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REVIEW ARTICLE

Research progress on immune checkpoint inhibitors in neoadjuvant therapy for gastric cancer

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Abstract

In recent years, immune checkpoint inhibitors (ICIs) have become an important treatment strategy for advanced gastric cancer. Immunotherapy has gradually transitioned from a later-line to a first-line treatment for advanced gastric cancer. Simultaneously, more and more researchers have begun to pay attention to whether immunotherapy can be used for resectable gastric cancer. The current use of ICIs in the neoadjuvant treatment of gastric cancer is still in its exploratory stage, with a number of clinical trials currently underway. However, the available data show good application prospects. This article reviews the research progress on ICIs in the neoadjuvant therapy for gastric cancer and evokes some unresolved problems.

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Gastric cancer is a common malignant tumor of the digestive system that ranks fifth in cancer incidence and fourth in mortality worldwide [1]. Approximately 44% of gastric cancer cases worldwide occur in China [2]. The China Gastrointestinal Cancer Surgery Union counted the gastric cancer surgery cases in 85 centers across the country from 2014 to 2016 and found that the proportion of locally advanced gastric cancers was as high as 70.8% [3]. The current treatment of resectable gastric cancer is based on clinical stage evaluation, and the importance of comprehensive perioperative treatment has been recognized; however, the perioperative treatment strategy for gastric cancer has not yet reached a global consensus [4–5]. In recent years, immune checkpoint inhibitors (ICIs) have gradually become a research hotspot in tumor immunotherapy. Based on the results of the CheckMate-649 study [6], in April 2021, the US Food and Drug Administration (FDA) approved nivolumab in combination with fluoropyrimidine- and platinum-containing chemotherapeutic drugs as a first-line treatment for patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma. This is the first FDA-approved first-line immunotherapy for gastric cancer. Immunotherapy has transitioned from the later-line treatment of gastric cancer to the first-line treatment and has evolvedas a neoadjuvant therapy. A number of clinical trials on neoadjuvant immunotherapy for gastric cancer are currently underway. This article reviews the research progress of ICIs in neoadjuvant therapy for gastric cancer.

Immune checkpoint inhibitors (ICIs)

Immune checkpoints, including programmed cell death receptor-1 (PD-1), programmed cell death ligand-1 (PD-L1), cytotoxic T lymphocyte-associated molecule-4 (CTLA-4), lymphocyte activation gene 3 (LAG3), and T cell immunoglobulin 3 (TIM3), are a class of molecules expressed on immune cells, antigen-presenting cells, and tumor cells that can regulate immune responses [7]. PD-1/PD-L1 and CTLA-4 inhibitors are the most widely used ICIs in clinical practice. PD-1/PD-L1 and CTLA-4 are negative regulators of T cell immune responses, and their inhibition enhances antitumor immune responses by blocking these factor-mediated immunosuppressive pathways [8].

PD-1 is an inhibitory receptor that is expressed on a variety of immune cells, such as activated T cells, B cells, and natural killer cells [9–10]. When it binds to PD-L1 expressed on tumor cells, it activates an

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immunosuppressive signaling pathway, resulting in tumor immune escape [11]. PD-1/PD-L1 inhibitors relieve the immunosuppression and restore the anti-tumor immune function of T cells by blocking the interaction between PD-1 and PD-L1 [12]. Common PD-1 inhibitors include pembrolizumab, nivolumab, camrelizumab, sintilimab, tislelizumab, and toripalimab. PD-L1 inhibitors include atezolizumab, avelumab, and durvalumab.

CTLA-4 is homologous to the immunostimulatory receptor CD28, but it binds to the CD80 (B7-1) and CD86 (B7-2) ligands expressed on antigen-presenting cells with a higher affinity than CD28. CTLA-4 and CD28 competitively bind to B7 ligands, thereby inhibiting T cell activation [13–15]. CTLA-4 inhibitors specifically bind to CTLA-4 and release T cellinhibition, thereby promoting their proliferation and activation [12, 16]. Tang *et al* proposed that anti-CTLA-4 antibodies exert therapeutic effects by selectively depleting T-regulatory cells in tumors [17]. However, their relevant mechanism of action is still under investigation. CTLA-4 inhibitors include ipilimumab and tremelimumab.

