


Current Molecular Targeted Agents for Advanced Gastric Cancer

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Abstract: Gastric cancer is the third leading cause of malignant tumor-related mortality worldwide. Traditional cytotoxic agents prolong the overall survival and progression-free survival of patients with advanced gastric cancer (AGC) compared to that with best supportive care. Due to the occurrence of serious adverse drug reactions that result in discontinued treatment, the survival benefit in AGC remains unsatisfactory. Systemic chemotherapy regimens have changed greatly, especially since the introduction of trastuzumab. Nevertheless, HER2 positivity is present in only approximately 20% of tumors. Due to the genetic heterogeneity and complexity of patients, there are many studies in progress that are exploring novel targeted drugs as an alternative to chemotherapy or adjuvant treatment in early-stage, progressive, and advanced gastric cancer. On the basis of the differences in gene expression profiles among patients, searching for specific and sensitive predictive biomarkers is important for identifying patients who will benefit from a specific targeted drug. With the development of targeted therapies and available chemotherapeutic drugs, there is no doubt that, over time, more patients will achieve better survival outcomes. Recently, immune checkpoint blockade has been well developed as a promising anticancer strategy. This review outlines the currently available information on clinically tested molecular targeted drugs and immune checkpoint inhibitors for AGC to provide support for decision-making in clinical practice.

Keywords: advanced gastric cancer, molecular targeted drugs, immune checkpoint blockade

Introduction

During the second half of the 20th century, there was a dramatic decline in gastric cancer (GC). However, GC still ranks as the third most common cause of malignant tumor mortality worldwide.¹ In 2012 alone, one million people were diagnosed with GC, making it the fourth most common cancer.² Although many factors, including genetic background, lifestyle (e.g., alcohol consumption, smoking habits, and diet), and *Helicobacter pylori* infection, have been demonstrated to be related to GC,³ the pathogenesis of GC is rather complicated and has not yet been well clarified. Due to its nonspecific symptoms, similar to dyspepsia, GC is usually misdiagnosed as gastritis and diagnosed late.⁴ The clinical outcome of GC depends on the tumor stage at diagnosis. Surgery, chemotherapy and radiation therapy are the most common treatments. Radical gastrectomy is the preferred approach for treating localized GC, but recurrence rates remain high. Patient prognosis is poor, with a five-year survival of less than 25% and a median overall survival (OS) of 7 to 10 months after diagnosis based on most large clinical studies.^{5,6} Traditional chemotherapeutic drugs, including 5-fluorouracil (5-FU), oral fluoropyrimidine, platinum agents, taxanes, irinotecan, and anthracyclines, aim to kill cancer cells.⁷

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Unfortunately, they are nonspecific and have serious adverse reactions. In addition, chemoresistance is another major obstacle for effective cancer therapy. Fortunately, in recent decades, the development of molecularly targeted agents that inhibit specific oncogenic signal pathways has promoted the personalization of cancer therapeutic treatment and has greatly improved the outcomes of GC.⁸ Moreover, systemic chemotherapy regimens for advanced gastric cancer (AGC) have progressed sharply, especially since the introduction of trastuzumab. Trastuzumab was approved in the United States for HER2-overexpressing AGC as the first-line treatment drug.⁹ However, due to the genetic heterogeneity and complexity of tumors, HER2 overexpression only occurs in approximately 20% of all GCs.¹⁰ In this scenario, other novel molecular targeted agents and immune checkpoint inhibitors have shown effectiveness after clinical verification for many years. For instance, vascular endothelial growth factor receptor-2 (VEGFR-2) inhibitors have been introduced into clinical practice.^{11,12} Some newly developed targeted therapies and their molecular targets are summarized in Figure 1.

This review outlines the currently available data on clinically molecular targeted agents and immune checkpoint inhibitors for AGC in order to provide strategies for decision-making in clinical practice.

Vascular Endothelial Growth Factor (VEGF) Inhibitors

Angiogenesis is necessary to promote the growth and metastasis of solid tumors. VEGF is considered an important driver of tumor angiogenesis.¹³ Thus, anti-VEGF inhibitors are attractive options that are making rapid progress. VEGF-A, -B, -C, -D, and placenta growth factor (PLGF) constitute the main structurally related ligands, among which VEGF-A is critical for the organization of the vasculature. Correspondingly, the related receptor tyrosine kinases (RTKs) include VEGFR-1, -2, -3, and neuropilins (NRPSs).¹⁴ The principal receptor that interacts with VEGF ligands with high affinity is VEGFR-2.¹⁵ Representative and approved VEGF inhibitors are discussed in detail below, and their relevant clinical trials are listed in Table 1.

