Review Article

Current status of novel agents in advanced gastroesophageal adenocarcinoma

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Abstract: Gastroesophageal (GE) adenocarcinomas are highly lethal malignancies and despite multiple chemotherapy options, 5-year survival rates remain dismal. Chemotherapy is the mainstay of treatment but patients are often limited by toxicity and poor performance status. Because of molecular heterogeneity, it is essential to classify tumors based on the underlying oncogenic pathways and develop targeted therapies that act on individual tumors. Trastuzumab, a human epidermal growth factor receptor type 2 (HER2) monoclonal antibody, was the first such agent shown to improve response rate, progression free survival (PFS), and overall survival (OS) when added to cisplatin based chemotherapy in patients with HER2 over-expressing GE junction (GEJ) and gastric adenocarcinomas. However, HER2 over expressing GE tumors are in the minority and the need for additional targeted agents is urgent. Though many agents are in development, incorporating targeted therapy in the treatment of GE cancers comes with a unique set of challenges. In this review, we outline oncogenic pathways relevant to GE adenocarcinomas, including HER2, epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), hepatocyte growth factor (HGF), and c-Met, and discuss recent trials with agents targeting these pathways.

Keywords: Gastric and esophageal adenocarcinoma; targeted therapy

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Introduction

Gastroesophageal (GE) adenocarcinomas are commonly diagnosed at an advanced stage and are extremely lethal, with median survival of less than 1 year for metastatic disease (1,2). Over the last 50 years, survival has improved only modestly despite considerable improvements in diagnosis, surgical techniques, and multidisciplinary approaches to care.

Chemotherapy remains the cornerstone of treatment for GE patients with locally advanced and metastatic disease. Many chemotherapy agents have activity including platinums, irinotecan, fluorouracil, taxanes and anthracyclines. Treatment with a combination of three agents has been shown to lead to modest improvements in survival compared to two agents, but at the expense of significant toxicity (3).

The pathogenesis of GE cancers involves multiple genetic and epigenetic alterations, chromosomal aberrations, gene mutations, and altered molecular pathways. During recent years, the molecular heterogeneity underlying carcinogenesis and metastasis has begun to be elucidated. Some of these molecular abnormalities and signaling pathways are amenable to pharmacological interventions (*Figure 1*). Targeted therapies been evaluated in the pre-clinical setting and are now rapidly moving to clinical trials (*Table 1*). The vascular endothelial growth factor (VEGF) receptor, epidermal growth factor receptor (EGFR), human epidermal growth factor receptor type 2 (HER2), insulin-like growth factor receptor (IGF-R), phosphatadylinositol 3-kinase (PI3k)/protein kinase B (Akt)/mammalian target of rapamyin (mTor) pathway, c-Met, fibroblast growth factor receptor (FGFR), poly [adenosine diphosphate (ADP)]-ribose polymerase (PARP) inhibitors, and immunotherapies

