Efficacy prediction of targeted therapy for gastric cancer: The current status (Review)

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Abstract. Despite significant progress in the treatment of gastric cancer (GC), the prognosis remains poor and the mortality is high. Targeted drugs have been incorporated into routine treatment to improve treatment efficacy. However, the therapy response is still below 50%. Therefore, there is a need to identify predictive factors for patient response to a specific drug in order to improve the efficacy of drug therapy. The present article reviewed the predictive factors for target therapy in GC, including epidermal growth factor receptor, human epidermal receptor 2, vascular endothelial growth factor family, molecules in the mesenchymal-epithelial transition pathway and the mammalian target of rapamycin. Additionally, the present review described the interactions between these molecules and signaling pathways.

Contents

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1. Introduction

Gastric cancer (GC) is the fourth-most common malignant neoplasm and the second leading cause of cancer-associated death worldwide (1). Although surgery is considered the only curative method for GC, a large number of patients are unable to undergo surgery because of advanced disease stage at diagnosis (2-4). Accordingly, chemotherapy is one of the options for the treatment of advanced gastric cancer (AGC). However, the response rate of first-line chemotherapy regimens in GC is ~40% In human epidermal receptor 2 (HER2)-positive patients, the response rate of first-line chemotherapy regimens using trastuzumab fails to reach 50% and the improvement of overall survival is limited (5). In patients who do not respond to chemotherapy, the benefit of chemotherapy is clearly limited, whereas the incidence of toxic reactions associated with the treatment is high (6). Therefore, it is important to identify patients who are sensitive to certain drugs. In addition, multidrug resistance (MDR) is an important contributor to drug non-response, and cellular resistance in AGC may be associated with the function of the MDR protein (7).

2. Anti-human epidermal growth factor receptor (EGFR) agents

Cetuximab and panitumumab are monoclonal antibodies against EGFR. Although several phase II clinical trials demonstrated the benefit of EGFR inhibitors in patients with GC (8,9), both randomized and open-label phase III trials of the drugs failed to prove the benefit of EGFR inhibitors in GC treatment. Cetuximab in Combination with Xeloda and Cisplatin in Advanced Esophago-gastric Cancer (EXPAND) clinical trial reported that cetuximab + cisplatin and capecitabine failed to improve the progression-free survival (PFS) (10). Furthermore, the Trial of Efficacy of Epirubicin, Oxaliplatin and Capecitabine (EOX) with/without Panitumumab in Previously Untreated Advanced Oesophagogastric Cancer (REAL3) showed that panitumumab + EOX did not increase the OS (11). Therefore, anti-EGFR treatments offer no survival benefits in non-selected patients with metastatic GC.

A previous study reported that wild-type KRAS proto-oncogene, GTPase (KRAS) could be a positive predictor of cetuximab efficacy in EGFR-positive gastric cancer cell lines (12) However, a prospective multi-center phase II trial

assessed biomarkers in patients with gastroesophageal cancer treated with cetuximab + irinotecan, folinic acid and 5-FU (13). The study analyzed mutations of the KRAS (exons 12 and 13), B-Raf proto-oncogene, serine/threonine kinase (V600E), and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit a (PIK3CA; exons 9 and 20) oncogenes, concluding that KRAS mutations were not suitable predictors of cetuximab efficacy (13).

Taken together, phase III clinical trials failed to confirm the efficacy of EGFR inhibitors in patients with GC and a phase II translational study did not identify any effective biomarkers for the prediction of cetuximab efficacy.

3. Anti-HER2 agents

Trastuzumab is a monoclonal antibody which binds to the extracellular domain of HER2 receptor (14). Trastuzumab is also the first approved targeted agent for the treatment of metastatic GC (5). HER2 is a promising predictive biomarker for the efficacy of trastuzumab efficacy (5).

