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REVIEW

Immunotherapy in Gastrointestinal Cancers: Current Insights

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Abstract: Gastrointestinal cancer is one of the most prevalent malignant tumors worldwide. The treatment landscape of gastrointestinal cancer has entered a new era with the advent of immunotherapy, which activates the immune system to identify and eliminate tumor cells. Immunotherapy has demonstrated high efficacy and tolerable toxicity profiles compared to conventional therapies. Immune checkpoint inhibitors including PD-1, PD-L1, CTLA-4 and LAG-3 in combination with targeted therapy or chemotherapy have been approved for the treatment of gastrointestinal tumors with good clinical patient benefit. In recent years, a variety of novel immunotherapeutic approaches have emerged. For example, adoptive T-cell therapy, such as claudin18.2-targeted CAR-T has achieved an objective remission rate of 48.6% in patients with advanced gastric cancer and gastroesophageal junction cancer. Oncolytic viruses inhibits tumor growth in both tumor lysis and immune activation, and is currently showing its efficacy against gastrointestinal tumors in some clinical trials. In addition, cancer vaccines, with their unique high degree of precision, have improved the effectiveness of individualized therapy. Personalized neoantigen vaccines combined with other immunotherapeutic drugs or chemotherapy, have shown some efficacy and safety in gastrointestinal patients. In this review, we summarize these recent advances in immunotherapy for the treatment of gastrointestinal tumors. Additionally, the challenges and limitations linked to immunotherapy were explored. This review will expand our understanding of clinical studies on immunotherapy in gastrointestinal cancer and assist in individualizing patient treatment strategies, maximizing therapeutic benefits, and improving patient prognosis.

Keywords: gastrointestinal cancer, immunotherapy, immune checkpoint inhibitors, adoptive T-cell therapy, oncolytic viruses, cancer vaccines

Introduction

Gastrointestinal cancer is a group of cancers with high prevalence worldwide. It includes gastric cancer (GC), esophageal cancer, colorectal cancer (CRC), hepatocellular carcinoma (HCC), pancreatic ductal adenocarcinoma (PDAC), and several others.[1] An earlier population-based systematic analysis described that the global lifetime risk of gastrointestinal cancer is one in 12, with one in 16 individuals experiencing mortality. Moreover, gastrointestinal cancer accounts for one-quarter of all cancer cases and one-third of cancer-related deaths.[2] Notably, the incidence of gastrointestinal cancer is rising among the younger populations, primarily attributed to smoking, alcohol consumption, poor dietary habits, obesity, and sedentary behavior.[3] The lifestyle changes may result in the presence of inflammatory factors in younger patients, affecting the function and activity of immune cells, weakening resistance to tumors, and thus the effectiveness of immunotherapy. Therefore, age is also an important stratification factor in terms of clinical trial design. Separate analysis of young and elderly patients can help to more accurately assess the efficacy and safety of immunotherapy in patients of different ages.

Immunotherapy is a promising approach in the treatment of gastrointestinal tumors and has made remarkable achievements, demonstrating survival breakthroughs and therapeutic paradigm innovations especially in specific subtypes of patients. Among them, immune checkpoint inhibitors (ICIs) have been widely investigated and approved for use in first- or second-line

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treatments.[4–6] In recent years, with the development of novel immunotherapies and new technologies, immunotherapies are no longer limited to immune checkpoints. New immunotherapies are being developed, including adoptive T-cell therapy (ACT), oncolytic viruses (OVs), and cancer vaccines,[7] as well as immunotherapies based on cytosolic vesicles, exosomes, and nanotechnology.[8–10] Among them, ACT, Ovs, and cancer vaccines have been demonstrated to have a favorable clinical response in Phase I and II clinical trials. They have revolutionized cancer treatment by optimizing treatment regimens in terms of precision, immune memory, and individualization dimensions, improving efficacy and extending treatment to a larger proportion of cancer patients.This review aimed to outline recent advances in clinical trials involving immune checkpoint inhibitors, ACT, OVs, and cancer vaccines for the management of gastrointestinal cancer (Figure 1). In addition, current challenges and limitations linked to immunotherapy were discussed.

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors (ICIs) are the mainstay of immunotherapy. They revolutionize gastrointestinal treatment and show outstanding clinical efficacy. Specifically, ICIs target the dysfunctional immune system and activate T cells to eliminate cancer cells by inhibiting immune checkpoints.[11] To date, most ICIs target programmed cell death receptor-1/programmed death ligand-1 (PD-/PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and have achieved long-term remission in patients with gastrointestinal tumors.[12,13]

PD-1/PD-L1 Inhibitors

PD-1 is an inhibitory receptor on T cells, and its ligand, PD-L1, is expressed on tumor cells. The binding of PD-1 to PD-L1 inhibits T-cell activity. PD-1/PD-L1 inhibitors reverse immunosuppression and enhance the killing of tumor cells through the blockade of the interaction between PD-1 and PD-L1.[14] While several PD-1/PD-L1 inhibitors have been approved, only