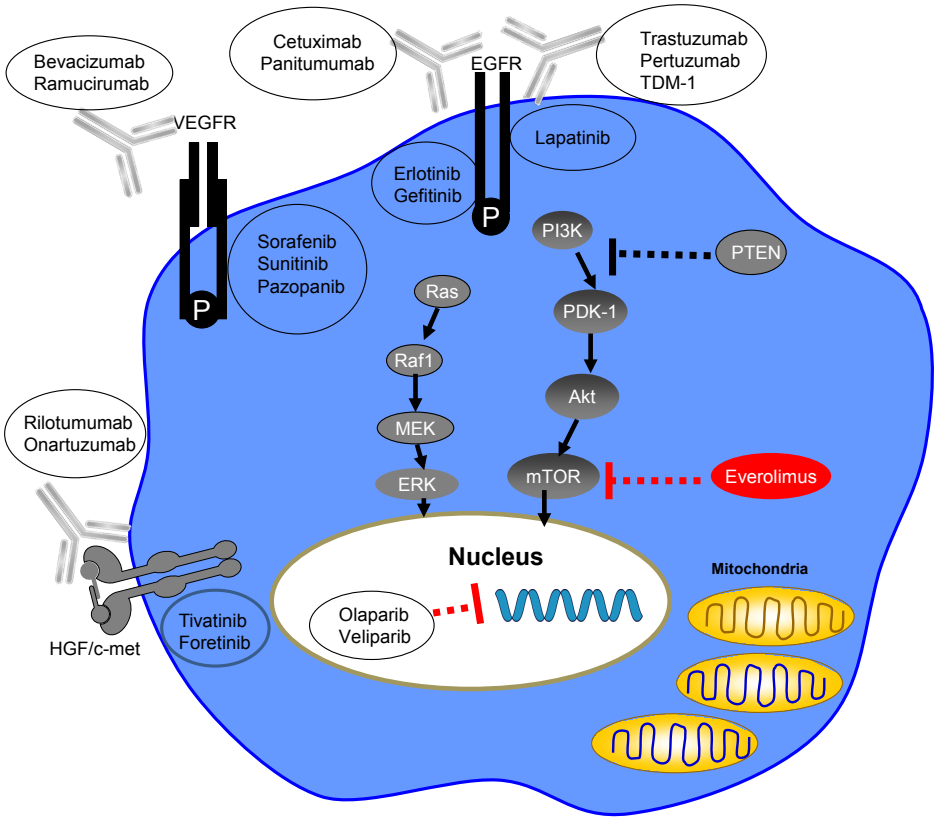

Figure 1 Targeted therapy in gastric cancer and sites of action. VEGFR, vascular endothelial growth factor receptor; EGFR, epidermal growth factor receptor; PI3K, phosphatadylinositol 3-kinase; PTEN, phosphatase and tensin homolog; PDK-1, phosphoinositide-dependent kinase 1; Akt, protein kinase B; mTOR, mammalian target of rapamyin; HGF, hepatocyte growth factor; MEK, mitogen-activated protein/extracellular signal-regulated kinase kinase; ERK, extracellular-regulated kinase.

have been investigated as therapeutics. We will discuss molecular targets and the novel drugs currently approved and in development for patients with GE.

HER2 inhibition

The HER2 receptor is a member of the EGFR/HER family involved with signal transduction, leading to cell growth and differentiation. The HER2 gene is a proto-oncogene, located at the long arm of human chromosome 17 (4), which encodes for a 185 KD transmembrane glycoprotein receptor with intracellular tyrosine kinase activity (5).

HER2 over-expression and amplification in GE ranges from 7-34% of patients, depending on the population studied. The primary tumor site appears to have higher concordance of HER2 amplification by immunohistochemistry (IHC) and fluorescence *in situ* hybridization (FISH) than regional lymph node or distant metastases (6-8). By consensus, HER2 is considered to be negative if IHC is 0 or 1+. HER2 is positive if IHC 3+. IHC of 2+ is considered equivocal and merits confirmatory testing with FISH (9).

Preclinical studies have shown that anti-HER2 therapies have significant activity for both *in vitro* and *in vivo* gastric cancer models (10,11). The most common approaches to targeting HER2 are through inhibition by monoclonal antibodies (trastuzumab and pertuzumab) or tyrosine kinase inhibitors (TKIs) (lapatinib). Both types of blockade have been examined in clinical trials of patients with GE cancers.

Trastuzumab, pertuzumab, and trastuzumab emtansine (TDM-1)

Trastuzumab is a humanized monoclonal antibody that has been approved by the US Food and Drug Administration (FDA) since 1998 for the treatment of breast cancer.

Table 1 Targeted agents and clinical trials for gastric and gastroesophageal cancers

Class	Agent	Clinical trials
VEGFR inhibitors		
Monoclonal antibody	Bevacizumab	Phase III
	Ramucirumab	Phase III
Receptor tyrosine kinase	Sunitinib	Phase II
	Sorafenib	Phase I/II
	Pazopanib	Phase II
	Vandetanib	Phase I/II
	Telatinib	Phase II
EGFR inhibitors		
Monoclonal antibody	Cetuximab	Phase III
	Panitumumab	Phase III
Receptor tyrosine kinase	Gefitinib	Phase III
	Erlotinib	Phase II
HER2 inhibitors		
Monoclonal antibody	Trastuzumab	Phase III
	Pertuzumab	Phase III
	TDM-1	Phase II/III
Receptor tyrosine kinase	Lapatinib	Phase III
c-Met inhibitors		
Receptor tyrosine kinase	Foretinib	Phase II
Monoclonal antibody	Rilotumumab	Phase II/III
	Onartuzumab	Phase II/III
PARP inhibitors		
	Olaparib	Phase II/III
	Veliparib	Phase I

VEGFR, vascular endothelial growth factor receptor; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor type 2; PARP, poly-adenosine diphosphate ribose polymerase.

Trastuzumab targets the extracellular binding domain of the HER2 receptor and has been combined with cytotoxic chemotherapy in patients with gastric and GE junction (GEJ) tumors in several trials. The trastuzumab for gastric cancer (ToGA) study was an internatinoal, open-label phase III trial that randomized patients with treatment naive metastatic or locally advanced unresectable gastric or GEJ adenocarcinoma with over-expressed HER2 to chemotherapy with trastuzumab versus chemotherapy alone. HER2 overexpression was defined as staining 3+ by IHC or by FISH positivity (12).

Patients received cisplatin plus fluoropyrimidine every 3 weeks for six cycles, with or without intravenous trastuzumab at 6 mg/kg after a one time loading dose of 8 mg/kg.

