

# Research progress in targeted therapy and immunotherapy for gastric cancer

Xuwei Li<sup>1</sup>, Jun Xu<sup>2</sup>, Jun Xie<sup>1</sup>, Wenhui Yang<sup>3</sup>

<sup>1</sup>Department of Biochemistry and Molecular Biology, Shanxi Key Laboratory of Birth Defect and Cell Regeneration, Shanxi Medical University, Taiyuan, Shanxi 030001, China;

<sup>2</sup>Department of Surgery, First Hospital of Shanxi Medical University, Taiyuan, Shanxi 030001, China;

<sup>3</sup>Cancer Center, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Third Hospital of Shanxi Medical University, Taiyuan, Shanxi 030032, China.

## Abstract

Gastric cancer (GC) is one of the most common malignant tumors worldwide. Its incidence ranks the 5th among all malignant tumors globally, and it is the 3rd leading cause of death among patients with cancer. Surgical treatment is the first choice in clinical practice. However, targeted therapy, immunotherapy, and other treatment methods have also become research hotspots at home and abroad with the development of individualized precision therapy in recent years, besides traditional radiotherapy and chemotherapy. At present, targeted therapy and immunotherapy are methods used for treating GC, and they have important clinical application value and prospects. This study aimed to review the research progress of targeted therapy and immunotherapy for GC, focusing on its mechanism of action and related important clinical trials, hoping to provide references for the clinical treatment of GC.

**Keywords:** Angiogenesis; Cytotoxic T lymphocyte-associated antigen-4; Epidermal growth factor receptor; Gastric cancer; Immunotherapy; Programed cell death ligand 1; Programed death-1; Targeted therapy; Vascular endothelial growth factor

## Introduction

Gastric cancer (GC) is one of the common malignant tumors worldwide. The estimates of the International Cancer Research Center of the World Health Organization<sup>[1]</sup> indicate that the incidence of GC ranks the 5th among all malignant tumors globally, and it is the 3rd leading cause of death among patients with cancer. China is a country with a high incidence and mortality of GC. More than 80% of patients with GC are in the advanced stage when they are diagnosed. Therefore, the burden of disease is severe.<sup>[2,3]</sup> Surgical treatment is the first choice in clinical practice. Targeted therapy, immunotherapy, and other treatment methods have also become research hotspots at home and abroad with the development of individualized precision therapy, besides traditional radiotherapy and chemotherapy.

Molecular targeted therapy has dramatically improved the prognosis of patients with certain malignant tumors, including breast cancer, colorectal cancer, esophageal cancer, and lung cancer, in the last 10 years.<sup>[4-11]</sup> The treatment and diagnosis of GC have made great progress with the in-depth study of the gene sequence and

molecular mechanism of GC. Targeted therapy can accurately identify and attack abnormal proteins in tumor cells, without causing damage to normal cells. It has several advantages, including high efficiency, low toxicity, and high directionality. Therefore, molecular targeted therapy has become a hotspot in treating GC. In recent years, immunotherapy has also saved many patients with GC, which is difficult to treat using traditional methods. It has the advantages that radiotherapy and chemotherapy do not have in treating advanced and recurrent GC. Immunotherapy prolongs the survival time of patients and has a long-lasting immune response effect. It is commonly used for treating GC and has important clinical application value and prospects.

This study aimed to systematically describe the research progress of targeted therapy and immunotherapy for GC. It focused on the mechanism of action and related

**Correspondence to:** Dr. Wenhui Yang, Cancer Center, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Third Hospital of Shanxi Medical University, Taiyuan, Shanxi 030032, China

E-Mail: yangwenhui-10012@163.com;

Prof. Jun Xie, Department of Biochemistry and Molecular Biology, Shanxi Key Laboratory of Birth Defect and Cell Regeneration, Shanxi Medical University, Taiyuan, Shanxi 030001, China

E-Mail: junxie@sxmu.edu.cn;

Prof. Jun Xu, Department of Surgery, First Hospital of Shanxi Medical University, Taiyuan, Shanxi 030001, China

E-Mail: junxuty@163.com

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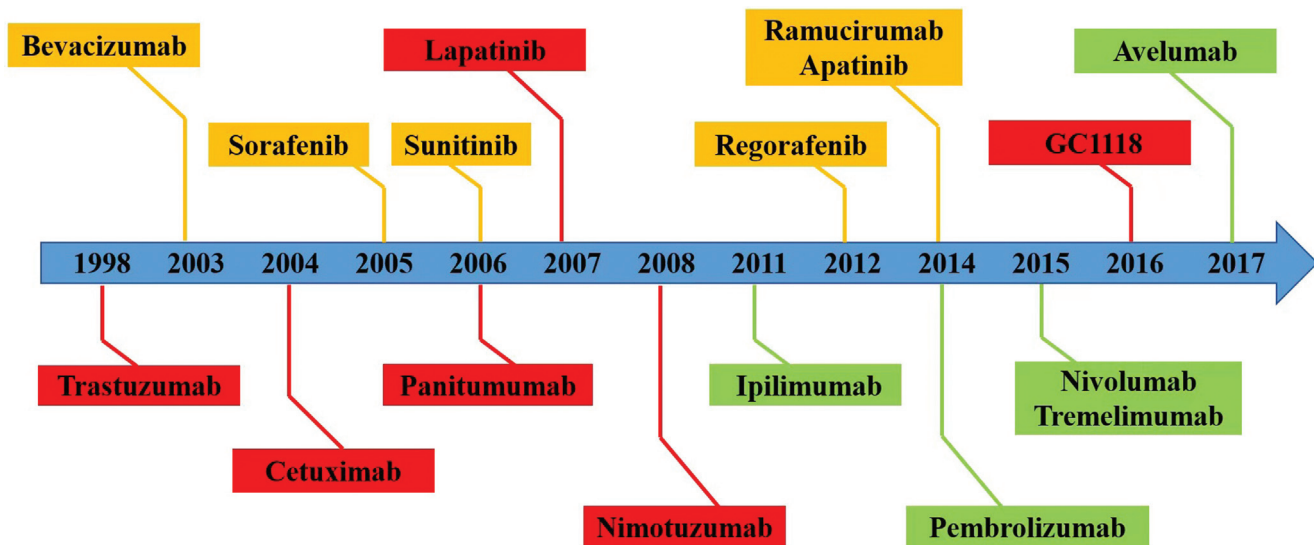
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**Figure 1:** Development schedule of targeted therapy and immunotherapy drugs for GC. GC: Gastric cancer. The time for each drug is the time when it was first approved by the Food and Drug Administration (FDA) or the time when it was first approved for marketing in China for treatment. Red represents epidermal growth factor receptor (EGFR) family-targeted drugs; yellow represents anti-angiogenesis-targeted drugs; and green represents immunotherapy drugs.

important clinical trials so as to provide references for clinically treating GC (see Figure 1 for the development schedule of all drugs).

**Epidermal growth factor receptor (EGFR) family-targeted drugs**

**Anti-EGFR antibodies**

The human EGFR family comprises four members: EGFR (also known as human epidermal growth factor receptor [HER] 1), HER2, HER3, and HER4. These receptors are essential for controlling the growth and differentiation of epithelial cells. Drugs targeting HER1 and HER2 are representative drugs among the targeted drugs for treating GC [Figure 2].