Neoadjuvant immune monotherapy

Nivolumab

A phase I clinical study of neoadjuvant nivolumab monotherapy for resectable gastric cancer was reported at the 2021 American Society of Clinical Oncology (ASCO) annual meeting [18]. A total of 31 patients received two cycles of neoadjuvant therapy, of which one discontinued the trial preoperatively due to disease progression. The remaining 30 patients underwent surgery, of which five (16.7%) achieved major pathological response (MPR), including one (3.3%) pathological complete response (pCR). Among seven patients with microsatellite instability-high (MSI-H), four (57.1%) achieved MPR (including one pCR). Treatment-related adverse events (TRAEs) occurred in seven patients (22.6%); one patient had grade 3 asymptomatic lipase elevation, and the rest developed grade 1–2 TRAEs. The results of the study showed that nivolumab is feasible and safe for neoadjuvant treatment of gastric cancer. However, because one patient had disease progression before surgery, the efficacy of immune monotherapy needs further validation.

Pembrolizumab

The 2021 ASCO annual meeting announced the results of an interim study on pre- and postoperative pembrolizumab and adjuvant chemoradiotherapy in patients with MSI-H, Epstein-Barr virus-positive, or PD-L1-positive locally advanced gastric cancer (NCT03257163) [19]. Of the 15 patients enrolled in the study, six had MSI-H status and two did not undergo surgical resection because they were considered too frail and were found to have peritoneal disease on exploration. Of the 13 patients that completed the operation, two (15.4%) MSI-H patients achieved pCR, five patients had downstaged clinical T stage, and two patients had downstaged clinical N stage. No recurrence was observed in the short-term follow-up (1–22 months). The incidence of specific adverse events was not disclosed.

It is worth noting that the patients who achieved pCR in the above two studies had an MSI-H status, and immunotherapy generally has a positive effect on MSI-H patients. Zhang *et al* reported a retrospective study of six patients with MSI-H gastrointestinal tumors [20], including four with gastric cancer and two with colorectal cancer. Two patients switched to immunotherapy after chemotherapy failure and were treated with nivolumab monotherapy and sintilimab combined with bevacizumab, respectively; three patients received ICIs combined with chemotherapy; and one patient received nivolumab combined with ipilimumab. Of these patients, five achieved pCR and one achieved clinical TNM downstaging after surgery. No grade 3–4 TRAES or surgery-related complications occurred. The median follow-up time was 10.5 (7–18) months after surgery, and no recurrence or long-term complications were reported. These data suggest the potential of MSI-H as a predictive marker for the efficacy of neoadjuvant therapy for gastric cancer.

Neoadjuvant immunotherapy combined with chemotherapy

Sintilimab in combination with chemotherapy

In 2021, the ASCO Gastrointestinal Cancers Symposium (ASCO-GI) reported a phase II clinical study on sintilimab combined with FLOT regimen (docetaxel + oxaliplatin + fluorouracil + leucovorin) as the neoadjuvant treatment of gastric or gastroesophageal junction adenocarcinoma (NCT04341857) [21]. The enrolled patients received four cycles of FLOT chemotherapy combined with three cycles of sintilimab before surgery and four cycles of FLOT chemotherapy after surgery. Seventeen patients underwent surgery with a pCR rate of 17.6% and an MPR rate of 58.8%. Grade 3–4 TRAEs included anemia (20%), leukopenia (10%), and abnormal liver function (5%). In the FLOT4-AIO study [22], the pCR and MPR rates following perioperative FLOT regimen chemotherapy were 16% and 37%, respectively. Therefore, compared with the FLOT4-AIO study, the combination of sintilimab and FLOT chemotherapy used in the NCT04341857 study improved the pCR rate and MPR rate, especially the MPR rate increased by 21.8%. The current survival rate of this study is still in the follow-up stage, and the efficacy and safety of the regimen need to be further confirmed.