Ramucirumab

Ramucirumab is a specific antibody against VEGFR-2 that blocks receptor binding to VEGF-A, -C and -D. Ramucirumab was initially approved in 2014 for patients with AGC/gastroesophageal junction (GEJ) adenocarcinoma.¹⁶ Ramucirumab has been proven to prolong OS and is considered a new therapy for AGC regardless of whether it is used as monotherapy or combined with paclitaxel.^{17,18} The REGARD trial reported that ramucirumab monotherapy offered

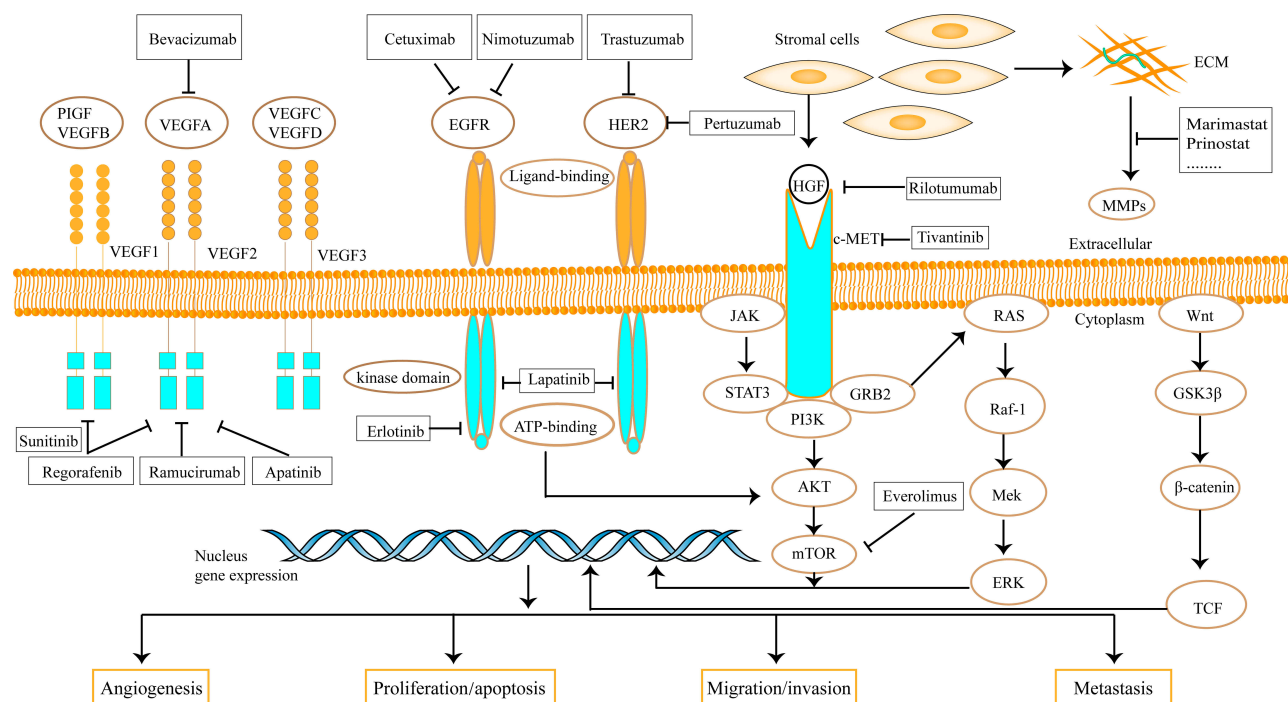


Figure 1 Molecular targeted agents and related action mechanism that are researched in AGC.

Table I Overview of Clinical Trials of Molecular Targeted Drugs in AGC

Reference	Phase	N	Treatment	PFS (m)	OS (m)	AE(Grade3–4)
Fuchs et al ¹⁷	III	238 117	Ramucirumab Placebo	2.1 1.3	5.2 3.8	Hypertension (8%) Fatigue (6%) Bleeding (3%)
Wilke et al ¹⁸	III	330 335	Ramucirumab + PTX Placebo + PTX	4.4 2.9	9.6 7.4	Bleeding (4%) Fatigue (12%) Hypertension (14%) Neuropathy (8%) Neutropenia (22%)
Fuchs et al ²⁰	III	326 319	Ramucirumab + FP Placebo + FP	5.7 5.4	11.2 10.7	Neutropenia (26%) Anaemia (12%) Hypertension (10%)
Shen et al ²⁶	III	100 102	XP + bevacizumab XP + placebo	6.0 6.3	11.4 10.5	Vomiting (22%) Neutropenia (14%) Nausea (9%)
Li et al ³⁰	II	48 47 46	Group A: Placebo Group B: apatinib 850mg Group C: apatinib 425mg	1.4 3.67 3.2	2.5 4.83 4.27	Hand-foot syndrome group B (4.26%) group C (13.04%) Hypertension group B (8.51%) group C (10.87%)
Li et al ³¹	III	176 91	Apatinib 850mg Placebo	2.6 1.8	6.5 4.7	Hypertension (4.5%) Hand-foot syndrome (8.5%) Proteinuria (2.3%)
Pavakis et al ⁴⁰	II	100 52	BSC + regorafenib BSC + placebo	2.6 0.9	5.8 4.5	GI disorders (11%) Infections (6%) Metabolism and nutrition disorders (4%)
Bang et al ⁵³	III	298 296	Cisplatin + Trastuzumab Capecitabine/fluorouracil	6.7 5.5	13.8 11.1	Nausea (67%) Vomiting (50%) Neutropenia (53%)
Thus et al ⁵⁸	II/III	228 117	Trastuzumab emtansine Taxane	2.7 2.9	7.9 8.6	Anaemia (26%) Thrombocytopenia (11%)
Kimura et al ⁵⁵	II	51	S-I + trastuzumab	5.1	15.8	Neutropenia (12.0%) Anemia (24.0%) Diarrhea (10.0%) Anorexia (12.0%)
Tabertero et al ⁶¹	III	388 392	Pertuzumab+Trastuzumab + XPF Trastuzumab+ XPF	8.5 7.0	17.5 14.2	Neutropenia (30%) Anemia (15%) Diarrhea (13%)
Satoh et al ⁶³	III	132 129	Lapatinib + PTX PTX	5.5 4.4	11 8.9	Diarrhea (18%) Neutropenia (31%) Leukopenia (24%)
Hecht et al ⁶⁴	III	272 273	CapeOX + lapatinib CapeOX + placebo	6.0 5.4	12.2 10.5	Diarrhea (12%) Nausea (6%) Vomiting (6%)

(Continued)

Table I (Continued).

