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REVIEW

Advances in targeted therapy for human epidermal growth factor receptor 2 positive in advanced gastric cancer

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Abstract

Emerging therapeutic methods represented by targeted therapy are effective supplements to traditional first-line chemoradiotherapy resistance. Human epidermal growth factor receptor 2 (*HER2*) is one of the most important targets in targeted therapy for gastric cancer. Trastuzumab combined with chemotherapy has been used as the first-line treatment for advanced gastric cancer. The safety and efficacy of pertuzumab and margetuximab in the treatment of gastric cancer have been verified. However, monoclonal antibodies, due to their large molecular weight, inability to penetrate the blood-brain barrier, and drug resistance, lead to decreased therapeutic efficacy, so it is necessary to explore the efficacy of other *HER2*-targeting therapies in gastric cancer. Small-molecule tyrosine kinase inhibitors, such as lapatinib and pyrrotinib, have the advantages of small molecular weight, penetrating the blood-brain barrier and high oral bioavailability, and are expected to become the drugs of choice for perioperative treatment and neoadjuvant therapy of gastric cancer after validation by large-scale clinical trials in the future. Antibo-drug conjugate, such as T-DM1 and T-DXd, can overcome the resistance of monoclonal antibodies despite their different mechanisms of tumor killing, and are a supplement for the treatment of patients who have failed the treatment of monoclonal antibodies such as trastuzumab. Therefore, after more detailed stratification of gastric cancer patients, various gastric cancer drugs targeting HER2 are expected to play a more significant role.

Key Words: Human epidermal growth factor receptor 2; Gastric cancer; Targeted therapy; Review

Core Tip: Human epidermal growth factor receptor 2 (*HER2*) is one of the most important targets in targeted therapy for gastric cancer. Trastuzumab combined with chemotherapy has been used as the first-line treatment for advanced gastric cancer. The safety and efficacy of pertuzumab and magtuximab in the treatment of gastric cancer have been verified. However, monoclonal antibodies, due to their large molecular weight, inability to penetrate the blood-brain barrier, and drug resistance, lead to decreased therapeutic efficacy, so it is necessary to explore the efficacy of other HER2-targeting therapies in gastric cancer.

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INTRODUCTION

Stomach cancer is currently the fifth most common cancer worldwide, with the fourth highest case fatality rate[1-4]. Surgical resection and multidisciplinary treatment combined with chemoradiotherapy, targeted therapy and immunotherapy are the main methods in the treatment of gastric cancer[5]. Because there are no obvious specific symptoms in the early stage, most patients are not diagnosed until the tumor has developed to an advanced stage, resulting in some patients losing the opportunity for surgical treatment[6-8]. The 5-year survival rate of early gastric cancer is 70%, that of advanced gastric cancer is 32%, and that of distant metastatic gastric cancer is only 6%[9]. Therefore, there is an urgent need to find more new and effective therapeutic targets[10-12]. With the development of precision medicine, the score of cancer. Sub-targeted therapy has become the main treatment method for gastric cancer. Human epidermal growth factor receptor 2 (*HER2*) is an important therapeutic target of the epidermal growth factor receptor (*EGFR*) family, with an average positive rate of 17.9% in gastric cancer. In 2010, the ToGA trial was the first to demonstrate that trastuzumab combined with chemotherapy extended survival[13]. At present, in addition to trastuzumab, there are many other *HER2*-targeting therapies still under study, such as monoclonal antibodies (trastuzumab, pertuzumab and magtuximab, *etc.*), antibo-drug conjugate (ADC), such as T-DM1, T-DXd, *etc.*, tyrosine kinase inhibitors (TKI) such as lapatinib, pyrrotinib, *etc.*[14-17].

Gastric cancer is a heterogeneous and highly aggressive malignancy with the 5th highest incidence and 3rd highest mortality worldwide[18]. Most patients are in the advanced stage when diagnosed, and the prognosis is very poor. Systemic therapy is currently the most important treatment for advanced gastric cancer, and *HER2* is an important therapeutic target for *HER2*-positive gastric cancer[19-22]. With the continuous optimization of *HER2*-targeting drugs and therapies, some gastric cancer patients have benefited from it. However, the high incidence of drug resistance and serious adverse reactions are still the bottlenecks limiting the application of *HER2*-targeted drugs[23]. Therefore, the development of novel anti-tumor drugs is of great significance for improving the long-term survival of patients with *HER2*-positive gastric cancer. ADCs are a new class of highly effective anti-tumor drugs, which are composed of specific targeted monoclonal antibodies, chemical junctions and small cytotoxic payloads[24]. Their main advantages are powerful therapeutic effect and moderate tissue toxicity[25]. In recent years, ADC has made great progress in the field of targeted therapy for HER2-positive advanced gastric cancer[26-30]. First of all, after years of development, a variety of ADCs, including DS-8201, RC48, *etc.*, have been used for second-line and postline treatment of gastric cancer. Secondly, with the progress of ADC bioengineering technology, including high ratio of drug antibodies, cleavable linkers, toxic payloads that can cause bystander effect, *etc.*, new ADCs can play a more significant therapeutic effect in the treatment of specific tumor targets. Some of these ADCs also have multi-targeting and can play an anti-cancer effect against multiple specific targets[31-33]. At the same time, the development of ADCs has reached the third stage, and the new generation of ADCs through site-specific coupling technology has higher homogeneity, more efficient cytotoxic payload, higher precision, and lower non-targeted toxic effects[34-36]. In addition, "target-free combination" therapy consisting of ADC and immune checkpoint inhibitors (ICI) may be a promising treatment strategy for advanced gastric cancer.

This reviews the progress and advantages of *HER2*-targeted therapies in the treatment of gastric cancer in recent years, and discusses the existing problems and future development directions.