In the Trastuzumab for GC (ToGA) phase III study, 594 GC/gastroesophageal junction cancer (GEJ), HER2 immunohistochemistry (IHC) 3+, or fluorescent *in situ* hybridization (FISH)-positive patients were randomly assigned to receive either chemotherapy (cisplatin combined with FU or capecitabine) + trastuzumab or chemotherapy alone (5). The OS and PFS significantly improved in patients treated with trastuzumab + chemotherapy. A post hoc analysis of OS by subgroups differentiated by protein expression level of HER2 showed the increased efficacy of trastuzumab associated with high expression of the protein (5). ToGA was a landmark study which utilized a targeted agent based on the measurement of a predictive biomarker, leading to a consensus about which patients may benefit from trastuzumab, the criteria for HER2-positive status being IHC3+ or IHC2+ and FISH+.

However, not all HER2-positive patients with GC benefit from trastuzumab. The efficacy prediction of trastuzumab has been investigated for years (15-19). In 2013, Gomez-Martin *et al* (16) reported that HER2 amplification, determined by the HER2/ centromeric probe for chromosome 17 (CEP17; 17p11.1-q11.1) ratio and HER2 copy number, demonstrated a significant positive correlation with sensitivity to HER2-targeted therapy and, therefore, could be considered a predictive factor of trastuzumab efficacy. Recently, Ock *et al* (17) reported a similar result to Gomez-Martin *et al* (16) indicating that HER2 gene amplification, identified using HER2/CEP17 ratio and HER2 copy number, may be a positive predictive factor for treatment outcome of trastuzumab-based chemotherapy, especially in patients with HER2 IHC <2+. However, another recent study evaluated the genomic alteration of HER2 using three different methods, including IHC, copy number variation and Ampliseq sequencing, and reported that the concomitant genomic alteration does not correlate with the treatment outcomes of HER2-targeted chemotherapy (18). In addition, Oyama *et al* (19) also tested the serum levels of HER2-extracellular domain (ECD) in patients with GC by chemiluminescent immunoassay and observed a correlation between HER2-ECD level and tissue HER2 status. The study also reported that alterations in the HER2-ECD level during chemotherapy positively correlated with therapy response in HER2-positive patients treated with trastuzumab-based chemotherapy. Accordingly, the researchers concluded that the serum HER2-ECD level could be a potential biomarker and monitoring marker for response to trastuzumab (19).

Lapatinib is a dual EGFR and HER2 inhibitor, the anti-cancer efficacy of which has been demonstrated in breast cancer (20), but not in GC. The Lapatinib Optimization Study in HER2 Positive GC (LOGiC) and Lapatinib Plus Paclitaxel Versus Paclitaxel Alone in the Second-Line Treatment of HER2-Amplified Advanced GC in Asian Populations (TyTAN) phase III trials were designed to evaluate the efficacy of lapatinib in patients with GC as first- and second-line treatments, respectively (21,22). Both trials failed to achieve the primary endpoint, although the subgroup analysis of the LOGiC cohort showed a significant OS benefit in Asian patients and patients <60 years of age. Similarly, the efficacy of treatment with lapatinib + paclitaxel improved in IHC3+ patients compared with IHC0/1+ and 2+ patients in the TyTAN trial (21,22). Because of the disappointing results of the aforementioned lapatinib clinical trials, a number of studies have investigated the molecular mechanisms (23-26).

HER2-targeted therapy has served an important role in GC drug treatments for a number of years (27-29), however, there are challenges associated with both intrinsic and acquired drug resistance. In 2014, Eto *et al* (24) analyzed the over-expression and suppression of the microRNA-21 (miR-21)/phosphatase and tensin homolog (PTEN) pathway in GC cell lines revealing that over-expression of miR-21 led to decreased sensitivity of GC cells to trastuzumab, while the suppression of miR-21 restored the trastuzumab-resistance in GC cell lines. Recently, Zhang *et al* (25) reported that PTEN deficiency is a predictive factor for the early resistance to HER2-targeted therapy, including trastuzumab and lapatinib. In 2014, Hong *et al* (26) established a lapatinib-resistant OE19 subclone from HER2-positive lapatinib-sensitive cell lines, in order to analyze the function of lapatinib resistance. The authors identified a novel acquired mutation, SrcE527K, that activated both the phosphatidylinositide 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways, and which may be a potential mechanism of lapatinib resistance, however, these findings require validation in primary tumor cells (26). Study by Hong *et al* (26) reported that the activation of the PI3K/protein kinase B (Akt) and MAPK pathways may be involved in HER2-targeted drug resistance.