EGFR is a tyrosine kinase receptor with both tyrosine kinase activity and ligand-binding ability. After activation, EGFR promotes tumor cell proliferation, infiltration, metastasis, and tumor angiogenesis by transmitting signals to the nucleus. EGFR is overexpressed in 27% to 64% of GCs<sup>[12,13]</sup> and is almost undetectable in non-cancerous gastric mucosa tissues. This overexpression is related to the high invasiveness and low survival of patients, suggesting that EGFR may be a reasonable therapeutic target.<sup>[14]</sup> Therefore, targeted therapeutic drugs for EGFR mainly inhibit the proliferation, infiltration, and metastasis of tumor cells by blocking the activation of downstream signal transduction pathways to achieve the purpose of treating GC.<sup>[15]</sup>

**Cetuximab**

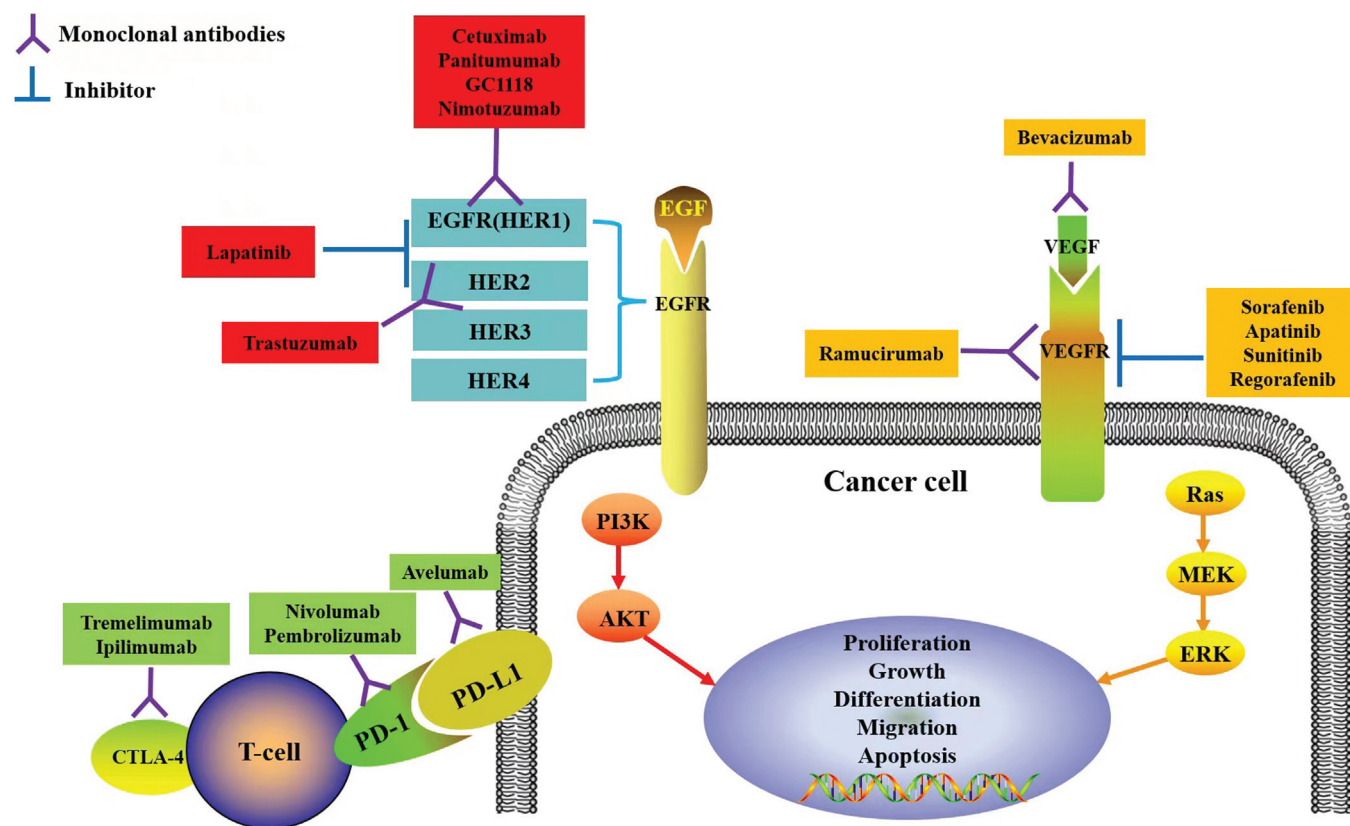
Cetuximab is a human–mouse chimeric monoclonal antibody that can selectively bind to EGFR immunoglobulin G (IgG)1. It exerts antitumor effects via the inhibition of tyrosine kinase activity. EGFR is overexpressed in many

tumors and can be activated by a large number of ligands. Cetuximab can bind to EGFR on the surface of tumor cells, thus inhibiting the interaction with its ligands and blocking the intracellular signal transduction pathway. This further inhibits cancer cell proliferation and induces cancer cell apoptosis.<sup>[16]</sup>

As early as >10 years ago, studies reported that tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib were not effective in treating GC, while monoclonal antibodies (mainly cetuximab) were found to be effective in some published experimental studies.<sup>[17,18]</sup> A randomized, multicenter phase II clinical study (NCT00477711) in China explored the efficacy of cetuximab combined with cisplatin and capecitabine (C + XP) in treating advanced gastric or esophagogastric junction adenocarcinoma. The study included 47 untreated patients with advanced gastric or esophagogastric junction adenocarcinoma. The results showed that the patient’s objective response rate (ORR) was 53.2%, and the median progression-free survival (mPFS) and median overall survival (mOS) were 5.2 and 10.8 months, respectively. This study showed that C + XP, as a first-line treatment for advanced gastric or esophagogastric junction adenocarcinoma, had good efficacy and tolerability, and EGFR overexpression might be a predictor of the treatment efficacy of cetuximab.<sup>[19]</sup>

**Panitumumab**

Panitumumab is the first fully humanized IgG2 monoclonal antibody that can target EGFR. It exerts an excellent inhibitory effect on epidermal growth factor receptors and is highly safe. It is a commonly used drug for treating gastrointestinal tumors. A study assessed the efficacy and safety of panitumumab plus first-line chemotherapy (docetaxel and cisplatin) in treating patients with advanced gastric or gastro-esophageal junction (GEJ)



**Figure 2:** Main molecules and their association with signaling pathways related to the occurrence and development of tumors, as well as available targeted therapies and immunotherapies for key molecular targets in GC. AKT: Protein kinase B; CTLA-4: Cytotoxic T lymphocyte-associated antigen 4; EGF: Epidermal growth factor; EGFR: Epidermal growth factor receptor; ERK: Extracellular regulated protein kinase; GC: Gastric cancer; HER: Human epidermal growth factor receptor; MEK: Mitogen-activated protein kinase kinase; PI3K: Phosphatidylinositol 3-kinase; PD-1: Programed death-1; PD-L1: Programed cell death ligand 1; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor.

adenocarcinoma. However, this study showed that adding panitumumab to standard chemotherapy as the first-line treatment did not improve the efficacy outcomes.<sup>[20]</sup>

### GC1118

GC1118 is a novel anti-EGFR antibody with a unique binding epitope and efficacy. It exhibited superior inhibitory activity against high-affinity EGFR ligands in terms of EGFR binding, triggering of EGFR signaling, and proliferation compared with cetuximab and panitumumab.<sup>[21]</sup>