A phase II clinical study of sintilimab combined

with oxaliplatin/capecitabine (CapeOx) as the neoadjuvant treatment of locally advanced resectable gastric/gastroesophageal junction adenocarcinoma was reported at the 2021 ASCO-GI [23]. The patients received three cycles of sintilimab combined with CapeOx regimen neoadjuvant therapy before surgery and three cycles of CapeOx regimen adjuvant chemotherapy postoperatively. Twenty-five patients completed three cycles of neoadjuvant therapy, one patient completed only 2 cycles due to grade 3 aspartate aminotransferase elevation, and 26 patients underwent surgery. The pCR and MPR rates were 23.1% and 53.8%, respectively. To assess the validity of positron emission tomography and computed tomography (PET-CT) evaluation, 18 patients underwent PET-CT scanning; of which, 11 patients (61.1%) showed partial metabolic remission. Six patients (23.1%) had grade 3 neoadjuvant TRAEs, including neutropenia, leukopenia, and thrombocytopenia. One patient developed hypothyroidism as agrade 1 immune-related adverse event (irAE). The pCR and MPR rates of this regimen exceeded the results of the study on sintilimab/FLOT combination and the safety was acceptable. However, whether PET-CT can better predict the response to focal immunotherapy remains to be explored [24–25].

Camrelizumab in combination with chemotherapy

The ChiCTR2000030610 study was a single-center, randomized, controlled clinical study evaluating FLOT chemotherapy combined with camrelizumab as a neoadjuvant therapy [26]. Twenty-four patients with locally advanced gastric and gastroesophageal junction adenocarcinoma were randomly divided into a FLOT (arm A) and a FLOT/camrelizumab (arm B) groups. Nineteen patients completed four cycles of neoadjuvant therapy and 17 underwent surgery. The R0 resection rate in arm B (100%) was higher than that in arm A (71.4%). In terms of tumor regression and lymph node downstaging, 10% and 60% of patients in arm B achieved TRG1 and ypN0, respectively, whereas no such observations were reported in arm A. No pCR was observed in either group; this may be related to the small number of enrolled patients, and the efficacy and safety of this regiment need to be further explored.

The 2021 ASCO meeting updated the results of a study on camrelizumab combined with FOLFOX regimen (oxaliplatin + fluorouracil + leucovorin) for the neoadjuvant treatment of resectable locally advanced gastric and gastroesophageal junction adenocarcinoma [27]. Of the 60 enrolled patients that received four cycles of neoadjuvant therapy, one was assessed for disease progression, three refused surgery, and four were found to have intra-abdominal metastases during surgery. The 52 surgically resected patients had pCR and MPR rates of 10% and 31%, respectively. Grade 3–4 TRAEs included leukopenia (17%). One patient had grade 3 irAEs (increased alanine and aspartate aminotransferases). The neoadjuvant combination of camrelizumab and FOLFOX is a safe and effective treatment option for patients with gastric or gastroesophageal junction adenocarcinomas.

Avelumab in combination with chemotherapy

The ICONIC study was a phase II clinical study of perioperative FLOT chemotherapy combined with avelumab for the treatment of resectable esophagogastric adenocarcinoma, and its interim safety results were announced at the 2021 ASCO-GI [28]. Of the 15 enrolled patients, two switched to alternative chemotherapy due to 5-fluorouracil cardiac toxicity. All patients underwent R0 resections. Grade 3–4 adverse events occurred in 9 patients (60%) and included neutropenia and diarrhea. Three patients developed Clavien-Dindo grade IIIa postoperative complications.

A phase II clinical trial of perioperative chemotherapy combined with avelumab in the treatment of locally advanced gastric and esophageal adenocarcinoma was reported at the 2021 ASCO Annual Meeting [29]. The patients were administered 4 cycles of avelumab and mDCF regimen (docetaxel + cisplatin + fluorouracil) before and after surgery. Surgery was completed in 27 patients, with MPR and pCR rates of 22% and 11%, respectively. Toxicity events included grade 4 neutropenia (two cases), pneumonia (one case), grade 3 stomatitis (two cases), and diarrhea (one case). The 12- and 24-month disease-free survival rates were 92% (95% CI: 0.83–1.00) and 77% (95% CI: 0.58–1.00), respectively. The combination of mDCF chemotherapy with avelumab showed promising safety and efficacy.

