

Targeted Therapies for Metastatic Esophagogastric Cancer

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Opinion statement

The prognosis and long-term survival for patients with metastatic esophagogastric cancer (EGC) is poor. Historically, the mainstay of treatment has been combination chemotherapy. More recently, a number of targeted therapies have been developed and are being studied with the goal of improving response rate and survival in patients with metastatic EGC. To date, the only targeted therapy which has been clinically approved is trastuzumab which targets the HER2/Neu oncogene. However, only a small group of patients with EGCs are HER2 amplified, and there are other important targets/pathways which play a role in the development of these cancers that are currently being studied. With the identification of these other clinically relevant pathways, it is anticipated that several other therapies will be approved in the future.

Introduction

Esophagogastric cancers (EGCs) are composed of tumors of three distinct anatomic areas and two distinct histological variants. Primary esophageal cancer includes both squamous cell and adenocarcinoma (AC) while tumors of the esophagogastric junction and the distal stomach are almost exclusively adenocarcinomas. Recent epidemiological trends have suggested that the incidence of esophageal and esophagogastric junction adenocarcinomas has been increasing over the last three decades. In contrast, the incidence of esophageal squamous cell carcinoma has decreased in the United States, while the incidence of gastric adenocarcinomas has decreased globally [1–5]. Despite continued research in the biology and treatment of EGC, the prognosis and long-term survival remains poor for most patients.

A study of a cancer registry in the United States found that the incidence of esophageal AC rose from 1.8 per 100,000 in 1987–1991 to 2.5 per 100,000 from 1992 to 1996 [6]. The estimated new cases of esophageal AC in the United States in 2009 were 16,470 [1]. This cancer has been noted to be more common in men and in whites compared to blacks. Possible risk factors include gastroesophageal (GE) reflux disease, smoking, and obesity. In contrast, the incidence of gastric AC has been declining both in the United States and worldwide. Despite its decreased incidence, this cancer remains one of the most common forms of cancer worldwide, accounting for nearly 10% of global malignancies [7, 8]. Possible risk factors include diets high in nitrosamine compounds and salt, obesity, smoking, prior gastric surgery, and

H. Pylori infection. The incidence of esophageal squamous cell carcinoma varies widely by geographic region, and is the most common in Asia, Africa, and Iran. Risk factors include smoking, alcohol abuse, diets high in nitrosamine compounds, preexisting esophageal disease, and human papillomavirus infection.

Patients with EGC may present in a wide variety of clinical scenarios. Common presenting symptoms include weight loss, dysphagia, epigastric or abdominal pain, early satiety, gastrointestinal bleeding, or anemia. Symptoms of advanced disease include tracheoesophageal fistulas, involvement of the recurrent laryngeal nerve, and gastrocolic fistulas. Patients with metastatic disease may present with liver enlargement secondary to liver metastases or ascites due to peritoneal deposits. Smaller lesions may be discovered incidentally on endoscopy or radiographic imaging done for other indications. The diagnosis is confirmed on tissue biopsy usually obtained by upper gastrointestinal endoscopy. Clinical staging often involves endoscopic ultrasound to assess depth of invasion and

regional lymph node involvement, and/or CT and PET scans to assess for distant disease.

Current treatment options for localized EGCs include surgery alone, combined modality strategies such as pre- or post-op chemotherapy with or without radiation, and definitive chemoradiation. In the metastatic setting, chemotherapy is the mainstay of treatment, but results in only modest improvements in survival with considerable toxicity. Most recent clinical trials have focused on the addition of targeted therapies to a chemotherapy backbone.

The prognosis of both locally advanced and metastatic EGC is poor. For locally advanced disease, surgery alone results in a 5-year survival of only 20–25% [9, 10]. Combined modality therapy increases the 5-year survival to approximately 30–35% [11–13]. Median overall survival in the metastatic setting is usually about 8–10 months [14].

Given the poor overall survival in the metastatic setting with standard chemotherapy, this article will focus on newer, targeted therapy options which are emerging for the treatment of metastatic EGC.