Reference	Phase	N	Treatment	PFS (m)	OS (m)	AE(Grade3–4)
Doi et al ⁸⁰	II	53	Everolimus	2.7	10.1	Anemia (11.3%) Hyponatremia (9.4%) Increased-GT (7.5%) Lymphopenia (7.5%)
Ohtsu et al ⁸¹	III	439 217	Everolimus + BSC Placebo + BSC	1.7 1.4	5.4 4.3	Anemia (16%) Decreased appetite (11%) Fatigue (8%)
Catenacci et al ⁸⁶	III	304 305	ECX + rilotumumab ECX + placebo	5.6 6.0	8.8 10.7	Neutropenia (29%) Anaemia (12%) Fatigue (10%)

Abbreviations: DCR, disease control rate; ECX, epirubicin + cisplatin + capecitabine; CapeOX, capecitabine + oxaliplatin; PTX, paclitaxel; XP, capecitabine + cisplatin; XPF, capecitabine + 5-fluorouracil + cisplatin; DOC/PTX, docetaxel/paclitaxel; FP, fluoropyrimidine and cisplatin m, months; AE, adverse events; OS, overall survival; PFS, progression-free survival; RR, response rate; GI, gastrointestinal; GT, glutamyltransferase; N, the total number of enrolled patients.

a 1.4-month improvement in the median OS (HR = 0.776; 95% CI, 0.603–0.998).¹⁷ The RAINBOW trial also suggested that ramucirumab plus paclitaxel increased median OS in patients who previously received paclitaxel alone. Of the enrolled patients, 330 were assigned to the combined medicine group and 335 were assigned to the paclitaxel alone group. The primary endpoint was OS, and in the combined medicine group, OS was significantly superior to that in the patients in the paclitaxel alone group (9.6 vs 7.4 months), with an HR of 0.807 (95% CI, 0.678–0.962).¹⁸ Both of these trials validated VEGFR-2 as a promising therapeutic target, and subgroup analyses showed that age had no impact on the efficacy of ramucirumab in AGC.¹⁹ On the basis of these meaningful results, the RAINFALL trial was designed to assess the efficacy of ramucirumab as a first-line therapy combined with cisplatin and fluoropyrimidine in patients with HER2-negative metastatic G/GEJ adenocarcinoma. Unfortunately, the primary endpoint of PFS was only prolonged by 0.3 months in the experimental group and therefore was not clinically significant. The second endpoint, median OS, was not different between the groups. As a result, ramucirumab is not recommended as a first-line therapy when combined with cisplatin and fluoropyrimidine for HER2-negative patients.²⁰ Ongoing trials combining ramucirumab with the FLOT regime or immune checkpoint inhibitors will provide additional benefit for specific intent to treat the population. The importance of looking for predictive biomarkers that reliably and consistently for anti-angiogenic therapies is being highlighted.

Bevacizumab

VEGF-A plays a critical role in the management of angiogenesis.²¹ Bevacizumab can suppress tumor growth as a specific monoclonal antibody targeting VEGF-A.²² A multicenter Phase II study suggested that bevacizumab combined with chemotherapy enhanced the primary endpoints median OS and PFS in G/GEJ adenocarcinoma.²³ Another phase II trial also achieved a promising result with a median PFS of 6.6 months and median survival of 11.1 months.²⁴ In terms of the compelling results, the large-scale AVAGAST trial also reported that bevacizumab prolonged PFS and significantly enhanced the overall response rate (ORR). Although the median OS was prolonged by 2 months, the primary objective in the trial was not reached. Subgroup analyses suggested a greater benefit in the European and Pan-American regions.²⁵ In the meantime, AVATAR, a Phase III trial specifically designed for Chinese patients, failed to reach its preplanned goal. The median OS and PFS were similar in both arms.²⁶ The different results between geographic regions may be attributed to the differences in prognostic factors and therapeutic schedules. In non-Asian regions, the efficacy of bevacizumab was strongly related to the levels of baseline plasma VEGF-A and tumor neuropilin-1.²⁷ However, it should be noted that although these studies generated evidence that supports bevacizumab as an effective VEGF-A antagonist, they lack combined pharmacokinetic data and information on potential biomarkers.²⁶

