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REVIEW

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Applications and challenges of immunotherapy in the management of gastric adenocarcinoma: current status and future perspectives

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Abstract

Gastric adenocarcinoma (GAC) remains a significant global public health challenge, characterized by high incidence and mortality rates. Progress in tumor immunology has introduced immune checkpoint inhibitors (ICIs) targeting the programmed cell death-1 (PD-1)/programmed cell death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) pathways, demonstrating substantial potential in GAC therapy. Clinical research indicates that ICIs, particularly when combined with chemotherapy or targeted therapies, significantly enhance treatment efficacy in advanced GAC and specific molecular subtypes, including microsatellite instability-high (MSI-H) and human epidermal growth factor receptor 2 (HER2)-positive patients. However, immunotherapy is also associated with a range of immune-related adverse events (irAEs), necessitating effective management strategies to ensure treatment safety and maintain patients' quality of life. Future studies should focus on identifying new therapeutic targets, optimizing patient selection, and developing personalized treatment approaches to further improve the efficacy and safety of immunotherapy in GAC.

Keywords Gastric adenocarcinoma, Immunotherapy, Immune checkpoint inhibitors, PD-1/PD-L1, CTLA-4, Immune evasion, Personalized treatment

Background

Gastric adenocarcinoma (GAC) remains a significant public health challenge worldwide. According to incidence statistics, GAC ranks as the fifth most common cancer globally and the third leading cause of cancer-related deaths [1]. Its incidence shows marked geographic variation, with higher rates in Asia, South America, Central America, and Eastern Europe, while lower rates are observed in Western Europe, North America, Africa, and Australia [2]. However, given the large populations in these regions, the absolute number of cases remains substantial. Notably, the incidence of GAC has been rising in South America in recent years, with a growing proportion of younger patients [2]. In the United States, the lack

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of standardized early screening and preventive measures means that many patients are diagnosed at an advanced, unresectable stage, resulting in an overall five-year relative survival rate of only 36.4% [3]. These realities underscore the inadequacy of current treatment strategies in improving patient outcomes, highlighting the urgent need for more effective therapeutic approaches.

In recent years, large-scale molecular studies have provided a more detailed framework for GAC classification. Based on molecular characteristics, The Cancer Genome Atlas (TCGA) has categorized GAC into four subtypes: Epstein-Barr virus (EBV)-positive, microsatellite instability-high (MSI-H), genomically stable (GS), and chromosomal instability (CIN) [4, 5]. This classification has laid a critical foundation for personalized precision medicine and novel drug development, as different subtypes exhibit distinct responses to immune checkpoint inhibitors (ICIs). MSI-H tumors are characterized by high tumor mutational burden (TMB) and increased neoantigen expression, leading to enhanced immune cell infiltration and favorable responses to PD-1/PD-L1 inhibitors. EBV-positive GAC exhibits high PD-L1 expression in both tumor and immune cells, along with a strong immune cell presence, suggesting increased sensitivity to ICIs. In contrast, CIN and GS subtypes tend to have lower immunogenicity and an immunosuppressive tumor microenvironment, resulting in reduced ICI efficacy [6]. Helicobacter pylori (H. pylori) infection, a major risk factor for gastric cancer, plays a complex role in tumor immune modulation. While chronic H. pylori infection induces persistent inflammation, it paradoxically promotes an immunosuppressive tumor microenvironment by enhancing TGF-β and IL-10 secretion, recruiting regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), and suppressing T cell activation [7]. These immune evasion mechanisms may contribute to reduced efficacy of immune checkpoint inhibitors. Although chronic inflammation theoretically increases tumor antigen presentation, studies suggest that H. pylori-associated immune suppression dampens anti-tumor immune responses [8]. The impact of H. pylori eradication on ICI efficacy remains an area of active investigation. Additionally, risk factors such as alcohol consumption, smoking, insufficient intake of fruits and vegetables, and various hereditary susceptibility syndromes (e.g., hereditary diffuse gastric cancer and Lynch syndrome) are commonly associated with GAC [9]. These factors vary in significance across different molecular subtypes, further emphasizing the need for more tailored therapeutic strategies. With an increasing understanding of molecular subtypes and risk factors, the field of personalized precision therapy for GAC is advancing rapidly.

In terms of traditional treatments, although radical surgery combined with chemotherapy and radiotherapy has improved outcomes for some patients, the overall efficacy remains limited. Recent advances in tumor immunology have brought new hope to GAC treatment [10]. The use of immune checkpoint inhibitors (ICIs) has not only provided additional survival benefits for patients with advanced disease but also inspired combination strategies targeting early-stage or resectable tumors [11]. In this context, this review focuses on the current status and cutting-edge developments in immunotherapy for GAC, as well as emerging therapeutic targets and future research directions.

Immunological basis and immune evasion mechanisms in gastric cancer

The development and progression of gastric adenocarcinoma are driven not only by intrinsic molecular changes in tumor cells but also by the influence of the surrounding immune microenvironment. The immune microenvironment of GAC comprises various immune cells, cytokines, and stromal components, primarily including tumor-infiltrating lymphocytes (TILs) and tumor-associated macrophages (TAMs) [12, 13]. TILs consist mainly of $CD4^+$ helper T cells, $CD8^+$ cytotoxic T cells, and regulatory T cells (Tregs) [14]. Their quantity and activation status are generally positively correlated with patient prognosis, indicating that an active immune response helps suppress tumor progression [15]. TAMs can be categorized into M1 and M2 phenotypes based on their polarization status; M1 macrophages exhibit anti-tumor activity, while M2 macrophages tend to promote tumor growth and suppress effective immune responses [16].