Targeted therapies

Anti-HER2 therapies

- HER2/Neu or ERBB2 is a member of the HER tyrosine kinase receptor family. When a peptide ligand binds to the extracellular domain of the HER2 receptor, homo- and heterodimerization of the receptor occurs leading to autophosphorylation of the kinase, and downstream growth signaling is activated. HER2 overexpression has been noted in many types of human cancers, most prominently in some breast cancers, and more recently in a subset of EGCs.
- HER2 overexpression has been variably noted in GE junction AC (mean 22%; range 0–43%) [15, 16]. The wide range of expression is due to receptor testing mechanisms based on immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH), as well as the variability in patients' cancer staging. In gastric and GE junction AC, some studies have shown a correlation between HER2 amplification by FISH and increasing depth of invasion, lymph node involvement, and distant organ metastasis, as well as overall poor survival [17]. To date, there is minimal data that have recorded comparisons between FISH and IHC in gastric cancers. However, based on extrapolation from the breast cancer literature, FISH is felt to be a more reliable and reproducible method for true HER2 amplification [18].
- Anti-HER2 therapies that have been evaluated in metastatic EGCs are the monoclonal antibody (moAb), trastuzumab, and the oral small molecule tyrosine kinase inhibitor, lapatinib.

Trastuzumab

- Trastuzumab (Herceptin, Genentech) is a humanized IgG1 moAb against the HER2 receptor. This drug likely exerts its effects through several mechanisms, including preventing dimerization of the receptor, increasing receptor endocytosis and destruction, inhibiting shedding of the extracellular domain, and inducing antibody dependent cytotoxicity [18]. It has been approved by the FDA for use as adjuvant therapy in combination with chemotherapy in HER2-amplified breast cancer and as monotherapy or combination therapy in metastatic breast cancer.
- A phase II study evaluating 21 patients with advanced gastric cancer and HER2 overexpression, who received trastuzumab and cisplatin showed an overall response rate of 35%, and stable disease in 17% [19]. Another phase II study of 16 HER2 positive patients with advanced gastric cancer treated with trastuzumab, cisplatin, 5-FU, and leucovorin found a response rate of 55%, and a median overall survival of 8 months [20].
- Because of its success in the treatment of HER2-amplified breast cancer, the phase III randomized ToGA trial evaluating trastuzumab in combination with chemotherapy was launched. The trial examined the addition of trastuzumab to a backbone of fluoropyrimidine (either capecitabine or 5-FU) and cisplatin chemotherapy for patients with HER2 positive advanced gastric or GE junction cancer [21]. The study enrolled patients with inoperable locally advanced, recurrent, or metastatic AC of the stomach or GE junction that were HER2 positive by FISH or 3+ positive by IHC. Of tumors from 3807 patients, 22.1% were found to be HER2 positive. Five-hundred ninety four patients were randomized, and 584 of these underwent treatment, with 20 among them having had locally advanced disease, and 564 metastatic disease. There was a statistically significant increase in overall response rate (47.3% vs 34.5%), median progression free survival (6.7 vs 5.5 months) and median overall survival (13.8 vs 11.1 months) in favor of the trastuzumab containing arm. There was no unexpected toxicity in the trastuzumab arm, but as expected there was an increased incidence of asymptomatic decrease in the left ventricular ejection fraction [22•]. Furthermore, in a recent analysis, quality of life was not compromised at all in the trastuzumab-treated group making this a clinically significant improvement [23]. The ToGA trial is the first positive phase III study of targeted therapy for the treatment of EGCs, and validated the role of trastuzumab chemotherapy combination as a new standard treatment for patients with HER2 positive EGCs.
- In the ToGA trial, trastuzumab was dosed at 8 mg/kg on Day 1 of cycle 1, followed by 6 mg/kg every three weeks until disease progression or unacceptable toxicity. The drug may enhance cardiotoxic effects of anthracyclines, neutropenic effects of immunosuppressants, and may increase the serum concentration of paclitaxel when given in combination. Typical side effects include cardiomyopathy, nausea, weakness, and infusion reactions.