TARGETED THERAPY FOR PATIENTS WITH *HER2* GENE POSITIVE GASTRIC CANCER

Many studies[37-40] have shown that the *HER2* gene is overexpressed in different tumors such as breast, ovarian, prostate, colorectal, and lung cancers. The *HER2* gene (also known as Neu or ErbB2) is located on human chromosome 17 (17q21) and encodes the transmembrane glycoprotein p185. Studies[41-45] have shown that the positive rate of *HER2* in gastric cancer is 4.4% to 53.4%, with an average of 17.9%[46-50]. The *HER2* protein has four extracellular domains with unique structural and functional features that interact with ligands and initiate signal transduction, domains I and III

have inherent ligand binding capabilities, domain II can form homologous or heterodimers with other *HER* molecules, and domain IV at the proximal end of the membrane[51-54]. Different ligands are involved in the proliferation and apoptosis of tumor cells by activating Ras/MAPK and PI3K-Akt by binding to different domains of *HER2* receptor[55]. In addition, *HER2* overexpression is closely related to the formation of neovascularization in gastric cancer[56-60]. At present, the recommended methods for detecting *HER2* expression are mainly immunohistochemistry, which can be combined with fluorescence *in situ* hybridization if necessary. Second-generation sequencing, although expensive, is also gaining interest as it helps to find mutations in *HER* genes. Liquid biopsy techniques can also obtain tumor lesion information by detecting circulating tumor cells or circulating tumor DNA. In gastric cancer, *Helicobacter pylori* infection was positively correlated with the positive rate of *HER2* in gastric cancer[61-65]. The difference in the positive rate of *HER2* in gastric cancer was statistically significant between the killed and non-killed groups, suggesting that the detection of *Helicobacter pylori* and *HER2* is of great significance for the detection of early gastric cancer and the evaluation of tumor malignancy[66]. At present, the correlation between HER2 overexpression and clinical outcome of gastric cancer is uncertain. Some studies[67-70] have shown that *HER2* positivity is associated with a significantly worse prognosis. Other studies[71-75] have found no correlation between *HER2* status and prognosis, so the prognostic value of *HER2* in gastric cancer remains uncertain and needs further study (Figure 1).

HER2 is currently the only clear therapeutic target for gastric cancer, and the ToGA trial is the first large-scale phase III clinical trial in the world to prove that targeted therapy for gastric cancer can prolong survival, making trastuzumab combined with first-line chemotherapy agents the standard first-line treatment for *HER2*-positive advanced gastroesophageal adenocarcinoma[76-80]. However, targeting *HER2* has achieved significant efficacy in the treatment of breast cancer, such as trastuzumab combined with paclitaxel or pertuzumab, the combination therapy of lapatinib and the combination therapy of the antibody coupling drug T-DM1, *etc.*, but these therapies have not achieved positive results in the targeted therapy of *HER2*-positive gastric cancer (Figure 2). At present, the combination of trastuzumab, pertuzumab and magtuximab with immunotherapy drugs is the main direction of clinical trials of targeted therapy for gastric cancer [81]. Due to the emergence of drug resistance, the efficacy of trastuzumab is not good in some patients, so TKI and ADC are the choice of targeted therapy for this part of patients[82-85].

MONOCLONAL ANTIBODY TARGETING HER2

Monoclonal antibodies targeting *HER2* recognize the *HER2* antigen through the Fab segment, and the Fc segment binds to immune cells to exert anti-tumor function through antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cell-mediated phagocytosis, and complement-dependent cytotoxicity[86-88]. Compared with other targeted drugs, *HER2*-targeting monoclonal antibodies have stronger anti-tumor specificity, but because of their relatively large molecular weight, they cannot cross the blood-brain barrier, so the treatment of patients with brain metastases has limitations (Figure 3).

TRASTUZUMAB

Trastuzumab is the only monoclonal antibody approved by the US Food and Drug Administration (FDA) for the first-line treatment of *HER2*-positive advanced gastric cancer[89-93]. It can bind to the extracellular domain IV of *HER2*, block the *HER2* signaling pathway and inhibit the proliferation of tumor cells[94]. The ToGA trial showed that overall survival (OS) in the trastuzumab plus chemotherapy group was superior to chemotherapy alone [median OS (mOS) 13.8 months *vs* 11.1 months] compared with the traditional standard chemotherapy regimens for gastric cancer (capecitabine/cisplatin or fluorouracil/cisplatin)[95]. The ToGA trial also yielded consistent results in subgroup analyses in Japan[96-98]. In addition to survival, patients' recovery adjustment time for health-related quality of life and absence of disease or toxic symptoms was also longer than that for chemotherapy alone[99]. In addition, in the HERXO trial, trastuzumab combined with capecitabine and oxaliplatin were significantly effective in the treatment of advanced gastric cancer patients (mOS was 13.8 months *vs* 7.1 months), the 18-month disease-free survival (DFS) rate was 71% in perioperative treatment of gastric cancer[100-104]. The main results of trastuzumab combined with capecitabine and oxaliplatin in the treatment of advanced gastric cancer were consistent with those of the CGOG1001 trial[105-108]. The above results further established the basic position of trastuzumab in the first-line treatment of gastric cancer.

In the second-line chemotherapy regimen for gastric cancer, 5-FU, calcium folinate, oxaliplatin, irinotecan, docetaxel and paclitaxel are the main chemotherapy drugs at present[109-112]. A clinical trial of trastuzumab combined with 5-FU, leucovorin, oxaliplatin, and docetaxel for perioperative treatment of gastric cancer (median DFS was 42.5 months) demonstrated the efficacy of trastuzumab in second-line chemotherapy for gastric cancer[113-115]. However, the combination of trastuzumab and paclitaxel in the treatment of advanced gastric cancer did not effectively prolong the survival of patients in the WJOG7112G trial and T-CORE1203 trial, which is consistent with the current mainstream view that trastuzumab is not a recommended choice in second-line chemotherapy for gastric cancer[116-118]. Therefore, the efficacy of trastuzumab in second-line chemotherapy for gastric cancer still needs to be further explored[119]. The drug resistance of trastuzumab is often the main reason limiting its efficacy[120]. The use of other drugs in combination with trastuzumab is still the main research direction of clinical trials.