The mesenchymal-epithelial transition (MET) pathway also serves a role in HER2-targeted drug resistance (30,31). Kim *et al* (30) established a lapatinib-resistant SNU216 cell line with an epithelial-mesenchymal transition (EMT) phenotype. The researchers analyzed EMT-associated extracellular molecules and genes and identified testican-1, an extracellular molecule, the inhibition of which decreased testican-1-induced, MET-dependent downstream signaling and restored sensitivity to lapatinib (30). Therefore, this molecule may contribute to lapatinib resistance. A recent multicenter clinical trial conducted by De Silva *et al* (31) collected biopsy samples from patients with oesophagogastric adenocarcinoma (OGA) treated with neoadjuvant chemotherapy + lapatinib. The molecular analysis showed a significant positive correlation between MET activation and phosphor(p)-Erk level (P=0.0005) and p-PI3K/total-PI3K ratio (P=0.0037), which

indicated that MET contributed to lapatinib resistance, whereas neither insulin-like growth factor receptor (IGFR) nor receptor tyrosine-protein kinase erbB-3 were associated with lapatinib resistance (31).

4. Anti-vascular endothelial growth factor (VEGF) or VEGF-receptor (VEGFR) agents

The VEGF family is involved in the angiogenesis of malignant neoplasms (32). Bevacizumab is a humanized VEGF-A antibody that has been successful used for the treatment of renal (33), colorectal (34) and lung (35) cancer. However, two phase III clinical trials of GC patients failed to achieve the primary endpoint (36,37). The Avastin in Gastric Cancer (AVAGAST) phase III study reported that bevacizumab + chemotherapy could be considered as a first-line treatment for patients with AGC, with improved PFS and tumor response rates, but not OS (36). The Bevacizumab plus Capecitabine and Cisplatin in Chinese Patients with Inoperable Locally Advanced or Metastatic Gastric or Gastroesophageal Junction Cancer (AVATAR) phase III study in China, with a design similar to that of the AVAGAST, also reported no difference in OS between the bevacizumab and placebo arms (37).

Based on the significant improvement in PFS in the AVAGAST trial, many oncologists believe it is important to identify patients who are sensitive to bevacizumab (38-41). In 2012, Yamashita-Kashima *et al* (38) reported that tumor VEGF levels and VEGF/basic fibroblast growth factor ratios were associated with bevacizumab sensitivity *in vitro*. Subsequently, Van Cutsem *et al* (39) hypothesized that angiogenic markers may be potential predictors for bevacizumab treatment outcome and conducted a study based on patients with AGC in the AVAGAST trial. They evaluated several angiogenic markers and found that plasma VEGF-A and neuropilin-1 were potential biomarkers for the prediction of treatment outcome in patients with AGC treated with chemotherapy + bevacizumab (39). In 2014, Han *et al* (40) analyzed bevacizumab pharmacokinetics in patients with AGC in the AVAGAST. The median clearance of bevacizumab was faster in patients with AGC compared with patients with other cancers (4.5 vs. 3 ml/day/kg), however, the mechanism of clearance remains unknown. The high clearance may contribute to the adverse treatment outcomes of bevacizumab (40). Recently, Hacker *et al* (41) evaluated angiopoietin-2 (Ang-2) expression in patients enrolled in the AVAGAS trial, reporting baseline plasma Ang-2 levels to be a prognostic biomarker for OS that was strongly positively associated with lymph node metastasis in AGC but not for bevacizumab efficacy. Therefore, although plasma VEGF-A and neuropilin-1 are potential biomarkers for bevacizumab treatment outcome, they remain to be validated (41).

Ramucirumab, a fully human monoclonal antibody against VEGFR-2, is the first drug approved by US Food and Drug Administration (FDA) for second-line treatment of AGC (42). A phase III clinical trial RAINBOW showed improved OS in the ramucirumab + paclitaxel arm compared with paclitaxel used as a single agent (43). Another phase III trial, REGARD, reported that ramucirumab as a single drug improved OS compared with that for the best supportive care [median OS: 5.2 months vs. 3.8 months, hazard ratio (HR) 0.776, 95% CI 0.603-0.998; P=0.047] (44). However, the predictive factors of treatment efficacy are lacking for ramucirumab (45).