A 2.7-month improvement in median overall survival (OS) for patients who received trastuzumab was demonstrated (median OS 13.8 months compared with 11.1 months). Response rate, time to progression, and duration of response were significantly higher in the trastuzumab plus chemotherapy group as well. Of note, the median survival in the chemotherapy only arm was higher than expected in this study, potentially related to the high proportion of Asian patients in the study (55%). The combination was generally well tolerated with only a slightly increased risk of asymptomatic left ventricular dysfunction and transfusion reaction. This study led to the first FDA approval for targeted therapy for gastric and GEJ adenocarcinoma in 2010 (13).

Based on these encouraging results, several other studies with trastuzumab are being conducted. The HELOISE trial (a study of herceptin in combination with cisplatin/capecitabine chemotherapy in patients with HER2-positive metastatic gastric or GEJ cancer) is currently recruiting patients to evaluate the optimal dose of trastuzumab in advanced gastric and GEJ tumors (14). In the non-metastatic setting, NCT01130337 is a phase II study which treats patients with trastuzumab, capecitabine, and oxaliplatin for three cycles prior to surgery. If an R0 or R1 resection is achieved, patients receive an additional three cycles of treatment. Trastuzumab will be continued for a total of 1-year (15). Similarly, the TOXAG study (a study of the combination of oxaliplatin, capecitabine, and herceptin and chemoradiotherapy in the adjuvant setting in operated patients with HER2+ gastric or GEJ cancer) is ongoing (16). The HER-FLOT study (Herceptin in combination with FLOT as perioperative treatment for patients with HER2-positive locally advanced esophagogastric adenocarcinoma) gives trastuzumab with FLOT (5FU, leucovorin, docetaxol, and oxaliplatin) for four cycles prior to surgical resection. Patients then receive an additional four cycles of chemotherapy with trastuzumab and nine additional cycles of trastuzumab alone (17). For locally advanced esophageal or GEJ adenocarcinoma, RTOG 1010 is a phase III trial which randomizes patients to weekly paclitaxel, carboplatin, and radiation with or without trastuzumab prior to surgery (18). The results of these studies could change the treatment paradigm for HER2 overexpressing GE cancers.

As resistance to HER2 therapy has begun to arise, there has been interest in the second generation HER2 targeting agent pertuzumab, which binds to a distinct site on the

HER2 (and potentially HER3) receptor and leads to the disruption of dimerization and blockade of downstream signaling. Based on pre-clinical work in GEJ, as well as the efficacy of the combination of trastuzumab and pertuzumab in breast cancer (19), the JACOB phase III study (a study of perjeta in combination with herceptin and chemotherapy in patients with HER2-positive metastatic GEJ or gastric cancer) randomizes patients with metastatic or locally advanced unresectable disease to first line cisplatin, fluoropyrimidine, and trastuzumab with or without pertuzumab (20).

TDM-1 is an antibody-drug conjugate which utilizes HER2 overexpression to deliver a cytotoxic agent directly to cancer cells is being evaluated in GEJ patients expressing HER2; a second line phase II/III trial of TDM-1 in advanced gastric cancer is currently recruiting; the study has three arms; TDM-1 at 3.6 mg/kg every 3 weeks, TDM-1 at 2.4 mg/kg every week, or physician's choice of single agent pa clitaxel or docetaxel (14).

Lapatinib

Lapatinib is an oral small molecule dual TKI of EGFR and HER2. It has been approved for the treatment of HER2-positive advanced breast cancer previously treated with trastuzumab and in conjunction with hormonal therapy for triple positive metastatic breast cancer (21-23).

Lapatinib has been evaluated in combination with standard chemotherapy in patients with gastric and GEJ adenocarcinomas. In the phase III LOGIC study (lapatinib optimization study in HER2-positive gastric cancer), patients with HER2 over-expressed advanced gastric and GEJ adenocarcinomas were randomized to chemotherapy (capecitabine and oxaliplatin) plus lapatinib versus placebo (24). This study did not meet its primary endpoint of improvement in OS, though certain subgroups (the Asian population and patients under age 60 years) were shown to have a benefit.

The second line phase III TyTAN trial (a phase III Asian study of tykerb in combination with paclitaxel as second-line therapy in gastric cancer) compared weekly paclitaxel with or without lapatanib in second line patients with HER2-positive advanced disease. Again, there was no OS or progression free survival (PFS) benefit for the lapatinib group, though there was a statistically significant increased response rate (25). At present, lapatinib is not ready for widespread implementation in GEJ but ongoing studies might better define its role in combination with other targeted agents.

Of the monoclonal antibodies, only trastuzumab is approved for locally advanced unresectable and metastatic GEJ and gastric cancers. However, with the results of adjuvant trastuzumab trials as well as the pertuzumab and TDM-1 studies, the role for monoclonal antibodies in GE cancers will likely expand significantly.

