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REVIEW

Advances in Immunotherapy and Targeted Therapy for Gastric Cancer: A Comprehensive Review

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Abstract

Gastric cancer remains one of the most prevalent and lethal malignancies worldwide, characterized by poor survival rates, particularly in advanced stages. In recent years, a paradigm shift in gastric cancer treatment has been witnessed with the introduction of immunotherapy and targeted therapies. This review provides a detailed examination of current immunotherapeutic strategies, including adoptive cell therapy (ACT), immune checkpoint inhibitors (ICIs), and cancer vaccines. Additionally, it explores advancements in targeted therapies, focusing on the human epidermal growth factor receptor 2 (HER2) and vascular endothelial growth factor receptor (VEGFR) signaling pathways, as well as emerging targets such as claudin 18.2. Clinical trials investigating chimeric antigen receptor T-cell (CAR-T) therapy, T-cell receptor-engineered T-cell (TCR-T) therapy, and natural killer (NK) cell-based treatments have shown promise, particularly when combined with conventional chemotherapeutic regimens. However, challenges such as cytokine release syndrome, immune-related toxicities, and scalability issues remain significant. The combination of immunotherapy with targeted therapies represents a promising approach to enhance treatment outcomes. Future directions emphasize the need to overcome resistance mechanisms and refine treatment strategies to improve efficacy while reducing adverse effects. This review aims to elucidate the current landscape of immunotherapy and targeted therapy in gastric cancer and to explore their potential in shaping the future of clinical management for this devastating disease.

Key words: immunotherapy; gastric cancer; targeted therapy; chimeric antigen receptor T-cell therapy

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Introduction

Gastric cancer ranks among the most prevalent and lethal malignancies worldwide, posing a significant global health burden. Recent epidemiological data indicate that gastric cancer as the sixth most common cancer in terms of incidence and the third leading cause of cancer-related mortality globally, with an annual incidence exceeding 1 million cases and approximately 769,000 deaths. Patients with advanced gastric cancer (AGC) patients face a poor prognosis, with a 5-year survival rate below 5% (Thrift and El-Serag, 2020).

A concerning trend has emerged in recent years, marked by a notable increase in gastric cancer incidence among individuals under 50 years of age. This alarming

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rise strongly correlates with helicobacter pylori infection and harmful lifestyle factors, particularly alcohol consumption and tobacco use (Christodoulidis et al, 2024). For early-stage gastric cancer, surgical intervention remains the primary treatment modality, with D2 lymph node dissection established as the standard procedure. However, significant challenges persist, including high recurrence rates even after curative surgery and limited treatment options for patients who develop resistance to conventional therapies. Furthermore, many patients are diagnosed at advanced stages, where traditional chemotherapy exhibits limited efficacy and considerable toxicity.

Recent years have witnessed remarkable advancements in immunotherapy for unresectable or metastatic gastric cancer, leading to a paradigm shift in treatment strategies (Guan et al, 2023). This progress is driven by extensive and rigorous clinical investigations. Various adoptive cell therapy approaches have emerged as promising options: chimeric antigen receptor T-cell (CAR-T), engineered to target specific tumor antigens through synthetic receptors; T-cell receptor-engineered T-cell (TCR-T), which recognize intracellular antigens presented by major histocompatibility complex (MHC) molecules; tumor-infiltrating lymphocytes (TILs), naturally occurring T cells isolated from tumors; cytokine-induced killer (CIK) cells, which exhibit both natural killer (NK) and T cell properties; and NK cells, which provide innate anti-tumor immunity. Each approach offers unique advantages and challenges regarding specificity, persistence, and safety profiles.

Additional immunotherapeutic strategies include immune checkpoint inhibitors (ICIs) and cancer vaccines, while targeted therapies focus on signaling pathways such as human epidermal growth factor receptor 2 (HER2) and vascular endothelial growth factor receptor (VEGFR), as well as novel targets like claudin 18.2 (CLDN18.2).

This comprehensive review aims to elucidate the current landscape and challenges associated with these immunotherapeutic and targeted approaches in the clinical management of gastric cancer, with a particular focus on addressing the urgent unmet needs in treating advanced and resistant disease.

Adoptive Cell Therapy

Adoptive cell therapy (ACT) is a cutting-edge therapeutic approach that utilizes the patient's endogenous immune cells to target and eradicate malignant cells selectively. The ACT protocol involves the isolation of patient-derived immune cells, predominantly T lymphocytes or NK cells, and their *ex vivo* manipulation or expansion, and subsequent reinfusion into the patient to enhance the host's anti-tumor immune response. ACT encompasses a diverse range of cellular therapies, including but not limited to CAR-T therapy, TCR-T therapy, TIL therapy, CIK cell therapy, and NK cell therapy. The salient characteristics of these distinct ACT modalities are shown in Table 1.

CAR-T Therapy

CAR-T therapy has gained widespread application in clinical trials and therapeutic interventions across various malignancies. While CAR-T therapy has demon-

Table 1. Advantages and disadvantages of various therapies in ACT.

Therapy	Advantages	Disadvantages
CAR-T	Highly specific and individualized treatment	Potential for severe immune-related adverse reactions
TCR-T	Not limited by cell surface antigens and applicable to tumor types ineffective for CAR-T	High antigen specificity requirements may cause damage to autologous tissues
NK	Applicable to various tumor types	Requires large-scale NK cell infusion in the short term, with relatively weak specificity and therapeutic effect
TIL	Effective against multiple tumor types	Time-consuming to obtain cells and unstable therapeutic effect
CIK	Non-MHC-restricted and antibody-dependent cellular cytotoxicity	Consistency and durability of efficacy need to be verified

ACT, adoptive cell therapy; CAR-T, chimeric antigen receptor T-cell; TCR-T, T-cell receptor-engineered T-cell; NK, natural killer; TIL, tumor-infiltrating lymphocyte; CIK, cytokine-induced killer; MHC, major histocompatibility complex.

strated remarkable efficacy in hematological malignancies, ongoing research is intensively focused on exploring its potential in solid tumors, including gastric cancer (Entezam et al, 2023). In gastric cancer research, multiple CAR-T therapeutic approaches targeting different molecular targets are under investigation. HER2-targeted CAR-Ts have shown objective response rates of 11.1–33.3% in phase I/II trials; Epithelial cell adhesion molecule (EpCAM)-targeted CAR-Ts have demonstrated promising safety profiles and initial efficacy signals in early-phase studies. Folate receptor 1 (FOLR1)-directed CAR-Ts have exhibited potent anti-tumor activity in preclinical models, with ongoing phase I trials assessing their clinical potential.

Notably, genetically engineered CAR-Ts designed to target HER2-positive tumor cells have exhibited pronounced antitumor efficacy in preclinical gastric cancer murine models, with tumor regression observed in 85–90% of treated animals (Xu et al, 2023). CLDN18.2, a membrane protein significantly upregulated in gastrointestinal adenocarcinomas, has emerged as a promising target in CAR-T research for gastric cancer. Current clinical trials evaluating CLDN18.2-targeted CAR-Ts (CT041) have yielded encouraging preliminary results, demonstrating an overall response rate of 33% in heavily pretreated patients with manageable safety profiles.

Recent clinical investigations have yielded promising results for combination therapy zolbetuximab, a monoclonal antibody targeting CLDN18.2, in specific patient cohorts. The target population includes patients with CLDN18.2-positive, HER2-negative, treatment-naïve locally advanced unresectable, or metastatic gastric cancer or gastroesophageal junction cancer (GEJC). Clinical data demonstrate that the combination of zolbetuximab with modified folinic acid, fluorouracil, and oxaliplatin (mFOLFOX6) or capecitabine plus oxaliplatin (CAPOX) regimen significantly improves progression-free survival (PFS) and overall survival (OS) in

these patients. This innovative combination therapy shows promise as a potential first-line treatment paradigm for the aforementioned patient subgroups (Shah et al, 2023). Despite these advancements, cytokine release syndrome and neurotoxicity associated with CAR-T therapy remain critical safety concerns, underscoring the need for effective mitigation strategies (Qi et al, 2022).

TCR-T Therapy

TCR-T therapy offers several distinct advantages over CAR-T therapy in certain contexts. TCR-Ts demonstrate superior proliferative capacity under high antigen pressure conditions and are not constrained by the expression of surface antigens on target cells, enabling versatile recognition of diverse epitopes (Wachsmann et al, 2022). Empirical evidence indicates that TCR-Ts can effectively mediate tumor lysis and clearance. Clinical trials investigating TCR-T therapy in hematological malignancies and various solid tumors have yielded promising efficacy results (Anderson and Chapman, 2024). Although TCR-T therapy has not yet achieved significant breakthroughs in gastric cancer treatment, its ability to recognize intracellular antigens offers substantial prospects for development in the field of cellular immunotherapy.