Gastric cancer can be broadly classified into "hot tumors" and "cold tumors" based on the degree of immune cell infiltration and tumor antigenicity [17]. Hot tumors are typically rich in active immune cell infiltration and respond well to immunotherapy. In contrast, cold tumors lack effective immune cell infiltration, exhibit a high degree of immune suppression, and generally show poor responses to current immunotherapy approaches [18, 19].

Several inhibitory co-stimulatory pathways play a "braking" role in immune regulation in gastric cancer, with the PD-1/PD-L1 and CTLA-4 pathways being the most critical [20]. Programmed cell death protein-1 (PD-1) and its ligand PD-L1 are important in gastric cancer immune regulation [21, 22]. When PD-L1 on tumor or immune cells binds to PD-1 on T cells, it activates an immunosuppressive signaling pathway, inhibiting T cell proliferation and activation, thereby reducing the immune system's ability to attack the tumor [23]. Immune checkpoint inhibitors (ICIs) that block PD-1/

PD-L1 interactions can reactivate T cells and enhance anti-tumor immune responses.

Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) primarily functions as a negative regulator during the early stages of T cell activation [24]. When B7 molecules on antigen-presenting cells bind to CTLA-4 on T cells, this interaction blocks the co-stimulatory interaction between B7 and CD28, limiting T cell proliferation and activation [25]. Recently, novel checkpoint molecules such as lymphocyte-activation gene 3 (LAG-3) [26], T cell immunoglobulin and mucin-domain containing-3 (TIM-3) [27], and T cell immunoreceptor with Ig and ITIM domains (TIGIT) have garnered increasing attention [28]. These molecules often work synergistically or complementarily with PD-1 and CTLA-4. Combining multiple checkpoint blockade strategies offers potential breakthroughs for patients with resistance or limited efficacy to existing treatments.

Gastric cancer cells employ various mechanisms to interact with their surrounding microenvironment, successfully evading immune surveillance and elimination. Firstly, gastric cancer cells can upregulate PD-L1 expression at the genetic or epigenetic level, broadly suppressing T cell function and weakening the body's anti-tumor immune response [29]. Secondly, the tumor microenvironment contains multiple suppressive cell types, such as regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and M2 macrophages. These cells secrete inhibitory factors such as TGF-β and IL-10, which suppress effector T cell proliferation and activation, forming an immunosuppressive network that facilitates immune evasion [30] (Fig. 1).

Furthermore, *Helicobacter pylori* infection induces chronic inflammation, alters the gastric mucosal immune microenvironment, and promotes the expression of inhibitory molecules like PD-L1 on epithelial and immune cells, further suppressing immune responses and enhancing tumor immune evasion [31]. The Epstein-Barr virus (EBV)-positive subtype of gastric cancer is often associated with high levels of immune cell infiltration [32]. Despite its high immunogenicity, interactions between the EBV genome and host cells induce epigenetic abnormalities, impacting the expression and function of immune-related genes. This complex regulatory mechanism can activate some immune responses while simultaneously suppressing effective tumor antigen presentation through chromatin remodeling and altered DNA methylation patterns, promoting immune evasion by tumor cells [33].

In conclusion, the immune microenvironment and immune evasion mechanisms in gastric cancer are intricately intertwined, presenting significant molecular and cellular complexity. A deeper understanding of these