EGFR inhibition

The EGFR is a trans-membrane glycoprotein receptor for the EGF family of extracellular protein ligands (26) and is overexpressed in several gastrointestinal (GI) malignancies. Ligand binding to the extracellular domain leads to EGFR activation and phosphorylation of the intracellular tyrosine kinase, which then directs activation of Ras/Raf/mitogen activated protein kinase (MAPK) or the Akt/mTOR pathway (27). EGFR overexpression occurs in 30-50% of GE. It is associated with older age, more aggressive histology, and advanced stage (28-30).

The most common approaches to inhibit the EGFR are by inhibition of the EGFR via monoclonal antibodies (i.e., cetuximab and panitumumab) or TKIs (i.e., gefitinib, erlotinib). Both methods have been studied in patients with GE.

Cetuximab

Cetuximab is an immunoglobulin G 1 (IgG1) type chimeric monoclonal antibody that binds to the extracellular domain of the human EGFR and competitively inhibits the binding of EGF and other ligands, as well as ligand-induced tyrosine kinase auto-phosphorylation. This antibody-receptor interaction prevents receptor dimerization and thereby blocks ligand-induced EGFR tyrosine kinase activation. Cetuximab also induces EGFR internalization, down-regulation, and degradation (31). It is currently approved for the treatment of advanced KRAS wild type colorectal cancer as well as squamous cell head and neck cancers (32,33).

Based on promising phase II data, the phase III trial EXPAND (erbitux in combination with xeloda and cisplatin in advanced GE) randomized 904 patients to cisplatin with capecitabine with or without cetuximab. However, no PFS or OS benefit for the cetuximab group was found (34). RTOG 0436 was a phase III trial which randomized patients with locally advanced esophageal cancer to weekly concurrent cisplatin (50 mg/m^2), paclitaxel (25 mg/m^2) for 6 weeks and daily radiation 50.4 Gy/1.8 Gy fractions ± weekly cetuximab (400 mg/m^2 day 1 then weekly 250 mg/m^2) for 6 weeks (35). No OS benefit to cetuximab was found.

Unlike in colorectal cancer, KRAS mutations have

not been shown to be a negative predictive biomarker for response to cetuximab in GE (36). Though other biomarkers including EGFR expression, copy number, and phosporylation have been evaluated, the sample sizes and retrospective nature of these analyses have precluded meaningful conclusions (37-40).

Panitumumab

Panitumumab is the first fully human IgG2 monoclonal antibody targeting EGFR. In gastric cancer, the REAL-3 study [a randomised open-labelled multicentre trial of the efficacy of epirubicin, oxaliplatin, and capecitabine (EOX) with or without panitumumab in previously untreated advanced oesophago-gastric cancer] did not show any benefit at preplanned interim analysis and was stopped early (41). However, these negative results may have been partly due to decreased doses of chemotherapy in the combination arm (42). In the single arm phase II ACOSOG Z4051 trial, patients with potentially resectable disease were given neoadjuvant docetaxel, cisplatin, and panitumumab as well as radiation (43). Some disease activity was found but at the expense of significant toxicity.

Gefitinib

Gefitinib is an oral EGFR TKI with promising activity against several types of malignancy in early phase trials. Based on phase II data (44), a phase III trial (NCT01243398) randomized patients with advanced GE to gefitinib versus placebo after progression on chemotherapy. The study is complete and the pending results will help better delineate the activity of gefitinib in GE (45).

Erlotinib

Erlotinib is another oral EGFR TKI, which has been approved in the US for the treatment of lung and pancreatic cancer. In a phase II analysis, erlotinib was found to be active in patients with GEJ cancer with a response rate of 9%, but with no responses in gastric cancer (46).

Vascular endothelial growth factor receptor (VEGFR) inhibition

Angiogenesis is an important aspect of tumorigenesis and is critical for tumor growth and survival. The VEGF plays a pivotal role in the control of angiogenesis, tumor growth, and metastasis in many human cancers (47) including GE, which makes it an attractive target for treatment. VEGF-A is an essential mediator of physiologic and pathologic angiogenesis (48), and its activities are mediated by two tyrosine kinase receptors, VEGFR-1 and VEGFR-2. Serum VEGF concentration has been related to metastasis and worse outcome in GE (49,50). Multiple agents have been developed to target the VEGF pathway, including monoclonal antibodies and TKIs.

Bevacizumab

Bevacizumab is a recombinant humanized IgG1 monoclonal antibody against VEGF, which has been shown to have efficacy in colorectal, lung, ovarian, and renal cell cancers (13,51-54). Side effects including thromboembolic events, gastrointestinal perforation, and hypertension have been demonstrated.