Atezolizumab in combination with chemotherapy

The DANTE study was a multicenter, phase IIb clinical study [30]. The 295 enrolled patients with resectable gastric or gastroesophageal junction adenocarcinoma were randomly divided into two groups: arm A received four cycles of FLOT/atezolizumab combination before surgery, followed by four cycles of FLOT/atezolizumab combination and eight cycles of atezolizumab; arm B received 4 cycles of FLOT chemotherapy before and after surgery. Twenty-three patients exhibited deficient mismatch repair (dMMR), and their pCR rate (47.8%) was higher than that of proficient mismatch repair (pMMR) patients (21.2%). Among dMMR patients, pCR and MPR rates were also higher in arm A (60% and 80%, respectively) than in arm B (38.5% and 53.9%, respectively). The data from the DANTE study once again demonstrated the favorable therapeutic effects of

immunotherapy in patients with MSI-H gastric cancer. Additionally, comparison of this study with the two aforementioned clinical trials on immune monotherapy revealed that atezolizumab combined with chemotherapy results in the highest pCR and MPR rates in patients with MSI-H gastric cancer.

Toripalimab in combination with chemotherapy

The Gastrim 001 study was a single-arm phase II clinical trial that assessed the effects of toripalimab/chemotherapy combination in patients with locally advanced resectable gastric/gastroesophageal junction adenocarcinoma [31]. The treatment plan consisted of four cycles of toripalimab combined with FLOT chemotherapy before and after surgery. Thirty-six patients were included, of which 28 had completed the surgery. The pCR and the MPR rates were 25% and 42.9%, respectively, higher than those of the FLOT4-AIO study. In terms of safety, eight patients developed Clavien-Dindo grade II postoperative complications and two had grade IIIa complications. Grade 3–4 adverse events included neutropenia (30.6%), leukopenia (25.0%), and anemia (5.6%). Among the three clinical studies using immunization combined with FLOT chemotherapy as the treatment plan, the most effective treatment was toripalizumab, followed by sintilimab and camrelizumab. The DANTE study was not included in this comparison because it analyzed patients according to dMMR and pMMR groups. Toripalimab combined with FLOT chemotherapy has high pCR and MPR rates, with good tolerability and safety.

Neoadjuvant immunotherapy combined with chemotherapy and targeted therapy

The 2021 ASCO Annual Meeting reported a phase II clinical study on camrelizumab, apatinib, and S-1 ± oxaliplatin in neoadjuvant/conversion therapy for gastric cancer treatment (cT4a/bN+M0) [32]. Twenty-five patients received at least two cycles of neoadjuvant therapy before surgery. Twenty-four patients completed the reassessment, and the tumor downstaging rate was 79.2%. Conversion failed in three cases and surgery was refused in two cases and postponed in one case because of immune-related pneumonia. Among the 18 patients who underwent R0 resection, the pCR and MPR rates were 16.7% and 27.8%, respectively. No TRAEs of grade 3 or higher were found.

Lin *et al* [33] and Zheng *et al* [34] conducted a study of S-1/oxaliplatin combined with apatinib (SOXA) as the neoadjuvant therapy for locally advanced gastric cancer, with pCR rates of 6.3% and 13.7%, respectively. However, camrelizumab, apatinib, and S-1 ± oxaliplatin neoadjuvant/conversion therapy for gastric cancer treatment (cT4a/bN+M0) achieved a higher pCR rate (16.7%) than those reported in the previous studies, suggesting that neoadjuvant immunetherapy combined with chemotherapy and antiangiogenic drugs may have a synergistic effect [35]. Preliminary results indicated that the treatment regimen is effective and safe. The multicenter phase II–III clinical trial DRAGON-IV/Ahead-G208 study on SOXA and camrelizumab for the perioperative treatment of resectable locally advanced gastric or esophagogastric junction adenocarcinoma is also underway, and we look forward to the results.

Neoadjuvant immunotherapy combined with chemoradiotherapy

Sintilimab in combination with chemoradiotherapy

The SHARED study was designed to evaluate the efficacy and safety of perioperative sintilimab combined with concurrent chemoradiotherapy (S-1 + Nab-PTX) for the treatment of locally advanced gastric or gastroesophageal junction adenocarcinoma [36]. Gastrectomy was completed in 19 patients, with pCR and MPR rates of 42.1% and 73.7%, respectively. Eleven (39.3%) patients had grade 3–4 TRAEs, including myelosuppression (39.3%) and increased transaminase levels (10.7%). The incidence of irAEs was 21.4%; these included one case of grade 4 hepatitis; the remaining irAEs were grade 1–2. Perioperative complications occurred in three patients. Despite the small sample size, the results of the SHARED study are encouraging. The final results of this study will be available once the follow-up of patients is completeand the survival data are reported.