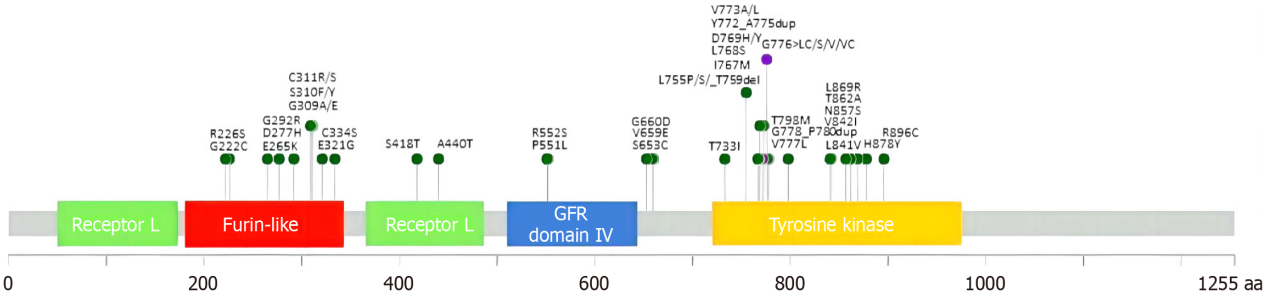

Figure 1 Human epidermal growth factor receptor 2 gene mutation site diagram. Created with BioRender.com (see Supplementary material).

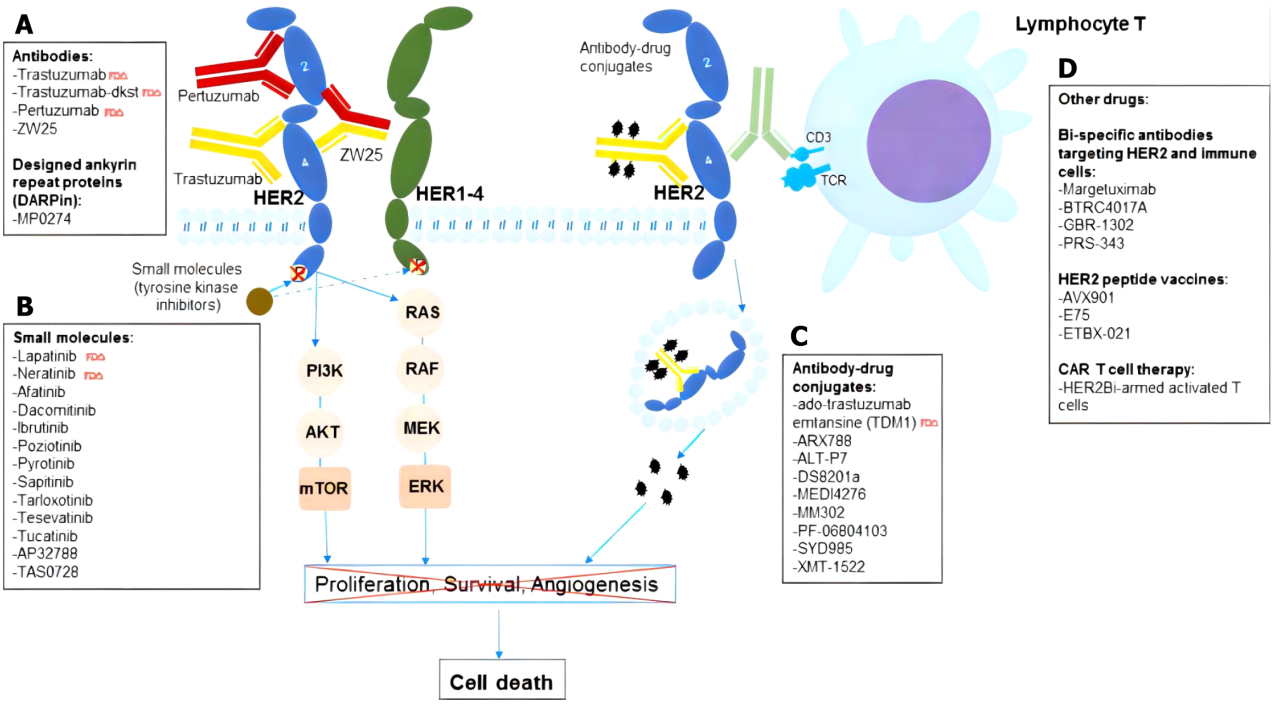

Figure 2 Activation pathway of human epidermal growth factor receptor 2 gene in gastric cancer immunotherapy. Created with BioRender.com (see Supplementary material).

PERTUZUMAB

Pertuzumab is a recombinant humanized monoclonal antibody that binds to the extracellular dimerization domain II of *HER2*, prevents the formation of ligand-induced *HER2* heterodimer, and can play a synergistic role with trastuzumab to inhibit tumor growth[121-126]. The JACOB trial applied pertuzumab and trastuzumab combined chemotherapy in the treatment of gastric cancer. The mOS of the pertuzumab group was 17.5 months, while that of the control group was 14.2 months.

mOS was extended by 3.3 months, but there was no statistical difference between the two, nor was it confirmed that the addition of pertuzumab effectively improved survival time[127-130]. Another clinical trial evaluating the dose and safety of pertuzumab in combination with trastuzumab, capecitabine, and cisplatin in patients with *HER2*-positive advanced gastric cancer showed that patients receiving a valley concentration (62.7 μg/mL) of pertuzumab (840 mg) every 3 wk had a higher response rate than those receiving the first week of pertuzumab loading dose (840 mg). Partial response rates (reduction in tumor volume) were 86% and 55%, respectively, in patients receiving weekly valley concentrations of 40.0 μg/mL of pertuzumab (420 mg)[131-134]. The INNOVATION trial applied pertuzumab combined with trastuzumab and chemotherapy drugs in perioperative chemotherapy for gastric cancer, which will further clarify the significance of pertuzumab in the treatment of gastric cancer[135].