Currently, several promising TCR-T approaches are under investigation for gastric cancer. New York esophageal squamous cell carcinoma-1 (NY-ESO-1)-targeted TCR-Ts were shown preliminary efficacy in phase I trials, with response rates of 20–30% in expression-positive patients (Singh et al, 2015). Melanoma-associated antigen A4 (MAGE-A4)-directed TCR-Ts are being evaluated in an ongoing clinical study, showing encouraging safety profiles; Human Leukocyte Antigen A*24:02 (HLA-A*24:02)-restricted TCR-Ts targeting multiple tumor-associated antigens are in early-phase trials (Dolton et al, 2023). These approaches demonstrate varying degrees of efficacy and safety profiles, with some showing particular promise in specific patient subgroups.

Despite these advances, TCR-T therapy faces several challenges. Low-affinity TCRs may confer enhanced safety profiles but potentially compromise anti-tumor efficacy, while high-affinity TCRs may elicit off-target toxicities against non-malignant tissues. Recent technological advances in TCR engineering, including affinity optimization techniques and the incorporation of safety switches, are being explored to address these challenges. Additionally, combination approaches with checkpoint inhibitors or other immunotherapies are being investigated to enhance TCR-T efficacy while maintaining acceptable safety profiles (Zhao et al, 2021).

NK Cell Therapy

NK cells, pivotal effectors of the innate immune system, play an indispensable role in the inhibition of gastric cancer initiation, progression, and metastasis. NK cells employ a multifaceted approach to exert their anti-neoplastic functions, including induction of gastric cancer cell death via antibody-dependent cell-mediated cytotoxicity (ADCC), release of cytolytic granules containing perforin and granzymes, secretion of pro-inflammatory cytokines such as interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α), and promotion of tumor cell apoptosis

through the engagement of death receptor pathways, namely First Apoptosis Signal/FAS Ligand (FAS/FASL) and TNF-Related Apoptosis-Inducing Ligand/TRAIL Receptor (TRAIL/TRAILR) complexes (Du and Wei, 2019). The study focusing on HER2-positive gastric cancer has demonstrated that the combinatorial approach of infusing *ex vivo* expanded and activated autologous NK cells with trastuzumab significantly augments the cytolytic capacity of NK cells against trastuzumab-targeted tumor cells (Lee et al, 2020). Furthermore, a cohort study encompassing 146 gastric cancer patients revealed that cases exhibiting high Cluster of Differentiation 56 (CD56) expression were associated with reduced tumor burden, enhanced surgical outcomes, and more favorable prognostic indicators. The study also elucidated a positive correlation between CD56 expression levels and NK cell density, lending further credence to the hypothesis that gastric cancer treatment efficacy is intimately linked to NK cell abundance (Sakamoto et al, 2015).

Notwithstanding the immense potential of NK cell-based immunotherapy, its clinical implementation is confronted by two principal challenges: the scalable production of NK cells in sufficient quantities for clinical application, and the augmentation of NK cell anti-tumor functionality. Addressing these challenges represents a critical frontier in the ongoing development and optimization of NK cell-based immunotherapeutic strategies.

TIL Therapy

Tumor-infiltrating lymphocyte (TIL) therapy is a personalized adoptive cell transfer method showing promise in inducing durable complete responses in patients unresponsive to standard treatments. Evidence indicated that neoantigen-reactive T cells primarily mediate tumor regression post-TIL infusion (Zhang et al, 2019). In advanced gastric cancer (AGC) patients, combining autologous TIL reinfusion with interleukin-2 (IL-2) led to complete tumor regression in 13% and tumor growth inhibition in 21.7% of cases, with the regimen being well-tolerated and free of severe adverse events (Faghfuri et al, 2022). Despite these positive outcomes, challenges such as lengthy *ex vivo* TIL expansion and the immunosuppressive tumor microenvironment hinder clinical implementation. Addressing these issues is essential to enhance the efficacy and practicality of TIL therapy.

CIK Cell Therapy

Cytokine-induced killer (CIK) cells are a heterogeneous population derived from peripheral blood mononuclear cells stimulated *ex vivo* with cytokines such as IFN-γ, IL-2, and anti-CD3 antibodies. The main effector subset co-expresses CD3 and CD56 markers. Studies have shown that adjuvant therapy with autologous CIK cells prolongs disease-free survival (DFS) and OS in post-operative and localized advanced gastric cancer (AGC) patients (Li et al, 2017; Shi et al, 2012). Although combining CIK cell therapy with chemotherapy improves survival outcomes in AGC patients, challenges remain in ensuring consistent and durable efficacy.

Table 2. Overview of immune checkpoint inhibitor studies in gastric cancer.

Inhibitor	Study	Study subjects (patients)	Study design	Results
PD-1 inhibitors	KEYNOTE-059 (Phase II)	AGC and GEJC	Pembrolizumab monotherapy	ORR was 11.6%, 2.3% patients had complete remission
	KEYNOTE-585 (Phase III)	Locally advanced resectable gastric cancer or gastroesophageal adenocarcinoma	Pembrolizumab + chemotherapy	Improved pCR, but did not significantly improve EFS
	KEYNOTE-859 (Phase III)	Locally advanced, metastatic HER2-negative gastric cancer or GEJC	Pembrolizumab + chemotherapy	Significant improvement in OS, manageable adverse reactions
	KEYNOTE-811 (Phase III)	HER2-positive gastric cancer or GEJC	Pembrolizumab + trastuzumab + chemotherapy	Significantly improved PFS, but did not improve OS
	ATTRACTION-4 (Phase III)	HER2-negative, unresectable advanced or recurrent gastric cancer or GEJC	Nivolumab + chemotherapy	Significantly improved PFS, but did not improve OS
	CheckMate-649 (Phase III)	AGC, GEJC, and esophageal adenocarcinoma	Nivolumab + chemotherapy	Combination therapy significantly improved OS and PFS compared to chemotherapy alone
	Li et al, 2023a (Phase I)	HER2-positive advanced gastric and GEJC	Pyrotinib + camrelizumab + chemotherapy	Showed good efficacy in first-line treatment, and ORR was 77.8%
	Lin et al, 2024 (Phase II)	Locally AGC	Camrelizumab + apatinib + chemotherapy	Combination therapy significantly increased pathological response, ORR, and R0 resection rate compared to chemotherapy alone
	DRAGON IV (Phase III)	AGC or GEJC	Camrelizumab + rivoceranib + chemotherapy	Combination therapy significantly improved pCR compared to chemotherapy alone, with manageable safety

Table 2. Continued.

Inhibitor	Study	Study subjects (patients)	Study design	Results
PD-L1 Inhibitors	JAVELIN Gastric 300 (Phase III)	AGC or GEJC	Avelumab monotherapy	No significant improvement in OS, PFS, or ORR compared to chemotherapy
	JAVELIN Solid Tumor (Phase Ib)	AGC or GEJC after chemotherapy	Avelumab monotherapy	Relatively low incidence of G3/4 adverse events, 1L group had extended median DOR
	JAVELIN Gastric 100 (Phase III)	AGC or GEJC	Avelumab monotherapy	After first-line induction chemotherapy, avelumab 1L group had better tolerability and more durable response, but no significant difference in median OS
	JVDJ (Phase Ia/b)	AGC or GEJC	Ramucirumab + durvalumab	Combination therapy showed enhanced efficacy and promising results in PD-L1 high-expression patients
	DURIGAST-PRODIGE 59 (Phase II)	AGC or GEJC	FOLFIRI + durvalumab ± tremelimumab	Expected safety observed with combination therapy
	MATTERHORN (Phase III)	Resectable gastric cancer and GEJC	Durvalumab + FLOT	Significant improvement in pCR with manageable safety
CTLA-4 Inhibitors	Lei et al, 2021 (Phase I/II)	Advanced GC/GEJC patients	Nivolumab ± ipilimumab biomarker analysis	CPS demonstrated superior predictive value for efficacy compared to TC score (positive tumor cells/total tumor cells), with objective response rate (ORR) reaching 19% in patients with CPS ≥5 and 26% in those with CPS ≥10
	CheckMate-032 (Phase III)	Metastatic esophagogastric cancer	Nivolumab + ipilimumab	Showed clinically meaningful antitumor activity, durable responses, good long-term survival rates, and manageable safety profile
	Kelly et al, 2020 (Phase Ib/II)	AGC and GEJC	Durvalumab monotherapy, tremelimumab monotherapy, durvalumab + tremelimumab	Low response rates observed with both monotherapy and combination therapy, and no new safety issues identified

PD-1, programmed cell death protein 1; AGC, advanced gastric cancer; GEJC, gastroesophageal junction cancer; ORR, objective response rate; pCR, pathological complete response; EFS, event-free survival; OS, overall survival; PFS, progression-free survival; HER2, human epidermal growth factor receptor 2; PD-L1, programmed death-ligand 1; DOR, duration of response; FOLFIRI, folinic acid, fluorouracil and irinotecan; FLOT, fluorouracil, leucovorin, oxaliplatin and docetaxel; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; CPS, combined positive score; GC, gastric cancer; TC, tumor cells.