Apatinib, a VEGFR-2 tyrosine kinase inhibitor, was approved by Chinese Food and Drug Administration (CFDA) for patients with AGC refractory to >2 lines of prior chemotherapy. The phase III trial showed that OS and PFS time improved in the apatinib group compared with the placebo group (46).

5. Anti-MET agents

MET receptor, a tyrosine kinase receptor activated by hepatocyte growth factor (HGF) or scatter factor (SF), results in the activation of downstream pathways, including the PI3K/Akt and RAS-MAPK pathways (47).

Rilotumumab, an investigational monoclonal antibody, inhibits the MET signaling pathway (48). Although a phase II trial reported that rilotumumab could improve PFS and OS in MET-positive GC/GEJ patients (49), a phase III study, RELOMET1, failed to confirm the OS or PFS benefit from rilotumumab (50). Another phase III study also failed to prove the OS benefit of MET inhibitor onartuzumab administered in combination with mFolFox6 (fluorouracil, oxaliplatin and leucovorin) in MET-positive patients with GC (51). Foretinib, an inhibitor targeting both receptor tyrosine kinase (RTK) encoded by MET proto-oncogene (cMET) and VEGFR2, was effective in MET-positive patients with AGC in a 2013 phase II study (52).

The frequency of MET inhibitor responsiveness is low, the molecular mechanism of which has been analyzed. A 2015 study reported that short-form recepteur d'origine nantais (RON) pathways conferred intrinsic cMET-targeted therapy resistance *in vivo* and *in vitro* (53). Another recent study demonstrated that co-amplification of driver oncogenes, including HER2 and MET, contributed to the acquired resistance to MET inhibitors (54). Ji *et al* (55) reported that high PI3K p110 α expression contributed to tyrosine kinase inhibitor resistance in GC xenografts. Musiani *et al* (56) reported that the induction of heat-shock protein 27 may limit the MET inhibitor efficacy in MET-positive patients with GC.

Furthermore, MET has cross-interactions with HER2 to modulate trastuzumab resistance (24), lapatinib resistance (57,58) and HER2 expression (59). Several *in vivo* and *in vitro* experiments (24-26) have shown that drug resistance in HER2-targeted treatments may be associated with the MET pathway, which has been explained in detail in the anti-HER2 agents section of the present article. In 2014, a review by Sukawa *et al* (58) reported that HER2 over-expression was significantly positively correlated with p-Akt expression in GC tissues. Furthermore, p-Akt expression correlated with poor prognosis. These results suggest that the PI3K/Akt pathway serves a role in HER2-positive GC. Furthermore, PIK3CA mutations and/or PTEN inactivation may affect the effectiveness of HER2-targeted therapy (58).

The above studies indicated that efficacy of MET inhibitors has not been confirmed in phase III clinical trials and conclusive evidence of predictive factors remains lacking. However, the MET pathway could partially explain the resistance to HER2 inhibitors.

Table I. Prospective clinical trials of monoclonal antibodies, mTOR inhibitors, and PD-1/PD-L1 and CTLA-4 antibodies in GC.