Camrelizumab in combination with chemoradiotherapy

The Neo-PLANET study was a phase II clinical study on neoadjuvant camrelizumab combined with chemoradiotherapy (oxaliplatin + capecitabine) for the treatment of locally advanced proximal gastric cancer [37]. Of the 36 enrolled patients, 33 were subjected to radical surgery; three patients were excluded from surgery because of liver metastasis, peritoneal metastasis, and surgery refusal. The pCR and MPR rates were 33.3% and 44.4%, respectively. Twenty-nine patients (80.56%) had grade 3–4 adverse events, including decreased lymphocyte count (75%) and leukopenia (5.6%). From the above-mentioned clinical studies, the efficacy of this regimen is second only to that obtained by sintilimab combined with concurrent chemoradiotherapy. However, the Neo-PLANET study had a high rate of grade 3–4 adverse events that required close monitoring.

Efficacy and safety

At present, the administration of ICIs in the perioperative period of gastric cancer is still being explored. Theoretically, due to the presence of the preoperative primary tumor, high levels of endogenous tumor antigens are present in the patient's body and can be presented to tumor-specific T cells by dendritic cells; these activated tumor-specific T cells can enter the blood circulation to act on metastatic lesions and enhance systemic anti-tumor immunity [38]. These effects may persist even after surgical resection of the primary tumor and regional lymph nodes. The long-term immune memory generated preoperatively may be superior to that induced by postoperative adjuvant therapy, thereby reducing the risk of recurrence [39]. Neoadjuvant therapy can increase the strength, breadth, and durability of tumor-specific T-cell responses compared with adjuvant therapy, which primarily targets micrometastases or residual lesions after resection [40]. A preclinical study also confirmed that neoadjuvant therapy, compared with adjuvant immunotherapy, can improve efficacy [41].

Owing to the different clinical characteristics and treatment plans of the patients enrolled in each clinical trial, the reported therapeutic effects also differ. Based on the existing studies, the efficacy of immune combination therapy is better than that of immune monotherapy and the combination of immune therapy and chemoradiotherapy has the best efficacy. Several previous studies have explored the application of neoadjuvant chemoradiotherapy in gastric cancer [42–46]. For example, the POET study included patients with locally advanced gastroesophageal junction adenocarcinoma and showed that neoadjuvant chemoradiation could significantly improve the pCR rate compared with neoadjuvant chemotherapy (15.6% *vs.* 2.0%) [42]. However, because most studies on neoadjuvant chemoradiation focus on gastroesophageal junction cancer, their validity for gastric corpus and distal gastric cancer is limited. The impressive pCR rate of 42.1% in the SHARED study is a significant improvement over the pCR rates in the RTOG 9904 (neoadjuvant chemoradiotherapy) and FLOT4-AIO studies (26% and 16%, respectively) [22, 44]. Whether the high pCR rate of neoadjuvant immunotherapy combined with chemoradiotherapy can be translated into long-term survival benefit is worth looking forward to. It is also worth noting that the results of some of the above clinical trials are not better than those on neoadjuvant chemo- and radiochemotherapy, possibly due to the small number of patients included. Additionally, whether the combination therapy can exert a synergistic effect needs to be determined in afollow-up with a large sample size. Owing to the lack of data on CTLA-4 inhibitors and dual immune combination therapy in clinical practice, it remains to be determinedwhether better treatments will be developed in the future.

