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REVIEW ARTICLE

# Targeted therapy of gastric cancer: current and prospective strategies*

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## Abstract

Gastric cancer is the third leading cause of cancer-related death worldwide. Surgery is currently the only curative treatment strategy. Chemotherapy has shown limited efficacy in advanced gastric cancer patients with a median overall survival of less than one year. Thus, new treatments are urgently needed. Trastuzumab and Ramucirumab are the only targeted therapies approved currently. Most Phase III clinical trials evaluating targeted drugs in gastric cancer have failed. This review will evaluate relevant clinical trials with targeted therapies performed in gastric cancer patients, discuss the possible reasons for the failure, and indicate new possibilities to enhance gastric cancer treatment.

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Gastric cancer is the third most common cause of tumor-related death globally, with about one million new cases diagnosed each year [1]. The epidemiology of gastric cancer has distinct regional differences: the highest mortality rate is in East Asia, and the lowest is in North America; non-cardia gastric adenocarcinoma is commonly seen in East Asia, Eastern and Central Europe, Latin America, and Africa, whereas gastroesophageal junction gastric adenocarcinoma and proximal gastric cancer are commonly seen in in Western Europe, North America, and Australia [2]. Surgery is the most important method for the comprehensive treatment of localized gastric cancer, but chemotherapy is the only standard treatment for recurrent or metastatic gastric cancer [3]. The median survival time of patients with unresectable gastric cancer is 8–11 months in Europe [4–5] and 13–16 months in East Asia [6–7].

To date, international large-scale oncogenomic studies have given detailed molecular typing on gastric cancer. The Cancer Genome Atlas (TCGA) project analyzed 295 primary gastric cancer tissues not subject to radiotherapy and chemotherapy, and classified gastric cancer into four subtypes: EBV positive (EBV), microsatellite instability (MSI), genomic stability (GS), and chromosomal instability (CIN) [8]. EBV-positive gastric cancer mostly takes places at the gastric fundus and gastric body, often concomitant with P1K3CA or ARID1A hypermutation, DNA hypermethylation, and high expression of PDL1/PDL2; MSI subtype gastric cancer is usually accompanied by a high mutation rate and hypermethylation; GS subtype gastric cancer is often associated with molecular change in the pathways relevant to cell adhesion and metastasis and ARID1A and RHOA mutations; CIN subtype gastric cancer is usually accompanied by mutation of TP53 and gene amplification of receptor tyrosine kinases (RTKs). Although this classification has no prognostic value, it provides a basis for the selection of gastric cancer therapy. The most recent molecular typing of gastric cancer adopted by the Asian Cancer Research Group (ACRG) is similar to that adopted by the TCGA—both containing the MSI subtype, but the MSS subtype adopted by ACRG is further divided into smaller subgroups according to the EMT and TP53 conditions. The MSS/EMT subtype has the worst prognosis and a high recurrence rate, whereas the MSI subtype has the best prognosis [9]. In general, these studies have deepened our understanding of the molecular mechanisms of gastric cancer and facilitated personalized therapy of this cancer.

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With the advancement of molecular biology research on gastric cancer, the demand for personalized therapy based on its molecular biology has emerged. The exploration of new, targeted therapeutic drugs and their joint application with other therapeutic tools is an urgent issue that should be addressed by researchers. This article elaborates on the current progress in targeted gastric cancer therapy, such as anti-EGFR, HER2, VEGF, and mTOR treatments, and suggests future strategies of targeted gastric cancer therapy.

## EGFR inhibitors

Human epidermal growth-factor receptors (HER) are a family of tyrosine kinase receptors, including EGFR/HER1, HER2/neu, HER3, and HER4 [10]. After binding with ligands, EGFR transforms into a homo- or heterodimer to activate the EGFR pathway and further affect multiple cellular physiological processes, including proliferation, adhesion, invasion, migration, and differentiation [11]. About 5% of gastric cancer patients show EGFR amplification with poor prognosis [8]. It has been confirmed by some studies that EGFR is an effective therapy target for tumors.