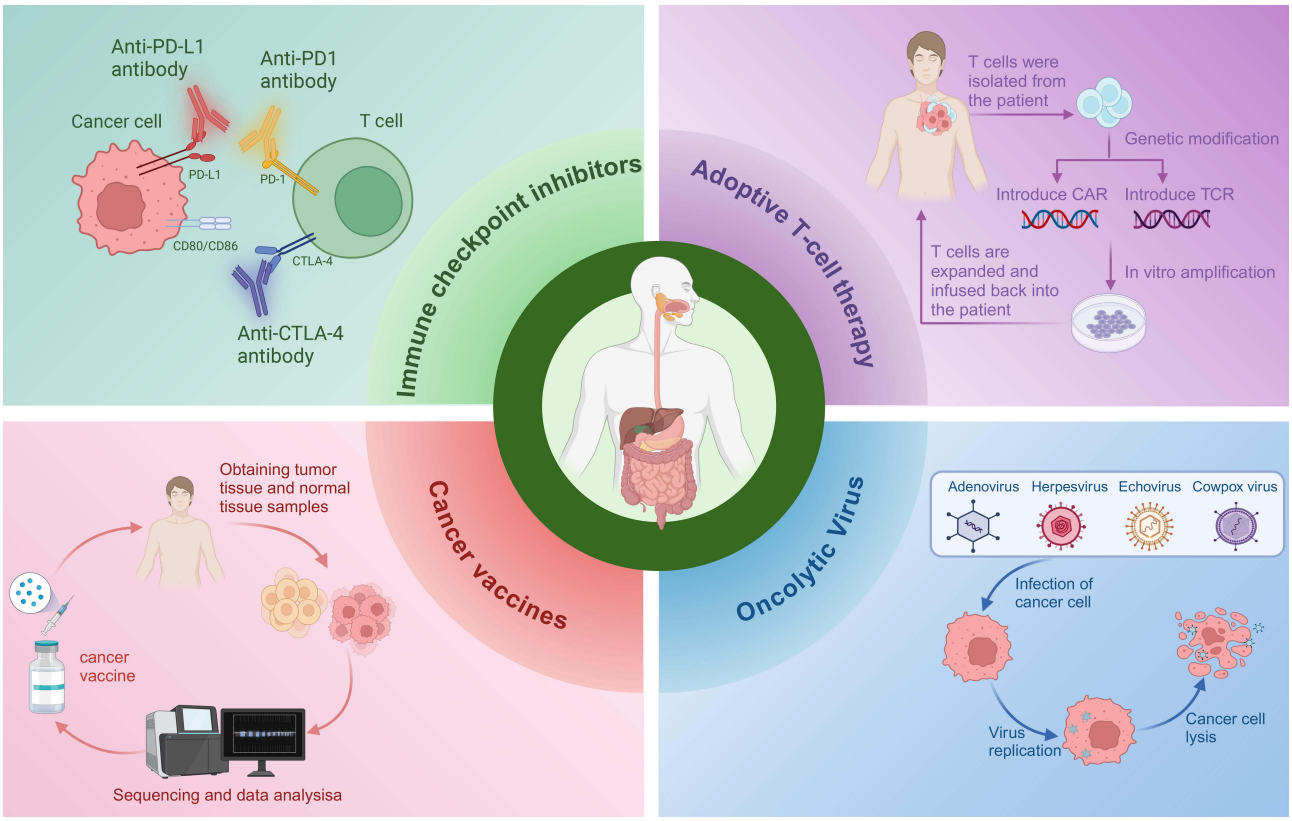

Figure 1 Immunotherapy in Gastrointestinal Cancers. Immunotherapy for gastrointestinal cancers includes immune checkpoint inhibitors, adoptive T-cell therapy, oncolytic virus therapy, and cancer vaccines. Created in BioRender. Ying, (**L**) (2025) https://BioRender.com/l79q414.

a limited number of PD-1/PD-L1 inhibitors, such as nivolumab, pembrolizumab, and atezolizumab, have been approved for the treatment of gastrointestinal tumors.[15,16]

PD-1/PD-L1 inhibitors show potential with lower toxicity and higher tolerability compared to other oncology drugs.[17,18] The results of several studies have shown that PD-1/PD-L1 inhibitor monotherapy for gastrointestinal tumors has good efficacy and safety in selected patients. For example, in gastric and colorectal cancer patients, most of them are microsatellite-stable (MSS), which have stable tumor cell genomes, low mutation loads, produce few neoantigens, and usually have more immune-suppressing cells in the tumor microenvironment, such as regulatory T-cells and myeloid suppressor cells, and are less responsive to immunotherapy. In contrast, the percentage of patients with high microsatellite instability (MSI) is around 15%, but MSI-type tumors have a defective DNA mismatch repair mechanism, which leads to the production of a large number of microsatellite sequence length changes during DNA replication, which increases the mutational load of the tumor cells and produces a large number of neoantigens, which can be recognized by the immune system as foreign substances, thus activating the immune system's tumor attack, with significant efficacy against immune checkpoint inhibitors.[19,20] Some results from s Phase III study of pembrolizumab indicated that its median progression-free survival (mPFS) was significantly better than that of chemotherapy (16.5 months vs 8.2 months) as a first-line treatment for metastatic microsatellite highly unstable (MSI-H) or mismatch repair-deficient (dMMR) CRC.[21] Also in a Phase 3 randomized clinical trial in untreated MSI-H patients with advanced gastric cancer, pembrolizumab monotherapy was found to be superior to chemotherapy alone.[22] In the clinic, pembrolizumab monotherapy or nivolumab combined with chemotherapy/ipilimumab is recommended for patients with MSI-H advanced gastric cancer. However, PD-1/PD-L1 inhibitor monotherapy presents limited results in terms of PFS and overall survival (OS) in most gastrointestinal patients such as MSS, and there may be a variety of reasons for this, including tumor heterogeneity, immune escape, and drug resistance.[23] In contrast, combination strategies (eg, integrating chemotherapeutic agents with targeted agents) are more promising for the treatment of gastrointestinal cancer.

The combination of PD-1/PD-L1 inhibitor and chemotherapy has garnered extensive attention in clinical trials, especially in patients with GC, esophageal cancer, and CRC, and yielded superior efficacy. For example, the combination of nivolumab with chemotherapy significantly extended OS and induced durable remission in patients with gastrointestinal tumors.[24] Similarly, the results of the phase 3 CheckMate 649 study that investigated the efficacy and safety of the combination of nivolumab with chemotherapy (XELOX every 3 weeks or FOLFOX every 2 weeks) for the treatment of advanced GC, gastroesophageal junction adenocarcinoma (GEJC), and esophageal adenocarcinoma.[25] Reported that compared to chemotherapy alone, OS (11.3 vs 14.0 months) and PFS (6.9 vs 7.5 months) were significantly longer using the combination of nivolumab with chemotherapy in the PD-L1 combined positive score (CPS) ≥1 cohort, and the results were generally consistent across different PD-L1 CPS subgroups. This study illustrated that nivolumab, in combination with chemotherapy, provided significant and clinically meaningful OS and PFS benefits for patients with PD-L1 CPS ≥5 and ≥1 and across the whole randomized population.Besides, pembrolizumab, another PD-1 inhibitor, in conjunction with chemotherapy, offers superior benefits in patients with gastrointestinal tumors. Results from a phase III KEYNOTE-859 study unveiled that among patients with advanced gastric cancer, the pembrolizumab and chemotherapy (fluorouracil +cisplatin/capecitabine+ oxaliplatin) group had a longer median OS (mOS) compared to the placebo-chemotherapy group, particularly in participants with a PD-L1 CPS of 1 or higher, wherein pembrolizumab conferred a significant and clinically meaningful improvement in OS (13.0 months vs 11.8 months).[26] In patients with previously untreated advanced esophageal squamous cell carcinoma, pembrolizumab, in combination with chemotherapy (5-fluorouracil and cisplatin), also improved OS (6.3 months vs 5.8 months) and maintained a manageable safety profile in the treated population.[27] It can be seen that different PD-1/PD-L1 inhibitors in combination with different chemotherapeutic agents resulted in an increase in mOS in patients, but different mOS outcomes were due to the different chemotherapeutic drug combinations and dosing regimens used in the studies, individual patient variability, and high or low tumor mutational load (TMB).