Lapatinib

- Lapatinib (Tykerb, GlaxoSmithKline) is an oral tyrosine kinase inhibitor (TKI) which has activity against both EGFR and HER2 kinases. The FDA has approved lapatinib in combination with

- capecitabine for treatment of HER2 positive breast cancer with prior progression on trastuzumab, an anthracycline, and a taxane.
- The Southwest Oncology Group (SWOG) performed a phase II study evaluating lapatinib as first-line therapy in 47 patients with advanced gastric cancer [24]. Only three patients (7%) had a documented partial response, median time-to-treatment failure was 2 months, and median overall survival was 5 months. The low overall survival rate in this study would suggest that lapatinib as a single agent will not prove to provide adequate disease control. A second phase II study evaluated lapatinib in 25 patients who were EGFR positive by IHC or HER2 positive by IHC or FISH whose disease had progressed through multiple prior therapies [25]. The overall response rate was 0%, but two patients had stable disease for 5 and 9 months, respectively. A third study evaluated 16 patients with HER2 amplified GE junction tumors [26]. This study was closed early due to lack of response and slow accrual. One patient achieved a durable complete remission (maintained at week 60), and another patient had stable disease at week 36.
 - Extrapolating from its success rate in breast cancer, two phase III studies are currently evaluating the role of lapatinib in combination with chemotherapy for the treatment of advanced EGC. The LOGIC trial is evaluating the combination of capecitabine/oxaliplatin ± lapatinib as first-line therapy for HER2 overexpressing EGCs. The TYTAN trial is an Asian study evaluating lapatinib in combination with paclitaxel as second-line therapy in gastric cancer. Both these studies are still in progress, and final results are pending.
 - Lapatinib is being dosed at 1250 mg/day in these trials. Lapatinib can enhance the QTc prolonging effects of many drugs, and increase or decrease the metabolism of CYP3A4 substrates. Side effects include but are not limited to fatigue, rash, diarrhea, cytopenias, and elevated transaminases and bilirubin.
 - Trials of anti-HER2 therapies that have been reported are shown in Table 1.

Anti-EGFR therapy

- EGFR or erbB1 is another member of the erbB tyrosine kinase family. Binding of ligand to the receptor causes dimerization either with itself or another member of the erbB family. Dimerization leads to tyrosine

Table 1. Summary of trials of anti-HER2/Neu-targeted therapies in metastatic EGCs

Agents	Trial design	Stage	Histology	No. of Pts	ORR	OS	Author
5-FU or capecitabine + Cis vs Trastuzumab + 5-FU or capecitabine + Cis	Randomized Phase 3	Locally advanced: 10	Gastric AC: 242	290	34.5%	11.1 mos	Bang <i>et al.</i>
		Locally advanced: 10	Gastric AC: 236	294	47.3%	13.8 mos	
Lapatinib	Phase 2	Metastatic	Gastric AC	47	7%	5 mos	Iqbal <i>et al.</i>
		Metastatic	Esophageal AC: 12	25	0%	NS	
Lapatinib	Phase 2	Her-2 amplified	GE junction AC: 13	16	6%	NS	Galsky <i>et al.</i>
		Metastatic	GE junction AC				
		Her-2 amplified					

- kinase phosphorylation and downstream signal activation. These downstream signals regulate the cell cycle, apoptosis, cell proliferation, and angiogenesis. EGFR is normally expressed in many tissues including the skin, gut, and kidney, and has been shown to be overexpressed in certain cancers. Overexpression by IHC or FISH in EGCs has been seen in 30–90% of tumors, and correlates with increased invasion, poorly differentiated histology, and worse prognosis. To date, there has been no correlation demonstrated between EGFR by IHC and response to anti-EGFR therapies. Finally, in contrast to adenocarcinoma of the lung, mutations in the EGFR kinase domain are exceedingly rare in gastric and esophageal cancers [27–30].
- *kras* is an oncogene downstream of EGFR, which is involved in signal transduction. Colon cancer patients with *kras* mutations do not seem to derive benefit from the anti-EGFR moAbs, cetuximab, or panitumumab. Little is known about the incidence of *kras* mutations or the significance of these mutations for treatment in patients with EGCs. In one study, none of the 38 patients was found to have mutated K-ras, and in another study two of 23 patients had a mutation suggesting that mutations in *kras* are exceedingly rare [31, 32].
 - Anti-EGFR therapies which have been evaluated in metastatic EGCs include the moAbs (cetuximab, panitumumab, and matuzumab) and oral, small molecule TKIs (erlotinib and gefitinib). It should be noted that unlike in the case with HER2 inhibitors, no EGFR-related criteria were required in selecting patients for the large majority of these trials.