Apatinib

Apatinib is a new VEGFR-2 RTK inhibitor that blocks the intracellular ATP-binding site. Therefore, it has certain inhibitory effects on PDGFR- β , c-Kit, and c-Src.^{28,29} It displays antitumor efficacy in cell experiments and animal studies.²⁹ On the basis of preclinical studies, the optimal protocol and manageable adverse profile of apatinib in metastatic GC was assessed in a phase II trial.³⁰ The patients were assigned to group A (placebo, $n = 48$), group B (850 mg apatinib once a day, $n = 47$), or group C (425 mg apatinib twice a day, $n = 46$). Among these groups, patients in group B had longer median OS and PFS and fewer adverse events.³⁰ Therefore, apatinib (850 mg once daily) was used in later phase III clinical trials. Compared to placebo, apatinib significantly improved OS and PFS.³¹ The CFDA (China Food and Drug Administration) has approved the drug to treat metastatic GC/GEJC after second-line chemotherapy.³² However, in the ANGEL trial (NCT03042611), a phase III study of apatinib monotherapy in AGC patients who have failed at least two prior lines of therapy, apatinib failed to significantly prolong the median OS. Subgroup analyses showed significant improvement of median OS and PFS in patients who endured three or more lines of therapy. In the meantime, inevitable treatment-related adverse events such as HFS and hypertension should not be ignored. As a third- or subsequent-line therapy, due to the convenient administration regimen and manageable safety profile, apatinib has been an emerging option for adult patients who progress or relapse after chemotherapy.

Other VEGF Inhibitors

Sunitinib can suppress tumor growth by inhibiting VEGF, PDGF, c-KIT, and FLT3 RTKs.³³ Based on the superior efficacy achieved in preclinical studies, the antitumor activity of sunitinib monotherapy was evaluated in patients who previously received treatment. However, among the 78 recruited patients in the phase II trial, only 2 patients had partial responses, suggesting that sunitinib lacks sufficient clinical evidence for AGC.³⁴ This conclusion was further confirmed by another independent phase II trial.³⁵

Orantinib is an orally active RTK inhibitor with wide spectrum activity that has been verified in clinical trials for GC. Nevertheless, two phase II studies have found that orantinib has no synergistic effect with S-1 or oxaliplatin (SOX) in AGC.^{36,37}

Regorafenib is a multikinase inhibitor that specifically targets angiogenic (VEGFR-1, VEGFR-2, and angiopoietin receptor Tie-2), stromal (PDGFR- β), and oncogenic (RAF, RET, and c-KIT) RTKs.^{38,39} In the INTEGRATE trial, regorafenib prolonged the PFS of 1.7 months in refractory AGC with an HR of 0.4 (95% CI, 0.28–0.59).⁴⁰ Further study verified that regorafenib improved deterioration-free survival without an excessively negative effect on quality of life.⁴¹ Therefore, the effect of regorafenib plus chemotherapy was assessed again in refractory GC through an ongoing multinational phase III trial named INTEGRATE II.⁴²

In addition, numerous anti-VEGF drugs are currently being explored in preclinical and clinical trials for AGC. Although aberrant angiogenesis is a key feature of solid tumors and the VEGF pathway is crucial in angiogenesis, the continuous progress in searching specific molecular biomarkers will be helpful for identifying priority patients who should benefit most from the addition of VEGF inhibitors.

Epidermal Growth Factor Receptor (EGFR) Antagonists

EGFR (ErbB-1/HER1), ErbB-2 (neu, HER2), ErbB-3 (HER3), and ErbB-4 (HER4) are the four definite receptors of the ErbB family, and they all have three common domains including a ligand-binding region, transmembrane domain and tyrosine kinase binding domain.^{43–45} Multiple studies have detected ErbB gene overexpression and mutations in colorectal cancer, GC, lung cancer, and ovarian cancer.^{46–49} Extensive preclinical studies and initial clinical trials have evaluated the practical value of inhibiting either EGFR or HER2 or both. The results suggested that targeting both EGFR and HER2 using two different antibodies has additive or even synergistic anti-GC effects.⁴⁴ In GC, 44% of EGFR receptors are overexpressed, making them an exciting therapeutic target.⁵⁰

Trastuzumab

Previous studies demonstrated that HER2 enhances proliferation and inhibits cell death.^{51,52} Treatment with trastuzumab, a HER2-targeted inhibitor, results in antibody-dependent cell-mediated cytotoxicity.⁵³ The ToGA trial verified that trastuzumab plus chemotherapy was more efficacious in patients with HER2 overexpression (immunohistochemistry (IHC) 2+ and fluorescence in situ hybridization (FISH) positive or IHC 3+); compared to patients with low HER2 expression (IHC 0 or 1+ and FISH positive), these patients had a longer median OS of 2.7 months (HR = 0.74; 95% CI, 0.60–0.91). An exploratory,