MAGTUXIMAB

Magtuximab is a monoclonal antibody with an engineered Fc domain that targets the *HER2* receptor[136]. The optimized Fc domain improves binding to CD16A, a low-affinity stimulatory receptor found on macrophages and natural killer

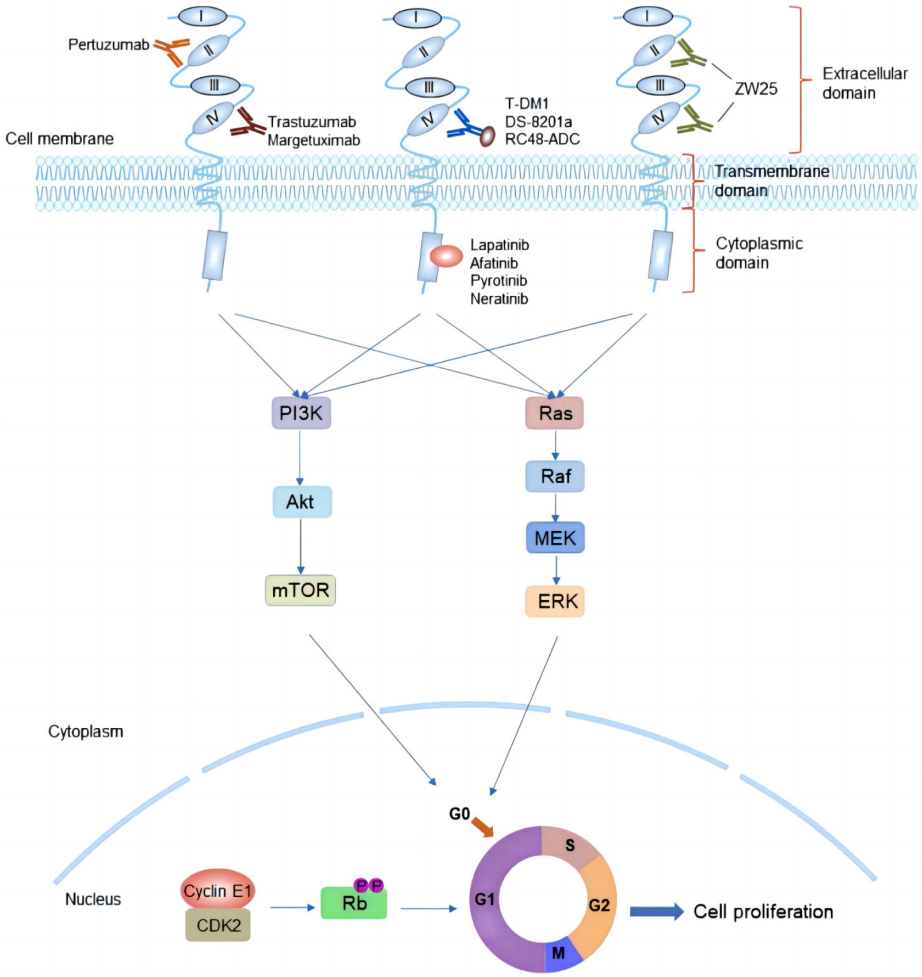

Figure 3 Mechanism of action of anti-human epidermal growth factor receptor 2 therapies in gastric cancer. Created with BioRender.com (see Supplementary material).

cells. The optimized Fc domain imparts enhanced ADCC action to the antibody[137-140]. A Phase I clinical trial evaluating magtuximab in patients with *HER2*-positive solid tumors, including gastric cancer, showed that 12% of patients were assessed as having a partial response and 50% were assessed as having stable disease. In addition, magtuximab combined with *PD-1* inhibitors inhibits tumor growth by enhancing innate immunity. The CP-MGAH22-05 trial evaluated the response of magtuximab in combination with pabolizumab in *HER2*-positive gastroesophageal adenocarcinoma patients with an objective response rate (ORR) of 18.48% and was safe and well tolerated[141-144]. The combination of an FC-optimized anti-*HER2* drug (Magtuximab) with an anti-*PD-1* checkpoint blocker (pembrolizumab) synergistically enhances the activity of these anti-tumor agents[145]. The MAHOGANY trial combined *PD-L1* inhibitor riflezumab with magtuximab in the first-line treatment of gastric cancer, and the results showed that ORR was 53%, the median duration of response was 10.3 months, and the disease control rate was 73%[146-148]. The above results suggest that the combination of dual-targeted drugs is effective in the treatment of gastric cancer.

TKI

HER2 is a transmembrane tyrosine kinase receptor, and TKI represented by Lapatinib blocks *HER2* signaling by competing with ATP in the catalytic domain of the *HER2* molecule, thereby preventing autophosphorylation and subsequent downstream signal transduction events[149]. In theory, TKI has an advantage over monoclonal antibodies because TKI binds to the intracellular domain and thus avoids monoclonal antibody resistance caused by the truncated form (P95) of *HER2* (Figure 4). Monoclonal antibody has a large molecular weight and cannot effectively cross the blood-brain barrier, which has certain limitations in the treatment of patients with brain metastases[150]. In contrast, TKI has a small molecular weight and can play a role across the blood-brain barrier. At the same time, TKI has good oral bioavailability and is an ideal therapeutic drug (Figure 5).