An experimental study showed that GC1118 alone or in combination with cytotoxic chemotherapeutics exerted a stronger antitumor effect on GC cells compared with cetuximab. It displayed good antitumor activity and tolerability, especially in GC and colorectal cancer. The advantages of strong antitumor effect and rare adverse reactions might provide a favorable basis for further research and development of GC1118 compared with other anti-EGFR antibodies.<sup>[22]</sup>

### Nimotuzumab

Nimotuzumab is a humanized IgG1 monoclonal antibody against EGFR, which exhibits antitumor effects by

regulating antibody-dependent cell and complement-dependent cytotoxicity, thus inhibiting tumor cell proliferation and angiogenesis. It can also selectively bind to cells expressing medium and high levels of EGFR, reducing the incidence of off-target toxicity. It has been approved for treating advanced head and neck cancer in China and other countries. Satoh *et al*<sup>[23]</sup> conducted a randomized phase II second-line study on high-grade GC. The subgroup analysis of this study showed an improvement in the progression-free survival (PFS) and overall survival (OS) of patients with EGFR-high-expressing tumors treated with nimotuzumab combined with irinotecan.

### HER2 antibody

HER2 is encoded by the *erb-b2* receptor tyrosine kinase 2 (*ERBB2*) gene on chromosome 17, which is a transmembrane glycoprotein with tyrosine kinase activity.<sup>[24]</sup> However, it lacks specific ligands and can only transmit cell growth signals through forming heterodimers with other HER family members.<sup>[25]</sup> These dimer reactions can lead to the phosphorylation of tyrosine residues and trigger downstream signal cascades, such as phosphatidylinositol 3-kinase/protein kinase B (Akt) signaling and Ras/mitogen-activated protein kinase kinase (MEK)/extracellular regulated protein kinases (ERK) signaling

cascades, which regulate cell survival, proliferation, differentiation, motility, apoptosis, invasion, migration, adhesion, and angiogenesis.<sup>[26]</sup>

HER2 can be expressed in many tissues, including the gastrointestinal tract, kidney, heart, and breast. It causes tumorigenesis by affecting the proliferation, apoptosis, adhesion, and migration of tumor cells. Abnormal HER2 protein overexpression is associated with some human gynecological tumors, such as ovarian cancer,<sup>[27]</sup> breast cancer,<sup>[28]</sup> and cervical cancer,<sup>[29]</sup> and non-gynecological tumors such as lung cancer<sup>[30]</sup> and bladder cancer.<sup>[31]</sup> It is one of the factors for poor prognosis. Therefore, HER2 is an important target for treating various types of cancer.<sup>[32]</sup>

Trastuzumab is a fully humanized monoclonal antibody against HER2.<sup>[33]</sup> It can bind to the extracellular region of HER2, cleave the receptor and cause blockage, and inhibit HER2 heterodimerization. Hence, it prevents HER2-mediated signal transduction and promotes antibody-dependent cytotoxicity, leading to the death of HER2-expressing cells.<sup>[34]</sup>

In 2010, a phase III randomized controlled trial (To-GA) proved for the first time that trastuzumab combined with chemotherapy significantly improved the survival of patients with HER2-positive advanced GC. It increased the OS to >1 year and the ORR from 34.5% to 47.3%.<sup>[35]</sup> At present, trastuzumab combined with chemotherapy has become the first-line treatment of choice for HER2-positive advanced GC. A cohort study using the Lombardy Health Care Database in Italy found that the mOS and restricted mean survival were 10.2 and 7.4 months, and 14.9 and 11.4 months, respectively, in the trastuzumab combined with chemotherapy group and standard chemotherapy group.<sup>[36]</sup> A large number of studies showed that trastuzumab combined with standard chemotherapy increased the mOS of patients with HER2-positive advanced GC. The latest Chinese Society of Clinical Oncology (CSCO) GC clinical guidelines,<sup>[2]</sup> the Japanese GC treatment guidelines, and the National Comprehensive Cancer Network (NCCN) GC clinical guidelines all recommend trastuzumab combined with fluorouracil or platinum for the first-line treatment of metastatic adenocarcinoma with high HER2 expression.<sup>[37,38]</sup>

The emergence of trastuzumab has changed the treatment model of HER2-positive GC. The treatment plan of trastuzumab combined with chemotherapy is significantly better than that of chemotherapy alone in terms of efficacy and safety. Trastuzumab monotherapy can be used for patients with more adverse reactions to chemotherapy. Moreover, trastuzumab-derived drugs less dependent on high HER2 expression have also emerged, providing a new option for treating patients with HER2-positive advanced GC.

### EGFR/HER2 tyrosine kinase inhibitor

Lapatinib is a selective intracellular tyrosine kinase inhibitor (TKI) that combines two targets of EGFR and HER2 in both directions. It can inhibit the autophosphor-

ylation sites on the receptors, thereby blocking the transduction of downstream signals and controlling the proliferation and metastasis of tumor cells.

A randomized, placebo-controlled phase II clinical study explored the efficacy of lapatinib combined with epirubicin + cisplatin + fluorouracil (ECF) in the first-line treatment of metastatic GC. The results of the study showed no statistically significant difference in PFS (8.0 *vs.* 5.9 months) and OS (13.8 *vs.* 10.1 months) between the lapatinib + ECF and the placebo + ECF groups ( $P > 0.05$ ), indicating that the lapatinib + ECF regimen was tolerable, but its curative effect did not meet expectations.<sup>[39]</sup> A phase III clinical trial TRIO-013/LOGiC randomly assigned 545 patients with untreated HER2-positive GC to receive capecitabine and oxaliplatin combined with lapatinib or placebo. The results showed that lapatinib increased the ORR from 39% to 53% and PFS from 5.4 to 6 months.<sup>[40]</sup>

### Anti-angiogenesis targeted drugs

Angiogenesis is a series of complex biological processes that generate new capillaries through the existing vascular network; it is jointly regulated by various angiogenesis-promoting and inhibitory factors. In 1971, Folkman proposed the hypothesis that tumor growth depended on angiogenesis,<sup>[41]</sup> which was later confirmed by many studies as one of the hallmarks of tumors. Local tumor infiltration and distant metastasis are angiogenesis dependent. Therefore, angiogenesis plays a vital role in the occurrence, development, and metastasis of tumors. At present, the angiogenesis signaling pathway has become a hotspot in oncology research. Especially, vascular endothelial growth factor (VEGF) and its receptor (vascular endothelial growth factor receptor [VEGFR]) have received maximum attention, and the progress has been relatively remarkable.