post hoc analysis supported that trastuzumab plus chemotherapy substantially increased OS (median overall survival 16.0 months) in patients with HER2 overexpression.⁵³ The subsequent phase II study also obtained a meaningful result.⁵⁴ As an adjunctive therapy combined with S-1 or B-DOCT, trastuzumab demonstrated promising antitumor effects and manageable adverse reactions in patients with HER2 overexpression.^{55–57} All clinical trials showed a synergistic antitumor effect of targeted agent trastuzumab and chemotherapy agents for patients with HER2 overexpression. The level of HER2 protein should be used as a biomarker to predict the clinical outcome and aid in chemotherapeutic selection in HER2-positive patients who received trastuzumab. Similar to trastuzumab, trastuzumab emtansine (comprised of trastuzumab and a tubulin inhibitor emtansine) was initially designed to inhibit HER2-mediated signaling and mediate antibody-dependent cellular cytotoxicity. However, GATSBY, a seamless, adaptive phase II/III study, revealed that trastuzumab emtansine did not benefit patients in terms of median OS (HR = 1.15; 95% CI, 0.87–1.51), and grade 3 or more adverse reactions, such as pulmonary toxicity, were higher in the trastuzumab emtansine group than in the taxane group. Imbalances in demographics or baseline disease characteristics, toxicity, drug administration and greater heterogeneity of HER2 expression are the main factors leading to the failure of trastuzumab emtansine.⁵⁸ Given these inconsistent observations, more evidence is needed for AGC in regard to using trastuzumab emtansine as a HER2-targeted second-line therapy, and the reason for these inconsistencies is worth pondering.

Pertuzumab

Pertuzumab is a humanized monoclonal antibody that binds to subdomain II to block HER2 heterodimerization. In HER2-positive breast cancer, pertuzumab and trastuzumab have complementary mechanisms and improve the rates of invasive disease-free survival.⁵⁹ It is logical to hypothesize that dual HER2-targeted therapy and chemotherapy have the potential to improve survival outcomes in patients with HER2-positive AGC. JOSHUA, a phase IIa trial, evaluated two different doses of pertuzumab in patients with HER2-positive AGC/GEJ cancer from the perspective of pharmacokinetic and safety files. A dosage of 840 mg q3w was considered optimum for maintaining trough concentrations above the target in at least 90% of patients.⁶⁰ Subsequently, the phase III study (JACOB trial) was designed to assess the efficacy of pertuzumab combined with trastuzumab and chemotherapy as the first-line setting in patients with HER2-positive

metastatic G/GEJ cancer. Although the median OS was prolonged by 3.3 months, there was no statistical significance.⁶¹ The negative result highlights the difference in HER2 biology between breast and gastric cancer. Furthermore, gastric cancer has characteristic HER2 heterogeneity, which may affect the activity of pertuzumab.

Lapatinib

Approximately 15–45% of GC patients have a overexpression of EGFR and HER2 tyrosine kinases, and lapatinib is a dual inhibitor that blocks autophosphorylation and downstream signaling.⁶² More importantly, HER2 status might be affected by different stages of the disease, host immune status, concomitant genomic alterations and prior first-line chemotherapy with or without trastuzumab. The TyTAN trial showed a prolonged median OS of 2.1 months with lapatinib plus paclitaxel as second-line therapy in Asian patients with HER2-amplified AGC.⁶³ Although the median OS and PFS were increased in lapatinib recipients, the change was not statistically significant. However, the ORR was significantly improved in the experimental group. Subgroup analyses showed clinically relevant OS and PFS gains in Chinese patients with HER2 overexpression (FISH positive and IHC 3+). The TRIO-013/LOGiC phase III trial also demonstrated that lapatinib combined with CapeOx did not improve OS for HER2-amplified GC.⁶⁴ Nevertheless, a subgroup analysis based on age showed that patients < 60 years of age had significant improvement (HR = 0.69; 95% CI, 0.51–0.94), but older patients had an unfortunate outcome (HR = 1.08; 95% CI, 0.81–1.45).⁶⁴ Since many factors, such as race, region, age, and sex, may influence drug effects, further studies need to be performed to choose an appropriate intent-to-treat population that could obtain a favorable prognosis from lapatinib therapy. Lapatinib could be an option for second-line therapy for AGC patients younger than 60 with HER2 overexpression (FISH positive and IHC 3+).

Other EGFR Inhibitors

In addition to trastuzumab and lapatinib, several other potential targeted inhibitors of EGFR and HER2 are under clinical development. Cetuximab is an anti-EGFR antibody. In patients with BRAF V600E-mutated colorectal cancer, cetuximab combined with encorafenib showed significant benefit with respect to OS and ORR (objective response rate).⁶⁵ However, the addition of cetuximab provided no additional benefit for AGC in the EXPAND trial. The median PFS was shortened by 1.2 months (HR = 1.09; 95% CI, 0.92–1.29).⁶⁶ Erlotinib is another small molecule inhibitor of EGFR that binds to its ATP

binding site and inhibits the intracellular phosphorylation of EGFR. Furthermore, MARK signaling, which inhibits proliferation and activation of the intrinsic apoptosis pathway, is blocked with erlotinib.⁶⁷ In both pancreatic cancer and non-small-cell lung cancer, erlotinib showed compelling results.^{68,69} A phase II trial showed that erlotinib has antitumor activity in patients with distal esophageal/GEJ adenocarcinomas but not in distal gastric tumors. Another phase II trial reached a similar conclusion in patients receiving erlotinib plus FOLFOX6 (oxaliplatin, fluorouracil, and leucovorin).^{70,71} Additionally, nimotuzumab is an EGFR inhibitor that has been used to treat EGFR-expressing 3+/4+ nasopharyngeal carcinoma in China. Nimotuzumab plus irinotecan (N-IRI) has shown potential improvement in the RR, PFS, and OS in the EGFR 2+/3+ subgroup of GC patients compared to that in the N-IRI treatment alone subgroup.⁷² According to the promising results, more new targeted agents will be approved in the future and will benefit an increasing number of patients.

