014	Improved efficacy with bevacizumab addition	OS 20.3 vs 15.6 mo; PFS 10.6 vs 6.2 mo	[14]
VEGF/VEGFR pathway	Bevacizumab + FOLFOX vs FOLFOX (E3200, advanced CRC)	Phase III	2004/ 2014	Superior PFS and OS with bevacizumab	OS 12.9 vs 10.8 mo; PFS 7.3 vs 4.7 mo	[15]
VEGF/VEGFR pathway	Ramucirumab+FOLFIRI vs placebo + FOLFIRI (RAISE, 2nd-line mCRC)	Phase III	2019	OS and PFS advantage	OS 13.3 vs 11.7 mo; PFS 5.7 vs 4.5 mo	[17]
Metabolism/ Hypoxia	Metformin (complex I inhibitor; radiosensitizer)	Various	2015/ 2016	Delayed DNA repair, G2/M arrest, apoptosis increase; effects pronounced in p53-deficient setting	Not reported	[18,19]
Metabolism/ Hypoxia	Nitroimidazoles (e.g., Nimorazole)	Preclinical/ Phase III (H&N)	2007/ 2019	Preclinical/early for CRC; Phase III ongoing/tested in head & neck cancer	Not reported	[20,21]
PD-1/PD-L1	Dostarlimab (MMR-D, stage II–III rectum)	Phase II	2022	After 6 months, 12/12 patients achieved a complete clinical response; no recurrence/ progression at 12 months	Not reported	[22]
PD-1/PD-L1	Camrelizumab + short-course RT + CAPOX vs CAPOX alone (UNION, LARC)	Phase III	2024	pCR 39.8% vs 15.3%; absolute difference 24.6%; OR 3.7; surgical complications similar	Not reported	[23]

DNA: Deoxyribonucleic Acid; 5-FU: 5-Fluorouracil; EBRT: External beam radiotherapy; CRT: Chemoradiotherapy; nCRT: Neoadjuvant chemoradiotherapy; MEK1/2: Mitogen-activated protein kinase kinase 1/2; EGFR: Epidermal growth factor receptor; LARC: Locally advanced rectal cancer; KRAS WT: KRAS wild type; RAS WT: RAS wild type; pCR: Pathological complete response; RaP/STAR-03: Rectal panitumumab/short-term accelerated radiotherapy trial; VEGF/VEGFR: Vascular endothelial growth factor / receptor; IRI: Irinotecan; LV: Leucovorin (Folinic Acid); mCRC: Metastatic colorectal cancer; FOLFOX: 5-FU, leucovorin, oxaliplatin; FOLFIRI: 5-FU, leucovorin, irinotecan; RAISE: Ramucirumab plus FOLFIRI in 2nd-line mCRC trial; G2/M: Gap 2/Mitosis cell cycle checkpoint; H&N: Head and neck; MMR-D: Mismatch repair deficient; RT: Radiotherapy; CAPOX: Capecitabine + oxaliplatin; UNION: Camrelizumab + CAPOX with/without short-course RT in LARC trial; OR: Odds ratio; OS: Overall survival; PFS: Progression-free survival

Ramucirumab (VEGFR-2 Monoclonal Antibody) blocks tumor vasculature by targeting VEGFR-2. The RAINBOW Phase III randomized, double-blind, placebo-controlled trial evaluated its efficacy in patients with advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma. The combination of ramucirumab and paclitaxel significantly improved overall survival compared with paclitaxel alone (OS: 8.71 months vs. 7.92 months).[32]

The REGARD Phase III randomized, double-blind trial compared ramucirumab with placebo in patients with advanced gastric or GEJ adenocarcinoma. Median overall survival was 5.2 months in the ramucirumab group versus 3.8 months in the placebo group (HR: 0.776; 95% CI: 0.603–0.998; p=0.047). This study demonstrated that ramucirumab could exert a measurable effect even as monotherapy, improving survival in patients with advanced esophageal and gastric adenocarcinoma.[33]

Anlotinib and Apatinib (VEGFR Tyrosine Kinase Inhibitors) have shown promising results in China-based clinical trials. The NCT02649361 Phase II randomized, double-blind, placebo-controlled trial in patients with advanced ESCC reported a median PFS of 3.02 months with anlotinib versus 1.41 months with placebo (HR: 0.46; 95% CI: 0.32–0.66; p<0.001). These findings support the potential efficacy of anlotinib in the treatment of ESCC, and it has subsequently been incorporated into the Chinese Society of Clinical Oncology (CSCO) clinical guidelines for advanced ESCC.[34]