Immune Checkpoint Inhibitors

Immune checkpoint molecules serve as crucial regulatory elements within the immune system, modulating immune responses to maintain self-tolerance and mitigate collateral tissue damage. Neoplasms exploit immune checkpoint pathways to circumvent immune surveillance and evade immunological destruction. This is achieved through the aberrant expression of immune checkpoint molecules, including programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). Immune checkpoint inhibitor (ICI) therapy aims to reinvigorate anti-tumor immune responses by disrupting these inhibitory signaling pathways through the administration of specific monoclonal antibodies. This therapeutic approach enhances the immune system's capacity to recognize and eliminate malignant cells. Table 2 presents a comprehensive overview of selected clinical studies investigating the efficacy of immune checkpoint inhibitors in the treatment of gastric cancer.

PD-1 Inhibitors

Pembrolizumab

Pembrolizumab, a humanized Immunoglobulin G4 (IgG4) monoclonal antibody targeting PD-1, has demonstrated significant clinical efficacy in advanced gastric cancer (AGC) treatment (Li et al, 2023a). In the KEYNOTE-059 study with 259 AGC patients, pembrolizumab monotherapy achieved complete responses in a subset, with an objective response rate (ORR) of 11.6% for those with combined positive score (CPS) $\geq$1 (Fuchs et al, 2018).

The subsequent study has explored the combination of pembrolizumab with chemotherapy. In KEYNOTE-811, for HER2-positive gastric or gastroesophageal junction cancer (GEJC), pembrolizumab with cetuximab and chemotherapy improved progression-free survival (PFS), though OS improvement was not statistically significant (Janjigian et al, 2023). Overall, pembrolizumab shows promise in AGC treatment, warranting further studies and long-term evaluations of its efficacy and safety.

Nivolumab

Nivolumab, a fully human IgG4 anti-PD-1 antibody, has shown efficacy in AGC. The ATTRACTION-4 study assessed nivolumab in combination with oxaliplatin-based chemotherapy as a first-line treatment, which prolonged median PFS without significantly extending median OS, and maintaining a manageable safety profile (Kang et al, 2022). The CheckMate-649 trial demonstrated significant improvements in OS, PFS, ORR, and response duration with nivolumab plus chemotherapy compared to chemotherapy alone in Chinese patients with AGC, GEJC, and esophageal adenocarcinoma. Additionally, it also showed enhanced OS and DFS in unresectable advanced or metastatic non-HER2-positive gastric cancer (Janjigian et al, 2021). These promising results led to Food and Drug Administration (FDA) and Chinese approvals of the combination of nivolumab and oxaliplatin-based chemotherapy as first-line treatment for AGC and GEJC patients.

Camrelizumab

Camrelizumab, a humanized anti-PD-1 IgG4 monoclonal antibody with high affinity, has shown promise in recent studies. Li et al (2023a) demonstrated that combining camrelizumab with pyrotinib and chemotherapy as first-line treatment for HER2-positive AGC and gastroesophageal junction adenocarcinoma resulted in high ORR. Lin et al (2024) reported in a phase II trial that camrelizumab combined with apatinib and chemotherapy as a neoadjuvant regimen for locally advanced AGC showed good tolerability, a higher major pathological response, and increased R0 resection rates. In the DRAGON IV trial, perioperative camrelizumab combined with rivoceranib and chemotherapy improved pathological complete response (pCR) compared to chemotherapy alone, while maintaining safety and surgical feasibility, offering a new perioperative treatment option for resectable AGC/GEJC (Li et al, 2023b). The efficacy of ICI in gastric cancer is influenced by factors such as Epstein-Barr virus (EBV) association and microsatellite instability-high (MSI-H) status, both of which correlate with a higher tumor mutational burden and enhanced neoantigen presentation, thus boosting T cell response.

PD-L1 Inhibitors

Avelumab

Avelumab, a humanized IgG1 monoclonal antibody specifically targeting PD-L1, functions by disrupting the PD-L1/PD-1 interaction, thereby reinvigorating antitumor immune responses. In the JAVELIN Solid Tumor study, avelumab was used as a first-line (1L) or second-line (2L) treatment for advanced gastroesophageal junction tumors, revealing low rates of Grade 3/4 adverse events (1L: 8.5%, 2L: 8.3%) and a prolonged median duration of response with an ORR 6.7% in the 1L cohort (Chung et al, 2019). The JAVELIN Gastric 100 study compared avelumab 1L maintenance therapy with continued chemotherapy post-capecitabine plus oxaliplatin (XELOX)/leucovorin, fluorouracil, and oxaliplatin (FOLFOX) and revealed that avelumab showed better tolerability and more durable responses with a 24-month OS of 22.1% vs 15.5% in the chemotherapy group. However, it did not significantly improve median OS in the CPS $\geq$1 subgroup (Moehler et al, 2021).

Durvalumab

Durvalumab, a high-affinity anti-PD-L1 IgG1 monoclonal antibody, inhibits the interaction between PD-L1 and both PD-1 and CD80 receptors on T cells. The JVDJ trial, which combined durvalumab with ramucirumab as second-line treatment for AGC and GEJC demonstrated enhanced efficacy with an ORR of 21%, a median PFS of 2.6 months, and a median OS of 12.4 months compared to durvalumab alone. The DURIGAST-PRODIGE59 trial evaluated durvalumab with folinic acid, fluorouracil and irinotecan (FOLFIRI), with or without tremelimumab, as second-line therapy for AGC. Both regimens exhibited acceptable safety profiles, with $\geq$Grade 3 treatment-related adverse events (TRAEs) in ~60% of patients (Evrard et al, 2022). The MATTERHORN study showed that adding durvalumab to perioperative fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) treatment significantly improved pathological complete response (pCR) with man-

ageable safety, supporting its use in resectable gastric cancer (GC) and gastroesophageal junction cancer (GEJC) (Oh et al, 2023).

CTLA-4 Inhibitors

Ipilimumab, a fully humanized IgG1 monoclonal antibody targeting CTLA-4, enhances T cell activation by specifically inhibiting the interaction between CTLA-4 and its ligands, thus augmenting antitumor immune responses. A clinical trial comparing ipilimumab monotherapy to best supportive care in AGC and GEJC was terminated early due to inadequate progression-free survival (PFS).

The CheckMate-032 study evaluated nivolumab monotherapy (NIVO) versus combinations: nivolumab 3 mg/kg + ipilimumab (IPI) 1 mg/kg (NIVO3 + IPI1) and nivolumab 1 mg/kg + ipilimumab 3 mg/kg (NIVO1 + IPI3) in AGC/GEJC patients. The NIVO1 + IPI3 regimen showed superior objective response rate (ORR) and PFS compared to NIVO3 and NIVO3 + IPI1, but with higher grade 3/4 TRAEs (Janjigian et al, 2018). In combination therapies, a recent study found that ipilimumab plus nivolumab did not significantly improve overall survival (OS) or ORR versus conventional chemotherapy in advanced gastroesophageal cancer but did enhance response durability (Shitara et al, 2022). Tremelimumab, another fully humanized anti-CTLA-4 antibody with a longer half-life, allows administration once every three months. Kelly et al (2020) reported that tremelimumab combined with durvalumab achieved OS comparable to other checkpoint inhibitor combinations, despite low response rates, and maintained an acceptable safety profile. The DURIGAST-PRODIGE59 trial assessed FOLFIRI with durvalumab, with or without tremelimumab, as second-line therapy for advanced gastric or gastroesophageal junction adenocarcinoma. It demonstrated expected safety profiles, supporting progression to phase II randomized trials.

Table 3 summarizes key clinical trials investigating immunotherapy agents, either as monotherapy or in combination with chemotherapy, across various treatment settings in gastric cancer, highlighting the evolving landscape of immunotherapeutic approaches in this malignancy.

Emerging Immune Checkpoint Inhibitors

Recent advances in immunotherapy have led to the identification of several promising novel immune checkpoint targets beyond PD-1/PD-L1 for gastric cancer treatment. One such approach is the B7 homolog 3 (B7-H3, also known as CD276)-targeted antibody-drug conjugate MGC018, which is under investigation in clinical trials (NCT05144529) and has shown promising preliminary efficacy. Another key area of focus is TIGIT inhibition, with tiragolumab being evaluated in the SKYSCRAPER-06 trial (NCT04866017) in combination with atezolizumab and chemotherapy for HER2-negative advanced gastric cancer. Additionally, savolitinib is being evaluated in a clinical trial (NCT04923932) for treating patients with gastric cancer and esophagogastric junction adenocarcinoma. Lymphocyte Activation Gene-3 (LAG-3)-targeted approaches have also shown particular promise, with relatlimab being investigated in combination with nivolumab (NCT04082364) and eftilagimod alpha demonstrating synergistic effects with PD-1 inhibitors in

Table 3. The Key Results of some immunotherapy studies in gastric cancer.