Author, year	Drug	Clinical Trial	Phase	Target	GC setting	Primary endpoint	Result	(Refs.)
Bang *et al*, 2012	Trastuzumab	ToGA	III	HER2	First-line	OS	Positive	(5)
Lordick *et al*, 2013	Cetuximab	EXPAND	III	EGFR1	First-line	PFS	Negative	(10)
Waddell *et al*, 2013	Panitumumab	REAL3	III	EGFR1	First-line	OS	Negative	(11)
Hecht *et al*, 2016	Lapatinib	LOGiC	III	HER2, EGFR	First-line	OS	Negative	(21)
Satoh *et al*, 2014	Lapatinib	TyTAN	III	HER2, EGFR	First-line	OS	Negative	(22)
Ohtsu *et al*, 2011	Bevacizumab	AVAGAST	III	VEGF-A	First-line	OS	Negative	(36)
Shen *et al*, 2015	Bevacizumab	AVATAR	III	VEGF-A	First-line	OS	Negative	(37)
Wilke *et al*, 2014	Ramucirumab	RAINBOW	III	VEGFR-2	Second-line	OS	Positive	(43)
Fuchs *et al*, 2014	Ramucirumab	REGARD	III	VEGFR-2	Second-line	OS	Positive	(44)
Catenacci *et al*, 2017	Rilotumumab	RELOMET1	Ib/II	MET	First-line	OS	Negative	(50)
Shah *et al*, 2017	Onartuzumab	NCT01662869	III	MET	First-line	OS	Negative	(51)
Ohtsu *et al*, 2013	Everolimus	GRANITE-1	III	mTOR	First-line	OS	Negative	(62)
Muro *et al*, 2016	Pembrolizumab	KEYNOTE-012	Ib	PD-L-1	Recurrent or matastatic	safety	Positive	(69)
Fuchs *et al*, 2017	Pembrolizumab	KEYNOTE-059	II	PD-1	>2 prior lines	ORR, AEs	Positive	(70)
Ohtsu *et al*, 2016	Pembrolizumab	KEYNOTE-061	III	PD-1	Second-line	OS, PFS in PD1+	Fail	(71)
Tabernero *et al*, 2016	Pembrolizumab	KEYNOTE-062	II	PD-1	First-line	ORR	NR	(72)
Moehler *et al*, 2017	Nivolumab+ Ipilimumab	CheckMate649	III	PD-1+CTLA-4	First-line	OS in PD-L1+	NR	(74)

GC, gastric cancer; PFS, progression-free survival; OS, overall survival; NR, not reported; PD-1, Programmed cell death 1; PD-L1, programmed death-ligand; CTLA-4, cytotoxic T-lymphocyteassociated antigen 4; mTOR, mammalian target of rapamycin; MET, mesenchymal-epithelial transition; VEGFR-2, vascular endothelial growth factor receptor 2; VEGF-A, vascular endothelial growth factor-A; HER2, human epidermal receptor 2; EGFR, epidermal growth factor receptor.

Table II. Potential predictive biomarkers for targeted therapy in GC.

Drug	Target	Biomarker	Study type	Result
Cetuximab	EGFR1	KRAS	*In vivo*	Wild-type KRAS is a positive predictor.
		KRAS	Phase II trial	KRAS mutations are not suitable predictors.
Trastuzumab	HER2	HER2 expression	Phase III trial	HER2-positive status of IHC3+ or IHC2+ and FISH+ is a positive predictor.
		HER2 gene amplification	Retrospective	HER2 gene amplification, identified as HER2/CEP17 (17p11.1-q11.1) ratio and HER2 copy number, is a predictive factor.
		HER2 gene amplification	Retrospective	HER2/CEP17 (17p11.1-q11.1) ratio and HER2 copy number are. predictive factors
		Concomitant genomic alteration of HER2	Retrospective	Concomitant genomic alteration of HER2 does not correlate with HER2-targeted chemotherapy.
		HER2-ECD	Retrospective	Serum levels of HER2-ECD are a potential predictor.
Bevacizumab	VEGF-A	VEGF/bFGF	*In vivo*	VEGF/bFGF is a potential predictor.
		VEGF-A		
Neuropilin-1	Retrospective	Plasma VEGF-A and neuropilin-1 are potential predictive factors.		
		Ang-2	Retrospective	Baseline plasma Ang-2 is not associated with bevacizumab efficacy.
Everolimus	mTOR	p-S6	Phase II trial	IHC≥2+ for p-S6 is associated with progression-free survival and disease control rate.

bFGF, basic fibroblast growth factor; p, phosphorylated; S6, S6 ribosomal protein; GC, gastric cancer; mTOR, mammalian target of rapamycin; VEGF-A, vascular endothelial growth factor-A; HER2, human epidermal receptor 2; EGFR1, epidermal growth factor receptor 1; KRAS, KRAS proto-oncogene, GTPase; IHC, immunohistochemistry; CEP17, centromeric probe for chromosome 17; ECD, extracellular domain; Ang-2, angiopoietin-2; FISH, fluorescent *in situ* hybridization.