The VEGF family includes VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor.<sup>[42]</sup> The receptors include VEGFR-1, VEGFR-2, and VEGFR-3. VEGFR is a tyrosine kinase receptor consisting of seven immunoglobulin homology domains, including a ligand-binding part and a split tyrosine kinase domain, which can transduce growth factor signals.<sup>[43]</sup> VEGFR2 is significantly expressed in vascular endothelial cells. It transmits pro-angiogenic signals and has strong tyrosine kinase activity. Therefore, the main and direct angiogenesis signal is generated by VEGFR2, which makes the therapy targeting VEGFR2 an essential strategy for antitumor therapy.<sup>[44]</sup>

Recent studies showed that the expression of VEGF and VEGFR was higher in GC tissues compared with normal gastric tissues, and it was related to the proliferation and invasion of GC cells.<sup>[45]</sup> The expression levels of VEGF-A, VEGF-C, and VEGF-D were higher in GC and precancerous tissues than those in normal gastric tissues. The positive expression rate of VEGF in GC tissues was about 17.6%, and the positive expression rate of VEGFR was 32.2% to 52.9%.<sup>[46]</sup> Some studies found that the higher the expression of VEGF, the worse the prognosis of

patients.<sup>[47]</sup> Therefore, blocking tumor angiogenesis to achieve the goal of antitumor therapy has been recognized as a new strategy for GC-targeted therapy.

### VEGF monoclonal antibody

Bevacizumab is the first recombinant humanized anti-VEGF monoclonal antibody and the first anti-angiogenic drug approved by the Food and Drug Administration (FDA) for clinical use. It can effectively prevent VEGF from binding to its receptors VEGFR-1 and VEGFR-2, thereby inhibiting vascular endothelial cell proliferation and angiogenesis.<sup>[48]</sup>

As early as in 2011, a phase III clinical study of GC (AVAGAST)<sup>[49]</sup> showed that bevacizumab combined with the capecitabine/cisplatin chemotherapy (XP) regimen significantly improved the mPFS and ORR in patients with advanced GC. The results of subgroup analysis showed regional differences. Americans benefited the most, followed by Europeans, while Asian patients did not benefit significantly. The AVATAR study was similar in design to AVAGAST. It was a randomized, double-blind, phase III clinical study involving patients with advanced GC in China. The addition of bevacizumab to capecitabine/cisplatin chemotherapy did not improve the prognosis. No difference in OS was found, and PFS was similar between the two groups.<sup>[50]</sup> The aforementioned two similar experiments showed noticeable regional differences in the therapeutic effect of bevacizumab combined with chemotherapy drugs.

*In vitro* studies on the efficacy of bevacizumab in GC<sup>[51]</sup> suggested that using bevacizumab before chemotherapy effectively improved the tumor control rate and reduced the tumor volume. Another phase II clinical trial<sup>[52]</sup> showed that bevacizumab combined with oxaliplatin and irinotecan followed by bevacizumab and docetaxel for treating unresectable locally advanced and metastatic GC displayed an excellent curative effect. The complete response rate (CR) reached 12.1%, and the partial response rate (PRR) was 39.4%. After the initial treatment using bevacizumab combined with docetaxel, capecitabine, and cisplatin for locally unresectable GC, the R0 resection rate reached 64.5%, the pathological CR rate was 12.9%, and the mOS reached 38.6 months after conversion therapy.<sup>[53]</sup> Chinese clinical studies<sup>[54]</sup> showed that bevacizumab combined with docetaxel, fluorouracil, and cisplatin chemotherapy significantly improved the quality of life of patients with GC and increased the treatment efficiency.

### VEGFR monoclonal antibody

Ramucirumab is a fully humanized IgG1 monoclonal antibody. It can specifically bind to VEGFR-2 and hence inhibit receptor-mediated downstream signaling events, including endothelial cell proliferation and migration, ultimately inhibiting tumor angiogenesis.<sup>[55]</sup>

The REGARD study<sup>[56]</sup> was a phase III clinical study evaluating ramucirumab as a single-drug *vs.* placebo second-line treatment of GC. The results showed that the

mOS was significantly longer in the ramucirumab group than in the placebo group (5.2 *vs.* 3.8 months,  $P = 0.047$ ). Ramucirumab single-agent second-line treatment prolonged the survival time of patients with GC. Another clinical study of the use of ramucirumab in the second-line treatment of GC (RAINBOW) evaluated the efficacy of ramucirumab combined with the chemotherapy drug paclitaxel in the second-line treatment of GC.<sup>[57]</sup> The results showed that ramucirumab combined with paclitaxel significantly prolonged OS and PFS compared with placebo plus paclitaxel. The aforementioned two clinical studies suggested that ramucirumab alone or combined with chemotherapy drugs prolonged the survival time of patients, with no significant increase in side effects. Based on the results of the aforementioned two clinical studies, ramucirumab was approved by the FDA in 2014 for second-line monotherapy or in combination with paclitaxel for treating GC. Ramucirumab was also the first drug found to be effective in the anti-angiogenesis treatment of GC. As a targeted anti-angiogenesis drug, ramucirumab had fewer side effects; also, combined chemotherapy did not increase chemotherapy-related side effects. Therefore, the studies used it for the first-line maintenance treatment of GC.

A double-blind, randomised, placebo-controlled, phase 3 trial aimed to assess whether the addition of ramucirumab, a VEGFR-2 antagonist monoclonal antibody, to first-line chemotherapy improves outcomes in patients with metastatic gastric or gastro-oesophageal junction adenocarcinoma. The RAINFALL trial<sup>[58]</sup> randomly assigned 645 patients with HER2-negative GC around the world to the ramucirumab + fluorouracil + cisplatin group (326 cases) or placebo + fluorouracil + cisplatin group (319 cases) in a ratio of 1:1. The study found that the combined use did not significantly improve the OS of patients with HER2-negative GC. Therefore, it is not currently recommended to add ramucirumab to fluorouracil and cisplatin chemotherapy as the first-line treatment for patients with metastatic gastric or GEJ adenocarcinoma.

A randomised, multicentre, double-blind, phase 3 trial—RAINBOW-Asia trial, aimed to evaluate the efficacy and safety of weekly paclitaxel with or without ramucirumab as second-line therapy for the treatment of advanced gastric or gastroesophageal junction adenocarcinoma. The RAINBOW-Asia trial published in 2021 confirmed that ramucirumab combined with paclitaxel could significantly prolong the mPFS time (4.14 *vs.* 3.15 months; HR = 0.765;  $P = 0.0184$ ) and OS time (8.71 *vs.* 7.92 months; HR = 0.963;  $P = 0.7426$ ) of patients compared with single-agent paclitaxel in the Chinese population.<sup>[59]</sup>

### VEGFR tyrosine kinase inhibitor

#### Sorafenib

Sorafenib is the first multitarget TKI that mainly targets Raf kinase, which has a broad-spectrum antitumor effect. It can not only inhibit the tyrosine kinase activity of VEGFR-2, VEGFR-3, platelet-derived growth factor receptor- $\beta$ , c-Kit, and other receptors, but also block

the signal transduction mediated by the RAF/MEK/ERK pathway and inhibit tumor proliferation.