Endostar (Recombinant Human Endostatin), developed by Chinese scientists, is a stable and soluble recombinant human endostatin. It inhibits tumor angiogenesis by suppressing VEGF and VEGFR expression and reduces tumor-associated lymphangiogenesis through inhibition of the VEGF-C signaling pathway. Phase II trials have shown that the combination of Endostar with chemotherapy produced promising tumor response rates in patients with advanced ESCC. Endostar was also found to be well tolerated and safe.[35]

Immunotherapies for Esophageal Cancer

PD-1/PD-L1 Inhibitors and Their Use Particularly in ESCC: Pembrolizumab (Keytruda) is a humanized monoclonal anti–PD-1 antibody. The KEYNOTE-181 Phase III randomized trial evaluated pembrolizumab monotherapy versus chemotherapy in patients with advanced or metastatic esophageal cancer. In PD-L1–positive patients, pembrolizumab significantly improved overall survival compared with chemotherapy (9.3 months vs. 6.7 months; HR: 0.69; p=0.0074).[36]

The KEYNOTE-590 Phase III randomized, double-blind trial compared pembrolizumab plus chemotherapy with chemotherapy alone in 749 patients with advanced EC or Siewert type 1 GEJ cancer. In PD-L1–positive patients, the combination significantly improved overall survival (13.5 months vs. 9.4 months; HR: 0.62; p<0.0001). Based on these results, pembrolizumab received approval for use in PD-L1–positive patients.[37]

Nivolumab is a human IgG4 anti–PD-1 monoclonal antibody. The ATTRACTION-03 Phase III randomized trial compared nivolumab with chemotherapy in patients with advanced or recurrent ESCC. Nivolumab significantly improved overall survival compared with chemotherapy (10.9 months vs. 8.4 months; HR: 0.77; p=0.019).[38]

The CheckMate 648 Phase III randomized trial assigned patients with advanced ESCC to receive nivolumab plus chemotherapy, nivolumab plus ipilimumab (a CTLA-4 inhibitor), or chemotherapy alone. In PD-L1–positive patients, the combination of nivolumab and chemotherapy significantly prolonged overall survival (15.4 months vs. 9.1 months; HR: 0.54; p<0.001). The combination of nivolumab and ipilimumab also improved overall survival (13.7 months vs. 9.1 months; HR: 0.64; p=0.001).[39]

The CheckMate 577 Phase III randomized, double-blind trial evaluated the use of nivolumab as adjuvant therapy in patients who underwent surgery following neoadjuvant chemoradiotherapy.[40] Nivolumab significantly reduced the risk of disease recurrence. Based on these findings, the FDA approved nivolumab as adjuvant therapy for patients with esophageal or GEJ cancer who had residual pathological disease after complete resection following neoadjuvant chemoradiotherapy.

Camrelizumab

Camrelizumab is a selective, humanized IgG4 monoclonal anti–PD-1 antibody. The ESCORT Phase III randomized trial compared camrelizumab with chemotherapy in patients with advanced ESCC. Overall survival was higher in the camrelizumab group (8.3 months vs. 6.2 months; HR: 0.71; p=0.0010).[41]

In the NICE study, 60 patients with locally advanced but resectable thoracic ESCC were enrolled to receive camrelizumab in combination with nab-paclitaxel or carboplatin. The pCR rate was 42.5%, indicating that the addition of camrelizumab to chemotherapy represents a promising neoadjuvant treatment strategy for locally advanced ESCC.[42]

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The ongoing NICE-2 trial aims to compare the efficacy of camrelizumab plus chemotherapy (IO-CT), camrelizumab plus chemoradiotherapy (IO-CRT), and CRT as preoperative treatments for locally advanced ESCC.[43] Based on the positive results from the aforementioned clinical trials, camrelizumab has now been approved as both a first- and second-line treatment for ESCC.

Sintilimab, toripalimab, and tislelizumab have demonstrated efficacy in China-based clinical trials for advanced ESCC. These agents represent promising drugs among PD-1/PD-L1–targeted immunotherapies.[24]

In patients with locally advanced ESCC, the combination of toripalimab (an anti–PD-1 monoclonal antibody) with definitive chemoradiotherapy—consisting of radiotherapy (50.4 Gy in 28 fractions) plus weekly intravenous paclitaxel (50 mg/m²) and cisplatin (25 mg/m²) has demonstrated promising efficacy with manageable toxicity.[44]

PD-1/PD-L1 Inhibitors and Their Use Particularly in EAC: Durvalumab has demonstrated benefit as adjuvant therapy following neoadjuvant chemoradiotherapy. Atezolizumab has shown potential as a neoadjuvant treatment. Immunotherapy appears particularly promising in EAC patients with high PD-L1 expression.[45,46]

In the KEYNOTE-585 trial, neoadjuvant and adjuvant pembrolizumab increased the pathological complete response rate compared with placebo but did not result in a statistically significant improvement in event-free survival.[47] This represents an important finding that may support the role of immunotherapy in patients with locally advanced resectable gastric or GEJ adenocarcinoma. The summary of major clinical trials concerning targeted agents and immune checkpoint inhibitors in esophageal cancer is presented in Table 2.