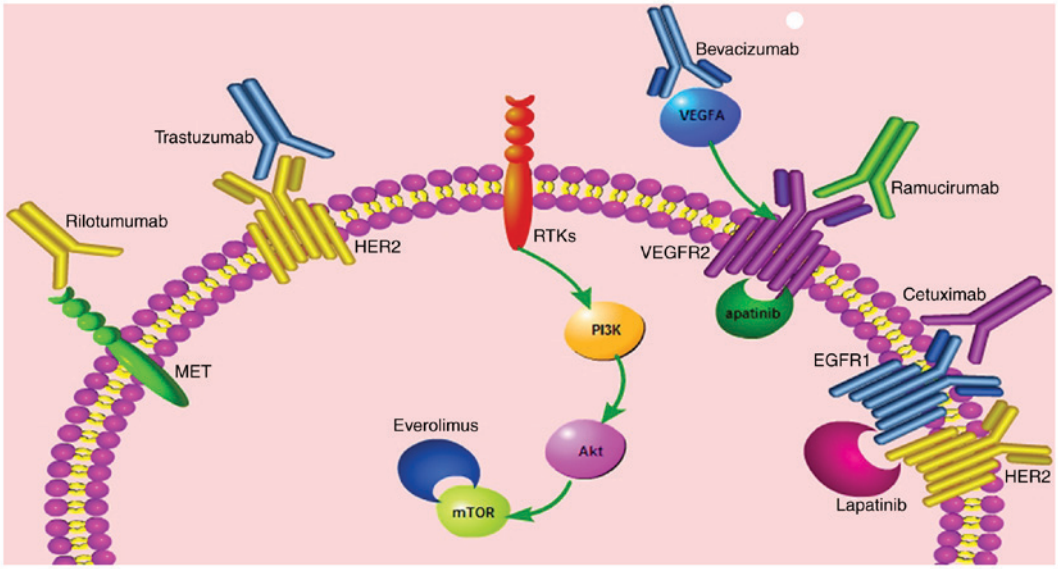

Figure 1. The mechanisms of targeted agents, including cetuximab, trastuzumab, lapatinib, bevacizumab, ramucirumab, apatinib, rilotumumab and everolimus. EGFR, epidermal growth factor receptor; HER2, human epidermal receptor 2; VEGFA, vascular endothelial growth factor A; MET, mesenchymal-epithelial transition; mTOR, mammalian target of rapamycin; RTK, receptor tyrosine kinase; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; VEGFR2, vascular endothelial growth factor receptor 2.

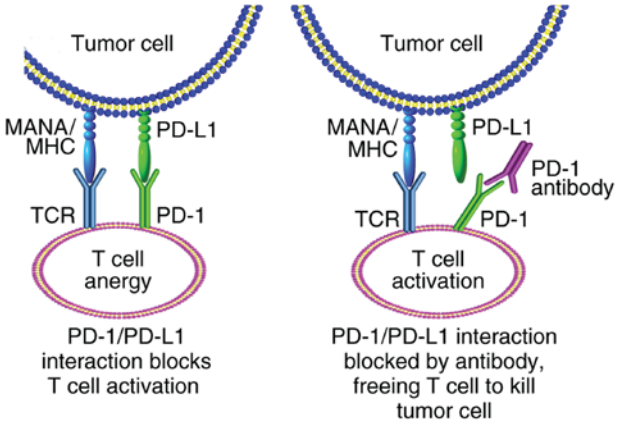

Figure 2. The mechanism of action of PD-1/PD-L1 agents. PD-1, programmed cell death 1; PD-L1, programmed death-ligand 1; MHC, major histocompatibility complex; MANA, mutant associated newborn antigen; TCR, T cell receptor.

6. Mammalian target of rapamycin (mTOR) inhibitors

mTOR, involved in the PI3K/Akt pathway, is a serine/threonine kinase that increases the production of proteins that stimulate cell growth, proliferation, angiogenesis and cell metabolism (60).

Everolimus is a mTOR inhibitor (61). Phase III study GRANITE-1 compared the effects of everolimus with the administration of placebo in patients with AGC with disease progression after one or two lines of chemotherapy and there was no significant difference in OS (62). To predict the efficacy of everolimus, Wainberg *et al* (63) conducted a phase II study, reporting a strong correlation between IHC staining ≥2+ for p-S6 ribosomal protein in tumor samples with improved PFS (P<0.0001) and disease control rate (P=0.0001) of patients, which indicated that p-S6 ribosomal protein could be a potential biomarker.