PI3K/Akt/mTOR Inhibitor

The PI3K/Akt/mTOR pathway has an important regulatory role in processes of cellular physiology, such as glucose homeostasis, protein synthesis, cell proliferation, growth, metabolism, survival, and angiogenesis.⁷³ Dysregulation of the PI3K/Akt pathway has been related to many cancers, making this pathway an important antitumor target.^{73–75} Several inhibitors targeting the pathway are currently under investigation, alone or in combination, in both solid tumors and hematologic malignancies.⁷⁶ Of them, everolimus has been extensively studied.

Everolimus has been demonstrated to have an encouraging clinical benefit in other cancers as an mTOR inhibitor.^{77,78} A Phase I trial showed that everolimus has strong antitumor activity in Japanese patients with AGC.⁷⁹ On the basis of the encouraging finding, a multicenter phase II trial showed that patients receiving everolimus achieved a primary endpoint disease control rate of 56%.⁸⁰ However, a later phase III trial called GRANITE-1 observed that everolimus only prolonged the median OS of 1.1 months (HR = 0.90; 95% CI, 0.75–1.08).⁸¹ In the RADPAC trial, everolimus combined with paclitaxel in patients with GC who progressed after first-line therapy containing fluoropyrimidine or platinum regimen did not show an improvement in OS or PFS.⁸² Thus, more high-quality clinical trials are needed to confirm the efficacy of everolimus, and potential specific biomarkers should be further explored.

HGF/c-MET Inhibitors

HGF/c-MET signaling is closely associated with the proliferation and aggressiveness of tumors.⁸³ Deepened scientific understanding of the relationship between c-MET and HGF has enhanced the development of these molecules as potential antitumor targets.⁸⁴ The c-MET inhibitor tivantinib combined with FOLFOX in AGC showed a good effect on ORR and PFS.⁸⁵

Not all inhibitors of HGF/cMET have the same antitumor efficacy. The HGF-targeted antibody rilotumumab led to a shorter median OS than placebo (8.8 vs 10.7 months) in MET-positive gastroesophageal cancer in the phase III RILOMET-1 trial.⁸⁶

In addition, onartuzumab is another anti-MET antibody. However, patients did not benefit from onartuzumab plus mFOLFOX6.⁸⁷ Although the HGF-cMET signaling pathway plays an essential and irreplaceable role in GC, few targeted drugs have shown efficacy in clinical trials.

Matrix Metalloproteinase (MMP) Inhibitors

Extracellular matrix enzymes are necessary for all stages of the tumor, including invasiveness, migration, apoptosis, immune surveillance, and metastasis.⁸⁸ There is no doubt that MMPs could be a target for anticancer drugs.⁸⁹ Several MMP inhibitors, such as marimastat, prinostat, and rebimastat, are currently in preclinical studies or clinical trials. However, so far, few MMP inhibitors are available on the market, and none of them present specific indications of antitumor activity.

Immune Checkpoint Inhibitors

Tumorigenicity is partly ascribed to the malfunction of the immune system.⁹⁰ Immune checkpoints refer to an inhibitory pathway that immune cells possess to regulate and control the durability of the immune response.⁹¹ CTLA-4 and PD-1 inhibit the immune response and thus enable tumor cells with immune escape from T cell-mediated killing. Inhibition of immune checkpoints has been well developed in the management of advanced GC and many other solid tumors.^{91–93} Table 2 lists the current immunologic checkpoint inhibitors and related clinical trials in AGC.

CTLA-4 Inhibitor

Ipilimumab is a monoclonal anti-CTLA-4 antibody (IgG1) that causes T-cell activation and tumor immunity. Adjuvant therapy for melanoma and non-small-cell lung cancer was stated as its use in the instruction manual.⁹⁴ In

Table 2 Summary of Clinical Trials of Immune Checkpoint Inhibitors in AGC

Reference	Phase	N	Treatment	PFS (m)	OS(m)	AE(Grade3–4)
Kang et al ¹⁰⁰	III	330 103	Nivolumab Placebo	1.61 1.45	5.26 4.14	Decreased appetite (1%) Diarrhoea (1%) Fatigue (1%)
Kato et al ¹⁰¹	III	152 74	Nivolumab Placebo	1.7 1.5	5.4 3.6	Decreased appetite (2%) Diarrhea (1.7%) Fatigue (0.7%)
Satoh et al ¹⁰²	III	330 163	Nivolumab: Tam+ + Tabm- Placebo: Tam+ + Tabm-	1.6 1.5	8.3, 4.8 3.1, 4.2	Pruritus (15.3%) Rash (13.6%) Interstitial lung disease (3.4%)
Boku et al ¹⁰⁵	III	21 19	Nivolumab + SOX Nivolumab + CapeOX	9.8 7.2	11.9 11.2	Neutropenia (14.3%) Neutropenia (16.7%) Nausea (11.1%)
Fuchs et al ¹¹⁰	II	259	Pembrolizumab	2	5.6	Fatigue (2.3%) Anemia (2.7%) Diarrhea (1.2%)
Shitara et al ¹¹²	III	296 296	Pembrolizumab PTX	1.5 4.1	9.1 8.3	Anemia (2%) Fatigue (2%)
Tabernero et al ¹¹³	III	257 256 250	P+C P C	—	12.5 10.6 11.1	—
Bang et al ¹¹⁶	III	185 186	Avelumab PTX/irinotecan	1.4 2.7	4.6 5.0	Elevated AST (2.2%) Elevated ALT (1.6%) Fatigue (0.5%)

Note: “—” means not research.