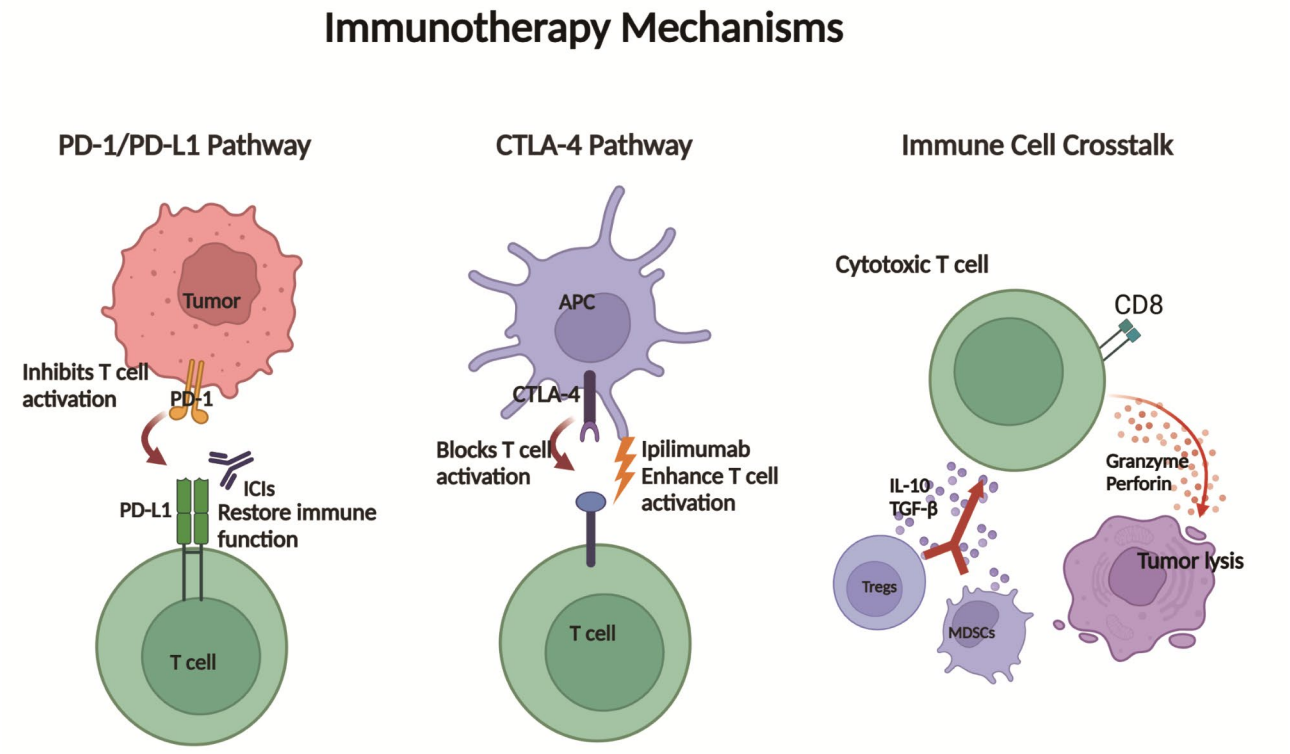

Fig. 1 The key immune regulatory pathways and interactions in the tumor microenvironment

mechanisms is crucial for developing more precise and effective therapeutic strategies.

Clinical application of ICIs in gastric cancer

PD-1/PD-L1 inhibitors

In recent years, the use of immune checkpoint inhibitors (ICIs) in treating gastric cancer has made significant strides, particularly with PD-1/PD-L1 inhibitors. Current research primarily focuses on monotherapy and first-line combination with chemotherapy. For monotherapy, pembrolizumab has shown promise in early clinical trials for advanced gastric cancer. In the Phase I KEYNOTE-012 study [34], 36 patients with PD-L1 positive advanced gastric cancer were treated with pembrolizumab, resulting in a 22% partial response rate, indicating initial activity in third-line and beyond settings. The subsequent Phase II KEYNOTE-059 [35] study reinforced these findings, reporting an objective response rate of 11.6%, a median progression-free survival of 2 months, and a median overall survival of 5.6 months in the third-line and beyond cohort (Cohort 1). Based on these results, the U.S. Food and Drug Administration (FDA) approved pembrolizumab in September 2017 for third-line treatment of patients with PD-L1 combined positive score (CPS) ≥ 1 locally advanced or metastatic gastric or gastroesophageal junction cancer (GC/GEJC). However, in the second-line KEYNOTE-061 study [36], pembrolizumab did not significantly outperform traditional chemotherapy in PD-L1 positive patients, suggesting variable efficacy depending on the treatment stage.

Nivolumab's efficacy as a third-line treatment in Asian populations was confirmed by the ATTRACTION-2 study [37]. This trial demonstrated a median overall survival (OS) of 5.26 months for the nivolumab group compared to 4.14 months for the placebo group, with a hazard ratio (HR) of 0.63. Additionally, the three-year OS rates reported at the 2020 ASCO-GI meeting were 5.6% versus 1.9% [38]. These findings led to the approval of nivolumab in Japan for third-line treatment of gastric cancer, showing particularly notable benefits in patients who had undergone at least four prior treatments.

In contrast, the JAVELIN Gastric 100 trial evaluated avelumab as maintenance therapy following first-line oxaliplatin/fluoropyrimidine chemotherapy [39]. The results indicated that avelumab maintenance did not significantly improve OS in the overall population or the PD-L1 tumor proportion score (TPS) ≥ 1 subgroup, although an exploratory analysis suggested a trend towards OS improvement in patients with PD-L1 CPS ≥ 1. This implies that single-agent PD-L1 inhibitors might have limited effectiveness as maintenance therapy, highlighting the need for further research to refine treatment strategies (Table 1).

Overall, PD-1/PD-L1 inhibitors have shown clinical activity in advanced gastric cancer, especially in later lines of treatment. However, their effectiveness is influenced by factors such as PD-L1 expression levels and molecular subtypes, driving the exploration of more combination-based treatment approaches. Recent studies have highlighted the critical role of post-translational modifications (PTMs) in regulating PD-L1 stability and function in tumor cells, particularly palmitoylation. For instance, PD-L1 palmitoylation mediated by DHHC3 suppresses its mono-ubiquitination and subsequent lysosomal degradation, thereby promoting tumor immune evasion [40]. In gastric cancer, Helicobacter pylori CagA upregulates the cholesterol metabolism enzyme SQLE, leading to increased synthesis of palmitoyl-CoA, which in turn enhances PD-L1 palmitoylation and inhibits its ubiquitination-mediated degradation. This process stabilizes PD-L1 expression and attenuates T-cell-mediated immune responses [41]. These findings suggest

Table 1 Summary of key clinical trials on immune checkpoint inhibitors in gastric cancer