A phase II clinical study showed that sorafenib combined with docetaxel and cisplatin achieved satisfactory results in treating metastatic or locally advanced GC and adenocarcinoma at the GEJ. The PRR was 41%, and the mOS was 13.6 months. Therefore, sorafenib combined with docetaxel and cisplatin was effective in treating GC or GEJ adenocarcinoma and was well tolerated.<sup>[60]</sup> The phase I dose study of sorafenib combined with FOLFOX4 (oxaliplatin/leucovorin/5-fluorouracil) showed that sorafenib 200 mg combined with FOLFOX4 twice a day was effective and safe in treating advanced GC and might be the appropriate option for subsequent phase II clinical studies.<sup>[61]</sup>

### Apatinib

Apatinib is a small-molecule TKI independently developed by China. It has been recommended by the CSCO GC clinical diagnosis and treatment guidelines as a third-line treatment for patients with metastatic GC.<sup>[2]</sup>

Apatinib can selectively target VEGFR2 and bind to its intracellular adenosine triphosphate-binding site, thereby inhibiting phosphorylation and downstream signaling pathways (including RAF/MEK/ERK signaling pathways). Consequently, VEGF-mediated endothelial cell migration, proliferation, and tumor microvessel density are reduced.<sup>[62]</sup> Cell and animal experiments showed that apatinib combined with chemotherapy reduced the invasion and migration ability of cells, increased the proportion of cell apoptosis, significantly reduced the expression of anti-apoptotic protein Bcl-2, and increased the expression of pro-apoptotic protein Bax. The tumor volume of the xenograft model was significantly suppressed, and the microvessel density was reduced.<sup>[63]</sup>

In a prospective, multicenter, observational study, the enrolled patients received apatinib monotherapy or apatinib plus chemotherapy. In the first-line treatment, the ORR in the apatinib single-agent and combination therapy groups was 9.09% and 16.42%, respectively, and the disease control rate (DCR) was 78.41% and 89.29%, respectively. Compared with monotherapy, the mPFS (6.18 *vs.* 3.52 months,  $P < 0.05$ ) and mOS (8.72 *vs.* 5.92 months,  $P < 0.05$ ) of patients receiving combination therapy were significantly prolonged. In second-line and third-line treatments, combination therapy showed a better trend in tumor response and survival outcomes compared with single-agent therapy. For all patients, apatinib combined with paclitaxel had longer PFS (8.88 *vs.* 6.62 months) than other combinations and might obtain a better survival benefit in the first-line treatment.<sup>[64]</sup>

A study recruited 337 patients with advanced GC who had undergone systemic chemotherapy but had progressed or relapsed. A total of 62 (18.4%), 102 (30.3%), and 173 (51.3%) patients received first-, second-, and third- or higher grade apatinib treatment, respectively. The mOS and mPFS were 7.13 and 4.20 months, respectively.<sup>[65]</sup>

Compared with the higher dose (675–850 mg) of apatinib, the lower daily dose (250 mg) of apatinib could achieve better OS and PFS while showing better safety in patients with advanced GC.<sup>[66]</sup>

### Sunitinib

Similar to sorafenib, sunitinib is also an oral, multitarget receptor TKI that inhibits tumor angiogenesis by inhibiting multiple tyrosine kinase targets.<sup>[67]</sup> A phase I clinical trial<sup>[68]</sup> showed that sunitinib combined with irinotecan + fluorouracil + calcium tetrahydrofolate (FOLFIRI regimen) effectively treated advanced gastric and GEJ adenocarcinoma, with a PRR of 35%; the median OS reached 12.4 months.

### Regorafenib

Regorafenib is an oral, multitarget phosphokinase inhibitor. It can inhibit the activity of a variety of protein kinases that promote tumor growth, such as VEGFR1–3, c-KIT proto-oncogene receptor tyrosine kinase, and endothelial cell TEK tyrosine kinase. Hence, tumor formation, tumor angiogenesis, and maintenance of tumor microenvironment signal transduction are inhibited. Regorafenib has been approved for treating metastatic colorectal cancer, advanced gastrointestinal stromal tumor, and liver cancer. Some researchers have applied it to advanced GC based on its broad-spectrum multitarget mechanism.

A phase II trial of modified combination of 5-fluorouracil, leucovorin and oxaliplatin (mFOLFOX6) combined with regorafenib as a first-line treatment<sup>[69]</sup> showed good efficacy, with an ORR of 56% and mPFS of 7.0 months. INTEGRATE was a phase II randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of regorafenib in second-line or third-line treatment for patients with advanced gastric adenocarcinoma.<sup>[70]</sup> The results showed that the mPFS of regorafenib was significantly improved compared with that of placebo (2.6 months for regorafenib and 0.9 months for placebo;  $P < 0.001$ ). However, the most common adverse reactions of regorafenib are gastrointestinal diseases, infections, and metabolic and nutritional disorders. Regorafenib is prone to liver damage; even deaths due to severe liver damage have occurred. Therefore, extreme caution is always required in the clinical use of regorafenib.

Important clinical trials of targeted therapy drugs for GC are shown in Table 1.

### Immunotherapy

The immune system of the normal body has the function of “immune surveillance”; it can specifically recognize tumor cells and exert killing effects.<sup>[71]</sup> The important biological feature of tumor cells is that they can evade the surveillance and killing of the immune system. When tumor cells change their characteristics (such as decreased expression of tumor antigens and major histocompatibility antigens, increased expression of inhibitory cytokines,

**Table 1: Important clinical trials of targeted therapy drugs for GC.**

Targeted drugs	Clinical trials	Research objects	Patient number	Groups	Results	Ref.
Cetuximab	Phase II clinical trial: NCT00477711	Unresectable or metastatic gastric or esophagogastric junction adenocarcinoma	47	Cetuximab combined with cisplatin and capecitabine	Cetuximab combined with cisplatin and capecitabine, as a first-line treatment for advanced gastric or esophagogastric junction adenocarcinoma, had good efficacy and tolerability.	[19]
Trastuzumab	Phase III clinical trial: To-GA	HER2-positive advanced gastric or gastro-oesophageal junction cancer	594	Trastuzumab + chemotherapy group ( <i>n</i> = 298) and chemotherapy alone group ( <i>n</i> = 296)	Trastuzumab combined with chemotherapy has become the first-line treatment of choice for HER2-positive advanced GC.	[35]
Bevacizumab	Phase III clinical trial: AVAGAST	Advanced GC	774	Bevacizumab + fluoropyrimidine-cisplatin group ( <i>n</i> = 387) and placebo + fluoropyrimidine-cisplatin group ( <i>n</i> = 387)	Bevacizumab combined with the capecitabine/cisplatin chemotherapy (XP) regimen significantly improved the median PFS and ORR in patients with advanced GC.	[49]
Ramucirumab	Phase III clinical trial: REGARD	Advanced gastric or gastro-oesophageal junction adenocarcinoma and disease progression after first-line platinum-containing or fluoropyrimidine-containing chemotherapy	355	Ramucirumab group ( <i>n</i> = 238) or placebo group ( <i>n</i> = 117)	Ramucirumab single-agent second-line treatment prolonged the survival time of patients with GC.	[56]
	Phase III clinical trial: RAINBOW	Advanced gastric or gastro-oesophageal junction adenocarcinoma	665	Ramucirumab + paclitaxel group ( <i>n</i> = 330) and placebo + paclitaxel group ( <i>n</i> = 335) and	The combination of ramucirumab with paclitaxel could be regarded as a new standard second-line treatment for patients with advanced GC.	[57]
Sorafenib	Phase II clinical trial	Metastatic or advanced adenocarcinoma of stomach or GEJ	44	Combined sorafenib, docetaxel and cisplatin group	Sorafenib combined with docetaxel and cisplatin effectively treated GC or GEJ adenocarcinoma.	[60]
Regorafenib	Phase II clinical trial: INTEGRATE	Advanced GC	147	Regorafenib group ( <i>n</i> = 97) and placebo group ( <i>n</i> = 50)	The median PFS of regorafenib was significantly improved compared with that of placebo.	[70]