Study name	Drug(s)	Setting	Key results
ATTRACTION-02	Nivolumab	3rd line and later	Established the role of Nivolumab in advanced gastric cancer
KEYNOTE-062	Pembrolizumab + chemotherapy	1st line	Did not demonstrate efficacy of combination
CheckMate 649	Nivolumab + chemotherapy	1st line	Positive results, especially in PD-L1 CPS ≥5
ORIENT-16	Sintilimab + chemotherapy	1st line	Positive results, especially in Chinese patients
RATIONALE-305	Tislelizumab + chemotherapy	1st line	Positive results, especially in PD-L1 high expression
KEYNOTE-859	Pembrolizumab + chemotherapy	1st line	Positive results
GEMSTONE-303	Sugemalimab + CAPOX	1st line	PFS and OS improved in PD-L1 ≥5%, and more benefit in PD-L1 ≥10%
AK104-302	Cadonilimab + chemotherapy	1st line	Significant OS benefit, including in PD-L1 CPS <5 population
KEYNOTE-158	Pembrolizumab	MSI-H/dMMR	ORR 31% (global), 63% (Chinese cohort)
KN035-CN006	Envafolimab	2nd line, MSI-H/dMMR	ORR 55.6%, 12-month OS rate 77.4%
ASTRUM-010	Serplulimab	MSI-H/dMMR	Approved for MSI-H/dMMR solid tumors after standard treatment failure
DANTE	Atezolizumab + FLOT	Perioperative	Improved pathological response
KEYNOTE-585	Pembrolizumab + chemotherapy	Perioperative	Increased pCR (12.9% vs 2.0%), and non-significant EFS improvement
ATTRACTION-5	Nivolumab + chemotherapy	Adjuvant	No significant RFS improvement, and benefit in PD-L1 ≥1% subgroup
DRAGON-IV/Ahead-G208	Apatinib + camrelizumab + SOX	Neoadjuvant	pCR rate 18.3% vs 5.0% in SOX alone
MATTERHORN	Durvalumab + FLOT	Neoadjuvant	pCR rate 19% vs 7%, pCR+pnCR 27% vs 14%

MSI-H, microsatellite instability-high; dMMR, deficient mismatch repair; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; EFS, event-free survival; RFS, recurrence-free survival; pCR, pathological complete response; pnCR, pathological near complete response; FLOT, fluorouracil, leucovorin, oxaliplatin and docetaxel; SOX, S-1 plus oxaliplatin; CAPOX, capecitabine plus oxaliplatin.

early-phase studies. Furthermore, the therapeutic portfolio is enriched by T-cell immunoglobulin and mucin domain-containing protein 3 (TIM-3) pathway inhibition, where agents like cobolimab (TSR-022) and sabatolimab (MBG453) are being evaluated in combination with other immunotherapeutic agents and standard chemotherapy protocols in advanced solid tumors, including gastric cancer. These novel checkpoint inhibitors, through their diverse mechanisms of action and potential synergistic effects, represent a significant advancement in the evolving paradigm of gastric cancer immunotherapy, though further clinical validation through ongoing trials remains crucial.

Immune-Related Adverse Events in Immune Checkpoint Inhibitors

Immune checkpoint inhibitors (ICIs) have demonstrated significant clinical efficacy in cancer immunotherapy for the treatment of various malignancies, including gastric and gastroesophageal junction cancer. However, the mechanism of action of ICIs carries the inherent risk of immune-related adverse events (irAEs), which results from disruptions in immune homeostasis. These events can manifest across multiple organ systems, including dermatologic manifestations, constitutional symptoms, hematologic abnormalities, and endocrinopathies, with varying degrees of severity. Fortunately, most irAEs are typically reversible with appropriate management.

In the phase Ib, KEYNOTE-012 clinical trial evaluating pembrolizumab monotherapy in advanced gastric and gastroesophageal junction cancer, common adverse events included nausea, vomiting, diarrhea, and thyroid dysfunction. These reactions were generally manageable and did not result in serious consequences. Joshi and Badgwell (2021) demonstrated that PD-1 inhibitors exhibited significantly lower overall adverse event rates compared to conventional chemotherapy, with manageable safety profiles.

Similarly, Pei et al (2023)'s meta-analysis involving 1589 patients treated with immune checkpoint inhibitors in advanced gastric and gastroesophageal junction cancer reported an overall incidence of immune-related adverse events of 16% for all grades, with anti-PD-1 inhibitors showing a higher incidence (20%) compared to anti-PD-L1 inhibitors (13%). The predominant manifestations included fatigue (14.1%), pruritus (10.3%), rash (9.8%), diarrhea (8.2%), hypothyroidism (7.0%), decreased appetite (6.1%), and nausea (5.7%), none of which resulted in severe adverse outcomes. Additionally, Wang et al (2019) reported adverse reactions associated with PD-1 inhibitor therapy included neutropenia (23%), leukopenia (17%), and nausea (3%). Only one patient (3%) experienced grade 3 adverse events, all of which improved with treatment, further demonstrating the overall controllability of PD-1 inhibitor-related adverse reactions.

Neoadjuvant Immunotherapy Combined with Chemotherapy

Recent studies have highlighted the potential of neoadjuvant immunotherapy combined with chemotherapy in the treatment of gastric cancer (GC) and gastroe-

sophageal junction (GEJ) adenocarcinoma (Table 4). These studies have demonstrated promising results, particularly in terms of pathologic complete response (pCR) rates, while survival benefits continue to require further investigation.

A meta-analysis (Yuan et al, 2023) of 20 prospective phase I trials (n = 753) reported a pCR rate of 21.7% (95% confidence interval [CI]: 18.1%–25.5%) and major pathologic response (MPR) rate of 44.0% (95% CI: 34.1%–53.8%). Treatment-related adverse events were observed in 89.1% of patients (95% CI: 82.7%–94.3%), with grade 3–4 events in 34.4%. The R0 resection rate was 98.9% and no significant differences in pCR were found between PD-L1-positive and negative patients (22.5% vs 21.2%, $p > 0.05$).

In another phase I single-arm trial by Wei et al (2023), 34 patients with locally advanced GC/GEJ adenocarcinoma received sintilimab plus chemotherapy with concurrent radiotherapy. The study achieved a pCR rate of 38.2% (95% CI: 22.2%–56.4%), an MPR rate of 79.4%, and R0 resection rate of 100%. The median DFS was 17.0 months, with a one-year survival rate of 92.6%. Higher pCR rates were observed in PD-L1-positive patients (CPS $\geq$5: 63.6% vs CPS $<$5: 28.6%, $p = 0.072$).

The KEYNOTE-585 phase III trial compared pembrolizumab plus chemotherapy to placebo plus chemotherapy in the neoadjuvant/adjuvant setting. The main cohort (n = 804) showed significantly higher pCR rates in the pembrolizumab group (12.9% vs 2.0%, $p < 0.0001$). Additionally, the three-year event-free survival (EFS) rates were 54% vs 44% (Hazard Ratio [HR] = 0.81, $p = 0.0198$), and median overall survival was 60.7 vs 58.0 months (HR = 0.90, 95% CI: 0.73–1.12). While the addition of pembrolizumab significantly improved pCR rates, the survival benefit requires further investigation as no statistically significant difference in OS was observed (Bang et al, 2019).

Overall, while neoadjuvant immunotherapy combined with chemotherapy has shown significant improvements in pCR rates, the impact on survival remains uncertain, and further investigation is needed to confirm the long-term benefits of these approaches in gastric cancer treatment.

Progress in Targeted Therapy for Gastric Cancer

Table 5 outlines key targeted therapies in gastric cancer, focusing on various molecular targets, their representative drugs, pivotal studies, and primary outcomes, demonstrating the diverse approaches in precision medicine for this malignancy.

HER2 Pathway

Trastuzumab, a humanized monoclonal antibody that specifically binds to the extracellular domain IV of HER2, prevents receptor dimerization and subsequent activation of downstream signaling pathways including phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) and mitogen-activated protein kinase (MAPK) cascades. Notably, exploratory analysis revealed that patients with immunohistochemistry 2+/fluorescence in situ hybridization positive (IHC2+/FISH+) or immunohistochemistry 3+ (IHC3+) status achieved an even more impressive OS of 16.0 months with this regimen. Despite the initial success, subsequent advances in anti-

Table 4. Three clinical trials of neoadjuvant immunotherapy combined with chemotherapy in gastric cancer.