Trial Name	Phase	Patient Population	Treatment	ORR (%)	PFS, months	Median OS (months)
KEYNOTE-012	1b	Recurrent/metastatic	Pembrolizumab	22%	1.9	11.4
KEYNOTE-059	2	Previously treated	Pembrolizumab	11.6% (overall), 15.5% (PD-L1+), 6.4% (PD-L1-)	2	5.6
ATTRACTION-2	3	Previously treated	Nivolumab vs. Placebo	11.2% vs. 0%	1.61 vs. 1.45	5.26 vs. 4.14
CheckMate-649	3	Untreated, unresectable	Nivolumab + Chemo vs. Chemo alone	60% VS. 45%	7.7 vs. 6.05	13.1 vs. 11.1
ATTRACTION-4	2–3	Untreated, unresectable	Nivolumab + Chemo vs. Placebo + Chemo	57% vs.48%	10.45 vs. 8.34	17.45 vs. 17.15
JAVELIN Gastric 100	3	Unresectable	Avelumab maintenance vs. Continued Chemo	13.3% vs. 14.4%	3.2	10.4 vs. 10.9
CheckMate-032	1–2	Chemotherapy-refractory metastatic	Nivolumab vs. Nivolumab + Ipilimumab	12% (Nivo 3 mg/kg), 24% (Nivo 1 mg/kg + Ipi 3 mg/kg), 8% (Nivo 3 mg/kg + Ipi 1 mg/kg)	8% (Nivo 3 mg/kg), 17% (Nivo 1 mg/kg + Ipi 3 mg/kg), 10% (Nivo 3 mg/kg + Ipi 1 mg/kg)	39% (Nivo 3 mg/kg), 35% (Nivo 1 mg/kg + Ipi 3 mg/kg), 24% (Nivo 3 mg/kg + Ipi 1 mg/kg)

that targeting extracellular PD-L1 binding alone may be insufficient to overcome immune resistance. Therapeutic strategies aimed at disrupting PD-L1 palmitoylation or its upstream regulators, such as DHHC3 and SQLE, may provide a more effective approach to enhancing the clinical efficacy of PD-1/PD-L1 inhibitors.

First-line combination with chemotherapy

Given the limited benefits of single-agent immunotherapy in later lines, researchers have moved PD-1/PD-L1 inhibitors into the first-line setting, combining them with chemotherapy to enhance overall treatment outcomes. In the Phase III KEYNOTE-062 trial [42], untreated patients with locally advanced or metastatic GC/GEJC and PD-L1 CPS ≥ 1 were randomized to receive either pembrolizumab plus chemotherapy or chemotherapy alone. The combination did not significantly outperform chemotherapy alone in median OS (12.5 months vs. 11.1 months, HR = 0.85, $P = 0.05$). Similarly, in the PD-L1 CPS ≥ 10 subgroup, there was no significant OS benefit (12.3 months vs. 10.8 months, HR = 0.85, $P = 0.16$). Despite these overall disappointing results, exploratory analyses revealed that patients with MSI-H or PD-L1 CPS ≥ 1 experienced significantly better OS with pembrolizumab compared to chemotherapy (HR = 0.29, 95% CI = 0.11–0.81).

In contrast, CheckMate-649, one of the largest global Phase III trials for gastric cancer, assessed nivolumab combined with chemotherapy (XELOX or FOLFOX) versus chemotherapy alone [43]. The combination therapy significantly extended median OS in the overall population (13.8 months vs. 11.6 months, HR = 0.80, $P = 0.0002$) and showed substantial improvements in objective response rate (ORR), progression-free survival (PFS), and OS in the PD-L1 CPS ≥ 5 subgroup (ORR 60% vs. 45%, OS 14.4 months vs. 11.1 months, HR = 0.71, $P < 0.0001$). Based on these results, the FDA approved nivolumab in April 2021 for first-line treatment of HER2-negative advanced or metastatic GC/GEJC, and esophageal adenocarcinoma.

Additionally, the Phase III ATTRACTION-4 trial in Asian populations evaluated nivolumab combined with chemotherapy [44]. While the trial showed a significant improvement in PFS (median PFS 10.45 months vs. 8.34 months), it did not demonstrate a statistically significant difference in OS. This discrepancy may be due to variations in subsequent treatments, patient characteristics, and biomarker distributions. Nonetheless, the results support the use of immunotherapy combined with chemotherapy in Asian patients, particularly regarding PFS.

Other PD-1 antibodies like camrelizumab and sintilimab have also shown encouraging results in combination with chemotherapy. For example, camrelizumab combined with CapeOx achieved an ORR of 65% (confirmed ORR of 44%) in a Phase II study for advanced or metastatic GC/GEJC [45]. Sintilimab combined with CapeOx in a Phase Ib study [46] reported an ORR of 85.0% and a pathological complete response (pCR) rate of 23.1% and major pathological response (MPR) rate of 53.8% in resectable locally advanced patients, further demonstrating the potential of immunotherapy combined with chemotherapy. These findings provide positive signals for subsequent larger Phase III trials.

In summary, combining immunotherapy with chemotherapy in first-line treatment for advanced or metastatic gastric adenocarcinoma has shown significant improvements, particularly for HER2-negative, PD-L1 CPS ≥ 5, or MSI-H patients. However, differences in trial outcomes highlight the need for optimized treatment protocols and precise patient selection in future research.

CTLA-4 inhibitors

CTLA-4 inhibitors represent another class of immune checkpoint inhibitors with relatively limited but promising applications in gastric cancer. Ipilimumab, a humanized IgG monoclonal antibody, was first approved by the FDA in 2011 for advanced melanoma. In the CheckMate-032 Phase I/II trial [47], ipilimumab at a dose of 3 mg/kg showed a 14% ORR in patients with advanced GC progressing after multiple lines of therapy. However, another Phase II trial found that ipilimumab as maintenance therapy following first-line chemotherapy in GC/GEJC patients did not significantly extend survival, indicating the limitations of monotherapy [48].