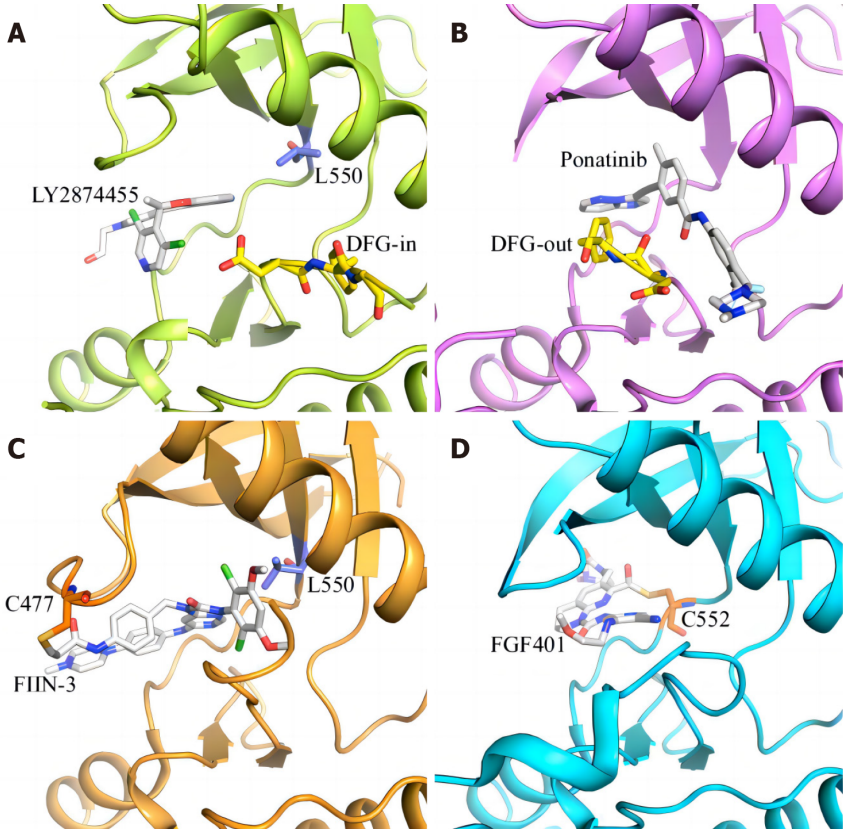

Figure 4 Strategies to overcome mutation-based TKI resistance. A: PDB: 5XFF; B: PDB: 4V01; C: PDB: 4R6V; D: PDB: 6JPJ. Created with BioRender.com (see Supplementary material).

LAPATINIB

Lapatinib is an oral TKI that blocks *HER1* and *HER2* tyrosine kinase activity by binding to the ATP-binding site of the intracellular domain of the recipient cell, thereby inhibiting tumor cell growth[151,152]. In the LOGiC trial, lapatinib was combined with first-line chemotherapy capecitabine plus oxaliplatin in the treatment of *HER2*-positive gastric cancer. mOS in the lapatinib group and placebo group was 12.2 months and 10.5 months, respectively[153-155]. Although the OS in the lapatinib group was longer, the difference was not statistically significant. In addition, the response rate was 53% in the lapatinib group compared with 39% in the placebo group, and the OS was prolonged in the Asian population and younger patients, suggesting that lapatinib may still play a large role in the treatment of gastric cancer. In the EORTC 40071 trial, mPFS was 8.0 months in the lapatinib group and 5.9 months in the placebo group, suggesting that lapatinib combined with epirubicin, cisplatin, 5-FU, and capecitabine can significantly improve PFS in gastric cancer. Lapatinib did not improve OS in chemotherapy for second-line gastric cancer (mOS 11 months *vs* 8.9 months for lapatinib and paclitaxel alone)[156-160]. In the treatment of metastatic gastric cancer, a trial found that PFS and OS were comparable when treated with lapatinib alone *vs* lapatinib combined with capecitabine after platinum therapy failed. In another trial, lapatinib was used as a neoadjuvant therapy for gastric cancer, but the complete response rate was only 8%[161-164]. Although the above trial results did not reach a consistent positive conclusion, it can suggest that lapatinib can still play a significant role in the treatment of gastric cancer after selecting the right target population.

PYROTINIB

Pyrrotinib is a novel and irreversible TKI with extensive anti-*EGFR* (*HER1*, *HER2* and *HER4*) activities[165]. By covalently binding to intracellular ATP binding sites, pyrrotinib inhibits the formation of homologous/heterodimer of *HER* family and self-phosphorylation, thereby blocking tumor cell cycle and limiting tumor development. mPFS of gastric cancer patients treated with pyrrotinib were 2.9 months, mOS was 5.9 months, disease control rate was 100%, and ORR was 50%, indicating that the treatment of pyrrotinib has a good effect on *HER2*-positive advanced gastric cancer patients, and its toxic effects can be well controlled[166-170]. In another retrospective study, gastric cancer patients treated with pyrrotinib had PFS of 142 d and mOS of 179 d, which also revealed that pyrrotinib has significant antitumor activity and good safety profile (Figure 6). However, the sample sizes collected in these trials are small, and the role of pyrrotinib in gastric cancer remains to be demonstrated by further larger clinical studies[171-173].