GC: Gastric cancer; GEJ: Gastro-oesophageal junction; HER2: Human epidermal growth factor receptor 2; ORR: Objective response rate; PFS: Progression-free survival.

and increased numbers of regulatory T lymphocytes and myelosuppressive cells),<sup>[72]</sup> they pass them to daughter cells. Also, the immune suppression is escaped and the apoptosis of immune cells is promoted, which is termed as “immune surveillance escape”.<sup>[73]</sup>

Several immune checkpoints are found on the surface of T lymphocytes. These “checkpoints” can inhibit the function of T cells under normal circumstances. At the same time, tumor cells can select these inhibitory mechanisms to protect T cells from their own tissues. The selective blocking of these natural inhibitory checkpoints can enable the continuous activation of T cells, thereby activating and promoting effective antitumor responses. Therefore, the immune checkpoint pathway is the main mechanism of tumor immune evasion. Tumor cells can regulate the activity of immune checkpoints through multiple channels and escape the surveillance of the immune system. Immune checkpoints mainly include programmed death-1 (PD-1) and its ligand programmed cell death ligand 1 (PD-L1) and cytotoxic T lymphocyte-associate antigen-4 (CTLA-4).<sup>[73,74]</sup>

PD-1 is expressed on immune cells or myeloid cells and provides a signal for terminating immune activity. PD-1 has two natural ligands, PD-L1 and PD-L2, which are mainly involved in negatively regulating T-cell activation. When PD-1 binds to PD-L1 in tumor tissues, it can inhibit the function of effector T cells, thereby inhibiting the antitumor immune response and promoting tumor growth. This is a potential mechanism for immune surveillance evasion.<sup>[75]</sup>

CTLA-4 is a member of the immune protein superfamily, which is expressed by activated cytotoxic T lymphocytes. Under normal circumstances, T cells can express CTLA-4 after activation. CTLA-4 competes with CD28 molecules expressed on the surface of T cells to bind to B7 molecules expressed by antigen-presenting cells. If the CD28 molecule fails to bind to the B7 molecule, the T cells cannot be activated, thereby reducing their ability to kill tumors.

The current research on treating GC with immune checkpoint inhibitors mainly includes PD-1 inhibitors nivolumab and pembrolizumab, PD-L1 inhibitor avelumab, and CTLA-4 immune checkpoint inhibitors tremelimumab and ipilimumab.

### PD-1 antibody

#### Nivolumab

Nivolumab is a highly selective and fully humanized IgG4 monoclonal antibody inhibitor.<sup>[76]</sup> It can bind to PD-1 on the surface of T cells, block the combination of PD-1 and its ligand PD-L1/2, restore the normal immune surveillance function of T cells, improve the lethality of T cells, and restore the antitumor effect of T cells.

Kang *et al*<sup>[77]</sup> conducted a randomized, double-blind, placebo-controlled phase III trial that explored the efficacy of nivolumab in treating GC. The study involved patients

with unresectable advanced or recurrent gastric or GEJ cancer who had received at most one chemotherapy regimen and had not received PD-1 treatment. A total of 493 cases were randomly divided into the nivolumab group ( $n = 330$ ) and placebo group ( $n = 163$ ). The average follow-up time in the two groups of patients was 8.87 and 8.59 months, mOS was 5.26 and 4.14 months, and the 12-month survival rates were 26.2% and 10.9%, respectively. The study suggested that nivolumab might be a new treatment option for advanced gastric or GEJ cancer. The Japanese subgroup study also showed that patients in the nivolumab group had better OS and a lower risk of death than those in the placebo group.<sup>[78]</sup>

Another phase II clinical trial (ATTRACTION-4) also evaluated the safety and effectiveness of nivolumab as a first-line treatment for unresectable advanced or recurrent HER2-negative GC or GEJ adenocarcinoma.<sup>[79]</sup> The study found that nivolumab combined with capecitabine and oxaliplatin was well tolerated and effective against unresectable advanced or recurrent HER2-negative GC or GEJ adenocarcinoma, indicating that nivolumab is expected to become the first immune checkpoint inhibitor approved for the first-line treatment of advanced HER2-negative GC. In short, nivolumab was safe and effective as a treatment for advanced GC. Its efficacy can be improved through combined application with another immunosuppressant or chemotherapeutic drug.

#### Pembrolizumab

Pembrolizumab is a highly specific PD-1 monoclonal antibody. Its mechanism of action is similar to that of nivolumab, but it has a different PD-1-binding site compared with nivolumab. Pembrolizumab can block PD-L1 receptors, make T cells get rid of the inhibitory effect of PD-L1, and make T cells mediate the antitumor effect against cancer cells.

In the field of GC research, a phase IB clinical study (KEYNOTE-012) explored the effect of pembrolizumab as a single agent in treating PD-L1-positive recurrence or metastasis of gastric/GEJ cancer.<sup>[80]</sup> Of the 39 patients enrolled, 66.7% had previously failed to receive third-line chemotherapy. The results showed that the PR rate was 22%, mPFS was 1.9 months, and mOS was 11.4 months. This result suggested that PD-L1 positivity could be used as a potential biomarker for pembrolizumab treatment.

The study by Le *et al*<sup>[81]</sup> included 86 patients with mismatch repair deficiency of 12 different tumor types who progressed after first-line treatment from September 2013 to September 2016 and were treated with pembrolizumab. The results showed that the objective imaging remission rate was 53% and the CR was 21%. Therefore, the FDA approved pembrolizumab in 2017 for the second-line treatment of high-microsatellite instability/DNA mismatch repair deficient solid tumors.

The KEYNOTE-059 trial<sup>[82]</sup> examined the efficacy of pembrolizumab in patients with advanced GC who progressed after second-line treatment. The results showed that the ORR was 11.6%, the CR rate was



2.3%, and the median response duration (MRD) was 8.4 months. The ORR and MRD of PD-L1-positive patients were higher than those of PD-L1-negative patients (15.5% and 16.3 months *vs.* 6.4% and 6.9 months, respectively). The aforementioned research results suggested that pembrolizumab had a noticeable effect in treating patients with advanced GC, especially PD-L1-positive patients. Both the CSCO 2019 version of the GC diagnosis and treatment guidelines and the NCCN 2019 version of the guidelines recommended pembrolizumab as the third-line treatment for advanced GC.

The KEYNOTE-061 trial<sup>[83]</sup> included 395 patients with advanced gastric or GEJ cancer who had a PD-L1 combined positive score (CPS) of 1 or higher, and they had previously received treatment and were randomly divided into the pembrolizumab group ( $n=196$ ) and paclitaxel group ( $n=199$ ). The results showed that the pembrolizumab group had no significant advantages over the paclitaxel group in terms of mPFS (1.5 *vs.* 4.1 months) and mOS (9.1 *vs.* 8.3 months). However, the incidence of grade 3 to 5 treatment-related adverse events was lower in the pembrolizumab group than that in the paclitaxel group (14% *vs.* 35%). The study showed that although pembrolizumab had no survival advantage over paclitaxel in treating advanced GC; it was less toxic and more tolerated by patients.

In the KEYNOTE-059 study, pembrolizumab alone or combined with cisplatin + 5-fluorouracil was used as the first-line treatment for advanced GC. They both showed good antitumor activity and were safe and tolerable.<sup>[84]</sup> The aforementioned studies showed that pembrolizumab had a significant therapeutic effect on advanced GC.