HEPATOCELLULAR CARCINOMA

HCC most commonly develops on the background of liver cirrhosis. The most frequent causes of cirrhosis include hepatitis B and C infections, alcohol consumption, and metabolic syndromes such as nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). Genetic mutations (e.g. TP53, TERT), epigenetic alterations, and dysregulation of signaling pathways (Wnt/β-catenin, JAK/STAT, PI3K/AKT/mTOR) contribute to tumorigenesis.[48] The Barcelona Clinic Liver Cancer (BCLC) staging system categorizes HCC into five major stages, and treatment strategies are determined according to these stages.[49]

Systemic Treatment Algorithm for HCC (BCLC Stage C) – Based on EMA and FDA Approvals

Following first-line treatment with atezolizumab/bevacizumab, scientific evidence remains insufficient, and no specific treatment algorithm has yet been established for this setting. Sorafenib is approved for the treatment of HCC regardless of prior therapy. Cabozantinib, ramucirumab, and regorafenib have been approved for patients previously treated with sorafenib. Ramucirumab is specifically preferred in tumors with an AFP level greater than 400 ng/mL.[50,51]

In the NRG/RTOG 1112 randomized trial, the efficacy of sorafenib (S) monotherapy was compared with that of stereotactic body radiotherapy followed by sorafenib (SBRT/S) in patients with advanced hepatocellular carcinoma (HCC). In this study, patients with newly diagnosed or recurrent HCC who were not candidates for surgery, transplantation, ablation, or transarterial chemoembolization were enrolled. Eligibility criteria included Zubrod performance status 0–2, Child–Pugh class A, BCLC stage B or C, and ≤5 tumors with a total liver tumor diameter ≤20 cm and extrahepatic metastasis ≤3 cm. Patients were randomized in a 1:1 ratio to receive either sorafenib (400 mg BID) or SBRT (27.5–50 Gy in 5 fractions, individualized according to mean liver dose and normal tissue constraints) followed by sorafenib 200 mg BID, with escalation to 400 mg BID on day 28 if tolerated. The primary endpoint was OS, and secondary endpoints included PFS, time to progression (TTP), and treatment-related adverse events (graded per CTCAE v4). Between April 2013 and March 2021, a total of 193 patients were enrolled from 23 centers, of whom 177 were deemed eligible (S, n=92; SBRT/S, n=85). The median age was 66 years, with 82% classified as BCLC stage C and 74% presenting with macrovascular invasion. Median follow-up was 13.2 months for all patients and 33.7 months for survivors. Among 153 death events, median OS was 12.3 months in the S arm and extended to 15.8 months in the SBRT/S arm (HR=0.77; one-sided p=0.055). In multivariate analysis, OS was significantly improved (HR=0.72; 95% CI 0.52–0.99; p=0.042). Median PFS increased from 5.5 months in the S arm to 9.2 months in the SBRT/S arm (HR=0.55; p=0.0001). TTP was also prolonged in favor of SBRT/S (HR=0.69; p=0.034). The incidence of ≥ grade 3 treatment-related adverse events was comparable between groups (S: 42%; SBRT/S: 47%; p=0.52). Grade 5 adverse events were observed only in the S arm.[52]

Table 2 Summary of key clinical trials for targeted agents and ICIs in esophageal cancer