Cetuximab

- Cetuximab (Erbix, Imclone Systems) is a partially humanized murine IgG1 moAb which binds EGFR and blocks ligand binding to the receptor, stimulates EGFR receptor endocytosis, and initiates immune-mediated cytotoxicity [33]. The FDA has approved cetuximab for use in irinotecan refractory colorectal cancer, and for use in combination with radiotherapy for treatment of locally advanced head and neck squamous cell carcinoma.
- In the metastatic setting, multiple trials have evaluated cetuximab with various chemotherapy regimens, including FOLFIRI (biweekly bolus 5-FU, leucovorin, irinotecan, and infusional 5-FU), FUFIRI (weekly irinotecan/infusional 5-FU/leucovorin), FOLFOX, FUFIX (weekly oxaliplatin/leucovorin/infusional 5-FU), 5FU/cisplatin, continuous infusion 5-FU/leucovorin/cisplatin, capecitabine/cisplatin, cisplatin/docetaxel, and oxaliplatin/irinotecan. The FOLFIRI trial was the only one which required tumors to be EGFR positive by IHC. The overall response rates in these trials were 40–69% and median overall survival was 9.5–17 months [31, 32, 34–41].
- The Cancer and Leukemia Group B (CALGB) recently reported results of a randomized phase II trial combining cetuximab with either ECF (epirubicin, cisplatin, and infusional 5-FU), cisplatin/irinotecan, or FOLFOX for the treatment of metastatic esophageal or GE junction cancers [42••]. Cetuximab plus ECF or FOLFOX had response rates greater than 40%. As the purpose of the trial was to determine the best chemotherapy backbone for further study, none of the arms contained a true control. Biomarker correlates including EGFR and *kras* are currently ongoing in this trial. Cetuximab is currently being tested in an ongoing randomized phase III trial in Europe.

- Cetuximab has also been evaluated in the second-line setting and beyond. Data from these studies suggest that this is not a promising approach. In a study done by SWOG in 55 patients with advanced esophageal and GE junction AC receiving cetuximab as second-line treatment, one patient had a confirmed partial response and median survival was 1.8 months [43–46].
- In these trials, cetuximab is usually dosed at 400 mg/m² on week 1 followed by 250 mg/m² weekly. Toxicities seen in the various studies include neutropenia, diarrhea, skin toxicity, and rare cases of anaphylaxis.

Panitumumab

- Panitumumab (Vectibix, Amgen) is a fully humanized IgG2 moAb against EGFR which has been approved by the FDA for treatment of chemorefractory EGFR-positive colorectal cancer. This drug is currently being evaluated for treatment of metastatic EGCs. In a phase I study which included three patients with EGC, one patient had stable disease for 7 months [47]. The REAL3 trial is currently being done in the UK to evaluate EOX (epirubicin, oxaliplatin, and capecitabine) ± panitumumab but at the planned doses, the trial has encountered significant toxicities including an 80% rate of grade 3 diarrhea [48]. As a consequence, the study was temporarily halted while formal dose-finding studies were conducted. The trial has now resumed with lower doses of both capecitabine and oxaliplatin with the standard dosing of panitumumab at 6 mg/kg every 2 weeks. The most common side effect is skin toxicity, diarrhea and electrolyte abnormalities (hypokalemia, hypomagnesemia).

Matuzumab

- Matuzumab, a humanized monoclonal Ab against EGFR, has been evaluated in Phase I studies for treatment of metastatic esophagogastric cancer. This drug has not yet received FDA approval. In one study, 1 of 2 patients with esophageal SCC had a durable 6-month partial response [49]. In another study, the drug was combined with ECX (epirubicin, cisplatin, and capecitabine) for first-line treatment of EGFR-positive gastric and GE junction AC [50]. Of the 21 patients, overall response rate in 20 patients was 65% and median time-to-progression was 5.2 months.

Erlotinib

- Erlotinib (Tarceva, Genentech) is a small molecule anti-EGFR tyrosine kinase inhibitor. It inhibits ATP binding within the tyrosine kinase domain leading to inhibition of autophosphorylation and signal transduction. The FDA has approved erlotinib for use as second or third-line treatment for non-small cell lung cancer, maintenance therapy for non small cell lung cancer, and as first-line treatment in combination with gemcitabine for pancreatic cancer.