### PD-L1 antibody

Avelumab is a highly specific anti-PD-L1 monoclonal antibody. It can intercept the immune checkpoint PD-1/PD-L1 pathway by blocking PD-L1, liberate normal T cells, activate the tumor immune system of the body, and achieve antitumor effects.

In a phase IB clinical trial evaluating the use of avelumab in treating advanced gastric or GEJ adenocarcinoma,<sup>[85]</sup> the patients were divided into two subgroups: sequential avelumab treatment after first-line chemotherapy and second-line avelumab treatment. The confirmed ORR was 6.7% in both subgroups, and the DCR was 56.7% and 28.3%, respectively. Further, mPFS was 2.8 and 1.4 months, respectively, and mOS was 11.1 and 6.6 months, respectively. The incidence of grade three and above adverse reactions was 8.7%. In a study of patients with GC in Japan,<sup>[86]</sup> the ORR was 10% and mOS was 9.1 months. The trial showed that avelumab improved the survival of patients with advanced gastric or GEJ adenocarcinoma and disease progression after chemotherapy with controllable safety.

Based on this, 371 cases of inoperable, recurrent, or metastatic GC or GEJ adenocarcinoma with disease progression after receiving two previous treatments were included in a randomized controlled phase III clinical trial

(JAVELIN Gastric300).<sup>[87]</sup> The results showed that mOS was 4.6 and 5.0 months, mPFS was 1.4 and 2.7 months, and ORR was 2.2% and 4.3%, respectively, in the avelumab and chemotherapy groups. The OS and PFS were not improved in the avelumab group compared with the chemotherapy group; however, the safety of avelumab treatment was superior. Hence, although avelumab failed as a third-line treatment for advanced GC, its safety was better.

An international phase III clinical trial focused on patients with advanced/metastatic HER2-positive GC or GEJ adenocarcinoma and analyzed the efficacy of avelumab maintenance therapy after first-line induction chemotherapy. The study included 499 untreated patients with locally advanced HER2-positive GC or GEJ adenocarcinoma. First, they received oxaliplatin + fluorouracil + leucovorin (FOLFOX) or oxaliplatin combined with capecitabine for 12 weeks. Then, the patients whose diseases were controlled were randomly divided into two groups in the ratio of 1:1. They received avelumab or continued the first-line chemotherapy until the disease progressed or intolerable adverse reactions occurred. The results showed that patients who received avelumab had a longer OS compared with patients who maintained first-line chemotherapy.<sup>[88]</sup> This study showed that avelumab maintenance therapy after first-line induction chemotherapy might serve as an alternative treatment strategy for patients with advanced GC or GEJ adenocarcinoma.

### CTLA-4 checkpoint inhibitor

#### Tremelimumab

Tremelimumab is a fully humanized anti-CTLA-4 monoclonal IgG2 antibody. A phase II clinical trial evaluated the efficacy of tremelimumab in patients with advanced GC and esophageal adenocarcinoma.<sup>[89]</sup> The patients enrolled in the study had received at least one platinum-based chemotherapy. A total of 18 patients participated in the trial. Patients received tremelimumab treatment every 3 months; the efficacy evaluation was also performed every 3 months. The results showed that one patient achieved partial remission after eight treatment cycles; the best curative effect for four patients during treatment was achieving stable disease, mPFS was 2.83 months, and mOS was 4.83 months. The overall efficacy was poor; however, tremelimumab showed long-lasting antitumor effects in patients with partial remission. This patient had multiple metastases at the time of enrollment. After 11 cycles of treatment, the OS time exceeded 32.7 months. The study found that tremelimumab had a poor anti-CTLA-4 effect on unscreened GC and esophageal adenocarcinoma, but it might achieve ideal and long-lasting effects in some special types of patients. This suggested that screening populations based on suitable molecular markers was of great significance for immunotherapy.

#### Ipilimumab

Ipilimumab is a fully humanized IgG1 monoclonal antibody against CTLA-4, which exerts antitumor immune effects by blocking the binding of CTLA-4 and B7 molecules.

The 143 patients enrolled in phase II clinical trial (NCT01585987) were randomly divided into the ipilimumab treatment group and the best supportive treatment group.<sup>[90]</sup> Immune-related PFS (irPFS) did not improve in the ipilimumab treatment group (2.92 *vs.* 4.90 months). Ipilimumab treatment failed to improve irPFS probably because patients who received disease control from first-line chemotherapy entered the ipilimumab treatment group, suspended effective chemotherapy, and were treated with ipilimumab only, which led to poor disease control.

Checkmate-032 was a phase I/II, randomized, open-label, solid-tumor cohort study.<sup>[91]</sup> It aimed to explore the efficacy and safety of nivolumab as a single agent or in combination with ipilimumab in treating solid tumors. A total of 160 patients were enrolled in one of the studies on the effectiveness and safety of nivolumab alone or in combination with ipilimumab in treating locally advanced or metastatic gastric or GEJ cancer. The study results showed that the ORR of combination was 14%, mPFS and mOS were 1.4 and 5.0 months, respectively, and the 6 and 12-month OS rates were 49% and 36%, respectively. Another phase I/II CheckMate-032 trial<sup>[92]</sup> found that the mOS of ipilimumab combined with nivolumab was 6.9 months, and the ORR could reach 24%. It suggested that ipilimumab combined with nivolumab had good antitumor activity in refractory GC.

Important clinical trials of immunotherapy drugs for GC are shown in Table 2.

## Summary and Outlook

While targeted therapy and immunotherapy for GC benefit many patients, they also face some problems and challenges.

### Problems and challenges

#### Targeted therapy appears to be resistant

The development of targeted therapy brings hope to the fight against cancer. It not only represents a new individualized treatment plan but also provides new biological insights for the treatment of GC. However, the success of this individualized treatment has encountered varying degrees of drug resistance (primary drug resistance and acquired drug resistance), which is still the main obstacle to clinical treatment. Therefore, it is advised to explore the development of the drug itself while investigating the mechanism of targeted drug resistance. It is hoped that by understanding the mechanism of drug resistance, we can find strategies to overcome drug resistance and improve the efficacy of treatment.

#### Duration of immunotherapy treatment is uncertain

The treatment duration of immune checkpoint inhibitors is uncertain, and the treatment period can range from four cycles to 1 to 2 years. Some patients can have a sustained effect after treatment in a short time. Some patients have a

better effect on the initial immunotherapy but relapse after a period. Therefore, it is necessary to explore the duration of treatment so as to obtain the maximum effect.

### Immune-related adverse events

Immunomodulators have immunotoxic reactions,<sup>[93]</sup> which can cause autoimmune or inflammatory side effects, which are called “immune-related adverse events” (irAEs). The specific antitumor immune response is a complex process jointly regulated by multiple molecules and signaling pathways. Hence, although immunotherapy benefits patients with cancer, it may also cause many irAE, such as skin toxicity, gastrointestinal toxicity, liver and endocrine toxicity, and other adverse reactions. These adverse reactions may be related to the imbalance of immune system regulation, but the specific mechanism is still unclear. Therefore, when immunotherapy brings benefits to patients with cancer, we must also pay attention to the adverse events caused by immunotherapy and provide timely preventive intervention or treatment.