### Cetuximab

Cetuximab is an IgG monoclonal antibody that binds to the extracellular domain of EGFR and prevents ligand binding to EGFR. A cetuximab-based prospective, multi-center phase II clinical trial showed that patients diagnosed with advanced gastric cancer or gastroesophageal junction adenocarcinoma but not previously treated, when treated with cetuximab in conjunction with cisplatin and capecitabine in the trial, had an objective response rate (ORR) of up to 53.2%, a median progression-free survival (PFS) time of 5.2 months, and a median overall survival (OS) time of 10.8 months [12]. However, the EXPAND trial showed that in patients already treated with both cisplatin and capecitabine, the combined use of cetuximab with them did not provide any additional benefit [13]. The REAL3 trial also confirmed that patients with advanced gastric cancer cannot benefit from anti-EGFR antibodies [14]. It has been experimentally confirmed that the effect of cetuximab is significantly related to EGFR amplification or high expression [15]. Similarly, a phase II clinical trial also confirmed that the effect of cetuximab in combination with chemotherapy is related to the number of EGFR amplifications [16]. However, in the EXPAND trial, there was no clear relationship between the immunohistochemistry score of EGFR and effect of cetuximab, and the relevant mechanism should be further researched.

### Nimotuzumab

Nimotuzumab is the first humanized monoclonal antibody that specifically binds EGFR. A phase II clinical trial of nimotuzumab enrolled 34 patients of recurrent or metastatic advanced gastric cancer, with the control group subject to standard DCF chemotherapy and the observation group subject to a joint treatment by DCF and Nimotuzumab, and found that the PFS and OS were 4.50 and 8.25 months in the control group, respectively, whereas they reached 6.50 and 12.50 months in the observation group, respectively; the difference was statistically significant, and there were no significant differences in toxicity and side effects between the two groups [17]. Another phase II clinical trial (NCT02370849) examined whether the use of nimotuzumab could benefit patients with advanced gastric cancer who initially received cisplatin-S1 chemotherapy and has been almost completed by now, with a result expected imminently. Japanese and Korean researchers initiated a phase III clinical trial (NCT01813253), in which the enrolled patients were those in a: first-line treatment group diagnosed with advanced or recurrent gastric cancer or with a gastroesophageal junction tumor and EGFR over-expression following the failure of 5-FU and cisplatin-based chemotherapy; second-line treatment group (control group) treated with irinotecan monotherapy; an observation group treated with both irinotecan and nimotuzumab, and this study is still recruiting suitable patients.

## HER2 inhibitors

HER2 is a member of the EGFR family, and different degrees of HER2 amplification have been observed in various tumors including breast, gastric, colorectal, and lung cancer [18]. The HER2 positive ratio of gastric cancer in different studies is mostly between 6%–30% [19–21]. FISH-positive gastric cancer tissues that also show HER2 overexpression (HER2 3+ or HER2 2+) detected with immunohistochemistry can be defined as HER2-positive tissues. Unlike breast cancer, HER2 expression in gastric cancer tissues is significantly heterogeneous, and therefore, the criteria for the determination of HER2 positivity are not the same. Many preclinical studies and clinical trials have confirmed the importance of HER2 status for targeted gastric cancer treatment.

### Trastuzumab

Trastuzumab is the first targeted drug approved for the treatment of gastric cancer. It can specifically bind to the HER2 extracellular domain. As a phase III clinical trial, the ToGA test is a milestone regarding the role of trastuzumab in gastric cancer treatment. In this trial, 594 patients with HER2-positive gastric cancer were

enrolled and randomly assigned to a group treated with chemotherapy alone and a group treated with both chemotherapy and trastuzumab [7], and the results showed that OS in the latter group was 2.7 months longer than that in the former group. Therefore, the results of this clinical trial were cited in the NCCN guideline in 2013, and to date trastuzumab has been recommended for first-line treatment of HER2-positive advanced gastric cancer. A second-phase clinical trial in South Korea studied the effect of the combined use of trastuzumab and XELOX in the treatment of HER2-positive advanced gastric cancer, with an ORR of 67% and a median PFS and OS of 9.8 and 21.0 months, respectively; the most common grade 3–4 toxic side effects were neutropenia (18%), anemia (11%), and peripheral neuropathy (11%). The results of this clinical trial suggested that the combined use of trastuzumab and XELOX is a tolerable and effective treatment method for advanced gastric cancer [22]. In addition, phase II clinical trials in Singapore and Japan confirmed that the treatment with both trastuzumab and S1-cisplatin/docetaxel was also effective for HER2-positive advanced gastric cancer [23–24].