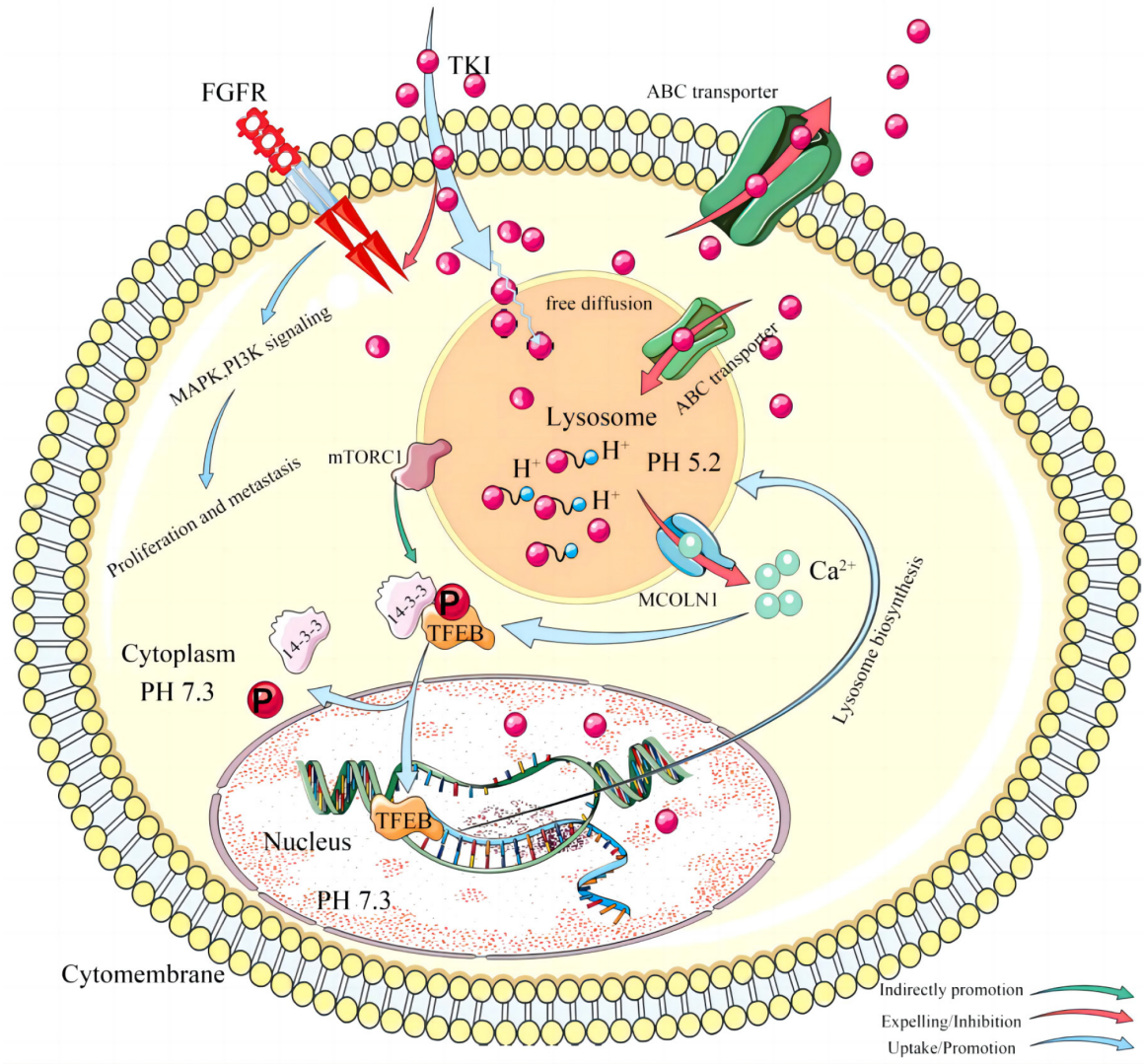

Figure 5 Schematic diagram of TKI-FGFR pathway activation in gastric cancer cells. Created with BioRender.com (see Supplementary material).

ADC

ADCs consist of recombinant monoclonal antibodies that are covalently bound to cytotoxic drugs. Antibodies can be internalized after binding with specific antigens on the surface of tumor cells, so that cytotoxic drugs can be released inside cells. Another ADC is designed to promote the release of drugs from target cells to extracellular space, or release cytotoxic drugs from antibodies after binding with internalized preantigens, which can achieve the purpose of killing target cells and surrounding cells. High levels of *HER2* expression are not necessarily required[174-176]. This may be beneficial for the treatment of stomach cancer. At present, the clinical ADCs for *HER2*-positive gastric cancer mainly include T-DM1 and T-DXd.

T-DM1

T-DM1 consists of trastuzumab and the small molecule microtubule inhibitor DM1 (maidensin)[177]. In the treatment of breast cancer, T-DM1 has achieved good efficacy and has been approved by the US FDA as a second-line treatment for *HER2*-positive advanced breast cancer. Based on this, many trials[178-180] have investigated its efficacy in the treatment of gastric cancer. The GATSBY trial evaluated the efficacy of T-DM1 and taxanes in *HER2*-positive advanced gastric or gastroesophageal junction carcinoma patients who had previously received chemotherapy and failed targeted therapy. The results showed that T-DM1 was not superior to taxanes in *HER2*-positive advanced gastric cancer patients who had previously received chemotherapy and failed targeted therapy (mOS was 7.9 months *vs* 8.6 months), and the results of the secondary efficacy endpoint PFS analysis did not reach a positive conclusion, which may be related to the *HER2*-positive patients with *HER2* negative conversion[181]. Therefore, there is still a need to explore other therapeutic drugs for these patients.

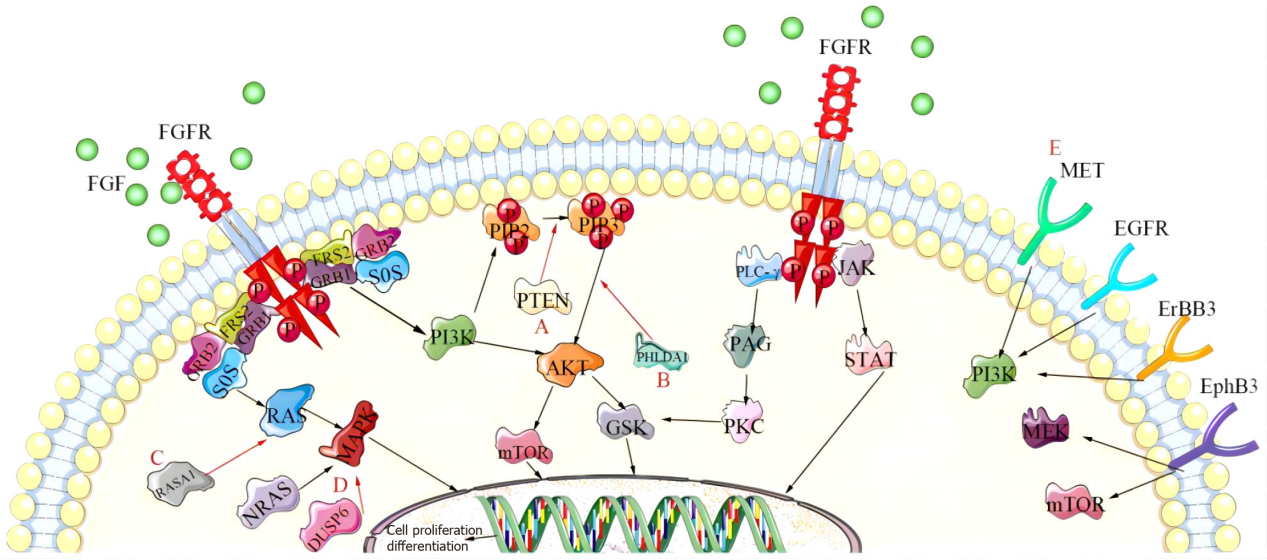

Figure 6 Mechanisms of alternative signaling activation induced FGFR-TKI resistance in gastric cancer. Created with BioRender.com (see Supplementary material).