Study	Study type	Sample size	Treatment regimen	Key outcomes
Yuan et al, 2023	Meta-analysis	753	Chemotherapy + immunotherapy	pCR rate: 21.7%; MPR rate: 44.0%; TRAEs: 89.1% (Grade 3–4: 34.4%); R0 resection rate: 98.9%; No significant difference in pCR and MPR based on PD-L1 status.
Wei et al, 2023	Phase I single-arm	34	Sintilimab + chemotherapy + radiotherapy (S-1 + nab-paclitaxel)	pCR rate: 38.2%; MPR rate: 79.4%; R0 resection rate: 100%; 1 year OS rate: 92.6%; Higher pCR rate in PD-L1 positive (CPS $\geq$5): 63.6% vs 28.6%.
Bang et al, 2019	Phase III randomized double-blind	1007	Pembrolizumab + chemotherapy vs placebo + chemotherapy	pCR rate: 13.0% vs 2.4%; 3-year EFS rate: 54% vs 44%; 3-year OS rate: 65% vs 60%; mEFS: 44.4 months vs 25.3 months mOS: 60.7 months vs 58.0 months (not significant).

pCR, pathologic complete response; MPR, major pathologic response; TRAEs, treatment-related adverse events; R0, complete resection with negative margins; PD-L1, programmed death-ligand 1; OS, overall survival; CPS, combined positive score; EFS, event-free survival; mEFS, median event-free survival; mOS, median overall survival; S-1, a combination drug consisting of tegafur, gimeracil, and oteracil potassium.

Table 5. Summary of targeted agents and their clinical trial results in gastric cancer.

Target	Representative drug	Key study	Main results
HER2	Trastuzumab	ToGA study	Trastuzumab + chemotherapy: OS 13.8 months, ORR 47%
	DS-8201	DESTINY-Gastric01	DS-8201 vs chemotherapy: ORR 51% vs 14%, OS 12.5 vs 8.4 months
	RC48	C008 study	Second-line or later treatment: OS 7.9 months, PFS 4.1 months, ORR 24.4%
	Pembrolizumab + Trastuzumab	KEYNOTE-811	Pembrolizumab + trastuzumab + chemotherapy vs trastuzumab + chemotherapy: PFS 10.0 vs 8.1 months
VEGF/VEGFR	Ramucirumab	RAINBOW-Asia	Ramucirumab + paclitaxel vs placebo + paclitaxel: PFS 4.14 vs 3.15 months, OS 8.71 vs 7.92 months
CLDN18.2	Zolbetuximab	SPOTLIGHT	Zolbetuximab + mFOLFOX6 vs placebo + mFOLFOX6: PFS 10.61 vs 8.67 months, OS 18.23 vs 15.54 months
		GLOW	Zolbetuximab + CAPOX vs placebo + CAPOX: PFS 8.21 vs 6.8 months, OS 14.39 vs 12.16 months
FGFR2b	Bemarituzumab	FIGHT	Bemarituzumab + mFOLFOX6 vs placebo + mFOLFOX6: PFS 9.5 vs 7.4 months
DKK1	Sirexatamab (DKN-01)	DisTinGuish	Tislelizumab + DKN-01 + XELOX: ORR 62%, ORR 90% in DKK1 high expression population

OS, overall survival; ORR, objective response rate; PFS, progression-free survival; mFOLFOX6, modified folinic acid, fluorouracil, and oxaliplatin; CAPOX, capecitabine plus oxaliplatin; XELOX, capecitabine plus oxaliplatin; ToGA, Trastuzumab for Gastric Cancer; DS-8201, trastuzumab deruxtecan; RC48, disitamab vedotin; VEGF/VEGFR, vascular endothelial growth factor/vascular endothelial growth factor receptor; CLDN18.2, claudin 18.2; FGFR2b, fibroblast growth factor receptor 2b; DKK1, dickkopf Wingless-Type Mouse Mammary Tumor Virus Integration Site Family (WNT) signaling pathway inhibitor 1 (Dickkopf-1).

HER2 therapy for advanced gastric cancer proved challenging. The TyTAN study (Satoh et al, 2014), which evaluated paclitaxel with or without lapatinib in the second-line setting. Similarly, the JACOB study (Tabernero et al, 2023), investigating dual HER2 blockade, showed a modest 3.3-month improvement in median OS (17.5 vs 14.2 months) but failed to demonstrate statistically significant OS prolongation with the addition of pertuzumab to trastuzumab plus chemotherapy.

Recent advances in anti-HER2 therapies for gastric cancer have predominantly centered on antibody-drug conjugates (ADCs). These sophisticated therapeutic agents combine the targeting precision of HER2 antibodies with potent cytotoxic payloads. While trastuzumab emtansine (T-DM1), which utilizes the antimicrotubule agent DM1, failed to demonstrate efficacy in gastric cancer due to its non-cleavable linker, next-generation ADCs have addressed these limitations. Trastuzumab deruxtecan (DS-8201) employs a topoisomerase I inhibitor payload with a novel cleavable tetrapeptide-based linker, allowing for improved payload delivery and potential bystander effects. Similarly, disitamab vedotin (RC48) utilizes a novel vedotin payload with optimized linker technology.

The C008 study (Peng et al, 2021) further demonstrated the efficacy of RC48 in HER2-overexpressing gastric cancer patients in the second-line or later setting. Key findings included a median OS of 7.9 months, median PFS of 4.1 months, and an overall ORR of 24.4%. Notably, patients with HER2 2+ status also derived benefit from RC48, a finding that challenges the traditional definition of HER2 positivity and potentially expands the eligible patient population by approximately 40%.

Concurrently, investigations into HER2-targeted bispecific antibodies such as zanidatamab (ZW25) and KN026 (anti-HER2 bispecific antibody), as well as Margetuximab with its optimized Fc segment, are ongoing. The landscape of first-line treatment for HER2-positive advanced gastric cancer has been further transformed by the KEYNOTE-811 study (Janjigian et al, 2023). At the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting, the first interim analysis of KEYNOTE-811 revealed a remarkable ORR of 74.4% for the pembrolizumab + trastuzumab + chemotherapy arm, representing a 22.7 percentage point improvement over trastuzumab plus chemotherapy alone. At the 2023 European Society for Medical Oncology (ESMO) Congress, the KEYNOTE-811 study unveiled its primary endpoint data for PFS and OS. In the intent-to-treat population, first-line pembrolizumab + trastuzumab + chemotherapy demonstrated a statistically significant improvement in median PFS compared to trastuzumab and chemotherapy alone (10.0 vs 8.1 months; HR = 0.72; $p = 0.0002$), translating to a 28% reduction in the risk of disease progression or death. Notably, in the subgroup of patients with PD-L1 CPS $\geq$1 (>80% of the study population), the PFS benefit was even more pronounced (10.8 vs 7.2 months; HR = 0.70), corresponding to a 30% risk reduction. While the analysis of the co-primary endpoint of OS is ongoing, preliminary data suggest a trend towards OS benefit with the triplet regimen in both the overall and PD-L1 CPS $\geq$1 populations.

The success of KEYNOTE-811 not only reshapes the first-line treatment paradigm for HER2-positive advanced gastric cancer but also opens avenues for investi-

gating the potential of combining targeted therapy, immunotherapy, and chemotherapy in the perioperative setting. Furthermore, the synergistic potential of immunotherapy and ADCs presents an exciting frontier for future research, potentially leading to more effective and personalized treatment strategies for gastric cancer patients. The rational sequencing and combination of HER2-targeted therapies represents a critical frontier in treatment optimization. Following progression on trastuzumab-based therapy, resistance mechanisms often involve HER2 pathway reactivation or alternate pathway upregulation. This understanding has led to several strategic approaches: (1) Continued HER2 blockade with alternative agents, as demonstrated by the efficacy of trastuzumab deruxtecan in trastuzumab-resistant disease; (2) Dual pathway inhibition, such as combining HER2 blockade with immune checkpoint inhibition as shown in KEYNOTE-811; and (3) Exploration of novel combinations with agents targeting resistance pathways such as PI3K inhibitors. Ongoing trials are investigating the optimal sequencing of these approaches and potential biomarker-driven selection strategies.

Targeting the VEGF/VEGFR Pathway

Apatinib mesylate is a highly selective small molecule tyrosine kinase inhibitor that targets the Adenosine Triphosphate (ATP) binding site of VEGFR-2. By blocking vascular endothelial growth factor (VEGF)-mediated endothelial cell migration, proliferation, and tumor angiogenesis, apatinib disrupts the tumor's blood supply and inhibits its growth. Approved by the National Medical Products Administration (NMPA) on 13 December 2014, apatinib is indicated for the treatment of advanced gastric cancer patients who have failed at least two lines of chemotherapy, addressing a significant unmet need in this patient population.

Ramucirumab, a fully human IgG1 monoclonal antibody, binds to the extracellular domain of VEGFR-2, preventing VEGF ligand binding and receptor activation. Unlike small molecule inhibitors, ramucirumab provides a complete extracellular blockade of VEGFR-2 signaling. On 18 March 2022, ramucirumab was approved as a second-line treatment for patients with advanced gastric cancer or gastroesophageal junction adenocarcinoma, broadening the treatment options available.

The approval was supported by the results of the phase III, randomized, double-blind RAINBOW Asia study (Xu et al, 2021), which demonstrated that the combination of paclitaxel and ramucirumab improved clinical outcomes. Specifically, the combination therapy achieved a notable improvement in median progression-free survival (4.14 vs 3.15 months) and median overall survival (8.71 vs 7.92 months). Moreover, the objective response rate (ORR) was enhanced by 6 percentage points (26.5% vs 20.5%) with the addition of ramucirumab. These findings underscore the potential of VEGFR2-targeted therapy in improving outcomes for patients with advanced gastric or gastroesophageal junction cancer.