### Pertuzumab

Pertuzumab is also a monoclonal antibody that specifically blocks the HER2 pathway. Monotherapy with pertuzumab has limited efficacy, but pertuzumab shows a synergistic effect with trastuzumab in HER2-positive breast cancer that progresses after trastuzumab treatment [25]. Currently, relevant clinical trials are investigating the role of the combined use of pertuzumab, trastuzumab, and chemotherapy in the treatment of gastroesophageal junctional tumors and gastric cancer, and in particular the INNOVATION (NCT02205047) trial is studying the efficacy of this regimen in new adjuvant therapy, whereas the JACOB (NCT01774786) trial studied the role of this regimen in the therapy of metastatic tumors and the results have not been reported.

### T-DM1

T-DM1 is a novel, targeted drug that couples trastuzumab with the anti-microtubule drug maytansine and has been approved for HER2-positive metastatic breast cancer. Preclinical studies have found that T-DM1 is effective in HER2-positive gastric cancer models [26]. Unfortunately, a randomized, open-label, phase II/III clinical trial has shown that T-DM1 is not superior to taxanes when used to treat the patients diagnosed with advanced HER2-positive gastric cancer and have been previously treated [27], which is a negative result with unknown reason, but may be interpreted by that after first-line treatment with both chemotherapy and trastuzumab, the HER2 status of some patients with gastric cancer changed, thereby affecting T-DM1 efficacy.

### Lapatinib

Lapatinib is a small-molecule tyrosine kinase inhibitor (TKI) that effectively inhibits HER2 kinase and slightly inhibits EGFR kinase. In the SWOG-S0413 phase II clinical trial, lapatinib monotherapy was used for first-line treatment of HER2-positive advanced or metastatic gastric cancer. However, this clinical trial did not reach the expected endpoint, with an ORR of only 11% and median OS 4.8 months [28]. A subsequent European Phase II clinical trial compared the efficacy of lapatinib and lapatinib with capecitabine in second-line treatment of HER2-positive gastric cancer, and only 2 of 37 enrolled patients showed objective relief, resulting in early closure of this clinical trial [29]. A phase III TRIO-013/LOGiC clinical trial found that the effects of the combined use of capecitabine and oxaliplatin–with or without lapatinib–on OS of patients with HER2-positive gastric cancer are not significant, but combined use of the former two with lapatinib can significantly prolong PFS of the patients [30]. TyTAN Phase III clinical trials have confirmed that administration of paclitaxel as a second-line treatment of HER2-positive advanced gastric cancer–with or without administration of lapatinib–does not provide survival benefits to patients [31], a result different from the positive results obtained in patients with breast cancer. A number of clinical trials are still ongoing.

### Afatinib

Afatinib has irreversible inhibitory effects on EGFR and HER2 tyrosine kinases and is approved for advanced non-small cell lung cancer and HER2-positive advanced breast cancer. Clinical trials on the effects of the combined use of afatinib and trastuzumab on HER2-positive metastatic refractory esophageal and gastric cancer are ongoing, and current data show that after four months of afatinib monotherapy, the disease control rate reached 42%, whereas the results of the combined use of the two drugs have not yet been reported.

## VEGF inhibitors

Angiogenesis can provide nutrients and oxygen to tissues while excreting metabolic waste and carbon dioxide, and has been considered one of the important causes resulting in tumor progression [32]. Tumor tissues secrete angiogenesis-related growth factors, such as VEGF, bFGF, and regulate angiogenesis by binding to receptors on the surface of epithelial cells. Binding of VEGF with the extracellular domain of its receptor phosphorylates its intracellular domain to activate the downstream pathway. Anti-vascular therapy is one of the important methods to treat cancer.