A number of clinical trials have also analyzed MSI-H patients, and the results have shown that these patients can achieve high pCR rates regardless of whether they receive immune monotherapy or combination therapy. Increasing evidence suggests that patients with MSI-H gastric cancer do not benefit from neoadjuvant chemotherapy [47–48]. Neoadjuvant immunotherapy may provide a new treatment option for these patients. However, the proportion of the MSI-H/dMMR population among gastric cancer patients is only 8%–10% [20], and MSI-H alone as the selection criterion for the appropriate population is limited. Therefore, the active search for markers or targets is critical for the precise treatment of gastric cancer. In recent years, the perioperative treatment of human epidermal growth factor receptor 2 (HER2)-positive gastric cancer has also attracted attention. Trastuzumab is a targeted therapy drug that specifically acts on HER2. The HER-FLOT study evaluated the administration of trastuzumab in combination with FLOT chemotherapy for the perioperative treatment of patients with HER2-positive gastric or esophagogastric junction adenocarcinomaand reported a pCR rate of 21.4% [49]. This phase II clinical trial confirmed the feasibility and effectiveness of trastuzumab combined with chemotherapy. However, there are currently no data on the application of immune combined anti-HER2 therapy in the perioperative period of HER2-positive gastric cancer. The KEYNOTE-811 study explored trastuzumab and chemotherapy combined with pembrolizumab as the first-line treatment for HER2-positive gastric or gastroesophageal junction cancer. The objective response rate was 74.4% (95% CI: 66.2–81.6) in the combined pembrolizumab group and 51.9% (95% CI: 43.0–60.7) in the control group; the incidence of adverse events was similar in both groups [50]. The high objective response rate of the KEYNOTE-811 study suggests that this treatment strategy has great potential for further development for the perioperative treatment of HER2-positive gastric cancer. Currently, most clinical trials use the clinical stage of patients as the main inclusion criteria. With the increasing understanding of the molecular typing of gastric cancer, the combination of MSI-H and other markers as inclusion criteria may more accurately screen the dominant population and improve the efficacy. It may also provide ideas for the design of clinical studies. Finally, in the NCT03257163 study, one patient was too frail to undergo surgery. Poor nutritional status increases the incidence of postoperative complications and affects the prognosis of patients with gastric cancer [51–52]. Therefore, clinically, the nutritional status of patients should be actively evaluated and nutritional support treatment should be provided accordingly.

In terms of safety, the most commonly observed grade 3–4 adverse reactions were chemotherapy-related bone marrow suppression and gastrointestinal reactions. Based on the available studies, the incidence of postoperative complications and irAEs is low, and the overall safety is acceptable. It is worth noting that although neoadjuvant immunotherapy combined with chemoradiotherapy achieved an outstanding efficacy, the incidence of adverse reactions also significantly increased. The incidences of irAEs in the SHARED study and grade 3–4 adverse events in the Neo-PLANET study were 21.4% and 80.56%, respectively. In addition, patients may need to delay surgery or suspend the follow-up treatment because of the disease progression or irAEs after neoadjuvant therapy. Researchers should carefully consider these potential risks in clinical practice and choose a treatment plan with a high disease control rate and safety to improve efficacy while minimizing adverse reactions. As most of the currently available data comes from phase II clinical trials with small samples and research is still in progress, the evidence is not yet strong and further data accumulation and evaluation are needed. The available data show the development prospects of ICIs as the neoadjuvant therapy of gastric cancer. We look forward to updating these data on efficacy, safety, postoperative recurrence and metastasis, and survival in the future multicenter, large-sample, and long-term follow-up phase III clinical trials. The ongoing phase III clinical trials of ICIs for the neoadjuvant treatment of gastric cancer are shown in Table 1.

Problems to be addressed

The exploration of biomarkers

Immunotherapy is not beneficial for all patients. To prevent disease progression due to unfavorable treatment plans or serious adverse reactions, it is crucial to find biomarkers that accurately screen beneficiaries. Currently, there are no clear biomarkers for neoadjuvant immunotherapy for gastric cancer. Potential predictive markers found in immunotherapy studies for advanced gastric cancer include PD-L1, tumor mutational burden, MSI-H, Epstein-Barr virus-positive, and gut microbiota [53]. Whether these can be used in the perioperative treatment of gastric cancer remains to be verified. We look forward to the identification of reliable biomarkers and multiple indicators that may help identify dominant populations, guide treatment, predict efficacy, and monitor prognosis.

Best treatment strategy

Several factors must be considered and optimized when establishing a treatment plan: the treatment mode; the dose, sequence, cycle, and interval of neoadjuvant therapy; the potential negative effects of neoadjuvant immunotherapy on surgery prospects; the need of adjuvant therapy after surgery; the adjuvant therapy regimen and timing of administration; the survival benefit of neoadjuvant or adjuvant immunotherapy; and the compromise between efficacy and safety. These factors still remain unresolved.