T-DXd

T-DXd is a novel ADC composed of trastuzumab, cleavable tetrapeptidase splitter and human DNA topoisomerase I inhibitor[182]. In the Phase I dose-escalation study of T-DXd in patients with advanced *HER2*-positive gastric cancer, the recommended dose of 5.4 mg/kg or 6.4 mg/kgT-DXd was administered intravenously every 3 wk, and 43.2% of patients responded objectively in the dose-expansion trial[183-185]. When T-DXd was used in *HER2*-positive gastric cancer patients who had previously failed treatment with two or more fluoropyrimidine, platinum-based drugs, and trastuzumab (or an approved biosimilar), the difference in OS was statistically significant (12.5 months *vs* 8.4 months)[186]. It provides a new and effective drug for *HER2*-positive gastric cancer patients who have failed chemotherapy and targeted therapy.

RESEARCH PROGRESS OF ADC AND ICI IN *HER2* ADVANCED GASTRIC CANCER

Immunotherapy is a new tumor treatment model. In advanced gastric cancer, the strategies of immunotherapy mainly include adoptive cell therapy, tumor vaccine and immune checkpoint regulation[187]. In recent years, the field of immunotherapy for advanced gastric cancer, especially targeted immune checkpoint therapy, has developed rapidly. The CheckMate 649 study established the important position of ICI in the immunotherapy of advanced gastric cancer. The latest research results were updated at the European Society of Medical Oncology Congress in 2022, which further confirmed the effect of nebuliuzumab combined with chemotherapy in the whole population, and the ORR of all randomized patients increased from 46% to 58%[188-190]. Both PFS and OS are extended and secure. These follow-up results further support the use of nabuliumab in combination with chemotherapy as the first-line standard of care for patients with advanced gastric cancer. In the Phase III KEYNOTE 062 trial, pembrolizumab, a *PD-1* inhibitor, was no less effective than chemotherapy as a first-line treatment for advanced gastric cancer, either alone or in combination with chemotherapy, and had fewer aes. *PD-1* inhibitors are also beneficial for the treatment of *HER2*-positive gastric cancer. In the Phase III KEYNOTE-811 study, adding pembrolizumab to trastuzumab plus chemotherapy for *HER2*-positive gastric cancer or gastroesophageal junction carcinoma, trastuzumab plus chemotherapy combined with pembrolizumab significantly reduced tumor size. The ORR of the patients was significantly improved. This study is another major breakthrough after the ToGA study, rewriting the first-line treatment guidelines for *HER2*-positive gastric cancer, and opening a new era of "immunotherapy + targeted therapy + chemotherapy" treatment for *HER2*-positive gastric cancer[191]. On this basis, a series of explorations have been carried out on new anti-*HER2* drugs and their combination methods. *ZW25*, a bi-specific antibody targeting the *ECD4* and *ECD2* domains of *HER2*, also achieved an ORR and a median PFS of 10.9 months similar to KEYMATe-811 in *HER2*-positive gastric cancer patients treated in combination with PD-1 inhibitors and chemotherapy[192]. In addition, cytotoxic T lymphocyte-associated antigen 4 (*CTLA-4*) is another important checkpoint (Figure 7).

However, *CTLA-4* checkpoint inhibitors have not been successful in gastric cancer. A *PD-1/CTLA-4* dual-target inhibitor currently under development, cadonilimab (AK104) is the first *PD-1/CTLA-4* bisspecific antibody. In a Phase I b/ II study of AK104 in combination with chemotherapy for the first-line treatment of gastric or gastroesophageal borderline cancer (NCT03852251), AK104 showed good anticancer activity and a manageable safety profile[193]. A Phase III study of AK104 combined with chemotherapy as first-line treatment for gastric or gastroesophageal borderline cancer (NCT05008783) is ongoing[194].