Furthermore, mTOR inhibitors interacted with other target agents (64-66). Recently, Zhu *et al* (64) investigated the interaction between BEZ235, a dual PI3K/mTOR inhibitor, and trastuzumab in HER2-positive GC, demonstrating anticancer activity in Her2-positive GC and synergy with trastuzumab both *in vivo* and *in vitro*. The interaction between mTOR inhibitor everolimus and VEGFR inhibitors, including sunitinib (65) and vatalanib (66), reportedly improved anticancer activity, resulting in a significant reduction of tumor burden and long-term tumor control.

7. Programmed cell death 1 (PD-1), programmed death-ligand (PD-L) 1 and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) antibodies

PD-1 is a negative costimulatory receptor expressed primarily on the surface of activated T cells (67). The binding of PD-1 to one of its ligands, PD-L1 or PD-L2, inhibits cytotoxic T-cell response (68). Phase Ib trial Keynote-012 has reported manageable toxicity and promising antitumor activity

of pembrolizumab (pembro) in patients with AGC (69). Phase II Keynote-059 reported that pembro exhibited encouraging efficacy and manageable safety in patients with gastric/gastroesophageal junction cancer (G/GEJ) who had received >2 prior lines of therapy, although the survival and bio-marker data have yet to be published (70). According to Keynote-059, pembro has been approved by FDA for the treatment of patients with G/GEJ who had received >2 prior lines of therapy. Further phase III trials (Keynote-061 and 062) (71,72) have yet to be published. On December 14th, Merck & Co., Inc. (Whitehouse Station, NJ, USA) officially announced the failure of Keynote-061. The company announced that the clinical trial did not achieve the primary endpoint of OS and the difference between PFS was not statistically significant. The results of Keynote-061 and 062 have yet to be published. In addition to pembro, a phase III trial for another PD1-targeted drug, nivolumab, is also in progress and the result are not available.

Ipilimumab is an anti-CTLA-4 antibody, the anti-tumor mechanism of which is based on upregulation of antitumor immunity (73). A phase III clinical trial CheckMate649 aimed to evaluate ipilimumab + nivolumab (nivo) or nivo + chemotherapy vs. chemotherapy alone as first-line treatment for advanced G/GEJ, of which the results have not been reported (74).

The details of the clinical trials are summarized in Table I. The details of potential predictive bio-markers for targeted therapy are summarized in Table II. The mechanisms of targeted drugs are illustrated in Figs. 1 and 2.

8. Conclusion

The present article reviewed the efficacy predictors of targeted agents in GC. A total of four drugs have been approved by FDA and CFDA. Firstly, HER2 is a bio-marker for trastuzumab in patients with GC and, therefore, HER2 analysis is recommended in patients with GC using standard test methods (HER2-positive status being IHC3+ or IHC2+ and FISH+) (5). HER2 amplification determined using HER2/CEP17 (17p11.1-q11.1) ratio and HER2 copy number may be a predictor in HER2-targeted chemotherapy, which requires verification in further prospective studies (16,17). In addition, the MET/PIK3CA/Akt pathway may be partially associated with HER2 resistance (24-26,30,31). Secondly, administration of ramucirumab, a VEGFR-2 antibody, is a standard therapy for second-line treatment of AGC (43,44). However, the predictive factors of treatment efficacy are lacking for ramucirumab. Thirdly, apatinib, a VEGFR-2 tyrosine kinase inhibitor, was approved by CFDA for the treatment of patients with AGC refractory to ≥2 lines of prior chemotherapy (46). Fourthly, pembro, a PD-1 antibody, has been approved by FDA in patients with G/GEJ who had received >2 prior lines of therapy (70). Lastly, the results of phase III studies suggest a modest and limited response to both cetuximab and bevacizumab in patients with GC (10,36,37), however, efficacy predictions are currently lacking.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

FW performed the literature search and wrote the article. ZX designed the review and drafted and revised the article.

Ethics approval and consent to participate

No applicable.

Consent for publication

No applicable.

Competing interests

The authors declare that they have no competing interests.

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