The combination of PD-1/PD-L1 inhibitors with targeted therapeutic agents is currently the main options for treatment of gastrointestinal tumors, especially HCC. The results of the global phase III IMbrave150 study[28] showed that atezolizumab-bevacizumab combination group had a significantly longer mPFS compared to the sorafenib group in patients with advanced HCC (6.8 months vs 4.3 months). Additionally, the one-year follow-up analysis showed[29] that the combination group had a significantly longer mOS (19.2 months vs 13.4 months), while tolerability and safety were

comparable between the two groups. ORIENT-32, a Phase II–III study involving sintilimab in combination with a bevacizumab analog for the treatment of advanced HCC,[30] uncovered a higher mPFS compared to the control group (4.6 months vs 2.8 months). However, although the mOS in the combination group had not yet been reached, it was significantly longer than in the control group (10.4 months). At the same time, the results of the phase III CARES-310 study investigating camrelizumab in combination with apatinib for advanced HCC[31] demonstrated significantly longer mPFS (5.6 months and 3.7 months) and mOS (22.1 months vs 15.2 months) compared with sorafenib. These results collectively suggest that PD-1/PD-L1 inhibitors, in conjunction with targeted therapeutic agents, represent a potential first-line treatment option for patients with advanced HCC. In addition, this combination has demonstrated satisfactory efficacy as a second-line treatment for other tumors. A recent Phase II OASIS trial reported[32] that the combination of nivolumab and anlotinib hydrochloride showed a significant efficacy and a manageable safety profile in patients with advanced gastric adenocarcinoma who had failed first-line treatment. Nevertheless, larger and more representative samples are warranted to validate these findings.

In recent years, triple therapy, that is, the combination of PD-1/PD-L1 inhibitors, targeted therapeutic agents, and chemotherapy, has been established as a potential therapeutic strategy for gastrointestinal tumors. Chen et al[33] concluded that the combination of camrelizumab, apatinib, and chemotherapy resulted in favorable clinical outcomes with a manageable safety profile in patients with untreated advanced GC, achieving an objective remission rate (ORR) of 76.5%, an mPFS of 8.4 months, and a 2-year OS rate of 62.8%. More importantly, a high ORR was also achieved in gastric cancer patients with low PD-L1 expression. However, this was a phase I study, and additional clinical trials are needed to corroborate these findings. The results of the phase III KEYNOTE-811 study demonstrated[34] that the combination of pembrolizumab, trastuzumab, and chemotherapy significantly improved PFS in patients with metastatic HER2-positive GC compared with placebo, especially in patients with tumors with a PD-L1 co-positive score of 1 or more. Therefore, this combination is a viable treatment option in patients with HER2-positive gastric cancer.

Taken together, these findings demonstrate the significant progress in the application of PD-1/PD-L1 inhibitors for the treatment of gastrointestinal tumors. In particular, PD-1/PD-L1 inhibitors, in conjunction with chemotherapy or targeted therapeutic agents, have been listed as a first-line treatment option for patients with gastrointestinal tumors. However, there are still some patients with gastrointestinal tumors who do not benefit from PD-1/PD-L1 inhibitors due to individual patient differences and drug resistance. Current challenges include optimizing predictive biomarkers for patients with MSS-type tumors, exploring new immune checkpoints, and novel combination therapy regimens.

CTLA-4 Inhibitors

CTLA-4 is a protein expressed on the surface of T cells and a key regulator of T cell homeostasis and self-tolerance by inhibiting T cell activity.[35] Currently the CTLA-4 inhibitors, ipilimumab and tremelimumab, are mostly used in combination with PD-1/PD-L1 inhibitors for the treatment of gastrointestinal tumors to enhance anti-tumorigenic effects.

The efficacy and safety of ipilimumab, in combination with nivolumab, has been extensively explored in gastrointestinal tumors. In patients with advanced gastroesophageal cancer who have undergone several treatments, ipilimumab in combination with nivolumab showed clinically meaningful antitumor activity and a manageable safety profile.[36] However, the results of the phase III clinical trial[25] and long-term follow-up[37] indicated that the OS of patients treated with ipilimumab in combination with nivolumab did not reach the predefined significance threshold in patients with PD-L1 CPS ≥5 compared to chemotherapy alone. In other words, no OS was comparable in patients with gastroesophageal cancer treated with the combination of ipilimumab and nivolumab compared to those who received nivolumab in combination with chemotherapy. Consequently, the combination of ipilimumab with nivolumab has not been used for the treatment of advanced gastroesophageal adenocarcinoma, whilst the use of nivolumab in combination with chemotherapy continues to be supported as the standard first-line treatment. In contrast, ipilimumab, in combination with nivolumab, showed clinical benefits in a non-randomized study enrolling patients with MSI-H or dMMR metastatic CRC.[38] The results of the phase III study revealed that at 24 months, patients who received ipilimumab in combination with nivolumab had a significantly longer PFS than those in the chemotherapy group, with progression-free survival rates of 72% and 14%, respectively. Moreover, the limiting mean survival time in the ipilimumab combined with the nivolumab group was 10.6 months longer than that of chemotherapy.[39] Therefore, ipilimumab, in combination with nivolumab, has been approved as a first-line treatment option for patients with

unresectable or metastatic MSI-H or dMMR CRC. In addition, ipilimumab in combination with nivolumab offers survival benefits for HCC patients as well with a manageable safety profile, promising ORR, and durable remission for patients who have progressed after prior sorafenib treatment or were unable to tolerate sorafenib.[40] A 5-year follow-up study reported an ORR of 34% and a mOS of 22.2 months, with no new safety signals identified, supporting its use as a second-line treatment for these patients.[41]

Tremelimumab, in combination with durvalumab, exerts antitumorigenic effects. However, its efficacy has been exclusively observed in HCC, with modest benefits in other gastrointestinal tumors.[42,43] A phase III study documented that tremelimumab, in combination with durvalumab provided sustained OS benefit in patients with unresectable HCC. Furthermore, this combination improved 3-year (19.8% vs 30.7%) and 4-year OS rates (15.1% vs 25.3%) in patients with disease control compared to sorafenib while maintaining a clinically meaningful and favorable safety profile.[44] This FDA-approved regimen is considered a well-tolerated and effective treatment option for patients with unresectable HCC.[45] In gastrointestinal tumors other than HCC, tremelimumab, in combination with durvalumab, must be followed by chemotherapy to achieve satisfactory efficacy.[46,47] Of note, a phase Ib/II study investigating the efficacy of tremelimumab in combination with durvalumab for the treatment of patients with metastatic colorectal cancer with RAS mutations demonstrated that the mPFS of tremelimumab in combination with durvalumab was 8.2 months, which exceeded the expected mPFS of 5–6 months.[48] The study emphasized the promising clinical efficacy of tremelimumab in combination with durvalumab chemotherapy in patients with unresectable MSS metastatic CRC, shifting the paradigm that targeted chemotherapy is the sole therapeutic option for MSS tumors and providing insights into the role of immunotherapy in patients with MSS metastatic CRC.

Botensilimab (AGEN1181; BOT) is a novel multifunctional Fc-enhanced anti-CTLA-4 antibody specifically designed to overcome the suppressive tumor microenvironment (TME) of immunologically "cold" tumors via multiple mechanisms of action[49,50] and to drive responses in patients with MSS or low tumor mutation burden (TMB) tumors. Its combination with balstilimab demonstrated a manageable safety profile and encouraging efficacy in heavily pretreated patients with MSS mCRC.[51] A randomized phase II study of this combination is ongoing (NCT05608044) and is expected to offer a novel treatment option for patients with MSS mCRC.