Promising phase II trial results in GE cancers led to AVAGAST (avastin in gastric cancer), a phase III multinational, randomized, placebo-controlled trial to evaluate the efficacy of adding bevacizumab to cisplatin based chemotherapy in the first-line treatment of advanced gastric cancer (55). Seven hundred and seventy-four patients from 17 countries were enrolled. Approximately 50% of patients were from Asia. Median OS was 12.1 months in the bevacizumab plus chemotherapy arm compared to 10.1 months with placebo plus chemotherapy arm [hazard ratio (HR) 0.87; 95% confidence interval (CI), 0.73 to 1.03; P=0.1002]. Though the trial did not meet its primary objective of OS, both median PFS and overall response rate (ORR) were significantly improved in the bevacizumab group. No bevacizumab-related safety signals were identified. The genetic heterogeneity of gastric cancer might explain the discordant results between the phase II and III trials. In addition, the patients with GEJ tumors on the AVAGAST study treated with bevacizumab arm had an exceptionally high response rate of 85% and improved OS. Asian patients showed better OS and PFS regardless of the treatment received when compared to European and Americans. Selection bias, sample size, and study design might have limited the conclusions of single-arm phase II studies.

In order to better select patients who might benefit from anti-VEGF therapy, a panel of tumor angiogenic factors was evaluated in the AVAGAST study, including EGFR, VEGF-A, VEGFR-1, VEGFR-2 and neuropilin (56). Low tumor neuropilin expression was associated with shorter

Table 2 Phase II/III trials targeting VEGFR in gastroesophageal cancers

Study	Phase	Setting	Treatment	Patients	PFS	OS
Shah *et al.* (61)	II	First line	Irinotecan, Cisplatin, and Bevacizumab	47	ORR: 6.5 mo	12.3 mo
Ohtsu *et al.*/ AVAGAST (55)	III	First line	Cisplatin/5FU ± Bevacizumab	774	38.0 *vs.* 29.5 mo, P=0.0121	12.1 *vs.* 10.1 mo, P=1.002
Fuchs *et al.*/ REGARD (57)	III	Second line	Ramucirumab *vs.* BSC	355	2.1 *vs.* 1.3 mo, P<0.0001	5.2 *vs.* 3.8 mo, P=0.047
Wilke *et al.*/ RAINBOW (59)	III	Second line	Paclitaxel ± Ramucirumab	665	4.4 *vs.* 2.9 mo, P<0.0001	9.6 *vs.* 7.4 mo, P=0.017
Yoon *et al.* (60)	II	First line	FOLFOX ± Ramucirumab	168	6.4 *vs.* 6.7 mo, P=0.89	11.7 *vs.* 11.5 mo, P not available, HR 1.08, 95% CI, 0.73-1.58

VEGFR, vascular endothelial growth factor receptor; PFS, progression free survival; OS, overall survival; ORR, overall response rate; mo, months; 5FU, 5-fluorouracil; BSC, best supportive care; FOLFOX, 5-fluorouracil, leucovorin, oxaliplatin; HR, hazard ratio; CI, confidence interval.

OS in the placebo group. Adding bevacizumab seemed to correct this effect as patients with low tumor neuropilin had an OS treatment HR numerically better than those with high neuropilin in the bevacizumab group. Neuropilin thus appeared to be a promising prognostic biomarker candidate, with potential predictive properties for bevacizumab as well. In addition, lower baseline plasma VEGF-A correlated with longer OS. Further evaluation of these biomarkers is ongoing.

Bevacizumab is being evaluated in the neoadjuvant setting in the United Kingdom. The MAGIC-B study (medical research council adjuvant gastric infusional chemotherapy) is assessing the role of bevacizumab for peri-operative chemotherapy in operable adenocarcinoma of the stomach and GEJ.

Ramucirumab

Ramucirumab is a fully human IgG1 monoclonal antibody that specifically and potently inhibits VEGFR-2. Ramucirumab has demonstrated efficacy and tolerability in several studies. The phase III REGARD study (ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma) randomized second line gastric or GEJ adenocarcinoma patients to single agent ramucirumab or best supportive care (BSC). They found a median OS of 5.2 months in the treatment arm compared to 3.8 months, with a P value of 0.042 (57). Based on this study, the FDA approved ramucirumab in 2014 for use as a single agent in gastric and GEJ cancer after progression on a platinum or fluropyrimidine containing regimen (58). This is the first approval of a biologic agent in an unselected GEJ population. Biomarker studies to better delineate the population most likely to benefit are ongoing.