Target/pathway	Drug/study	Phase	Year	Histology	Clinical findings	OS/PFS	Ref. no
EGFR pathway	Nimotuzumab	Phase II	2021	SCC	Combination with nCRT; increased endoscopic complete response; safe	Not reported	[25]
EGFR pathway	Cetuximab (SAKK 75/08)	Phase III	2018	SCC>Adeno	Neoadjuvant CRT+surgery; reduced local recurrence; OS benefit particularly in SCC	Not reported	[26]
EGFR pathway	Icotinib	Phase II	2016	SCC	Efficacy in EGFR+ ESCC; OS benefit with RT	Not reported	[27]
EGFR pathway	Gefitinib (COG)	Phase II/III	2017	SCC	No benefit in general population; potential benefit in EGFR amplification	Not reported	[28]
HER2 pathway	Trastuzumab (ToGA)	Phase III	2010	Adeno	Combination with chemotherapy; OS advantage in HER2+ EAC	Not reported	[29]
HER2 pathway	Trastuzumab (RTOG-1010)	Phase III	2022	Adeno	Addition to neoadjuvant CRT did not show OS benefit	Not reported	[30]
VEGF/VEGFR pathway	Bevacizumab (ST03)	Phase II/III	2017	Adeno	Potential efficacy in HER2+ EAC; increased post-op complications	Not reported	[31]
VEGF/VEGFR pathway	Ramucirumab (RAINBOW)	Phase III	2014	Adeno	Combination with paclitaxel; OS: 8.71 vs 7.92 months	OS 8.71 vs 7.92 mo	[32]
VEGF/VEGFR pathway	Ramucirumab (REGARD)	Phase III	2014	Adeno	Monotherapy; OS: 5.2 vs 3.8 months	OS 5.2 vs 3.8 mo	[33]
VEGF/VEGFR pathway	Anlotinib, apatinib	Phase II	2021	SCC	Advanced ESCC; PFS: 3.02 vs 1.41 months	PFS 3.02 vs 1.41 mo	[34]
VEGF/VEGFR pathway	Endostar	Phase II	2021	SCC	Combination with chemotherapy; improved response rate in advanced ESCC	Not reported	[35]
PD-1/PD-L1	Pembrolizumab (KEYNOTE-181)	Phase III	2020	SCC+Adeno	Compared with chemotherapy; OS: 9.3 vs 6.7 months in PD-L1+ patients	OS 9.3 vs 6.7 mo	[36]
PD-1/PD-L1	Pembrolizumab+CT (KEYNOTE-590)	Phase III	2021	SCC+Adeno	Combination with chemotherapy; OS: 13.5 vs 9.4 months	OS 13.5 vs 9.4 mo	[37]
PD-1/PD-L1	Nivolumab (ATTRACTION-3)	Phase III	2019	SCC	Compared with chemotherapy; OS: 10.9 vs 8.4 months	OS 10.9 vs 8.4 mo	[38]
PD-1/PD-L1	Nivolumab + CT/ + Ipilimumab (CheckMate 648)	Phase III	2022	SCC	OS: 15.4 vs 9.1 months (PD-L1+); Nivo+Ipi: OS 13.7 vs 9.1 months	OS 15.4 vs 9.1/13.7 vs 9.1 mo	[39]
PD-1/PD-L1	Nivolumab (adjuvant, CheckMate 577)	Phase III	2021	SCC+Adeno	Reduced recurrence risk in residual disease after neoadjuvant CRT	Not reported	[40]
PD-1/PD-L1	Camrelizumab (ESCORT)	Phase III	2020	SCC	Compared with chemotherapy; OS: 8.3 vs 6.2 months	OS 8.3 vs 6.2 mo	[41]
PD-1/PD-L1	Camrelizumab+ nab-paclitaxel/ carboplatin (NICE)	Phase II	2022	SCC	Locally advanced ESCC; pCR 42.5%	Not reported	[42]
PD-1/PD-L1	Camrelizumab+ CRT/CT (NICE-2)	Phase III (ongoing)	2022	SCC	Evaluation of IO-CT and IO-CRT arms ongoing	Not reported	[43]
PD-1/PD-L1	Sintilimab/ Toripalimab/ Tislelizumab	Phase II/III	2023	SCC	Efficacy in advanced ESCC in China	Not reported	[24,44]
PD-1/PD-L1	Durvalumab (adjuvant)	Phase II	2021	Adeno	Adjuvant benefit after neoadjuvant CRT	Not reported	[45]
PD-1/PD-L1	Atezolizumab (neoadjuvant)	Phase II	2021	Adeno	Neoadjuvant treatment, feasibility study	Not reported	[46]
PD-1/PD-L1	Pembrolizumab (KEYNOTE-585)	Phase III	2024	Adeno (GEJ/ Gastric)	Neoadjuvant+adjuvant; increased pCR; no significant improvement in EFS	Not reported	[47]

SCC: Squamous cell carcinoma; Adeno: Adenocarcinoma; nCRT: Neoadjuvant chemoradiotherapy; CRT: Chemoradiotherapy; RT: Radiotherapy; OS: Overall survival; PFS: Progression-free survival; EAC: Esophageal adenocarcinoma; GEJ: Gastroesophageal junction; PD-1: Programmed death-1; PD-L1: Programmed death ligand-1; CT: Chemotherapy; Ipi: Ipilimumab; IO: Immuno-oncology; pCR: Pathological complete response; EFS: Event-free survival; EGFR: Epidermal growth factor receptor; HER2: Human epidermal growth factor receptor 2; COG: Cancer oesophagus gefitinib trial; ToGA: Trastuzumab for gastric cancer trial; RTOG: Radiation therapy oncology group

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CONCLUSION

In conclusion, the addition of SBRT significantly improved OS, PFS, and TTP compared with sorafenib monotherapy in patients with advanced HCC. No substantial increase in adverse events was observed. These findings suggest that the integration of SBRT into systemic therapy may provide a meaningful contribution to the management of advanced HCC and represent a safe therapeutic option.

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