- SWOG performed a phase II evaluation of erlotinib in refractory-advanced gastric and GE junction AC [51••]. Interestingly, in this trial in the patients with gastric primaries, there were no responses. However, in the 44 patients with GE junction tumors, the overall response rate was 9% and median time-to-failure was 2 months. Based on these results, we recently completed a trial investigating the addition of erlotinib to modified FOLFOX6 chemotherapy restricting the trial to gastroesophagus junction tumors only [52]. In this phase II trial of 38 patients, the response rate was 50% with an overall survival of 11 months.
- Erlotinib is dosed at 150 mg daily. Antacids can decrease serum concentration of erlotinib, and erlotinib may increase or decrease metabolism of CYP3A4 substrates. Possible side effects include rash, diarrhea, nausea, and decreased appetite.

Gefitinib

- Gefitinib (Iressa, AstraZeneca Pharmaceuticals) is also a small molecule TKI. It has been used for the treatment of locally advanced or metastatic non-small cell lung cancer after failure of platinum-based and docetaxel therapies. Studies using gefitinib as a single agent for treatment of EGC have also only produced modest results. Gefitinib was studied in a phase II evaluation as second-line treatment for 28 patients [32]. One patient had a 3-month partial response, and 10 patients had stable disease. Another study evaluated gefitinib as either first or second-line therapy for esophageal and GE junction adenocarcinoma [53]. The overall response rate was 11%, but overall survival was 4.5 months.
- Gefitinib is dosed at 500 mg daily. Gefitinib may increase or decrease the metabolism of CYP3A4 substrates, and can enhance the anticoagulant effect of warfarin. Possible side effects include rash, diarrhea, and nausea.
- Based on the number of trials that have been done to date, it seems likely that to achieve improved outcomes, these agents will also need to be added to a chemotherapy backbone.
- Trials of anti-EGFR therapies that have been reported are shown in Table 2.

Anti-vascular endothelial growth factor

- Vascular endothelial growth factor (VEGF) is a regulator of angiogenesis. It plays a role in endothelial cell mitogenesis and migration, remodeling of the extracellular matrix, increased vascular permeability, and maintenance of survival for newly formed blood vessels [54]. VEGF is overexpressed in 30–60% of patients with esophageal cancer, and some studies have shown a correlation between VEGF overexpression, advanced stage, and poor survival [55–59].
- Anti-VEGF therapies which have been studied include the moAb, bevacizumab, as well as the multi-target TKIs, sunitinib, sorafenib, and telatinib.