The targeting of the VEGF/VEGFR pathway has opened new opportunities for combination therapies. Evidence suggests that anti-angiogenic therapies like ramucirumab may synergize with immunotherapy by normalizing tumor vasculature and improving immune cell infiltration. Several ongoing trials are exploring

the combination of VEGFR inhibitors with immune checkpoint inhibitors. Additionally, switching between anti-angiogenic agents, such as transitioning from ramucirumab to apatinib, is being investigated to overcome resistance mechanisms. Combining anti-angiogenic therapy with other targeted treatments, such as HER2-targeted therapies in HER2-positive cancers, is another promising approach under investigation. The optimal sequencing and timing of these combination therapies remain a key area of research.

CLDN18.2 Monoclonal Antibodies

Breakthrough Research on CLDN18.2-Targeted Monoclonal Antibodies: SPOTLIGHT and GLOW Trials

Claudin 18.2 (CLDN18.2) is a four-transmembrane domain protein essential for tight junction formation between epithelial cells. Unlike its isoform CLDN18.1, which is expressed in the lung, CLDN18.2 is predominantly found in differentiated gastric mucosa cells. During malignant transformation, CLDN18.2 is exposed on the surface of cancer cells in approximately 30–40% of gastric cancer cases, making it a promising target for antibody-based therapies.

In 2023, CLDN18.2-targeted monoclonal antibodies have emerged as a promising new approach for the first-line treatment of advanced HER2-negative gastric cancer. The GLOW study, led by Professor Xu Ruihua with Shah as the first author (Shah et al, 2023) employed CAPOX as the chemotherapy backbone and also yielded positive outcomes. Both studies demonstrated statistically significant improvements in PFS and OS, with the GLOW study showing particularly pronounced benefits in the Asian subgroup. These findings hold significant implications for guiding treatment decisions, as they highlight the potential of CLDN18.2-targeted therapies in improving outcomes for advanced gastric cancer patients.

Prospects of CAR-T Therapy CT041 in CLDN18.2-Positive Gastric Cancer

At the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting, CARsgen Therapeutics presented promising results from their CAR-T product CT041. In a phase Ib trial (Botta et al, 2024) involving 14 patients with CLDN18.2-positive advanced gastric cancer who had progressed on two prior lines of therapy, 8 patients (57.1%) achieved partial remission at the first tumor assessment following the initial CT041 infusion. Investigator-assessed outcomes showed an impressive objective response rate of 57.1% and a disease control rate of 78.6%. The study reported a median progression-free survival of 5.6 months and a median overall survival of 10.8 months. Currently, a phase II study (Qi et al, 2024) comparing CT041 to the investigator's choice of treatment is ongoing in China. This randomized controled trial aims to further validate the efficacy and safety of CT041 in a larger patient population, potentially paving the way for its regulatory approval and clinical implementation.

Other Targets

Fibroblast growth factor receptor 2b (FGFR2b)-Targeted Therapy: The FIGHT trial (Wainberg et al, 2022) evaluated FGFR2b therapy in HER2-negative gastric/gastroesophageal junction adenocarcinoma patients. In the bemarituzumab-mFOLFOX6

(N = 77) and placebo-mFOLFOX6 (N = 78) arms, respectively, 59.7% and 66.7% of patients were FGFR2b-positive in ≥10% of tumor cells. The median PFS (95% CI) was 9.5 months (7.3–13.7) with bemarituzumab-mFOLFOX6 and 7.4 months (5.7–8.4) with placebo-mFOLFOX6 (HR, 0.72; 95% CI: 0.49–1.08) (Wainberg et al, 2024). Patients with IHC2+/3+ ≥10% had higher 12-month survival rates (70.2% vs 49.5%).

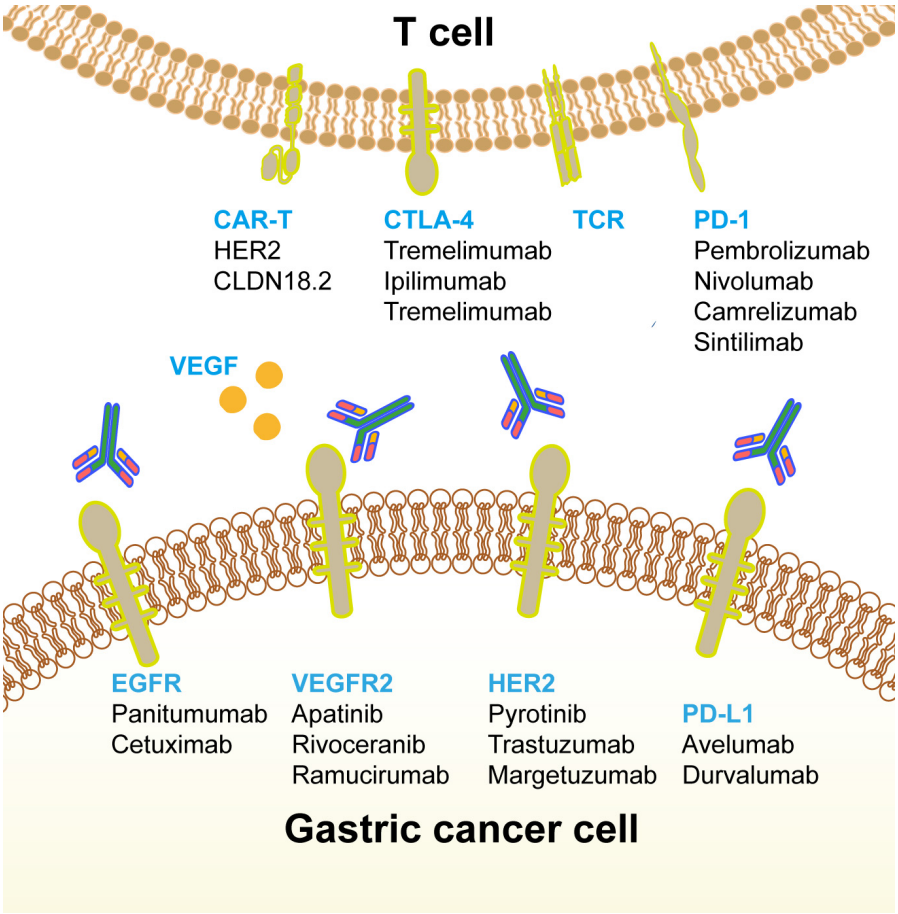

Fig. 1. Immunotherapy and major therapeutic targets for gastric cancer. Some elements are adapted from literature (Guan et al, 2023) (BioMed Central, available under the CC BY 4.0 IGO (https://creativecommons.org/licenses/by/4.0/)). CAR-T, chimeric antigen receptor T-cell; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; TCR, T cell receptor; PD-1, programmed cell death protein 1; EGFR, epidermal growth factor receptor; VEGFR2, vascular endothelial growth factor receptor 2; HER2, human epidermal growth factor receptor 2; PD-L1, programmed death-ligand 1; CLDN18.2, claudin 18.2; VEGF, vascular endothelial growth factor. Fig. 1 was created using Adobe Illustrator CC 2023 (Adobe Inc., San Jose, CA, USA).

DKK1 (dickkopf Wingless-Type Mouse Mammary Tumor Virus Integration Site Family (WNT) signaling pathway inhibitor 1, Dickkopf-1)-Targeted Therapy: DKK1, an inhibitor of the WNT/β-catenin pathway, is highly expressed in gastric cancer cells and associated with advanced stages, metastasis, lymph node infiltration, and vascular invasion.

Sirexatamab (DKN-01) is a monoclonal antibody targeting DKK1. In the DisTinGuish study, the combination of Tislelizumab + DKN-01 + XELOX as first-line therapy achieved an ORR of 62%, with a particularly high response rate of 90% in patients with high DKK1 expression.

Other Therapeutic Targets: Ongoing research is exploring additional targets in gastric cancer, including Mesenchymal-Epithelial Transition factor (cMET), Trophoblast cell-surface antigen 2 (TROP-2), and Focal Adhesion Kinase (FAK), with promising therapies under investigation to enhance the clinical management of this challenging disease.

Collectively, Fig. 1 depicts the therapeutic targets and their corresponding drugs at the interface between T cells and gastric cancer cells, highlighting key immune checkpoints (CAR-T, CTLA-4, TCR, PD-1) and tumor-associated targets (VEGF, epidermal growth factor receptor (EGFR), VEGFR2, HER2, PD-L1), along with their respective monoclonal antibodies and small molecule inhibitors in gastric cancer treatment.