Tremelimumab, a selective humanized IgG2 CTLA-4 antibody, enhances T cell activity by blocking CTLA-4. In a Phase Ib/II trial, twelve patients with advanced gastric/GEJC received tremelimumab as second-line treatment, resulting in a median PFS of 1.7 months and a median OS of 7.7 months [49]. Although overall efficacy was modest, a few patients exhibited durable anti-tumor responses, with OS exceeding 32.7 months, suggesting that combining CTLA-4 inhibitors with biomarker-driven strategies might hold greater promise.

Dual checkpoint blockade has also been explored in gastric cancer. In the CheckMate-032 trial [50], the combination of nivolumab and ipilimumab was tested in patients with metastatic or unresectable solid tumors, including gastric cancer. The combination achieved a higher ORR (24%) compared to monotherapy (12%), though overall OS was similar (6.9 months vs. 6.2 months). Notably, in PD-L1 positive and MSI-H subgroups, the dual therapy significantly extended survival rates (50% vs. 13–29%), indicating enhanced efficacy for specific patient populations. Building on this, the NO LIMIT Phase II trial is evaluating the combination of nivolumab and low-dose ipilimumab in first-line treatment of MSI-H advanced GC/GEJC, with initial results showing positive trends awaiting further validation [51].

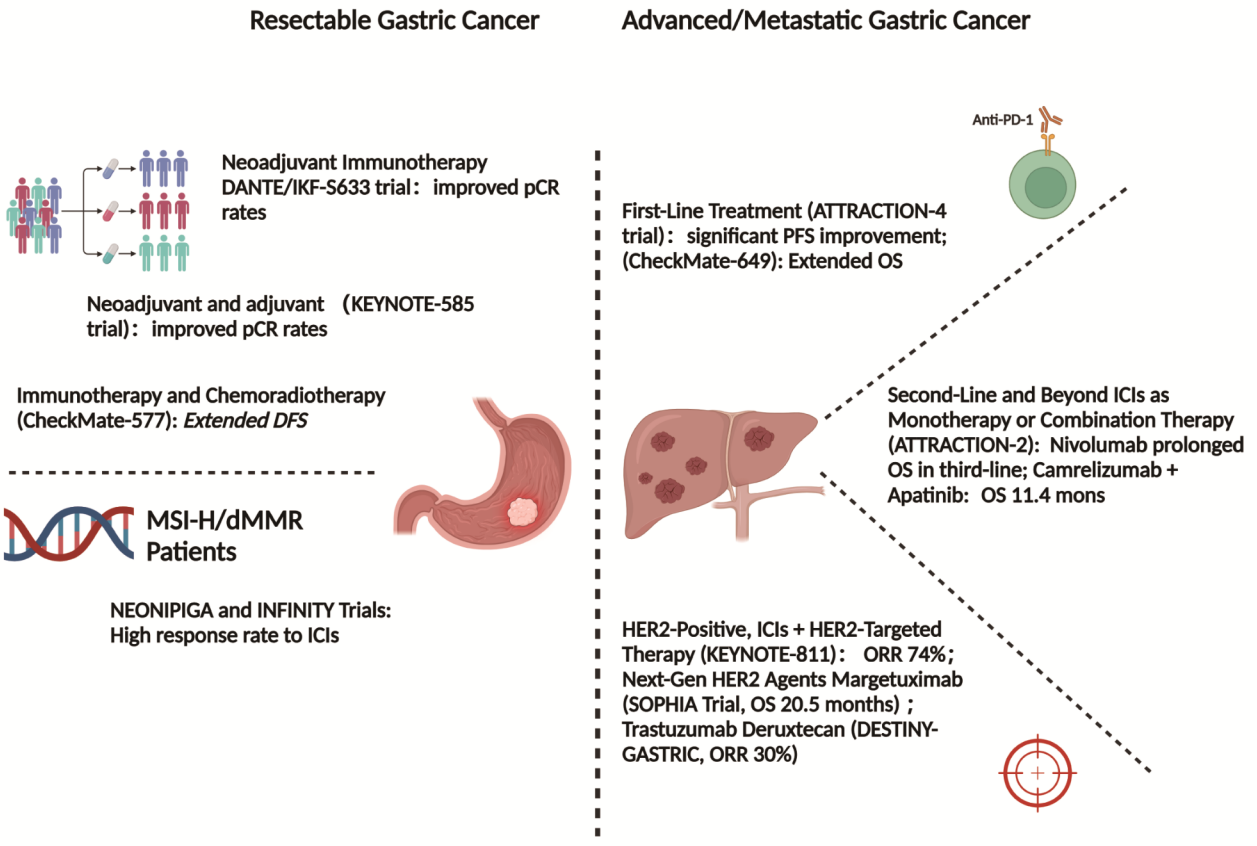

Fig. 2 Immunotherapy for resectable and advanced/metastatic gastric cancer

In conclusion, while CTLA-4 inhibitors alone have limited efficacy in gastric cancer, their combination with PD-1/PD-L1 inhibitors, especially in specific molecular subtypes like MSI-H/dMMR, may achieve better therapeutic outcomes. Future research should focus on optimizing combination regimens and using precise biomarkers to identify patients who are most likely to benefit from dual immune checkpoint blockade strategies.

Applications of immunotherapy across different clinical stages

Immunotherapeutic strategies and their efficacy vary according to different clinical stages. This section provides a comprehensive examination of the current status and advancements in immunotherapy for locally resectable and advanced or metastatic gastric cancer (Fig. 2).