The phase III RAINBOW study (a global, phase III, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of metastatic GEJ and gastric adenocarcinoma following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy rainbow) randomized 665 second line advanced gastric or GEJ adenocarcinoma patients to paclitaxel with or without ramucirumab. Median OS was 9.6 months in the combination arm versus 7.4 months for paclitaxel alone. Patients in the combination arm had more neutropenia and hypertension (59). These findings will likely lead to approval of ramucirumab in combination with paclitaxel by the FDA later this year. However, a front line phase II study of ramucirumab with or without FOLFOX did not show an improvement in the primary endpoint of PFS (60). The results of the major trials involving bevacizumab and ramucirumab are described in *Table 2*.

Another approach to targeting the VEGF pathway is through so-called dirty kinase inhibitors, which inhibit the VEGF receptor as well as FLT-3, c-kit, and RET. Several TKIs are currently being evaluated and are described below.

Sunitinib

Sunitinib is an oral multi-targeted TKI of VEGFR, platelet-

derived growth factor receptors (PDGFRs), c-kit, RET, and FLT3 that has been approved for the treatment of advanced renal cell carcinoma and imatinib resistant or intolerant gastrointestinal stromal tumors.

Several trials have evaluated single agent sunitinib in the treatment of GEJ. In a phase II second line trial of single agent sunitinib in 78 patients with advanced gastric and GEJ cancer, two patients had partial response and 25 patients had stable disease for ≥6 weeks. Median PFS was 2.3 months and median OS was 6.8 months (95% CI, 4.4-9.6 months) (62). Sunitinib has also been evaluated in combination with chemotherapy. A second line phase II trial randomized 107 patients to docetaxel with or without sunitinib. The time to progression was not significantly different (3.9 months in the sunitinib arm versus 2.6 months), but there was an increased response rate of 41.4% compared to 14.3% (63).

Similar to other TKIs, sunitinib has multiple drug interactions and can lead to QTc prolongation and changes in the metabolism of CYP3A4 substrates. Common toxicities include hypertension, hand-foot syndrome, and liver dysfunction.

Sorafenib

Sorafenib is a potent inhibitor of the Raf tyrosine kinase and several other receptor tyrosine kinases, including VEGFR-2, VEGFR-3, and PDGFR-β. Sorafenib has been approved for the treatment of both renal cell carcinoma and hepatocellular carcinoma based on the results of phase III trials (64,65). In tumor xenograft models, sorafenib effectively inhibited tumor growth and angiogenesis in gastric tumors (66).

Sorafenib has been evaluated for the treatment of advanced GEJ in several studies, both in combination with chemotherapy and as a single agent. Though one phase II study of 44 second line gastric cancer patients which combined sorafenib with docetaxel and cisplatin showed an impressive median PFS of 5.8 months and median OS of 13.6 months (67), other studies have not found these results and have been terminated early because of low response rates (68,69).

Pazopanib

Pazopanib is an oral agent which inhibits angiogenesis through multiple pathways, including the VEGFR, the PDGFR, as well as c-kit. It has been approved by the FDA for use in the treatment of metastatic renal cell carcinoma as well as metastatic soft tissue sarcoma based on the results of phase III trials (70,71). Pazopanib has also been shown to have activity in metastatic thyroid cancer (72).

Pazopanib is currently being evaluated with chemotherapy in two GEJ trials. The phase II PaFLO trial (FLO ± pazopanib as first-line treatment in advanced gastric cancer) randomized first line advanced gastric cancer patients to 5-fluorouracil, leucovorin, and oxaliplatin with or without pazopanib and is currently accruing patients (73). Another first line phase II trial adds pazopanib to capecitabine and oxaliplatin in advanced gastric cancer patients and is also recruiting (74). The results of these studies will help determine if pazopanib has a role in the treatment of advanced GE cancer.

IGF-1 inhibition

The IGF-1 receptor belongs to the insulin receptor family. IGF-1R is expressed on the cell surface and phosphorylation of intracellular substrates leads to activation of the MAPK and PI3K/Akt pathways which promotes tumor growth, progression and invasion in several cancers, including GE (75).

In GE, IGF-1R expression in resected tumors correlates with poorer clinical outcomes (76). IGF-1R signaling has been associated with resistance to cytotoxic therapy and inhibition of IGF-1R enhances tumor cell apoptosis in numerous models (77). The IGF-1R pathway can be targeted through monoclonal antibodies, IGF-1R antisense/small interfering ribonucleic acid (siRNA), and receptor tyrosine kinases.

In a study of 86 patients with resected gastric tumors, patients with low expression of both IGF-1R and EGFR had significantly longer OS compared to those who lack the low co-expression (76). A phase I trial of docetaxel combined with CP-751,871, an IGF-1R antibody, has demonstrated promising results and warrants further investigation (78).

Fibroblast growth factor (FGF) TKIs

FGF and its signaling receptors have multiple biological properties including cell proliferation, differentiation, motility, and transformation (79,80). FGFR2 is amplified in poorly differentiated gastric cancer (scirrhous cancer) with malignant phenotypes (81), which makes it a potential molecular target for treatment.