Abbreviations: Tam+, trastuzumab (HER2+); Tabm-, HER2-; OS, overall survival; PFS, progression-free survival; ORR, overall response rate (nivolumab + SOX vs nivolumab + CapeOX = 66.7% vs 70.6%; pembrolizumab = 11.6%); P+C, pembrolizumab + chemotherapy; P, pembrolizumab; C, cisplatin+5-FU/capecitabine; N, the total number of enrolled patients; mo, months; AE, adverse events; PTX, paclitaxel; SOX, oxaliplatin + tegafur; CapeOX, capecitabine + oxaliplatin.

the CheckMate-032 study, ipilimumab plus nivolumab demonstrated significant and durable antitumor activity in chemotherapy-refractory esophagogastric cancer.⁹⁵ However, immune-related progression-free survival (irPFS) (4.90 versus 2.92 months) was not improved by ipilimumab monotherapy, resulting in study cessation.⁹⁶

PD-1/PD-L1 Inhibitors

To maintain an immunosuppressive microenvironment and avoid being killed by immune surveillance, tumor cancers must activate the PD-1/PD-L1 signaling pathway.⁹⁷ Tumor size, lymph node metastasis, and depth of invasion are related to the pathway; thus, inhibition of the pathway is a reasonable tactic. Moreover, high PD-1/PD-L1 expression is present in 65% of GC patients, making the pathway a promising antitumor target.^{98,99}

Nivolumab

The PD-1 inhibitor nivolumab showed significant antitumor efficacy in the ATTRACTION-2 trial. Nivolumab extended the median OS by 1.12 months (HR = 0.63; 95% CI, 0.51–0.78) in Asian patients who had received two or more previous chemotherapy regimens.¹⁰⁰ A subsequent analysis of a Japanese subpopulation found that nivolumab improved OS (5.4 vs 3.6 months) and reduced the risk of death (HR = 0.58; 95% CI, 0.42–0.78).¹⁰¹ Because the trial did not take into account HER2 status, evidence on whether patients who had previously been treated with trastuzumab influenced the efficacy of nivolumab was offered in a randomized phase III clinical trial. In both the trastuzumab+ and trastuzumab-groups, nivolumab prolonged the median OS by 5.2 months, (HR = 0.38; 95% CI, 0.22–0.66) and 0.6 months (HR = 0.71; 95% CI, 0.57–0.88), respectively. Thus, nivolumab treatment remained efficient regardless of HER2-positive or -negative

status.¹⁰² The ATTRACTION-4 trial suggested that nivolumab plus chemotherapy had a good objective response in approximately two-thirds of patients as a first-line therapy, higher than that in the SOX or CapeOX alone groups.^{103–105}

Pembrolizumab

Pembrolizumab is a monoclonal IgG4-kappa antibody that blocks PD-1 binding to PD-L1 and PD-L2.¹⁰⁶ Pembrolizumab was approved in 2017 for PD-L1-positive AGC as a third-line (or higher) agent.^{107,108} In the KEYNOTE-012 study, pembrolizumab had a 22% ORR in PD-L1-positive AGC.¹⁰⁹ Because of this result, cohort 1 of a 3-cohort KEYNOTE-059 trial evaluated the antitumor activity in patients who had experienced second- or more subsequent-line treatment. Ninety-five PD-L1-positive patients (42.4%) exhibited shrinkage of tumors; these patients also exhibited a higher ORR than PD-L1 negative patients (15.5% vs 6.4%).¹¹⁰ The following cohort 2 (combination therapy) and cohort 3 (monotherapy) trials showed that the ORR was 60.0% with pembrolizumab versus 25.8% with placebo.¹¹¹ In the KEYNOTE-061 trial, patients who failed first-line chemotherapy containing platinum and fluoropyrimidine or trastuzumab who received pembrolizumab had a median OS that was 0.8 months longer than that in the paclitaxel group.¹¹² The PFS was not different in either arm. Compared with paclitaxel, pembrolizumab had a more favorable safety profile and longer duration of response. Post hoc exploratory subgroup analyses suggested that patients who have a better Eastern Cooperative Oncology Group (ECOG) performance status, overexpression of PD-L1, and high microsatellite instability benefit more from pembrolizumab monotherapy. On the basis of the results, the KEYNOTE-062 trial compared the efficacy of pembrolizumab with pembrolizumab plus chemotherapy and chemotherapy alone in the first-line setting for AGC patients who were PD-L1 positive (CPS ≥ 1) and HER2 negative. The median OS with pembrolizumab monotherapy was noninferior to that with chemotherapy alone. However, there was a significant improvement in patients with CPS ≥ 10 (17.4 vs 10.8 months, HR = 0.69; 95% CI, 0.49–0.97). The combination group did not significantly prolong PFS and OS compared with that with chemotherapy alone. As a result, in PD-L1 positive patients (CPS ≥ 10), pembrolizumab monotherapy is recommended as an ideal option.¹¹³