Immunotherapy for resectable gastric cancer

For patients with locally resectable gastric adenocarcinoma, radical surgical resection remains the primary treatment modality. However, perioperative adjuvant therapies, such as neoadjuvant chemotherapy and adjuvant chemotherapy, are crucial for improving patient prognosis. In recent years, immunotherapy has been actively explored as a component of neoadjuvant or adjuvant treatment to further enhance therapeutic outcomes.

Current research on neoadjuvant and adjuvant immunotherapy

Neoadjuvant immunotherapy aims to reduce tumor size preoperatively using ICIs, thereby increasing resectability rates and decreasing postoperative recurrence risks. Multiple clinical trials are evaluating the efficacy of PD-1/PD-L1 inhibitors during the neoadjuvant phase. For instance, the DANTE/IKF-S633 trial (Phase II/III) assessed the efficacy of atezolizumab combined with the FLOT regimen (fluorouracil, leucovorin, oxaliplatin, and docetaxel) in resectable gastroesophageal adenocarcinoma. Interim results indicated a significant increase in the pathological complete response rate among subgroups with PD-L1 CPS > 10 and MSI-H/dMMR, suggesting potential benefits of immunotherapy in specific molecular subtypes [52].

Adjuvant immunotherapy involves the use of ICIs post-surgery to eliminate potential micrometastases, thereby prolonging disease-free survival (DFS) and OS. The KEYNOTE-585 (Phase III) trial compared pembrolizumab with placebo in combination with platinum and fluoropyrimidine-based perioperative chemotherapy [53].

Although improvements in pCR rates and median event-free survival were observed in the FLOT chemotherapy subgroup, statistical significance was not achieved, indicating the need for larger-scale follow-up data to validate long-term effects.

Additionally, the MATTERHORN (Phase III) trial [54] evaluated durvalumab in combination with FLOT during the perioperative period. Interim analysis revealed an increase in the pCR rate from 7 to 19% in the combination therapy group, though the impact on primary endpoints EFS and OS requires further observation. The ATTRACTION-5 (Phase III, Asia) trial compared nivolumab with placebo in combination with FOLFOX adjuvant chemotherapy, showing no significant improvement in recurrence-free survival (RFS), highlighting challenges in the application of immunotherapy during the adjuvant phase [55].

Immunotherapy for MSI-H/dMMR patients

High microsatellite instability (MSI-H) and deficient mismatch repair (dMMR) are molecular subtypes of gastric adenocarcinoma highly sensitive to immunotherapy [56]. For this subtype, recent NCCN guidelines recommend preoperative use of nivolumab combined with ipilimumab, single-agent pembrolizumab, or tremelimumab combined with durvalumab [57]. The NEONIPIGA (Phase II) trial demonstrated that approximately 59% of MSI-H/dMMR gastric cancer patients achieved pCR following neoadjuvant nivolumab combined with ipilimumab and subsequent postoperative nivolumab therapy [58]. Similarly, the INFINITY trial (Phase II) employing tremelimumab combined with durvalumab preoperatively in MSI-H patients achieved a pCR rate of approximately 60% [59]. These findings indicate that immunotherapy not only enhances pathological response rates but may also significantly extend survival in locally resectable MSI-H/dMMR gastric cancer patients, establishing it as a preferred treatment option for this subgroup.

Immunotherapy combined with perioperative chemoradiotherapy

To further enhance perioperative treatment efficacy, researchers are investigating strategies that combine ICIs with traditional chemotherapy or radiotherapy. Immunotherapy regimens combined with chemotherapy aim to achieve synergistic effects through the tumor-killing actions of chemotherapeutic agents and the immune-activating effects of ICIs. For example, the CheckMate-577 study demonstrated that nivolumab combined with neoadjuvant chemoradiotherapy significantly extended DFS in patients with esophageal or gastroesophageal junction cancer undergoing surgery, providing robust clinical evidence for incorporating immunotherapy into neoadjuvant treatment regimens [60].

Moreover, radiotherapy, as a local treatment modality, can directly kill tumor cells and release neoantigens, potentially enhancing the immune system's recognition and attack on tumors. Studies have shown that radiotherapy can upregulate PD-L1 expression on tumor cells, thereby inducing immune suppression and mitigating some benefits of radiotherapy [61]. Consequently, combining PD-1/PD-L1 inhibitors with radiotherapy holds promise for blocking immunosuppressive signals and achieving synergistic effects, thereby improving overall treatment outcomes.

Immunotherapy for advanced or metastatic gastric adenocarcinoma

Treatment strategies for advanced or metastatic gastric adenocarcinoma primarily rely on the detection of molecular biomarkers such as HER2, MSI/dMMR, and PD-L1 expression levels. These biomarkers not only guide the selection of targeted therapies but also play a crucial role in the application of immunotherapy.

First-line treatment: immunotherapy combined with chemotherapy becoming standard

In first-line treatment, the combination of immunotherapy with chemotherapy is increasingly becoming the standard regimen for HER2 negative advanced gastric adenocarcinoma. The CheckMate-649 trial, one of the largest global Phase III clinical studies, evaluated nivolumab combined with chemotherapy (XELOX or FOLFOX) versus chemotherapy alone [62]. Results demonstrated that the combination therapy significantly extended median OS in the overall population (13.8 months vs. 11.6 months, HR = 0.80, $P = 0.0002$) and markedly improved objective response rate, progression-free survival, and OS in the PD-L1 CPS ≥ 5 subgroup (ORR 60% vs. 45%, OS 14.4 months vs. 11.1 months, HR = 0.71, $P < 0.0001$) [63]. Consequently, the FDA approved nivolumab combined with chemotherapy in April 2021 for first-line treatment of HER2-negative advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.