Table 2. Summary of trials of anti-EGFR-targeted therapies in metastatic EGCs

Agents	Trial design	Stage	Histology	No. of Pts	ORR	OS	Author
Cetuximab + FOLFIRI	Phase 2	Metastatic EGFR+	Gastric AC: 34 GE Junction AC: 4	38	44% (of 34)	16 mos	Pinto <i>et al.</i>
Cetuximab + FUFIRI	Phase 2	Metastatic	Gastric AC: 34 GE junction AC: 15	49	42% (of 48)	16.6 mos	Kanzler <i>et al.</i>
Cetuximab + FUFOX	Phase 2	Metastatic	Gastric AC: 27 GE junction AC: 25	52	65% (of 46)	9.5 mos	Lordick <i>et al.</i>
Cetuximab + FOLFOX	Phase 2	Metastatic	Gastric AC	40	50%	9.9 mos	Han <i>et al.</i>
Cetuximab + oxaliplatin/CPT	Phase 2	Metastatic	Gastric AC	51	63% (of 35)	9.5 mos	Woell <i>et al.</i>
Cetuximab + Cis/docetaxel	Phase 2	Unresectable Metastatic	Gastric AC: 40 GE junction AC: 8	48	41% (of 42)	NS	Pinto <i>et al.</i>
Cetuximab + Cis/capecitabine	Phase 2	Metastatic	Gastric AC	49	48% (of 47)	NS	Zhang <i>et al.</i>
Cetuximab + CI 5-FU/LV/Cis	Phase 2	Metastatic	Gastric AC	35	69%	14.5 mos	Yeh <i>et al.</i>
Cetuximab + 5-FU/Cis vs 5-FU/Cis	Randomized	Metastatic	SCC	32	19%	9.5 mos	Lorenzen <i>et al.</i>
Cetuximab	Phase 2	Metastatic	Esophageal AC	30	13%	5.5 mos	Gold <i>et al.</i>
Cetuximab + Cis/CPT	Phase 2 2nd line	Metastatic	Esoph ageal or GE junction AC: 6	55	2%	4.0 mos	Ku <i>et al.</i>
Cetuximab + docetaxel	Phase 2 2nd line	Metastatic	NS	7	11%	NS	Tebbutt <i>et al.</i>
Cetuximab + CPT	Phase 2 2nd line	Metastatic	Esoph ageal or GE junction AC: 19 Gastric AC: 8	38	6% (of 35)	5.2 mos	Schonnemann <i>et al.</i>
Cetuximab + ECF vs Cetuximab + IC vs Cetuximab + FOLFOX	Randomized Phase 2	Metastatic	Esophageal or GE junction AC: 222 SCC: 23	245	58% 38% 51%	10 mos 8.6 mos 10 mos	Enzinger <i>et al.</i>
Matuzumab + ECX	Phase 1 Phase 1	Metastatic Metastatic	Esophageal AC: 5 GE junction AC: 7 Gastric AC 9	2 21	50% 65% (of 20)	NS NS	Vanhoefter <i>et al.</i> Rao <i>et al.</i>
Panitumumab	Phase 1	Metastatic	NS	3	0%	NS	Figlin <i>et al.</i>
Erlotinib + FOLFOX	Phase 2 1st line	Metastatic	GE junction AC	38	50%	11 mos	Wainberg <i>et al.</i>
Erlotinib	Phase 2 2nd ^t line	Metastatic	Gastric AC: 26 GE junction AC: 44	70	0% 9%	3.5 mos 6.7 mos	Dragovich <i>et al.</i>
Gefitinib	Phase 2 2nd line	Metastatic	Esophageal and GE junction AC: 26 SCC: 1	36	3% (of 28)	5.5 mos	Janmaat <i>et al.</i>
Gefitinib	Phase 2 1st/2nd line	Metastatic	AdenoSCC: 1 Esophageal and GE junction AC	27	11%	4.5 mos	Ferry <i>et al.</i>

Bevacizumab

- Bevacizumab (Avastin, Genentech) is a humanized IgG1 mAb against VEGF. The FDA has approved bevacizumab for the treatment of metastatic colon cancer, metastatic nonsquamous non-small cell lung cancer, progressive glioblastoma, and metastatic renal cell carcinoma.
- Several phase II studies of bevacizumab for treatment of metastatic EGC showed encouraging results. One study combined bevacizumab with cisplatin/irinotecan for 47 patients, and showed an overall survival of 12.3 months [60]. Another study combined bevacizumab with docetaxel/cisplatin/irinotecan in 44 patients, and showed overall response rate of 67% and overall survival of 16.2 months [61]. Other evaluations in combination with various chemotherapy regimens have shown similar overall response rates [62, 63]. Bevacizumab has also been evaluated in the second-line setting in combination with docetaxel with an overall response rate of 24% in 17 evaluable patients [64]. Given the promising phase II data, the phase III AVAGAST study was launched to evaluate first-line fluoropyrimidine (5-FU or capecitabine) and cisplatin plus bevacizumab or placebo in patients with advanced gastric cancer [65••]. There were 774 patients enrolled in this trial, and approximately 95% had metastatic disease. Despite some advantages, there was no statistically significant difference in median overall survival (10.1 months with chemotherapy vs 12.1 months with chemotherapy plus bevacizumab). Interestingly, there was a statistical advantage in the bevacizumab groups for both response rate (29.5% for placebo vs 38% for bev) and PFS (5.3 months for placebo vs 6.7 months for bev). Furthermore, in a subset analysis of geographical regions, patients in the Americas did have an advantage in overall survival (6.8 months for placebo vs 11.5 months for bev). While the Americas cohort was small (approximately 150 patients), these results are provocative and suggest that the geographical heterogeneity of these disease may also reflect differences in responses to targeted agents. Additional studies with bevacizumab in EGC that are currently ongoing may provide additional insight into the appropriate patients for this agent (Table 3).
- Bevacizumab is dosed at 7.5 mg/kg every three weeks. Possible side effects include hypertension, thromboembolic events, and gastrointestinal perforation or bleeding.