In summary, only nivolumab/durvalumab in combination with CTLA-4 inhibitors has been examined in clinical trials involving patients with gastrointestinal tumors and has shown outstanding clinical benefits, whereas other PD-1/PD-L1 inhibitors combined with CTLA-4 inhibitors necessitate further exploration in the future. Overall, the number of CTLA-4 inhibitors is relatively limited compared to PD-1/PD-L1 inhibitors, with only three approved drugs, including candonilimab, a dual immune-target inhibitor, ipilimumab, and tremelimumab. Nonetheless, several CTLA-4 inhibitors are under development, signaling the importance and therapeutic potential of the CTLA-4 target.

Dual Immune Target Inhibitors

Cadonilimab is an innovative bispecific antibody drug targeting two immune checkpoints, namely human PD-1 and CTLA-4. It blocks the interaction between PD-1 and CTLA-4 with their ligands, thereby promoting tumor-specific T-cell immune activation and inhibiting tumor growth.[52] A multicenter, open-label, phase Ib/II trial indicated that cadonilimab showed encouraging tumor response rates with a manageable safety profile. In the esophageal squamous cell carcinoma cohort, the median follow-up duration was 17.9 months, with an ORR of 18.2%. In the HCC cohort, the median follow-up duration was 19.6 months, with an ORR of 16.7%.[53] These results highlight the potential of cadonilimab for the treatment of advanced solid tumors. Qiang et al[54] demonstrated that cadonilimab, in combination with lenvatinib, showed promising efficacy and manageable toxicity. In addition, a retrospective study corroborated the efficacy and safety of this combination therapy, which improved prognosis as a first-line treatment.[55] Therefore, cadonilimab, in combination with lenvatinib, may provide a new treatment approach for patients with advanced HCC. Cadonilimab in combination with chemotherapy yielded favorable outcomes in the treatment of gastrointestinal tumors. The phase Ib/II COMPASSION-04 trial showed that in HER2-negative GC/GEJC patients, the mPFS and OS of patients treated with cadonilimab in combination with chemotherapy were 8.18 months and 17.48 months, respectively. At the same time, the mOS was 20.32 months in patients with PD-L1 CPS ≥5 and 17.64 months in patients with PD-L1 CPS <1.[56] Thus, cadonilimab in

combination with chemotherapy showed promising clinical activity and manageable safety in patients with HER2-negative GC/GEJC.

The aforementioned studies have demonstrated the feasibility and superior safety of dual immune-targeted inhibitors in the treatment of gastrointestinal tumors and positioned dual immune-targeted inhibition as a reliable treatment option. However, current clinical trial results remain sub-optimal, with only one drug marketed for clinical use. Thus, further in-depth research and exploration are needed in the future.

Novel Immune Checkpoint Inhibitors

At present, PD-1/PD-L1 and CTLA-4 are the most extensively studied immune checkpoints, with significant breakthroughs achieved. However, some patients experience poor outcomes or develop resistance to PD-1/PD-L1 and CTLA-4 inhibitors.[57] Hence, there is an urgent need to develop additional new immune checkpoint inhibitors. Recently, several studies have focused on novel immune checkpoints, including lymphocyte activation gene-3 (LAG-3), T cell immunoreceptor with Ig and ITIM domain (TIGIT),T-cell immunoglobulin and mucin domain-containing T-cell immune receptor (TIM-3), and glucocorticoid-induced tumor necrosis factor receptor (GITR).[58] Drugs targeting these immune checkpoints are advancing into clinical trials, providing new therapeutic options and hope for patients.

To date, over 20 LAG-3 inhibitors have been evaluated in clinical trials for cancer immunotherapy; however, only relatlimab has been FDA-approved and is indicated for use in combination with nivolumab for the treatment of pediatric and adult patients aged 12 years and older with unresectable or metastatic melanoma.[59] Several trials have been conducted to investigate the clinical efficacy of this combination therapy in gastrointestinal tumors. For instance, a phase Ib study demonstrated the safety and feasibility of this combination for the treatment of resectable GC/GEJC.[60] The phase II RELATIVITY-060 study suggested[61] that in patients with GC/GEJC whose tumors expressed LAG-3 ≥1%, the combination of relatlimab, nivolumab, and chemotherapy, despite having an acceptable safety profile, did not provide significant benefits, with no improvement in mPFS or mOS compared to nivolumab in combination with chemotherapy. Notwithstanding, a trend toward improved PFS was observed in patients with LAG-3 expression ≥5%. Therefore, relatlimab + nivolumab + chemotherapy may be more suitable for patients with high LAG-3 expression. Moreover, a short-term neoadjuvant regimen of relatlimab plus nivolumab demonstrated potent anti-tumor efficacy in patients with locally advanced dMMR colon cancer.[62] Michael et al[63] exposed that the administration of relatlimab combined with nivolumab monoclonal antibody in previously treated patients with MSI-H/dMMR metastatic CRC had an ORR of 50%, a median duration of remission (DOR) of 42.7 months, and an mPFS of 27.5 months, implying that this combination provided durable clinical benefits and was well tolerated. In addition, a recent phase I study found that the new LAG-3 inhibitor (IBI110) in combination with sintilimab was well tolerated in Chinese patients with advanced solid tumors. Noteworthily, the ORR of HER-2 negative GC patients receiving IBI110, sintilimab, and chemotherapy in this study was 70.6%, highlighting the potential of this combination.[64] Clinical trials involving the efficacy and safety of relatlimab in HCC are also ongoing (NCT04658147 and NCT05337137). These findings reflect the therapeutic benefit of LAG-3 inhibitors in combination with other drug therapies in patients with gastrointestinal tract. However, further studies are needed to optimize this treatment option.

Like LAG-3, TIGIT inhibitors synergize with PD-1/PD-L1 inhibitors and significantly increase anti-tumor CD8+ T cells.[65] Tiragolumab is a human anti-TIGIT monoclonal antibody, which is well tolerated as monotherapy or in combination with atirizumab in solid tumors and has shown promising antitumor activity in combination therapy in immunotherapy-primed patients with non-small cell lung and esophageal cancer.[66] The results of a phase I study in Japan (jRCT2080224926) found that atiragolumab combined with atezolizumab was well tolerated in patients with non-small cell lung, pancreatic and bile duct cancers.[67] The latest Phase 1b-2 multicenter study found that in unresectable hepatocellular carcinoma, the objective remission rate was 43% in the tiragolumab in combination with atezolizumab plus bevacizumab group, compared with 11% in the atezolizumab in combination with bevacizumab group. Therefore, the addition of tiragolumab, a TIGIT monoclonal antibody, to atezolizumab and bevacizumab is more clinically effective than atezolizumab plus bevacizumab alone.[68] The ongoing Phase 3 IMbrave152/SKYSCRAPER-14 study (NCT05904886) is investigating tiragolumab plus atezolizumab plus bevacizumab as a novel first-line treatment option for patients with unresectable hepatocellular carcinoma.