Avelumab

Avelumab specifically targets PD-L1 and further blocks the binding between PD-L1 and PD-1.¹¹⁴ Avelumab has been approved for use in G/GEJ cancer.¹¹⁵ However, the

JAVELIN Gastric 300 trial showed that avelumab monotherapy did not achieve a satisfactory result due to its inability to extend OS, PFS, and ORR in patients with G/GEJ cancer.¹¹⁶ Along with the adjustment of patients, a phase I trial in Japanese patients observed that avelumab exhibited durable antitumor activity with an ORR of 10%. The primary endpoints of PFS and OS were 2.4 and 9.1 months, respectively.¹¹⁷ In another single-arm phase Ib trial, avelumab showed compelling results in AGC regardless of whether it was used as a first- or second-line therapy.¹¹⁸ However, as first-line maintenance therapy in the JAVELIN Gastric 100 trial (NCT02625610), avelumab did not show better efficacy than the continuation of chemotherapy in patients with advanced GC/GEJC who did not progress after 12 weeks of first-line oxaliplatin/fluoropyrimidine chemotherapy. However, compared with chemotherapy, avelumab had a longer duration of response and lower incidence of treatment-related adverse events. Thus, the design of further clinical trials should focus on the choice of highly selective drugs for highly selected patients.

Other Immune Checkpoint Inhibitors

Currently, many phase I or phase II trials of other PD-L1 antibodies are underway.¹¹⁹ Among other immune checkpoint inhibitors, atezolizumab, an anti-PD-L1 antibody, has revealed encouraging response rates and favorable safety profiles in urothelial carcinoma and lung cancer.^{120,121} Like atezolizumab, durvalumab, a high-affinity PD-L1 antibody, also exhibited promising results in solid tumors.^{122,123} However, neither showed a beneficial effect in AGC. As far as we know, immune checkpoint inhibitors are being developed in various types of cancers and certainly provide hope for cancer patients.

Conclusion and Future Perspectives

This review is an update on targeted therapy agents for AGC. Ramucirumab and apatinib have been approved in AGC as second- and third-line therapy agents with prolonged OS and PFS. Trastuzumab is considered the primary agent in HER2/neu-positive GC. Lapatinib could be an option for second-line therapy of AGC patients younger than 60 with HER2 overexpression (FISH positive and IHC 3+). Bevacizumab, regorafenib and everolimus also showed good effects, with prolonged median OS and improved disease control rate in AGC. Pembrolizumab is already approved for recurrent locally advanced or metastatic GC/GEJC with PD-L1 expression (CPS ≥ 1). With the progress regarding

molecular targeted agents and immune checkpoint inhibitors, a wider group of patients should benefit. Most of the targeted drugs and immune checkpoint inhibitors have manageable adverse events and longer durable responses than traditional chemotherapies. As second- and subsequent-line therapy, these drugs always show compelling efficacy. However, even with the introduction of immune checkpoint inhibitors, there is still a large number of patients who fail to derive clinical benefit.¹²⁴

Although research on molecular targeted agents has obtained promising results and many clinical trials involving targeted therapy agents are ongoing, efforts are still needed to select an optimal therapeutic scheme for AGC. Furthermore, we have only limited knowledge of the signaling pathway of the tumor at present. The reason why the effects of drugs targeting the same signaling pathway are not equivalent is worth exploring. For every nonspecific molecular targeted drug, the optimal time, sequence and combination should be carefully chosen in the clinic. Moreover, currently, molecular targeted drugs or immune checkpoint inhibitors are effective only for specific patients with known overexpression or activation of the targets, and the clinical benefit is modest. Many other related pathways are involved in the occurrence and development of AGC. With the advancement of network pharmacology and gene sequencing, more potential antitumor targets will be found to develop new drugs. Therefore, it is imperative to find specific clinical biomarkers for various patient subpopulations with AGC. Additionally, it is important to evaluate the influence of race, region, optimal dose, adequate endpoints, and individual chemotherapy regimens when designing a new high-quality, well-designed clinical trial.

Abbreviations

GC, gastric cancer; AGC, advanced gastric cancer; G/GEJ, gastric or gastroesophageal junction cancer; PD-1, programmed cell death 1; OS, overall survival; VEGF, vascular endothelial growth factor; NRPs, neuropilins; HR, hazard ratio; CI, confidence intervals; PDGFR, platelet-derived growth factor receptor; EGFR, Epidermal growth factor receptor; PI3K, phosphatidylinositol 3'-kinase; AKT, protein kinase B; mTOR, mammalian target of rapamycin; HGF, hepatocyte growth factor; MMPs, Matrix metalloproteinases; CTLA-4, Cytotoxic T lymphocyte-associated antigen 4; BSC, best supportive care; PFS, progression-free survival; CPS, combined positive score; ORR, objective response rate; RR, response rate; GI, gastrointestinal; GT,

glutamyltransferase; AE, adverse events; FDA, Food and Drug Administration; TKI, tyrosine kinase inhibitors; RTKs, receptor tyrosine kinases; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data; SSN took part in drafting the article, GPY and HWL revised it critically for important intellectual content; All authors have read and approved the final version manuscript to be published. All authors agreed to be accountable for all aspects of the work.

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Disclosure

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