Sunitinib

- Sunitinib (Sutent, Pfizer) is an oral multi-target TKI that has activity against the VEGF receptor. The FDA has approved sunitinib for first-line therapy for advanced renal cell carcinoma and for imatinib resistant gastrointestinal stromal tumors. In a phase II study, 78 patients received sunitinib as second-line treatment for advanced EGC [66]. Two patients had partial response, and 25 had stable disease for at least 6 weeks. Median overall survival was 6.8 months. In this study, sunitinib was dosed at 50 mg/day with four weeks on, two weeks off. There are no major contraindications to administration of this drug. Sunitinib has multiple drug interactions including enhancing the QTc prolonging the effects of other agents, and increasing or decreasing the metabolism of CYP3A4 substrates. Possible toxicities include hyper-

Table 3. Summary of selected additional trials of novel therapeutics in metastatic EGCs

Agents	Trial design	Stage	Histology	No. of Pts	ORR	Median OS	Author
Bevacizumab + Cis/CPT	Phase 2	Metastatic	Gastric AC: 24 GE junction AC: 23	47	65%	12.3 mos	Shah <i>et al.</i>
Bevacizumab + docetaxel/Cis/5-FU	Phase 2	Metastatic	Gastric AC: 22 GE junction AC: 22	44	67% (of 37)	16.2 mos	Kelsen <i>et al.</i>
Bevacizumab + docetaxel/Cis/CPT	Phase 2	Metastatic	Gastric AC: 12 Esophageal AC: 10 GE junction AC: 7 SCC: 3	32	63% (of 30)	NS	Enzinger <i>et al.</i>
Bevacizumab + docetaxel/oxaliplatin	Phase 2	Metastatic	Gastric and GE junction AC	23	59%	NS	El-Rayes <i>et al.</i>
Bevacizumab + docetaxel	Phase 2	Metastatic	Gastric AC: 6 Esophageal AC: 15 GE junction AC: 4 SCC: 1	26	24% (of 17)	NS	Enzinger <i>et al.</i>
Bevacizumab + Capecitabine/Cis vs Placebo + Capecitabine/Cis	Phase 3	Inoperable	Gastric and GE junction AC	387	38%	12.1 mos	Kang <i>et al.</i>
Sunitinib	Phase 2	Metastatic	Gastric and GE junction AC	387	29.5%	10.1 mos	Bang <i>et al.</i>
Sorafenib + docetaxel/Cis	Phase 2	Metastatic	Gastric and GE junction AC	42	2.6%	6.8 mos	Bang <i>et al.</i>
Sorafenib + capecitabine/Cis	Phase 1	Inoperable	Gastric and GE junction AC	44	38.5%	14.9 mos	Sun <i>et al.</i>
Everolimus	Phase 2	Metastatic	Gastric AC	21	62.5% (of 16)	Not reached	Kim <i>et al.</i>
Foretinib	Phase 2	Metastatic	Gastric, GE junction, Esophageal AC	54	0%	Not reached	Yamada <i>et al.</i>
Marimastat vs Placebo	Phase 3	Inoperable	Gastric and GE junction AC	64	0%	NS	Jhawer <i>et al.</i>
Bryostatatin-1 + paclitaxel	Phase 2	Metastatic	Gastric and GE junction AC	185	NS	NS	Bramhall <i>et al.</i>
Bryostatatin-1 + paclitaxel	Phase 2	Metastatic	Gastric and GE junction AC	184	29% (of 35)	8 mos	Ajani <i>et al.</i>
	Phase 2	Metastatic	GE junction and esophageal AC	24	27% (of 22)	8.3 mos	Ku <i>et al.</i>

tension, cytopenias, transaminitis or elevated alkaline phosphatase and bilirubin, and hand-foot syndrome.