The combination of TIM-3 inhibitors with PD-1 inhibitors exhibits potent antitumor activity and is well tolerated in patients with advanced solid tumors.[69] Besides, this combination is associated with a manageable safety profile in patients with advanced MSI-H/dMMR solid tumors and favorable survival outcomes in patients with MSI-H/dMMR solid tumors not previously treated with PD-1/PD-L1 inhibitors. However, it is worthwhile acknowledging that its clinical activity is limited in patients with MSI-H/dMMR tumors refractory to prior PD-1/PD-L1 inhibitor therapy.[70] Thus, further exploration of its resistance profile is needed in follow-up studies.

The discovery of novel immune checkpoints for LAG-3 and TIM-3 has provided valuable insights for the development of a new generation of immunotherapeutic drugs. However, in gastrointestinal tumors, only LAG-3 and TIM-3 inhibitors have progressed to clinical trials. Other potential targets play decisive roles in gastrointestinal tumor progression and immune microenvironment and have been exclusively investigated in preclinical studies.[71,72] However, the development of drugs targeting these checkpoints remains in the early stages, with several challenges and a lack of robust clinical data to support their efficacy and safety.

Adoptive T-Cell Therapy

Adoptive T-cell therapy (ACT), which utilizes tumor-infiltrating lymphocytes (TILs) or T-cells genetically engineered to express tumor-recognizing receptors, can mediate tumor regression in patients with metastatic cancers and has emerged as a powerful and potentially curative therapy for a wide range of cancers. ACT includes TIL therapy, chimeric antigen receptor T-cell (CAR-T) therapy, and T-cell receptor-engineered T-cell (TCR-T) therapy.[73] Of these, TIL therapy has not yet been explored in gastrointestinal tumors, whilst CAR-T and TCR-T therapies have shown preliminary efficacy in gastrointestinal tumors and may lead to significant breakthroughs in the future.

CAR-T therapy modifies T cells through genetic techniques to express CAR on their surface, which recognizes specific antigens on the surface of cancer cells and activates T cells. Although it has made significant progress in the treatment of hematological malignancies, its efficacy in solid tumors remains limited. To overcome these challenges, Zheng et al[74] designed CAR-T cells using a synthetic Notch (synNotch) receptor, which induces localized tumor-specific secretion of extracellular matrix (ECM)-degrading enzymes at the tumor site, which induces tumor regression by targeting ECM and enhancing CAR-T infiltration, resulting in solid tumor clearance. More importantly, this therapy is non-toxic in vivo and provides a strategy for targeting ECM-rich solid tumors. Claudin18.2 (CLDN18.2) protein is an isoform of claudin18, a member of the tight junction protein family, with limited expression in normal tissues. However, it is frequently aberrantly expressed during the development and progression of various primary malignant tumors, especially in cancers of the digestive system. Abnormal expression of Claudin18.2 leads to its exposure from the gastric mucosa, making it a unique potential target for antitumor therapy.[75] CT041 is a CAR-T therapy containing expression targeting CLDN18.2. CT041 therapy is well tolerated in patients with CLDN18.2-positive GI cancers, regardless PD- L1 expression status, and is effective independent of prior treatment with anti-PD-1/PD-L1 inhibitors.[76] Two patients with CLDN18.2-positive PDAC who failed chemotherapy were treated with CTO41 and showed excellent tumor control.[77] Thus, CT041 could provide clinical benefits to patients without effective treatment options. Furthermore, CAR-GPC3 T-cell therapy shows potential for the treatment of HCC. The high expression of phosphatidylcholine-3 (GPC3) in tumor cells is associated with a poorer prognosis in HCC. CAR-GPC3 T therapy has an acceptable safety profile in patients with advanced HCC.[78]

TCR-T therapy involves the recognition of antigens presented by major histocompatibility complex (MHC) molecules, including those located intracellularly, through genetically modified TCRs, which expands treatment options beyond extracellular antigens. In addition, owing to the natural properties of TCR signaling, TCR-T cells have greater persistence and infiltration capacity in solid tumors.[79] In a phase II single-arm study, seven patients with metastatic mismatch repair proficient (pMMR) CRC tolerated TCR-T cell therapy, which mediated tumor regression.[80] In addition, Maggadottir et al[81] investigated a clinical protocol using mRNA TCR-modified T cells to treat patients with progressive, refractory metastatic MSI-H CRC. As anticipated, the treatment was well tolerated, and despite the advanced stage of the cancer, the patients were stable, with a post-treatment survival of 6 months. These findings conjointly confirm the feasibility of TCR-T therapy in solid tumors. However, the limited sample size warrants further phase I/II studies.

ACT features ex vivo-grown patient-derived T cells, and although this therapy has shown significant therapeutic effects in hematologic malignancies, its application in gastrointestinal tumors is still at an infant stage and faces many challenges and limitations. First, there is a high degree of antigenic heterogeneity in gastrointestinal tumors, where different tumor cells may express different antigens or vary in the expression of the same antigen. This makes it difficult to find a specific antigenic target for ACT that can universally recognize all tumor cells, resulting in limited therapeutic efficacy and only a small group of patients benefiting from ACT. For example, the expression level of Claudin18.2 in gastric cancer cells may vary significantly across patients and different tumor sites, affecting the efficacy of CAR-T cell therapy targeting Claudin18.2. Studies have confirmed that gastric cancer patients with CLDN18 positivity and over-expression in epithelial cells suggest a favorable prognosis for CAR T therapy.[82] Secondly, there is a complex tumor microenvironment in gastrointestinal tumors, including immunosuppressive cells, suppressors, hypoxia and tumor metabolism. It is not conducive to the infiltration of T cells into tumor tissues, and it also inhibits the activation and proliferation of permissive T cells, which reduces the killing ability of ACT on tumor cells.[83] Finally, most of the antigens targeted by CAR-T or TCR-T cells in gastrointestinal tumors are not specific for cancer cells and are also expressed in non-malignant tissues, leading to potential targeting/debridement toxicity.[84] Therefore, more advanced technologies and clinical studies are required to validate its effectiveness and safety. Currently, clinical studies investigating ACT for the management of gastrointestinal tumors are actively underway (Table 1), and ACT is anticipated to become an important therapeutic approach for cancer in the future.