### Clinical application and prospects

#### Screening of suitable biomarkers

In recent years, the success of tumor molecular targeted drugs and immune checkpoint inhibitors in clinical practice has reinvented the model of tumor treatment and has epoch-making significance in tumor treatment. However, the current practice of targeted therapy and immunotherapy still has many unsolved problems. Therefore, we urgently need to find valuable biomarkers to screen suitable populations for targeted therapy and immunotherapy so as to achieve individualized treatment of tumors.

#### Multitarget drugs and combination drugs

The marketing of targeted therapy and immunotherapy drugs has brought new hope to patients with cancer, and many patients with cancer have achieved complete remission in clinical practice. However, more deficiencies have been exposed with more clinical data. At present, combination medication is the main direction to improve the therapeutic effect.

The causes and mechanisms of tumors are complex and changeable. It is difficult to achieve a cure only for a single target. The development of multitarget antitumor drugs and combination therapy drugs is very important. For example, multiple-target antitumor drugs such as sorafenib and sunitinib, which are already on the market, have significant clinical effects. Most of the combination drugs are still in the clinical research and development stage and are currently divided into three types: (1) combination drugs with the same target; (2) combination drugs with the same target but different sites; and (3) multitarget combination drugs, such as targeted drugs for EGFR and drugs for another target (anti-angiogenesis drugs) at the same time. Of course, the combination of chemotherapy and molecular targeted drugs is also a promising treatment regimen.

**Table 2: Important clinical trials of immunotherapy drugs for GC.**

Targeted drugs	Clinical trials	Research objects	Patient number	Groups	Results	Ref.
Nivolumab	Phase III clinical trial: ATTRACTION-2 Phase III clinical trial: ATTRACTION-4	Advanced gastric or gastro-oesophageal junction cancer Advanced gastric/ GEJ cancer	493 39	Nivolumab group ( <i>n</i> = 330) or placebo group ( <i>n</i> = 163) Nivolumab + S-1 plus oxaliplatin group ( <i>n</i> = 21) and nivolumab + capecitabine plus oxaliplatin ( <i>n</i> = 18)	Nivolumab might be a new treatment option for advanced GC. Nivolumab combined with capecitabine and oxaliplatin was well tolerated and effective against unresectable advanced or recurrent HER2-negative GC or GEJ adenocarcinoma.	[77] [79]
Pembrolizumab	Phase II clinical trial: KEYNOTE-059	Previously treated gastric or gastroesophageal junction cancer	259	Pembrolizumab monotherapy	Pembrolizumab had an apparent effect in treating patients with advanced GC with MMR deficiency, especially PD-L1-positive patients.	[82]
	Phase III clinical trial: KEYNOTE-061	Advanced gastric or gastro-oesophageal junction cancer	395	Pembrolizumab group ( <i>n</i> = 196) and paclitaxel group ( <i>n</i> = 199)	Although pembrolizumab had no survival advantage over paclitaxel in treating advanced GC, it was less toxic and more tolerated by patients.	[83]
Avelumab	Phase III clinical trial: JAVELIN Gastric300 Phase III clinical trial: JAVELIN Gastric 100	Unresectable, recurrent, locally advanced, or metastatic GC/GEJ cancer Locally advanced/metastatic HER2-GC/GEJ adenocarcinoma	371 499	Avelumab group ( <i>n</i> = 185) and chemotherapy group ( <i>n</i> = 186) Avelumab group and chemotherapy group ( <i>n</i> = 250) continue ( <i>n</i> = 249)	Although avelumab failed as a third-line treatment for advanced GC, its safety was better. Avelumab maintenance therapy after first-line induction chemotherapy might be an alternative treatment strategy for patients with advanced GC or GEJ adenocarcinoma.	[87] [88]
Tremelimumab	Phase II clinical trial	Metastatic gastric and esophageal adenocarcinomas	18	Tremelimumab group	Tremelimumab had a poor anti-CTLA-4 effect on unscreened GC and esophageal adenocarcinoma, but it might achieve ideal and long-lasting effects in some special types of patients.	[89]
Ipilimumab	Phase I/II clinical trial: CheckMate-032	Locally advanced or metastatic chemotherapy-refractory gastric, esophageal, or gastroesophageal junction cancer	160	Nivolumab 3 mg/kg group ( <i>n</i> = 59), nivolumab 1 mg/kg + ipilimumab 3 mg/kg group ( <i>n</i> = 49), nivolumab 3 mg/kg + ipilimumab 1 mg/kg group ( <i>n</i> = 52)	Ipilimumab combined with nivolumab had good antitumor activity in refractory GC.	[92]

CTLA-4: Cytotoxic T lymphocyte-associate antigen-4; GC: Gastric cancer; GEJ: Gastro-esophageal junction; HER2: Human epidermal growth factor receptor 2; MMR: Mismatch repair; PD-L1: Programmed cell death ligand 1.

### Choice of dosage

Although combined medication can improve the therapeutic effect of tumors, the increase in therapeutic drugs may cause more adverse reactions. Therefore, the way to use a smaller dose to bring better efficacy is an important direction for future research. However, more clinical studies are still needed to explore the dosages of single drugs and combination drugs, as well as the efficacy of different doses.

### Ideas to address irAE

The field of immunotherapy-related adverse reactions is also a hotspot in immunotherapy research. If we can find out what kind of people may have irAE before treatment and carry out strict monitoring and early treatment, it will be critical to the clinical practice of immunotherapy. However, a better predictive marker is still not available for many serious irAEs. The ideal solution to irAE is to develop drugs that target tumor-specific immunosuppressive signaling pathways or only activate the tumor local immune response. However, overlaps may occur between patients with better tumor response and those who experience irAE, causing difficulties in avoiding irAE. With the widespread application of immune checkpoint inhibitors in various tumor types, molecular studies and clinical data analysis of large-scale specimens may bring more hope to this field.

Remarkable progress has been made in domestic and foreign research on molecular targeted therapy and immunotherapy for GC in recent years, which has continuously promoted the advancement of precision medicine. The occurrence and development of GC are related to various signaling pathways. Hence, further research is needed for exploring the mechanism of pathogenesis and development of GC. Although good results have been achieved in the research of molecular targeted therapy and immunotherapy for GC, many clinical trials are still in progress. While targeted therapy and immunotherapy benefit many patients, they also face many problems and challenges. The current clinical research results are largely unsatisfactory due to the high heterogeneity of GC, the lack of clear tissue or serological markers, and the rapid drug resistance to targeted drugs. Targeted therapy is moving ahead in the direction of precision medicine, and immunotherapy is also developing rapidly. Therefore, the follow-up studies must further increase research efforts, striving to achieve more breakthroughs. In the course of treatment, it is necessary to not only maximize the benefit of patients but also reduce the occurrence of adverse reactions.

In summary, GC treatment still has a long way to go. GC has its own unique laws and strong heterogeneity. Future studies should innovate research methods and identify people who really benefit. New breakthroughs in the treatment of GC can only be made if individualized treatment is given based on different molecular types and different pathological characteristics. Also, more targeted and immunotherapy drugs should be developed to overcome problems and challenges so as to further improve

the OS and quality of life of patients with GC. The next 10 years will be a critical period in the development of targeted tumor therapy and immunotherapy. The related research results of basic medicine, translational medicine, and clinical medicine will play an important role in it and benefit more patients with cancer.

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### Conflicts of interest

None.

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