In preclinical models, AZD2171, a highly potent oral VEGF, FGFR1, PDGFRB, and VEGFR-2 TKIs, led to tumor inhibition in gastric cancer xenografts in a dose-dependent fashion. The most potent antitumor activity was

seen in xenografts over-expressing FGFR2. These results suggest that AZD2171 might be clinically beneficial in patients with FGFR2 expressing gastric tumors (82).

Ki23057, a broad-range TKI of FGFR2, also inhibits FGFR1, FGFR2, and VEGF2 tyrosine kinases. It inhibits the proliferation of gastric scirrhous cancer cells with FGFR2 gene amplification only. Oral administration of Ki23057 inhibits the growth and peritoneal dissemination of gastric cancer cells through FGFR2-RAS/extracellular-regulated kinase (ERK) inhibition, rather than through FGFR2-PI3k-AKT signaling inhibition (83). To our knowledge, no clinical trials are currently available for this compound in GE.

c-Met TKIs

C-Met is a receptor tyrosine kinase that is expressed in epithelial and endothelial cells. Overexpression of c-Met and activating c-Met mutations have been widely documented in many tumor types including GE and have been correlated with poorer outcomes (84,85). Hepatocyte growth factor (HGF), its ligand, is expressed by cells of the mesenchymal lineage.

A phase II study examined the safety and efficacy of two dosing schedules of foretonib (GSK1363089), an oral small-molecule inhibitor of c-Met and VEGFR-2, as a single agent in patients with metastatic gastric adenocarcinoma. Foretonib was well tolerated but demonstrated minimal antitumor activity in a c-Met unselected population (86).

A phase II study of rilotumumab (a human monoclonal antibody directed against HGF) showed more efficacy in a subset of patients with increased MET expression by IHC (87). Based on this data, the phase III RILOMET-1 trial [an international phase III multicenter, randomized, double-blind, placebo-controlled trial of rilotumumab plus epirubicin, cisplatin, and capecitabine (ECX) as first-line therapy in patients with advanced MET-positive gastric or GEJ adenocarcinoma] is currently recruiting (88). However, a double blind randomized first line phase II study of this combination (ECX with or without rilotumumab) was recently found to be negative for improved PFS (89).

Onartuzumab (a humanized monovalent antibody directed against MET) is also being evaluated in a first line, randomized phase III trial in MET-positive, HER2-negative GE patients in combination with FOLFOX. This study is ongoing and should be complete in 2015 (90).

PI3 kinase pathway inhibition

The PI3K enzymes are involved in the phosphorylation of membrane inositol lipids (91). The activation of PI3K generates the second messenger phosphatidylinositol 3,4,5-trisphosphate (PIP3) from phosphatidylinositol 4,5-bisphosphate (PIP2). This recruits proteins to the cell membrane, including the Akt/PKB kinases, resulting in their phosphorylation by phosphoinositide-dependent kinase 1 (PDK1) and by PDK2 (92,93).

Dysregulation of the PIP3/Akt/mTOR pathway can occur secondary to oncogenic mutations of PIK3CA (94), loss of phosphatase and tensin homolog (PTEN) function (95,96), mutation of Akt/PKB isoforms (97), or upstream activation through other pathways like IGF-1R. Abnormal expression of the PTEN protein in gastric cancer is found in 11% of tumors and is related to the tumor differentiation, advanced staging, and chemoresistance (98). Upregulation of the PI3k/Akt/mTOR downstream pathway correlates with a worse prognosis and may contribute to the resistance to chemotherapy (99).

Everolimus is an oral mTOR inhibitor that has shown anticancer activity both in phase I and II studies (100,101). The phase III GRANITE-1 trial (safety and efficacy of everolimus monotherapy plus BSC in patients with advanced gastric cancer) was performed for further evaluation. Six hundred and fifty-six second or third line advanced gastric cancer patients were randomized to everolimus as monotherapy or placebo with BSC. The median OS was not significantly different, at 5.39 months in the everolimus group compared to 4.34 months in the placebo group (102).

PARP Inhibitors

The function of PARP is to repair single stranded breaks (SSBs). If these SSBs are not repaired, they become double stranded breaks (DSBs) at the next fork replication, which leads to cell death. As cancer therapeutics, the PARP inhibitors prevent the cancer cell's SSB repair mechanism and ultimately allow tumor cell death to occur (103). These agents have shown activity in ovarian and breast cancer, particularly in patients with BRCA1 or BRCA2 gene mutation.

The PARP inhibitor olaparib was studied in a second line phase II trial for metastatic or recurrent GE. Patients received paclitaxel with or without olaparib (104). Though PFS was not significantly different, OS was improved in the

olaparib group. Because preclinical data had shown more olaparib sensitivity in patients with low ataxia telangiectasia mutated (ATM) protein (105), this study performed a subset analysis in which low ATM patients were found to have improved OS with olaparib. Based on these results, an ongoing phase III study of second line GE randomizes patients to paclitaxel with or without olaparib (106). A phase I study of another PARP inhibitor veliparib with FOLFIRI is also currently recruiting (107).