Oncolytic Virus

Oncolytic viruses (OVs) are genetically engineered virus-based tumor-targeted immunotherapies that offer novel and promising therapeutic options for the conventional treatment of patients with gastrointestinal tracts. They can directly lyse cancer cells while preserving healthy cells. Ovs-based immunotherapy can induce tumor regression by killing tumor cells, releasing antigens, and recruiting innate effector cells to the tumor site to elicit an immune response, thus converting "cold" tumors into "hot" tumors and inducing tumor regression.[85] Common OVs include adenovirus, herpesvirus, echovirus, and cowpox virus.[86]

H101 (Oncorine), a human recombinant adenovirus type 5 engineered by removing the gene E1B, is responsible for encoding the anti-apoptotic E1B55K protein that inactivates p53. It was approved for the treatment of advanced nasopharyngeal carcinoma (NPC) in 2005 and was the first OV to receive regulatory approval.[87] H101 infection induces downregulation of CD47 in cancer cells which in turn induces phagocytosis of tumor cells by macrophages and activation of CD8+ T cells and may enhance the therapeutic efficacy of PD-1 blockade in cancer.[88] A single-arm

Table 1 Investigational Clinical Studies on ACT in Gastrointestinal Cancers

Agent	Target	Phase	Conditions	NCT number	Status	Study Start
CAR-T	Autologous GPC3 CAR-T Cells (CBG166)	I	Advanced Hepatocellular Carcinoma	NCT06461624	Recruiting	2024
CAR-T	TM4SF1-positive chimeric antigen receptor T-cell therapy	Not Applicable	The TM4SF1-positive Tumors of Digestive System	NCT05673434	Not yet recruiting	2023
CAR-T	Mesothelin/GPC3/GUCY2C Targeted CAR-T	I	Pancreatic Cancer	NCT05779917	Recruiting	2023
CAR-T	CEA-targeted CAR-T	I	CEA-positive Advanced/Metastatic Malignant Solid Tumors	NCT06010862	Recruiting	2023
CAR-T	AZD6422	I	Advanced or Metastatic CLDN18.2+ GI Tumors	NCT05981235	Recruiting	2023
TCR-T	Mutant KRAS G12V-specific TCR transduced autologous T cells	I/II	Advanced Pancreatic Cancer	NCT04146298	Recruiting	2021
ACT	Regorafenib + PD-1 + iNKT cells	II	Hepatocellular Carcinoma	NCT05962450	Recruiting	2023
ACT	pTTL	I/IIa	Advanced Colorectal Cancer	NCT05908643	Recruiting	2023

study of H101 in combination with nivolumab in patients with advanced HCC who had failed prior systemic therapy conducted by Li et al[89] found that this combination was potentially efficacious, safe, and well tolerated, with an ORR of 11.1% and a mOS of 15.4 months. The combination is also more suitable for patients with low AFP levels. Another oncolytic adenovirus, LOAd703, harbors a transgene encoding TMZ-CD40L and 4–1BBL. It infects neighboring immune and stromal cells to induce CD40L and 4–1BBL expression.[90] The results of a non-randomized, single-center phase I/II group 1 study performed by Musher B L et al[91] demonstrated that LOAd703 combined with albumin conjugated paclitaxel and gemcitabine for the treatment of patients with advanced pancreatic ductal adenocarcinoma was feasible and safe, with the majority of adverse events being grade 1–2, and the maximum tolerated dose was never reached. The proportion of CD8 effector memory cells and adenovirus-specific T cells increased after LOAd703 injection in 15 of 16 patients for whom T-cell assays were available. Among 18 patients for whom activity could be assessed, eight (44%) achieved an objective response. An additional sub-study group 2 is ongoing (NCT02705196).

OH2 was developed by genetically modifying the HG52 strain of herpes simplex virus type 2, enabling the virus to selectively replicate in tumors. OH2 therapy effectively activates systemic immunity and induces a sustained anti-tumor immune response. A major effect of OH2 on systemic immunity was the promotion of Ccl5 production, which correlated with clinical response.[92] A phase I/II study of OH2, either as a single agent or in combination with the anti-PD-1 antibody HX008, for the treatment of advanced solid tumors yielded safe results.[93] Encouraging anti-tumor activity was observed in patients with metastatic rectal and esophageal cancers, with durations of response (DOR) of 11.25+ and 14.03+ months for the two responders treated with single-agent OH2 and DOR of 1.38+ and 2.56+ months for the two responders in the combination cohort. OH2 is anticipated to be evaluated in more gastrointestinal tumor samples in the future for its benefits.

Pelareorep (Reolysin®), an echidna orphan virus type 3 Dearing strain, is a double-stranded RNA virus that selectively replicates in KRAS-mutant cells. Pelareorep enhances anti-tumor immunity by activating the innate and adaptive host immune system through dendritic cells, natural killer cells and effector T cells.[94] T-cell infiltration and PD-L1 upregulation in tumor tissues of patients treated with Pelareorep.[95] It induces apoptosis and cell death through an autophagic mechanism in KRAS-mutant CRC.[96] Pelareorep, in combination with FOLFIRI and bevacizumab, was found to be well tolerated in a phase I dose-escalation clinical trial that recruited patients with KRAS-mutant oxaliplatin-refractory/intolerant mCRC.[97] In addition, a phase Ib single-arm study undertaken by Devalingan et al[95] determined that Pelareorep in combination with pembrolizumab and chemotherapy for the treatment of patients with PDAC did not result in significant toxicity. Among 10 out of 11 patients assessed for efficacy, three patients demonstrated long-term efficacy with an overall mPFS of 2.0 months and a mOS of 3.1 months.

Pexa-vec (pexastimogene devacirepvec, JX-594) is a cowpox virus genetically modified to express immune-enhancing human granulocyte-macrophage colony-stimulating factor (hGM-CSF). It exerts significant antitumor effects through oncolysis, anti-angiogenesis, immunostimulatory activity, and increased CD8+ T cells.[98] In the clinical setting, Pexa-vec is predominantly used in combination regimens for the treatment of gastrointestinal tumors. Monge et al[99] evaluated the safety and efficacy of Pexa-vec in combination with durvalumab with and without tremelimumab in patients with standard chemotherapy-refractory pMMR mCRC in a phase I/II trial. The results showed good toxicity and tolerability. However, mPFS was only 2.3 months, which was comparable to the results noted with third-line therapies approved for mCRC.[100] A randomized phase III study initiated by Abou-Alfa et al[101] in the same year revealed that Pexa-Vec, in combination with sorafenib, failed to yield increased clinical benefits compared to sorafenib in the treatment of patients with advanced HCC. The results of these two studies suggest that Pexa-vec still faces challenges in the treatment of gastrointestinal tumors, highlighting the need for more rational drug combinations and study design protocols.

To date, OVs have shown promising safety and efficacy in clinical trials involving gastrointestinal tumors, with improvements in their translation to clinical practice. However, based on the findings of ongoing clinical studies (Table 2), most of which are in relatively early stages (phase I/II). Several challenges persist, including host antiviral immunity, OV penetration and spread, patient selection, and optimization of dosage and drug combination strategies. It is hoped that additional OVs will be approved for the treatment of gastrointestinal tumors.