### Bevacizumab

Bevacizumab is a humanized IgG1 monoclonal antibody that binds to VEGF and inhibits the VEGF/VEGFR signaling pathway. A phase II clinical trial with 35 patients investigated the efficacy of capecitabine, oxaliplatin, and bevacizumab in metastatic esophageal cancer and gastric cancer, and found that the median PFS and OS were 7.2 and 10.8 months, respectively, the response rate was 51.4%, and drug-related toxicity was tolerable [33]. The AVAGAST trial enrolled 774 patients with advanced gastric cancer who were treated with either 7.5 mg/kg bevacizumab or placebo and simultaneously received chemotherapy with both cisplatin and capecitabine, and found that the median OS and PFS for the bevacizumab patients were 12.1 and 6.7 months, respectively, whereas they were 10.1 and 5.3 months in the placebo group, respectively, indicating that the combined treatment with bevacizumab and chemotherapy significantly prolonged PFS and increased ORR, but the clinical trial did not reach its primary endpoint OS [34]. Recently, Shen *et al* initiated a randomized, double-blind phase III clinical trial, in which Chinese patients with inoperable locally advanced or metastatic gastric cancer were treated with both bevacizumab and capecitabine-cisplatin. A total of 202 patients (102 in the placebo group and 100 in the bevacizumab group) were enrolled in the clinical trial. The results showed that there was no significant difference in OS and PFS between the two groups, and the patients could tolerate the treatment with both bevacizumab and capecitabine-cisplatin [35].

### Ramucirumab

Ramucirumab is a novel IgG1 monoclonal antibody that specifically binds to the extracellular domain of VEGFR2 and inhibits the VEFGR2-related pathway. The REGARD trial (NCT00917384) enrolled patients with metastatic gastric or gastroesophageal junctional tumors who had received an unsuccessful platinum- or fluorouracil-based first-line treatment. A total of 335 patients were randomly divided–at a ratio of 2:1–into a ramucirumab group (8 mg/kg/2 weeks) and a placebo group, and all the patients received best support treatment. Median OS and PFS were 5.2 and 2.1 months in the ramucirumab group, respectively, whereas they were 3.8 and 1.3 months in the placebo group, respectively, indicating that ramucirumab provide survival benefit to these type of patients [36]. Another phase III clinical trial (RAINBOW trial) examined the role of the combined use of ramucirumab and paclitaxel in the treatment of patients with advanced gastric cancer after first-line treatment failure. The patients in the ramucirumab group had longer OS than the placebo group (9.6 vs. 7.4 months), and the combined use of ramucirumab and paclitaxel significantly delayed disease progression (PFS 4.4 vs. 2.9 months) [37]. In first-line treatment, some clinical trials have demonstrated that ramucirumab has no significant effects on OS and PFS in terminal patients receiving mFOLFOX6 chemotherapy. Based on the above results, ramucirumab has been approved for patients with gastric cancer who have received an unsuccessful platinum- or fluorouracil-based first-line treatment.

### Apatinib

As a small-molecule, targeted drug independently developed by China for the treatment of advanced gastric cancer, apatinib is the only oral drug targeting gastric cancer and is an effective VEGFR2 inhibitor. Phase III clinical trials show that apatinib significantly increases OS and PFS by 55 days (195 days in the apatinib group vs. 140 days in the placebo group) and 28 days (78 days in the apatinib group vs. 53 days in the placebo group), respectively, in patients with advanced gastric cancer who have received an unsuccessful second-line treatment [38].

## Multi-target TKI

### Sorafenib

Sorafenib is a multi-target TKI that can effectively inhibit the BRAF, VEGF, PDGFR, and Ras/Raf/MERK/ERK pathways. A total of 40 patients were enrolled in the GEMCAD study, in which 2.5% of the patients were evaluated as CR, and 47.2% of the patients were evaluated as SD; grade 3–4 toxic side effects were neutropenia (9.8%), thrombocytopenia (7.3%), neurotoxicity (4.9%), and diarrhea (4.9%); the median PFS and OS were 3 and 6.5 months, respectively; patients with first-line treatment progression time (TTP) > 6 months had a median OS of 9.7 months, whereas patients with a TTP < 6 months had a median OS of 5.6 months. Therefore, TTP in first-line treatment is an effective predictor of prognosis [39]. ECOG5203 studied the role of sorafenib combined with docetaxel and cisplatin in first-line treatment of advanced and metastatic gastric cancer; 44 patients with gastric cancer were included in the trial, with a median PFS and OS of 5.8 and 13.6 months, respectively; the most common toxic side effect was neutropenia; the results of this clinical trial suggest that sorafenib combined with chemotherapy is an effective treatment option in patients with advanced gastric cancer, which needs to be verified with larger clinical studies [40]. Clinical trials about the effect of sorafenib combined with both capecitabine and platinum-based drugs in advanced gastric cancer (NCT00565370) are also in progress.