Similarly, the ATTRACTION-4 trial assessed the efficacy of nivolumab combined with chemotherapy [44]. While the trial demonstrated a significant improvement in PFS (median PFS 10.45 months vs. 8.34 months), it did not achieve statistical significance in OS. This discrepancy may be attributed to variations in subsequent treatment strategies, patient population characteristics, and biomarker distributions. Nonetheless, the ATTRACTION-4 results support the use of immunotherapy combined with chemotherapy in Asian populations, particularly regarding PFS.

Additionally, other PD-1 antibodies, such as camrelizumab and sintilimab, have shown promising results when combined with chemotherapy. In a Phase II clinical study, camrelizumab combined with CapeOx (capecitabine and oxaliplatin) for first-line treatment of advanced or metastatic GC/GEJC patients achieved an ORR of 65% (confirmed ORR 44%), indicating a high remission rate [64]. Sintilimab combined with CapeOx in a Phase Ib study for locally advanced or metastatic GC/GEJC patients achieved an ORR of 85.0%, with a pCR rate of 23.1% and a major pathological response rate of 53.8% in resectable locally advanced cases, further demonstrating the potential of immunotherapy combined with chemotherapy [46]. These studies provide positive signals for subsequent larger-scale Phase III clinical trials.

In summary, immunotherapy combined with chemotherapy has demonstrated significant efficacy improvements in first-line treatment of advanced or metastatic gastric adenocarcinoma, particularly for HER2-negative, PD-L1 CPS ≥ 5, or MSI-H patients. The combination regimen is progressively establishing itself as the new standard of care. However, variations in outcomes across different clinical trials indicate that optimizing treatment protocols and precise patient selection remain critical areas for future research.

Second-line and later treatments: feasibility of immunotherapy as monotherapy or combination therapy in specific populations

In second-line and subsequent treatments, immunotherapy continues to be an important therapeutic option, especially for patient populations with specific biomarker positivity. The ATTRACTION-2 trial demonstrated that nivolumab significantly prolonged OS in Asian patients with advanced gastric cancer as a third-line or later treatment (5.26 months vs. 4.14 months, HR = 0.63, $P < 0.0001$) and substantially increased the 1-year OS rate (26.6% vs. 10.9%) [65]. This outcome underscores the significance of immunotherapy in later-line treatments, particularly for patients with high PD-L1 expression levels.

The KEYNOTE-059 three-cohort study further explored the application of pembrolizumab across different treatment stages [66]. In the third-line or later treatment cohort (Cohort 1), pembrolizumab achieved an ORR of 11.6% and a median OS of 5.6 months, demonstrating moderate activity in later-line settings. However, the KEYNOTE-061 s-line treatment study did not show pembrolizumab to be significantly superior to traditional chemotherapy, indicating variability in efficacy across different treatment stages [67]. This highlights the necessity for precise biomarker-driven patient selection to identify those most likely to benefit from immunotherapy.

Moreover, there are explorations into combining immunotherapy with other agents in later-line treatments. For example, camrelizumab combined with apatinib in second-line treatment of GC/GEJC achieved a confirmed ORR of 16.0%, with median PFS and OS of 2.9 months and 11.4 months, respectively, demonstrating feasibility [68]. Although the efficacy requires further validation, these studies lay the groundwork for diversifying immunotherapeutic approaches in later-line treatments.

HER2-positive patients: combining with trastuzumab and next-generation HER2 agents

HER2 overexpression is a significant molecular marker in advanced gastric adenocarcinoma, present in approximately 15–20% of advanced gastric cancer patients [69]. The ToGA trial established trastuzumab combined with platinum and fluoropyrimidine-based chemotherapy as a first-line treatment for HER2-positive advanced gastric cancer, significantly extending OS (13.8 months vs. 11.1 months) and ORR (47% vs. 35%) compared to chemotherapy alone [70].

Building on this foundation, the KEYNOTE-811 Phase III trial investigated the efficacy of pembrolizumab combined with trastuzumab and platinum-based chemotherapy in HER2-positive advanced gastric cancer patients [71]. Interim analysis revealed a significantly higher ORR in the combination group compared to the control group (74% vs. 52%, $P = 0.00006$), supporting the incorporation of immunotherapy in HER2-positive patient treatment regimens. Based on these results, the FDA granted accelerated approval in May 2021 for pembrolizumab combined with trastuzumab and chemotherapy for first-line treatment of HER2-positive gastric and gastroesophageal junction cancer patients.

Margetuximab, an anti-HER2 antibody with optimized Fc receptor affinity, received orphan drug designation from the FDA in June 2020 for the treatment of esophagogastric cancer based on positive results from the SOPHIA Phase III trial [72]. In the Phase II CP-MGAH22–05 study, margetuximab combined with pembrolizumab in second-line treatment of HER2-positive gastric/GEJC adenocarcinoma, particularly in PD-L1-positive populations, achieved an ORR of 44%, median PFS of 4.8 months, and median OS of 20.5 months, demonstrating favorable efficacy and tolerability [73].