Sorafenib

- Sorafenib (Nexavar, Bayer), like sunitinib, is also a multi-targeted TKI with activity against the VEGF receptor. The FDA has approved sorafenib for treatment of advanced renal cell carcinoma and hepatocellular carcinoma. The Eastern Cooperative Oncology Group performed a phase II study of sorafenib with docetaxel/cisplatin for first-line treatment of 53 patients with metastatic or unresectable gastric or GE junction AC, with overall response rate of 38.6% and median overall survival 14.9 months [67]. Sorafenib is dosed at 400 mg twice daily. Sorafenib may increase serum concentration of doxorubicin and irinotecan, and may decrease serum concentration of fluorouracil. Side effects are similar to those of sunitinib.

Telatinib

- Finally, telatinib is a small molecule oral TKI which selectively targets the VEGF and platelet-derived growth factor (PDGF) receptors. The drug has not been FDA approved. Preliminary results from a phase II study was recently reported evaluating telatinib in combination with capecitabine and cisplatin as first-line treatment in patients with advanced cancer of the stomach or GE junction [68].

mTOR inhibitors

- The mTOR pathway is a downstream component of the phosphatidylinositol 3-kinase/Akt kinase signaling pathway. This pathway regulates cell growth and metabolism by acting as a sensor for nutrients and growth factors. In gastric cancer, upregulation of this pathway has been linked to poor prognosis [69].

Everolimus

- Everolimus (Afinitor, Novartis) is an oral mTOR inhibitor which is approved by the FDA for treatment of sunitinib or sorafenib resistant renal cell carcinoma. A Japanese phase II study evaluated using everolimus in 53 treatment-refractory gastric cancer patients [70••]. Although there were no responses, a decrease in tumor size from baseline was observed in 45% of patients, and median overall survival was 10.1 months. The GRANITE-1 study is a phase III study currently evaluating everolimus plus supportive care vs placebo plus supportive care for treatment of advanced gastric cancer after progression on prior chemotherapy. Results of this study are pending. Everolimus is dosed at 10 mg daily. Everolimus has multiple drug interactions including interactions with CYP3A4 inducers and inhibitors. Side effects include stomatitis, edema, hypertension, rash, fatigue, cytopenias, rise in creatinine, and cough.

Other targets

- Other targets that have been evaluated in a small number of clinical studies include c-MET, matrix metalloproteinases (MMPs), and protein kinase C.
- C-MET is the receptor for hepatocyte growth factor. Ligand binding to the receptor stimulates tyrosine kinase phosphorylation, further signal cascade, and cell proliferation. The c-MET protein has been found to be overexpressed in some EGCs and correlates with a poor prognosis. A phase II study evaluated two dosing schedules for GSK1363089 (foretonib), a dual MET/VEGFR2 inhibitor in patients with metastatic gastric cancer [71]. The study found that c-MET amplification in metastatic gastric cancer is rarer than anticipated (3/43 patients). However, the lack of a well-validated method to assess c-MET expression/mutation/amplification makes any conclusive interpretations premature. The best response was stable disease noted in 15% and 21% of the two different cohorts. Unfortunately, amplification of the MET oncogene was not associated with a higher response rate. Other clinical trials of various c-MET inhibitors (TKI's and monoclonal antibodies) are ongoing.
- MMPs are proteolytic enzymes that break down components of the extracellular matrix and play a role in cell growth and repair. Marimastat, an MMP inhibitor was evaluated in a phase III study vs placebo in 369 patients with metastatic or inoperable GE junction AC [72]. At the end of 2 years, there was a small but significant difference in overall survival (160 vs 138 days) and 2-year survival (9% vs 3%) favoring the marimastat group ($P = 0.02$). However, this class of drugs is no longer being tested in clinical trials in EGC.
- Finally, protein kinase C mediates anti-apoptotic signals. Bryostatin-1 is an inhibitor of protein kinase C. Two different phase II studies have evaluated bryostatin-1 in combination with paclitaxel for treatment of EGC [73, 74]. Both studies suggested that this may be an active combination, but the drug was not further evaluated because of significant grade 3/4 myalgias which occurred in about half the patients. Nonetheless, other PKC inhibitors are under investigation in a variety of malignancies including gastric cancers.

Conflicts of interest Dr. Wainberg has consulted for and accepted honoraria from Genentech.

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