### Sunitinib

Sunitinib is a multi-target TKI that inhibits PDGFR, RET, Flt-3, and VEGFR. A phase II clinical trial of

sunitinib in second-line treatment of advanced gastric cancer showed that median PFS and OS were 2.3 and 6.8 months, respectively; 32.1% of the patients had a SD time not less than 6 weeks; this clinical trial did not reach its primary study endpoint, namely ORR. The above results indicated that sunitinib monotherapy has limited clinical significance in second-line treatment of advanced gastric cancer [41]. In addition, a number of phase I clinical trials explored the safety and efficacy of sunitinib combined with chemotherapy in patients with advanced gastric cancer [42–43].

## mTOR inhibitors

The activation of the PI3K/Akt/mTOR signaling pathway is closely related to chemotherapy resistance and prognosis. It has been reported that the mTOR pathway is activated in about 60% of gastric cancer patients, and the activation of this pathway is closely related to the disease progression, thereby making mTOR a potentially effective therapeutic target for gastric cancer [44–45].

Everolimus is an oral mTOR inhibitor that specifically binds its extracellular receptor FKBP12 and exhibits antitumor activity in the treatment of a variety of tumors [46]. A phase I clinical trial demonstrated that capecitabine combined with everolimus showed good tolerability and clinical efficacy in patients with refractory gastric cancer, with a recommended dose of 5 g everolimus administered twice daily [47]. A multicenter everolimus-related phase II clinical trial enrolled 53 patients with refractory metastatic gastric cancer and found that, although no patient achieved CR or PR, the disease control rate reached 56.0%, with a median PFS and OS of 2.7 and 10.1 months, respectively, suggesting that everolimus monotherapy has a very good disease control rate in patients with refractory advanced gastric cancer [48]. The phase III GRANITE study, a clinical trial, showed that everolimus, compared to best support treatment, did not significantly improve median OS (5.4 vs. 4.3 months) and PFS (1.7 vs. 1.4 months) in patients with advanced gastric cancer who showed progression of the disease after first- or second-line treatment [49].

## Other targeted drugs

Clinical trials for MET inhibitors, ADP ribose polymerase inhibitors, heat-shock protein 90 inhibitors, and FGFR2 inhibitors are underway to evaluate the efficacy and safety of these drugs in patients with gastric cancer.

## Summary

Gastric cancer research has made considerable progress in recent years, but the prognosis of gastric cancer patients has not been significantly improved. Trastuzumab combined with chemotherapy is the standard first-line treatment for HER2-positive advanced gastric cancer, and ramucirumab is approved for second-line treatment. Based on clinical trial data, apatinib may be one of the options for advanced gastric cancer patients who have received unsuccessful first-line chemotherapy. However, whether patients with advanced gastric cancer would benefit from TKI drugs remains yet to be confirmed by more data from phase III clinical trials. Clinical trials report inconsistent results about anti-EGFR drugs in the treatment of gastric cancer, and the main reason may be the difference in enrolled patients among the clinical trials. Everolimus monotherapy achieved good results in phase II clinical trials, but phase III clinical trials have shown that everolimus failed to provide significant survival benefits to patients with advanced gastric cancer. It expected to see increased efficacy of pertuzumab combined with both trastuzumab and chemotherapy in patients with advanced gastric cancer.

Despite the entry of an increasing number of molecularly targeted drugs into clinical trials, the progress achieved in gastric cancer is much less than that in other tumors, which may be accounted for by the following reasons. First, there have been few large-scale molecular genomics studies of gastric cancer until recent years when some large-scale comprehensive molecular typing studies have emerged to provide new ideas for targeted gastric cancer therapy. For example, EBV-positive and MSI patients usually show PIK3CA mutation and CIN patients usually show amplification of tyrosine kinase receptors, which provides a valid basis for the personalized selection of proper targeted therapeutic drugs in the treatment of gastric cancer patients [8]. Second, gastric cancer tumors are a type of highly heterogeneous tumors, showing heterogeneity within a tumor, and heterogeneity between the primary and metastatic tumors—a problem resulting in considerable difficulties for targeted gastric cancer therapy, and presently cannot be solved [50]. Finally, targeted therapy combined with immunotherapy may bring new hope to gastric cancer patients, especially those with MSI-H; however, further investigation in large clinical trials is necessary. With personalized tumor therapy, more preclinical and clinical studies could be expected to enhance prognosis for gastric cancer patients.

### Conflicts of interest

The authors indicated no potential conflicts of interest.

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