Table 2 Investigational Clinical Studies on OVs in Gastrointestinal Cancers

Target	Phase	Conditions	NCT Number	Status	Study Start
OH2 injection	I/II	Solid Tumor Gastrointestinal cancer	NCT03866525	Recruiting	2019
IDOV-SAFE	I	Advanced Malignant Solid Tumor of Digestive System	NCT06380309	Recruiting	2024
H101+Camrelizumab	II	Advanced Pancreatic Cancer	NCT06196671	Not yet recruiting	2024
LOAd703	I/IIa	Pancreatic Cancer	NCT02705196	Recruiting	2016
Oncolytic virus+Camrelizumab+AG (Gemcitabine +Capecitabine)	Preoperative Therapy	Patients With Borderline Resectable and Locally Advanced Pancreatic Cancer	NCT06346808	Not yet recruiting	2024
OH2 Injection	Ib/II	Pancreatic Cancer	NCT04637698	Terminated	2021
RP2/RP3+Atezolizumab+ bevacizumab	II	Advanced Microsatellite Stable and Mismatch Repair Proficient Colorectal Carcinoma	NCT05733611	Active, not recruiting	2023
OH2 injection administered by transcatheter Intraarterial infusion	I	Advanced hepatocellular carcinoma	NCT05698459	Recruiting	2023
CF33-hNIS or CF33-hNIS+Pembrolizumab	I	Metastatic or Advanced Solid Tumors	NCT05346484	Recruiting	2022
BioTTT001+SOX+ Toripalimab	I	Peritoneal Metastases From Gastric Cancer	NCT06283121	Not yet recruiting	2024
BioTTT001+Toripalimab+ Regorafenib	I	Liver Metastases From Colorectal Cancer	NCT06283134	Not yet recruiting	2024
T3011+Toripalimab+ regorafenib	I	Liver Metastases From Colorectal Cancer	NCT06283303	Not yet recruiting	2024
RP2+Atezolizumab+ bevacizumab	II	Advanced Hepatocellular Carcinoma	NCT05733598	Recruiting	2024
VG161+ Nivolumab	Ib/IIa	Metastatic Gastric Cancer	NCT06008925	Recruiting	2022
VG161+camrelizumab	Ib/IIa	Advanced Primary Hepatocellular Carcinoma	NCT06124001	Not yet recruiting	2023
H101+Tislelizumab+ lenvatinib	Ib	Advanced Pancreatic Cancer	NCT05303090	Recruiting	2022

Cancer Vaccines

With the continuous advancement of medical technology, cancer vaccines, which employ tumor antigen-specific cellular immune responses to target and eliminate tumor cells, have progressively emerged as a new research hotspot in tumor therapy. Cancer vaccines include vaccines targeting DNA or mRNA, virus-like particle vaccines, and peptide vaccines. These different types of cancer vaccines offer new hope for the treatment of gastrointestinal tumors.[102,103]

GNOS-PV02 is a personalized neo-antigenic DNA vaccine that encodes up to 40 patient-specific neoantigens, designed for patients with advanced HCC. In a phase I/II clinical trial,[104] the GNOS-PV02 vaccine, in combination with pembrolizumab, demonstrated favorable efficacy in patients with advanced HCC. Of the 36 patients evaluated, eight patients experienced substantial tumor shrinkage, while three patients experienced complete tumor disappearance, yielding an ORR of 30.6%, which is double the historical ORR for anti-PD-1 monotherapy in HCC.[23,105] In addition, 20 out of 36 patients had effective disease control, with a disease control rate of 55.6%, and experienced only low-grade side effects. The results from this study suggest that the development of a personalized therapeutic cancer vaccine (PTCV) is feasible and can be combined with anti-PD-1 therapy to induce clinical responses in patients with advanced HCC.

Autogene cevumeran is an mRNA-individualized cancer vaccine designed for postoperative adjuvant therapy in patients with PDAC. The vaccine drives de novo synthesis and expansion of CD8 T cells. Eight of the 16 patients in a phase I trial responded positively to the Autogene cevumeran vaccine, with six of them remaining disease-free at an average follow-up of 3 years.[106] The results of this study are promising and are expected to lead to new therapeutic approaches for this patient population with very limited treatment options. Although mRNA cancer vaccines still face challenges in practical application, such as tumor heterogeneity, vaccination routes, and tumor microenvironment, mRNA vaccines are expected to provide more effective options for the treatment of gastrointestinal tumors in the future.[107] Clinical trials on mRNA vaccines are currently underway (Table 3), reflecting the rapid development of mRNA vaccines in the field of gastrointestinal tumor therapy.

Table 3 Investigational Clinical Studies on mRNA Vaccines in Gastrointestinal Cancers

Target	Phase	Conditions	NCT Number	Status	Study Start
Personalized mRNA Tumor Vaccine	Not Applicable	Advanced Esophageal Cancer and Non-small Cell Lung Cancer	NCT03908671	Recruiting	2019
Personalized mRNA Vaccine iNeo-Vac-R01	I	Advanced Digestive System Neoplasms	NCT06019702	Recruiting	2023
iNeo-Vac-R01 in combination with standard adjuvant therapy	I	Advanced Digestive System Neoplasms	NCT06026774	Recruiting	2023
XP-004 Personalized mRNA Tumor Vaccine Combined With PD-1 Inhibitor	I	Postoperative Adjuvant Therapy for Pancreatic Cancer	NCT06496373	Recruiting	2024
Neoantigen mRNA Personalised Cancer vaccine in combination with Stintilimab I injection	Not Applicable	Liver Cancer	NCT05761717	Not yet recruiting	2023
KRAS Neoantigen mRNA Vaccine (ABO2102)	Early Phase I	Participants With KRAS-mutated Advanced Pancreatic Cancer	NCT06577532	Recruiting	2024
HBV mRNA vaccine	I	Patients With HBV-positive Advanced Hepatocellular Carcinoma	NCT05738447	Recruiting	2023
XH001 (Neoantigen Cancer Vaccine) Sequential Combination With Ipilimumab and Chemotherapy	Not Applicable	Resected Pancreatic Cancer	NCT06353646	Recruiting	2024
Neoantigen mRNA Vaccines	I	Resectable Pancreatic Cancer	NCT06326736	Recruiting	2024
Personalized Neoantigen Vaccine	Not Applicable	Advanced Gastric Cancer, Esophageal Cancer and Liver Cancer	NCT05192460	Recruiting	2022
Neoantigen vaccine (IPM511)	Not Applicable	Advanced Hepatocellular Carcinoma	NCT05981066	Recruiting	2023
Personalized Tumor Vaccines mRNA-0217/S001 and Pabolizumab	Early Phase I	Advanced Pancreatic Cancer	NCT05916261	Recruiting	2023

ELI-002 7P is a peptide vaccine against KRAS mutant cancers. In the Phase I AMPLIFY-201 clinical trial, the ELI-002 7P vaccine showed promising potential. Among 20 patients with PDAC and five patients with CRC, 84% of patients developed an immune response. Some patients exhibited stronger responses that may potentially yield superior anti-tumor effects.[108] The ELI-002 2P vaccine has shown great potential and is expected to alter the therapeutic landscape for PDAC and other KRAS-mutant cancers. The vaccine is currently undergoing a phase II clinical trial (NCT05726864). On the other hand, HER-Vaxx (IMU-131) is a B-cell peptide-based vaccine that primarily targets HER2-overexpressing malignancies. In a phase I pilot study, HER-Vaxx was well tolerated and safe in patients with gastroesophageal adenocarcinoma (GEA).[109] A subsequent phase II study showed[110] a 40% OS benefit following the administration of HER-Vaxx in combination with chemotherapeutic agents for the treatment of GEA patients. In this trial, HER-Vaxx not only induced a HER2-specific humoral response but also counteracted immune tolerance, thus contributing to the improved efficacy of SOC chemotherapy in vaccinated gastric cancer patients. Based on existing evidence of equivalent therapeutic efficacy, the proposed vaccination approach could serve as an alternative to trastuzumab therapy in cases where it is unavailable or toxicity occurs. Peptide vaccines in gastrointestinal tumor therapy are undergoing intensive exploration, with a significant increase in the number of ongoing clinical projects in recent years (Table 4), aiming to identify more tumor-specific antigens to aid in controlling cancer progression.