Furthermore, next-generation HER2-targeted agents such as trastuzumab deruxtecan have shown superior efficacy compared to chemotherapy in the DESTINY-GASTRIC series of trials, with an ORR of up to 30%, providing additional treatment options for HER2-positive patients [74]. These findings indicate that combining immunotherapy with HER2-targeted therapies can further enhance treatment efficacy and improve survival outcomes for patients with HER2-positive advanced gastric cancer.

In conclusion, immunotherapy combined with chemotherapy has demonstrated significant efficacy enhancements in first-line treatment of advanced or metastatic gastric adenocarcinoma, particularly for HER2-negative, PD-L1 CPS ≥ 5, or MSI-H patients, establishing it as a new treatment standard. However, discrepancies in clinical trial outcomes suggest that further optimization of treatment protocols and precise patient selection remain crucial areas for future research. Additionally, the integration of immunotherapy with targeted therapies, especially in HER2-positive patients, offers promising avenues for improving therapeutic outcomes and patient survival.

Safety management of immunotherapy

The application of immunotherapy in gastric adenocarcinoma has significantly improved patient survival, yet the occurrence of immune-related adverse events (irAEs) necessitates vigilant safety management [75]. irAEs refer to autoimmune-like toxicities that arise from immune checkpoint inhibitors disrupting immune tolerance, leading to inflammation in normal tissues. Common irAEs, including thyroid dysfunction, rash, colitis, hepatitis, and pneumonitis, are primarily attributable to ICIs activating the immune system to target normal tissues. The severity of irAEs is graded according to the Common Terminology Criteria for Adverse Events (CTCAE), where grade 1 (mild) irAEs are asymptomatic or cause mild symptoms that can be managed with symptomatic treatment and close monitoring. Grade 2 (moderate) irAEs may require treatment interruption and corticosteroid administration, while grade 3–4 (severe or life-threatening) irAEs often necessitate permanent discontinuation of ICIs, high-dose corticosteroids, and additional immunosuppressive therapy [76]. Certain studies suggest that patients who experience irAEs may exhibit a more favorable treatment response, potentially reflecting heightened immune system activity [77]. For instance, a phase III clinical trial in patients with high-risk stage III melanoma demonstrated that pembrolizumab significantly prolonged recurrence-free survival (RFS) compared to placebo, and treatment-related adverse events, including irAEs, were reported in 14.7% of patients receiving pembrolizumab [78]. However, this association requires further investigation. When ICIs are combined with chemotherapy or radiotherapy, the risk of compounded toxicity increases, necessitating optimized treatment regimens and enhanced patient education. Regular follow-up and functional assessments are essential to promptly identify and address these adverse events [79].

Outlook and conclusions

Advances in understanding the molecular characteristics and immune microenvironment of GAC offer promising avenues for the future of immunotherapy. Novel targets, such as CLDN18.2, FGFR2b, and TROP-2, are highly expressed in GAC and present opportunities for innovative treatment strategies. For instance, CLDN18.2 is a promising target for CAR-T cell therapy, and bispecific or multispecific antibodies targeting multiple immune pathways may further enhance therapeutic efficacy [80]. Moreover, integrating genomic, transcriptomic, and immunomic data to develop multiparametric predictive models can help identify patients who are most likely to benefit from ICIs. Biomarkers such as MSI-H, *PD-L1* overexpression, and high tumor mutational burden (TMB) can guide personalized treatment strategies, potentially improving outcomes. In the clinical setting, neoadjuvant immunotherapy shows potential to reduce tumor size and lower postoperative recurrence risk. Optimizing strategies for patients with weak responses, including novel immune drugs and more sensitive biomarkers, may further expand the benefits of immunotherapy [81].

Immunotherapy's role in GAC treatment continues to grow, offering significant prognostic benefits, particularly for certain molecular subtypes. However, challenges such as treatment resistance, lack of response, and irAE management remain pressing. The integration of multi-omics technologies to identify new targets and the development of innovative immunotherapeutic approaches, such as oncolytic viruses and nanoparticle-based drug delivery systems, may further enhance efficacy while reducing toxicity. Additionally, real-world evidence and health economics analyses can support broader access to immunotherapy. By refining therapeutic strategies and advancing precision medicine, the survival and quality of life of GAC patients may be further improved.

Abbreviations

GAC	Gastric adenocarcinoma
ICI	Immune checkpoint inhibitor
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
MSI-H	Microsatellite instability-high
HER2	Human epidermal growth factor receptor 2
irAE	Immune-related adverse event
TIL	Tumor-infiltrating lymphocyte
TAM	Tumor-associated macrophage
Treg	Regulatory T Cell
MDSC	Myeloid-derived suppressor cell
TGF-β	Transforming growth factor beta
IL-10	Interleukin-10
EBV	Epstein-barr virus
LAG-3	Lymphocyte-activation gene 3
TIM-3	T cell immunoglobulin and mucin-domain containing-3
TIGIT	T cell immunoreceptor with Ig and ITIM domains
NCCN	National comprehensive cancer network
CAR-T	Chimeric antigen receptor T cell
TMB	Tumor mutational burden
pCR	Pathological complete response
DFS	Disease-free survival
OS	Overall survival
PFS	Progression-free survival
ORR	Objective response rate

FLOT	Fluorouracil, leucovorin, oxaliplatin, and docetaxel
CPS	Combined positive score
TPS	Tumor proportion score

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Z. C.: Conceptualization, Investigation, Writing - original draft; Y. M.: Conceptualization, Writing - review & editing; J.C.: Supervision, Project administration, Writing - review & editing.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

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Competing interests
The authors declare no competing interests.

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