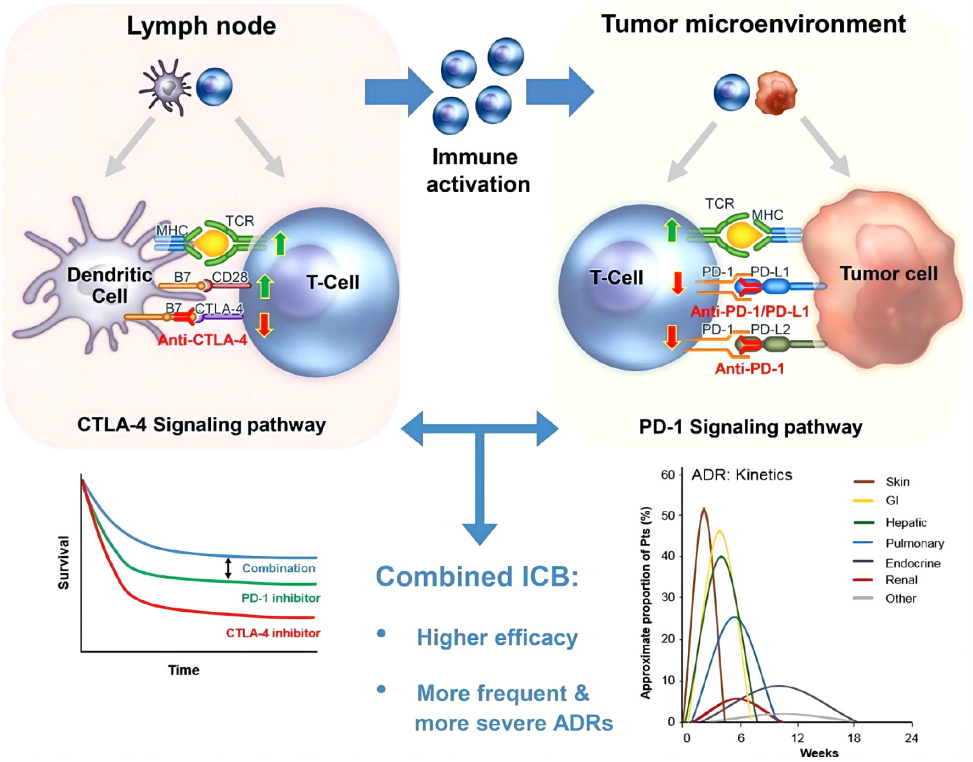

Figure 7 Schematic diagram of the effect of PD-1/CTLA-4 signaling on the immune microenvironment of gastric cancer. ICB: Immune checkpoint blockade; ADR: Adverse drug reaction; MHC: Major histocompatibility complex. Created with BioRender.com (see Supplementary material).

ADC can improve the degree of T lymphocyte infiltration in gastric cancer tissue, enhance the anti-tumor immune response, and thus improve the therapeutic effect of *PD-1* inhibitors. Therefore, a promising therapeutic strategy is ADC combined with ICI. ADC enhances anti-tumor immune response in the following three aspects: First, ADC can induce anti-tumor immune activity by releasing cytotoxic payloads within cancer cells; Secondly, ADC can significantly improve the immune response by directly killing cancer cells or non-targeted cancer cells through enrichment on the tumor surface; Third, cytotoxic payloads can induce antigen-presenting dendritic cells to mature to enhance anti-tumor immune responses. At present, some preclinical studies have confirmed the potential of ADC combined with ICI in the treatment of gastric cancer. Sato *et al*[195] found that XMT-1522 can induce immune cell death *in vitro* and enhance CD8+T cell infiltration and PD-1 expression level of CD8+ cells after treating multiple gastric cancer cell lines. Yuan *et al*[196] found that T-DXd could increase the number of tumor infiltrating dendritic cells and up-regulate their CD86 expression. In addition, T-DXD also increased the number of tumor-infiltrating CD8+T cells and enhanced the expression levels of *PD-L1* and major histocompatibility complex class I molecules on tumor cells. When combined with ICI, both XMT-1522 and T-DXd showed synergistic antitumor activity. Therefore, the combination therapy composed of ADC and ICI shows an anticancer effect of "1 + 1 > 2", which is expected to become a promising treatment strategy for *HER2*-positive gastric cancer, but it needs to be confirmed by large randomized controlled clinical studies.

CHALLENGES IN THE APPLICATION AND DEVELOPMENT OF ADCS

As the fastest growing *HER2*-targeting drug at present, ADC faces three major challenges in the application and development process: First, how to improve the uptake of ADC by tumor cells is the main difficulty in its development [197]. ADC mainly relies on the high expression of target antigen on the surface of cancer cells to ensure its effective endocytosis and release cytotoxic payloads. The killing effect of *HER2* ADC is closely related to the expression level of *HER2* on the surface of gastric cancer cells, and requires high expression of *HER2* on the surface of gastric cancer cells. Gastric cancer limits the therapeutic effectiveness of existing ADCs. Therefore, improving the cancer cell uptake of ADC can significantly improve its anticancer activity, especially for *HER2*-low expressing gastric cancer. Second, non-targeted toxicity is one of the main factors leading to the failure of ADC clinical trials. Non-targeted toxicity is associated with a variety of factors, including mAb, cytotoxic payloads, linkers and target antigens, as well as the internalization of ADC by cancer cells, non-specific binding of antibodies to Fc receptors, premature hydrolysis of linkers to release payloads, and the "bystander" effect of overstrong ADCC action on normal cells. Thirdly, low expression of target antigen is another important factor in off-target toxicity of ADC[198]. ADC resistance is another problem that needs to be overcome. The results suggest that ineffective internalization of ADC and lysosomal degradation may be the main mechanism of T-DM1 inactivation. It is also possible that cancer cells develop resistance to T-DM1 through upregulation of the drug efflux pump or by alternating the use of tubulin/microtubule-associated proteins. In addition, trastuzumab related changes

may also contribute to the development of T-DM1 resistance, including reduced *HER2* expression levels, the emergence of a truncated form of *HER2*, or mutations in the *ERBB2* gene. At the same time, some key issues should also be addressed in the future, including optimizing each ADC component to improve its anti-cancer activity; Accelerate the exploration of other targets in addition to *HER2*, such as ADCs against Trop-2, C-MET, claudin 18.2, and guanylate cyclase C.

CONCLUSION

Since the ToGA trial started the treatment of *HER2*-positive gastric cancer with trastuzumab, trastuzumab has played a huge role in the first-line treatment of gastric cancer, but in the second-line treatment, the efficacy of trastuzumab is not significant due to the emergence of drug resistance. At the same time, both pertuzumab and magtuximab have shown certain clinical application value in the treatment of gastric cancer. Small molecule TKI drugs lapatinib and pyrrotinib have shown certain efficacy in some clinical trials, but when combined with chemotherapy drugs, they do not significantly improve the survival rate of all patients. However, they still show irreplaceable therapeutic effects in some gastric cancer patients. In addition, the ADC drug T-DM1 did not significantly extend survival in patients with gastric cancer who had failed chemotherapy or targeted therapy, but T-DXd may be the treatment of choice for this subset of patients. Therefore, more detailed classification of *HER2*-positive gastric cancer patients is needed, which will help the use of various targeted drugs to better exert anti-tumor effects. At present, many drugs are still under study, such as monoclonal antibody initumab, TKI drugs lenatinib, Tucatinib, and ADC SYD985, which may play a good anti-tumor role in the treatment of gastric cancer in the future. At the same time, it is also expected that new and more effective anti-tumor drugs will be developed against the target *HER2*.

FOOTNOTES

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