In summary, cancer vaccines are feasible, safe, and immunologically active in gastrointestinal tumors and represent a major breakthrough in the treatment of patients with gastrointestinal tumors. Notably, mRNA vaccines and peptide vaccines have shown promise in the treatment of gastrointestinal tumors and are expected to offer more therapeutic options and hope for patients, potentially prolonging PFS and improving the quality of life of patients.

Challenges and Future Strategies in Immunotherapy

Although immunotherapy has shown great advantages in the development of gastrointestinal tumors, it faces multifaceted challenges that limit its clinical application.

One of the great challenges facing immunotherapy is biomarkers. Although biomarkers such as MSI, DMMR, TMB, and PD-L1 expression are currently available, not all patients benefit from immunotherapy based on these biomarkers. Therefore, new markers are urgently needed. Gastrointestinal tumors are highly heterogeneous tumors involving multiple

Table 4 Investigational Clinical Studies on Peptide Vaccines in Gastrointestinal Cancers

Target	Phase	Conditions	NCT Number	Status	Study Start
Pooled Mutant KRAS-Targeted Long Peptide Vaccine Combined with Nivolumab and Ipilimumab	I	Resected MMR-p Colorectal and Pancreatic Cancer	NCT04117087	Recruiting	2020
Personalized Tumor Neoantigen-based Peptide Vaccine Combined with Conventional Second-line Therapy	Not Applicable	Colorectal Cancer	NCT06751914	Recruiting	2024
Personalized Tumor Neoantigen-based Peptide Vaccine Combined with Conventional Third-line Therapy	Not Applicable	Colorectal Cancer	NCT06751966	Recruiting	2024
DNAJB1-PRKACA Fusion Kinase Peptide Vaccine Combined With Nivolumab and Ipilimumab	I	Fibrolamellar Hepatocellular Carcinoma	NCT04248569	Recruiting	2024
Nivolumab with Ipilimumab Combined with TGFβ-15 Peptide Vaccine	I	Refractory Pancreatic Cancer	NCT05721846	Recruiting	2023
Personalized Peptide Vaccine	I	Advanced Pancreatic Ductal Adenocarcinoma or Colorectal Adenocarcinoma	NCT02600949	Recruiting	2016
Mutant KRAS -Targeted Long Peptide Vaccine	I	Pancreatic Cancer	NCT05013216	Recruiting	2022
Mutant KRAS-Targeted Long Peptide Vaccine Combined With Balstilimab and Botensilimab	I	Stage IV MMR-p Colorectal Cancer and Pancreatic Ductal Adenocarcinoma	NCT06411691	Recruiting	2024
Peptide Vaccine Plus Durvalumab and Tremelimumab	I	Biliary Tract Cancers	NCT06564623	Recruiting	2025
Peptide-based hepatocellular carcinoma vaccine IMA970A Plus Montanide in Combination with Durvalumab	I	Hepatocellular Carcinoma	NCT06218511	Recruiting	2022
DNAJB1-PRKACA Fusion Transcript-based Peptide Vaccine Combined with Immune Checkpoint Inhibition	I	Fibrolamellar Hepatocellular Carcinoma and Other Tumor Entities Carrying the Oncogenic Driver Fusion	NCT05937295	Recruiting	2023

biomarkers. The same immunotherapy responds differently to different patients, leading to the challenge of individual differences in immunotherapy. Current advances in genome sequencing, including technologies such as single-cell sequencing and immune cell identification strategies, hold significant implications for identifying new predictive biomarkers, which will enable accurate selection of patients most likely to benefit from immunotherapy and facilitating personalization of therapies for each patient.[111] Another reason why gastrointestinal patients do not benefit from immunotherapy may be the inefficiency of immune monotherapy, and the effectiveness of combination therapy is to be explored. The process of combination therapy is complex and involves multiple factors such as combination partnering, dosing and dosing regimen, which requires more research and clinical data to optimize.

For novel immunotherapies such as ACTs, OVs and cancer vaccines, the issues and challenges are different from those of immune checkpoint inhibitors. There is a high degree of antigenic heterogeneity in gastrointestinal tumor cells, and different tumor cells may express different antigens, which makes it difficult for ACT to find an antigenic target that can universally recognize and effectively kill all tumor cells, resulting in limited therapeutic efficacy. However, with the development of antigen screening techniques, more methods can be applied to identify and explore novel target antigens in the future, such as whole exome sequencing combined with mass spectrometry, neoantigen screening through inventory-shared neoantigen peptide libraries, and discovery of neoantigens through endocytosis.[112,113] A critical challenge faced by OVs is off-target toxicity. After systemic administration, OVs are prone to accumulate rapidly in the liver, leading to hepatotoxicity. Therefore, it is vital to thoroughly assess potential off-target toxicity during the design and development of oncolytic viruses. One effective approach to address this issue is to minimize toxicity and enhance the tumor-targeting ability of oncolytic viruses to limit the potential for off-target toxicity and improve the safety of oncolytic viruses.[114] The efficacy and applicability of various types of cancer vaccines are limited, and their delivery in a safer and more controlled manner is crucial for maximizing their efficacy. For instance, the use of advanced biomaterials and drug delivery systems, including nanoparticles and exosomes, might enhance their efficacy while concomitantly mitigating toxic side effects.[115–117] A common challenge for novel immunotherapeutic regimens is the complexity of preparation and high cost, making them unaffordable for many patients and limiting their widespread use in the clinic.

Summary

Immunotherapies have opened a new era in the treatment of gastrointestinal cancers, offering renewed hope to patients. With the development of precision medicine technology, exploring biomarkers based on new technologies such as artificial intelligence, histology and high-throughput screening will help improve the precision of immunotherapy. The development of novel immunotherapies such as ACT, OVs and cancer vaccines is expected to bring longer-term survival benefits to patients. However, they also face limitations and challenges. Further research and development are warranted to address these challenges and provide more effective and safe treatment options for patients.

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Disclosure

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