Conclusion

Significant advancements have been achieved in both the research and clinical application of immunotherapy for gastric cancer, offering novel therapeutic prospects for patients with advanced gastric cancer (AGC), particularly those ineligible for surgical intervention or presenting with metastatic disease. The implementation of PD-1 and PD-L1 inhibitors in gastric cancer treatment has demonstrated remarkable efficacy, while diverse cell-based immunotherapeutic approaches have garnered substantial attention from the scientific community. Moreover, immunotherapy has shown the potential to not only enhance patient survival rates but also mitigate treatment-related adverse events. These achievements underline the importance of immunotherapy as a critical component in the management of gastric cancer, providing promising avenues for improving patient outcomes. As technological innovations continue to progress and our understanding of tumor immunology deepens, immunotherapy for gastric cancer is poised to emerge as a cornerstone of future treatment paradigms, potentially improving quality of life for patients.

Key Points

- Significant advancements in CAR-T, TCR-T, and NK cell therapies show promise for gastric cancer treatment.
- Focus on HER2, VEGFR, and claudin 18.2 aims to improve outcomes in advanced gastric cancer.
- Issues like cytokine release syndrome and immune toxicities present major hurdles.
- Combining immunotherapy with targeted therapies could enhance treatment effectiveness.
- Emphasizing refining strategies to overcome resistance and reduce side effects in gastric cancer treatment.

Availability of Data and Materials

All data analyzed in this review are included in the cited articles and are available in published literature.

Author Contributions

HY and SY designed the research study. HY and MB drafted and revised the manuscript. MB participated in data interpretation. MC and JF were responsible for data collection and analysis. All authors contributed to revising the manuscript critically for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

References

Anderson GSF, Chapman MA. T cell-redirecting therapies in hematological malignancies: Current developments and novel strategies for improved targeting. Molecular Therapy. 2024; 32, 2856–2891. https://doi.org/10.1016/j.ymthe.2024.07.028

Bang YJ, Van Cutsem E, Fuchs CS, Ohtsu A, Tabernero J, Ilson DH, et al. KEYNOTE-585: Phase III study of perioperative chemotherapy with or without pembrolizumab for gastric cancer. Future Oncology. 2019; 15: 943–952. https://doi.org/10.2217/fon-2018-0581

Botta GP, Chao J, Ma H, Hahn M, Sierra G, Jia J, et al. Metastatic gastric cancer target lesion complete response with Claudin18.2-CAR T cells. Journal for Immunotherapy of Cancer. 2024; 12: e007927. https://doi.org/10.1136/jitc-2023-007927

Christodoulidis G, Koumarelas KE, Kouliou MN. Revolutionizing gastric cancer treatment: The potential of immunotherapy. World Journal of Gastroenterology. 2024; 30: 286–289. https://doi.org/10.3748/wjg.v30.i4.286

Chung HC, Arkenau HT, Lee J, Rha SY, Oh DY, Wyrwicz L, et al. Avelumab (anti-PD-L1) as first-line switch-maintenance or second-line therapy in patients with advanced gastric or gastroesophageal junction cancer: Phase 1b results from the JAVELIN solid tumor trial. Journal for ImmunoTherapy of Cancer. 2019; 7: 30. https://doi.org/10.1186/s40425-019-0508-1.

Dolton G, Rius C, Wall A, Szomolay B, Bianchi V, Galloway SAE, et al. Targeting of multiple tumor-associated antigens by individual T cell receptors during successful cancer immunotherapy. Cell. 2023; 186: 3333-3349.e27. https://doi.org/10.1016/j.cell.2023.06.020

Du Y, Wei Y. Therapeutic Potential of Natural Killer Cells in Gastric Cancer. Frontiers in Immunology. 2019; 9: 3095. https://doi.org/10.3389/fimmu.2018.03095

Entezam M, Sanaei MJ, Mirzaei Y, Mer AH, Abdollahpour-Alitappeh M, Azadegan-Dehkordi F, et al. Current progress and challenges of immunotherapy in gastric cancer: A focus on CAR-T cells therapeutic approach. Life Sciences. 2023; 318: 121459. https://doi.org/10.1016/j.lfs.2023.121459

Evrard C, Aparicio T, Soularue E, Le Malicot K, Desramé J, Botsen D, et al. Safety of FOLFIRI + Durvalumab +/- Tremelimumab in Second Line of Patients with Advanced Gastric Cancer: A Safety Run-In from the Randomized Phase II Study DURIGAST PRODIGE 59. Biomedicines. 2022; 10: 1211. https://doi.org/10.3390/biomedicines10051211

Faghfuri E, Shadbad MA, Faghfouri AH, Soozangar N. Cellular immunotherapy in gastric cancer: adoptive cell therapy and dendritic cell-based vaccination. Immunotherapy. 2022; 14: 475–488. https://doi.org/10.2217/imt-2021-0285

Fuchs CS, Doi T, Jang RW, Muro K, Satoh T, Machado M, et al. Safety and Efficacy of Pembrolizumab Monotherapy in Patients With Previously Treated Advanced Gastric and Gastroesophageal Junction Cancer: Phase 2 Clinical KEYNOTE-059 Trial. JAMA Oncology. 2018; 4: e180013. https://doi.org/10.1001/jamaoncol.2018.0013

Guan WL, He Y, Xu RH. Gastric cancer treatment: recent progress and future perspectives. Journal of Hematology & Oncology. 2023; 16: 57. https://doi.org/10.1186/s13045-023-01451-3

Janjigian YY, Bendell J, Calvo E, Kim JW, Ascierto PA, Sharma P, et al. CheckMate-032 Study: Efficacy and Safety of Nivolumab and Nivolumab Plus Ipilimumab in Patients With Metastatic Esophagogastric Cancer. Journal of Clinical Oncology. 2018; 36: 2836–2844. https://doi.org/10.1200/JCO.2017.76.6212

Janjigian YY, Kawazoe A, Bai Y, Xu J, Lonardi S, Metges JP, et al. Pembrolizumab plus trastuzumab and chemotherapy for HER2-positive gastric or gastro-oesophageal junction adenocarcinoma: interim analyses from the phase 3 KEYNOTE-811 randomised placebo-controlled trial. Lancet. 2023; 402: 2197–2208. https://doi.org/10.1016/S0140-6736(23)02033-0

Janjigian YY, Shitara K, Moehler M, Garrido M, Salman P, Shen L, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet. 2021; 398: 27–40. https://doi.org/10.1016/S0140-6736(21)00797-2

Joshi SS, Badgwell BD. Current treatment and recent progress in gastric cancer. CA: a Cancer Journal for Clinicians. 2021; 71: 264–279. https://doi.org/10.3322/caac.21657

Kang YK, Chen LT, Ryu MH, Oh DY, Oh SC, Chung HC, et al. Nivolumab plus chemotherapy versus placebo plus chemotherapy in patients with HER2-negative, untreated, unresectable advanced or recurrent gastric or gastro-oesophageal junction cancer (ATTRACTION-4): a randomised, multicentre, double-blind, placebo-controlled, phase 3 trial. The Lancet. Oncology. 2022; 23: 234–247. https://doi.org/10.1016/S1470-2045(21)00692-6

Kelly RJ, Lee J, Bang YJ, Almhanna K, Blum-Murphy M, Catenacci DVT, et al. Safety and Efficacy of Durvalumab and Tremelimumab Alone or in Combination in Patients with Advanced Gastric and Gastroesophageal Junction Adenocarcinoma. Clinical Cancer Research. 2020; 26: 846–854. https://doi.org/10.1158/1078-0432.CCR-19-2443

Lee SC, Shimasaki N, Lim JSJ, Wong A, Yadav K, Yong WP, et al. Phase I Trial of Expanded, Activated Autologous NK-cell Infusions with Trastuzumab in Patients with HER2-positive Cancers. Clinical Cancer Research. 2020; 26: 4494–4502. https://doi.org/10.1158/1078-0432.CCR-20-0768

Lei M, Siemers NO, Pandya D, Chang H, Sanchez T, Harbison C, et al. Analyses of PD-L1 and Inflammatory Gene Expression Association with Efficacy of Nivolumab ± Ipilimumab in Gastric Cancer/Gastroesophageal Junction Cancer. Clinical Cancer Research. 2021; 27: 3926–3935. https://doi.org/10.1158/1078-0432.CCR-20-2790

Li S, Bao J, Li X, Yang Q, Xu J, Chen S, et al. Multicenter phase I dose escalation and expansion study of pyrotinib in combination with camrelizumab and chemotherapy as first-line treatment for HER2-positive advanced gastric and gastroesophageal junction adenocarcinoma. eClinicalMedicine. 2023a; 66: 102314.

https://doi.org/10.1016/j.eclinm.2023.102314

Li T, Qian C, Gu Y, Zhang J, Li S, Xia N. Current progress in the development of prophylactic and therapeutic vaccines. Science China. Life Sciences. 2023b; 66: 679–710. https://doi.org/10.1007/s11427-022-2230-4