Choice of the surgery timing

The optimal timing for surgery after neoadjuvant chemotherapy in patients with gastric cancer is still controversial [54–56]. A preclinical study, where a mouse model of breast cancer received immunotherapy before surgery, showed that different surgical intervals after neoadjuvant therapy affect survival [57]. Exploring the optimal duration of immunotherapy action may help determine the timing of surgery.

Endpoints of clinical trials

Overall survival is the generally accepted gold standard to measure the benefit of a treatment. However, determining the overall survival requires an extended

Table 1 Ongoing phase III clinical trials on immune checkpoint inhibitors as a neoadjuvant treatment of gastric cancer

ClinicalTrials.gov Identifier	Phase	Cases	Treatment method	Primary outcome	Estimated primary completion date
NCT04882241	III	120	pembrolizumab + chemotherapy	EFS, pCR rate, OS, The percentage of participants who experience at least one AE, The percentage of participants who discontinue study treatment due to an AE	2025.10.31
NCT03221426	III	1007	pembrolizumab + chemotherapy	EFS, pCRrate, OS, The percentage of participants who experience at least one AE, The percentage of participants who discontinue study treatment due to an AE	2024.06.28
NCT04208347	II/III	258	camrelizumab + apatinib + chemotherapy	MPR	2021.07
NCT04592913	III	900	durvalumab + chemotherapy	EFS	2025.02.14
NCT04139135	III	642	HLX10 + chemotherapy	3-year EFS rate	2023.10.15

Note: AE, adverse events; EFS, event-free survival; MPR, major pathological response; OS, overall survival; pCR, pathological complete response

follow-up, which increases the trial costs [58]. Scholars have suggested MPR as a surrogate endpoint in studies related to neoadjuvant chemotherapy in resectable lung cancer [59]. Most studies on neoadjuvant immunotherapy now use MPR or pCR as the primary endpoint; however, their prognostic value is inconclusive. At present, survival data are still being followed up. The relationship between pathological remission and remission degree and long-term survival, as well as whether there are other surrogate endpoints, such as the lymph node status, remains to be determined [60–61].

Efficacy assessment

Previous studies have reported that patients who received neoadjuvant immunotherapy showed tumor enlargement on preoperative imaging, but postoperative pathological evaluation was based on the pCR or MPR [62]. This discrepancy between imaging and pathological evaluations is a pseudoprogression, a phenomenon that may result from transient immune cell infiltration in the tumor bed [63]. Hyperprogression, another specific immune response pattern characterized by accelerated disease progression and shortened survival, is also of concern [64]. Failure to correctly identify pseudo- and hyperprogression in a timely manner may result in delayed surgery or even loss of the opportunity for surgical resection. With the continuous improvement of the efficacy evaluation criteria, researchers have developed a number of response evaluation criteria in solid tumors (RECISTs) for immunotherapy, such as the immune-related RECIST (irRECIST), immune-modified RECIST (imRECIST), and immune RECIST (iRECIST). However, these new criteria cannot assess hyperprogression, and it is unclear whether they should be used in clinical practice [65]. Additional efficacy assessment tools are also being explored, such as circulating tumor DNA [66] and PET-CT [67–69].

Some scholars have also explored the pathological evaluation standard and proposed immune-related pathologic response criteria for the immunotherapy of non-small cell lung cancer; these have been extended to multiple tumor types and need to be further verified and standardized [70–71].

Epilogue

ICIs have shown promising potential in the neoadjuvant therapy for gastric cancer, especially neoadjuvant immunotherapy combined with chemoradiotherapy. However, questions such as the optimal treatment strategy and the timing of surgery remain to be answered, and the current survival data are immature. Thus, more large-scale clinical trials are still needed. In addition, because gastric cancer is a highly heterogeneous tumor, a future development trend will be the search for reliable biomarkers to screen beneficial populations, formulate personalized targeted treatment plans, and achieve precise treatment.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Author contributions

All authors contributed to data acquisitionand interpretation, and reviewed and approved the final version of this manuscript.

Data availability statement

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Ethical approval

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