Immunotherapy

Cancer evades host immune recognition through multiple mechanisms acquired during tumor evolution (108). By blocking negative immune regulatory pathways and thereby allowing increased immune activity, cancer immunotherapy is a novel way to attack tumor cells. With the approval of therapies like ipilumamb for melanoma, there has been increased interest in immunotherapy for other diseases. Ipilumamb releases negative immune regulatory pathway by blocking cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), an inhibitory receptor.

The immunotherapy agent nivolumab has also been recently evaluated in cancer. This drug function by blocking binding of receptor inhibitor programmed cell death 1 (PD-1) that is expressed on T-cells to programmed cell death ligand 1 (PDL-1) which prevents T cell death. A phase I trial of nivolumab included patients with gastric adenocarcinoma. Unfortunately, these patients were not included in the efficacy analysis (109).

Pembrolizumab is another agent that blocks the binding of PD-1 and PDL-1 (as well as PDL-2). A phase IB study of pembrolizumab in recurrent and metastatic gastric and GEJ adenocarcinoma patients with PD-L1 tumor positivity by IHC was presented at ESMO 2014 (110). Tolerability as well as anti-tumor activity was demonstrated. Another anti-PDL-1 agent, MEDI4736, has shown activity in gastric cancer (111).

The combination of CTLA-4 and PDL-1 blocking agents has also been investigated. In melanoma, this grouping has been shown to improve response rate and survival in melanoma compared to each drug alone, suggesting synergistic activity of these agents (112). Based on promising pre-clinical data, the combination of MEDI4736 and tremilumumab (an anti-CTLA-4 agent) is being investigated in patients with advanced solid tumors, including gastric cancer (113). Immunotherapy could provide an unmet clinical need to patients with advanced GE cancers who might not benefit or be able to tolerate further traditional chemotherapy.

Guanylyl cyclase C (GCC) inhibitor

GCC, a trans-membrane cell surface receptor, is expressed on normal intestinal tissue but also expressed on the tumor cells of patients with gastrointestinal malignancies. Expression has been shown to be a good prognostic marker (39). Based on preclinical data that GCC on tumor cells has alterations in epithelial junctions, an antibody-drug conjugate MLN0264 was developed to preferentially target tumor cells. Based on promising phase I results (114), a phase II study of MLN 0264 in previously treated patients with gastric and GEJ cancers whose tumors express GCC by IHC is currently recruiting patients (115).

Conclusions

Together, GE cancers are among the most common malignancies worldwide (116). At diagnosis, approximately 50 percent of patients have disease that extends beyond locoregional confines. Cytotoxic agents have been the mainstay of systemic treatment for decades but carry significant toxicity.

During recent years, several molecular abnormalities underlying GE carcinogenesis have been identified. This has stimulated the search for targeted therapeutic approaches, and many studies are incorporating these agents with chemotherapy as described in this review.

The highly complex nature of the underlying molecular abnormalities and concurrent aberrations in multiple signaling pathways in GE cancers has been established (117). Because of the inherent redundancies in tumor molecular pathways, targeted agents used as monotherapy or even added to a chemotherapy backbone are unlikely to result in dramatic improvements in efficacy. However, pursuing multiple targets simultaneously might be logistically difficult given the current limited understanding of how to combine targeted agents, the issue of designing multi-sponsor trials, as well as the potential for additional toxicities. In the future, molecular profiling will play a role in identifying the specific patient who might benefit from targeted therapy, validate whether the drug inhibits the target, and determine if the tumor having the target is of functional importance.

To better achieve this goal of personalized cancer care, biomarkers should be utilized to predict the efficacy and toxicity of anticancer agents, as with HER2 overexpression

prior to trastuzumab use. However, though selecting patients based on predictive factors is ideal, the lack of validated biomarkers in GE and the diversity of molecular alterations acquired during malignant transformation, recurrence or metastasis makes biomarker incorporation into clinical trials difficult.

Finally, the failure of phase III trials to demonstrate survival benefit despite promising results from phase II studies indicates the need to change the current evaluation system. Targeted agents often result in stable disease rather than disease response, which make assessment more challenging. OS should remain the primary end point of clinical trials because of the short survival in GE cancers.

Apart from the molecular targeted therapies described in this article, many other agents are currently being evaluated in GE cancers. Adequately powered, randomized trials are necessary to define the role of targeted therapies in advanced GE. Further work is needed to determine the optimal use of targeted therapy, validate biomarkers, and bring personalized medicine to GE adenocarcinomas.

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