Li Y, Wang C, Xu M, Kong C, Qu A, Zhang M, et al. Preoperative NLR for predicting survival rate after radical resection combined with adjuvant immunotherapy with CIK and postoperative chemotherapy in gastric cancer. Journal of Cancer Research and Clinical Oncology. 2017; 143: 861–871. https://doi.org/10.1007/s00432-016-2330-1

Lin JX, Tang YH, Zheng HL, Ye K, Cai JC, Cai LS, et al. Neoadjuvant camrelizumab and apatinib combined with chemotherapy versus chemotherapy alone for locally advanced gastric cancer: a multicenter randomized phase 2 trial. Nature Communications. 2024; 15: 41. https://doi.org/10.1038/s41467-023-44309-5

Moehler M, Dvorkin M, Boku N, Özgüroğlu M, Ryu MH, Muntean AS, et al. Phase III Trial of Avelumab Maintenance After First-Line Induction Chemotherapy Versus Continuation of Chemotherapy in Patients With Gastric Cancers: Results From JAVELIN Gastric 100. Journal of Clinical Oncology. 2021; 39: 966–977. https://doi.org/10.1200/JCO.20.00892

Oh DY, Janjigian YY, Al-Batran SE, Wainberg ZA, van Cutsem E, Molena D, et al. 129O pathological complete response (pCR) to durvalumab plus 5-fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) in resectable gastric and gastroesophageal junction cancer (GC/GEJC): Interim results of the global, phase III MATTERHORN study. Annals of Oncology. 2023; 34: S1520–S1521. https://doi.org/10.1016/j.annonc.2023.10.265

Pei WG, Chen WZ, Wu YK, Tan SX, Jie ZG. Immune-related adverse events associated with immune checkpoint inhibitors for advanced gastric and gastroesophageal junction cancer: A meta-analysis. World Journal of Gastrointestinal Oncology. 2023; 15: 352–367. https://doi.org/10.4251/wjgo.v15.i2.352

Peng Z, Liu T, Wei J, Wang A, He Y, Yang L, et al. Efficacy and safety of a novel anti-HER2 therapeutic antibody RC48 in patients with HER2-overexpressing, locally advanced or metastatic gastric or gastroesophageal junction cancer: A single-arm phase II study. Cancer Communications. 2021; 41: 1173–1182. https://doi.org/10.1002/cac2.12214

Qi C, Zhang P, Liu C, Zhang J, Zhou J, Yuan J, et al. Safety and Efficacy of CT041 in Patients With Refractory Metastatic Pancreatic Cancer: A Pooled Analysis of Two Early-Phase Trials. Journal of Clinical Oncology. 2024; 42: 2565–2577. https://doi.org/10.1200/JCO.23.02314

Qi CS, Gong JF, Li J, Liu D, Qin YR, Ge S, et al. Claudin18.2-specific CAR T cells in gastrointestinal cancers: Phase 1 trial interim results. Nature Medicine. 2022; 28: 1189-1198. https://doi.org/10.1038/s41591-022-01800-8

Sakamoto N, Ishikawa T, Kokura S, Okayama T, Oka K, Ideno M, et al. Phase I clinical trial of autologous NK cell therapy using novel expansion method in patients with advanced digestive cancer. Journal of Translational Medicine. 2015; 13: 277. https://doi.org/10.1186/s12967-015-0632-8

Satoh T, Xu RH, Chung HC, Sun GP, Doi T, Xu JM, et al. Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of HER2-amplified advanced gastric cancer in Asian populations: TyTAN–a randomized, phase III study. Journal of Clinical Oncology. 2014; 32: 2039–2049. https://doi.org/10.1200/JCO.2013.53.6136

Shah MA, Shitara K, Ajani JA, Bang YJ, Enzinger P, Ilson D, et al. Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial. Nature Medicine. 2023; 29: 2133–2141. https://doi.org/10.1038/s41591-023-02465-7

Shi L, Zhou Q, Wu J, Ji M, Li G, Jiang J, et al. Efficacy of adjuvant immunotherapy with cytokine-induced killer cells in patients with locally advanced gastric cancer. Cancer Immunology, Immunotherapy. 2012; 61: 2251–2259. https://doi.org/10.1007/s00262-012-1289-2

Shitara K, Ajani JA, Moehler M, Garrido M, Gallardo C, Shen L, et al. Nivolumab plus chemotherapy or ipilimumab in gastro-oesophageal cancer. Nature. 2022; 603: 942–948. https://doi.org/10.1038/s41586-022-04508-4

Singh N, Kulikovskaya I, Barrett DM, Binder-Scholl G, Jakobsen B, Martinez D, et al. T cells targeting NY-ESO-1 demonstrate efficacy against disseminated neuroblastoma. Oncoimmunology. 2015; 5: e1040216. https://doi.org/10.1080/2162402X.2015.1040216

Tabernero J, Hoff PM, Shen L, Ohtsu A, Shah MA, Siddiqui A, et al. Pertuzumab, trastuzumab, and chemotherapy in HER2-positive gastric/gastroesophageal junction cancer: end-of-study analysis of the JACOB phase III randomized clinical trial. Gastric Cancer. 2023; 26: 123–131. https://doi.org/10.1007/s10120-022-01335-4

Thrift AP, El-Serag HB. Burden of Gastric Cancer. Clinical Gastroenterology and Hepatology. 2020; 18: 534–542. https://doi.org/10.1016/j.cgh.2019.07.045

Wachsmann TLA, Wouters AK, Remst DFG, Hagedoorn RS, Meeuwsen MH, van Diest E, et al. Comparing CAR and TCR engineered T cell performance as a function of tumor cell exposure. Oncoimmunology. 2022; 11: 2033528. https://doi.org/10.1080/2162402X.2022.2033528

Wainberg ZA, Enzinger PC, Kang YK, Qin S, Yamaguchi K, Kim IH, et al. Bemarituzumab in patients with FGFR2b-selected gastric or gastro-oesophageal junction adenocarcinoma (FIGHT): a randomised, double-blind, placebo-controlled, phase 2 study. The Lancet. Oncology. 2022; 23: 1430–1440. https://doi.org/10.1016/S1470-2045(22)00603-9

Wainberg ZA, Kang YK, Lee KW, Qin S, Yamaguchi K, Kim IH, et al. Bemarituzumab as first-line treatment for locally advanced or metastatic gastric/gastroesophageal junction adenocarcinoma: final analysis of the randomized phase 2 FIGHT trial. Gastric Cancer. 2024; 27: 558–570. https://doi.org/10.1007/s10120-024-01466-w

Wang F, Wei XL, Wang FH, Xu N, Shen L, Dai GH, et al. Safety, efficacy and tumor mutational burden as a biomarker of overall survival benefit in chemo-refractory gastric cancer treated with toripalimab, a PD-1 antibody in phase Ib/II clinical trial NCT02915432. Annals of Oncology. 2019; 30: 1479–1486. https://doi.org/10.1093/annonc/mdz197

Wei J, Lu X, Liu Q, Fu Y, Liu S, Zhao Y, et al. Neoadjuvant sintilimab in combination with concurrent chemoradiotherapy for locally advanced gastric or gastroesophageal junction adenocarcinoma: a single-arm phase 2 trial. Nature Communications. 2023; 14: 4904. https://doi.org/10.1038/s41467-023-40480-x

Xu RH, Zhang Y, Pan H, Feng J, Zhang T, Liu T, et al. Efficacy and safety of weekly paclitaxel with or without ramucirumab as second-line therapy for the treatment of advanced gastric or gastroesophageal junction adenocarcinoma (RAINBOW-Asia): a randomised, multicentre, double-blind, phase 3 trial. The Lancet. Gastroenterology & Hepatology. 2021; 6: 1015–1024. https://doi.org/10.1016/S2468-1253(21)00313-7

Xu X, Chen J, Li W, Feng C, Liu Q, Gao W, et al. Immunology and immunotherapy in gastric cancer. Clinical and Experimental Medicine. 2023; 23: 3189–3204. https://doi.org/10.1007/s10238-023-01104-2

Yuan Z, Cui H, Wang S, Liang W, Cao B, Song L, et al. Combining neoadjuvant chemotherapy with PD-1/PD-L1 inhibitors for locally advanced, resectable gastric or gastroesophageal junction adenocarcinoma: A systematic review and meta-analysis. Frontiers in Oncology. 2023; 13: 1103320. https://doi.org/10.3389/fonc.2023.1103320

Zhang D, He W, Wu C, Tan Y, He Y, Xu B, et al. Scoring System for Tumor-Infiltrating Lymphocytes and Its Prognostic Value for Gastric Cancer. Frontiers in Immunology. 2019; 10: 71. https://doi.org/10.3389/fimmu.2019.00071

Zhao Q, Jiang Y, Xiang S, Kaboli PJ, Shen J, Zhao Y, et al. Engineered TCR-T Cell Immunotherapy in Anticancer Precision Medicine: Pros and Cons. Frontiers in Immunology. 2021; 12: 658753. https://doi.org/10.3389/fimmu.2021.658753