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REVIEW

Targeted therapy for esophagogastric cancers: a review

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Abstract: The incidence of esophagogastric cancers is increasing rapidly in the Western population. Despite better understanding of the biology and intense research in the treatment of these cancers, the long-term survival remains poor both in the locally advanced and metastatic settings. The addition of combined modality strategies has resulted in modest improvement in 5-year survival rates. A number of biologic agents targeting epidermal-derived growth factor receptor, vascular endothelial derived growth factor and its receptor, and mammalian target of rapamycin (mTOR) are being currently evaluated in Phase II and III clinical trials. Some of these, like trastuzumab, cetuximab, and bevacizumab, have shown promising results. This review provides a brief overview of the recent developments in biologic agents for the treatment of esophagogastric cancers.

Keywords: adenocarcinoma, squamous cell carcinoma, VEGF, trastuzumab, Her2-positive EGC

Introduction

Esophagogastric cancers (EGCs) include tumors involving the esophagus, gastroesophageal junction (GEJ), and stomach. While the tumors involving the esophagus can be of either adenocarcinoma (AC) or squamous cell carcinoma (SCC) histology, tumors involving the GEJ and stomach are almost exclusively of AC type. The EGCs constitute a significant problem worldwide. The incidence of EGC-AC is increasing rapidly in the Western population.[1] There are demographic variations in the incidence of these tumors, and there has been a major change in the epidemiological trend towards AC histological subtype in the Western world over the last two decades.[2–4] Globally, SCC is still the most common subtype of esophageal cancer, but AC is now the most prevalent in the West.

Despite greater understanding of the biology and intense research in the treatment of EGC, the prognosis and long-term survival remains poor for both locally advanced and metastatic disease, with a case–fatality ratio of 84% (esophageal) and 75% (gastric), respectively.[5] Current treatment options for locally advanced disease include surgery alone, combined modality treatment (perioperative chemoradiotherapy, or chemotherapy), or definitive chemoradiation therapy. The 5-year survival rates for locally advanced disease with surgery alone are only 20%–25%.[6,7] Poor outcomes with surgery alone have led to the evaluation of combined modality approaches to improve the survival. Such therapy has now become the standard of care for locally advanced disease. However, the addition of combined modality strategies results in modest improvement in 5-year survival rates to only 30%–35%.[7–10]

Palliative chemotherapy is the current treatment approach practiced by medical oncologists worldwide for metastatic disease. The objective response rate (ORR) with palliative chemotherapy for metastatic disease is only 20%–40%, with a median overall survival (OS) of 8–10 months.[11] Various combination chemotherapy regimens have been used with addition of a third drug but have achieved a modest benefit only at the cost of increased toxicity in this cohort of patients with increased comorbidites.[12,13]

The lack of any further significant benefit in OS and ORR with cytotoxic chemotherapy seems unlikely though not impossible and has lead investigators to believe that a plateau has been reached. Therefore, in the era of intense translational research and personalized therapy, the focus of current clinical trials has shifted to integrating molecular targeted therapies into current treatment strategies and to exploiting the molecular abnormalities that are involved in the etiology and pathogenesis of these tumors. The molecular targets currently being evaluated in various Phase II and III clinical trials include the epidermal-derived growth factor receptor (EGFR) with subtypes ERBB-1, ERBB-2 (Her2/neu), ERBB-3 and ERBB-4, vascular endothelial derived growth factor (VEGF) and its receptor (VEGFR), and mammalian target of rapamycin (mTOR). The focus of this review is to evaluate the current evidence for molecular-targeted agents in the management of EGC.

Potential targets and biologic agents

HER2/neu tyrosine kinase receptor

Her2/neu is a member of the ERBB tyrosine kinase (TK) receptor family. Peptide ligands bind to its extracellular domain, leading to receptor homo- and hetero-dimerization followed by auto-phosphorylation of the kinase. Her2/neu has been variably expressed in EGC (AC) (mean 23%; range 0%–43%).[14,15] Approximately 25% of advanced gastric cancers (GCs) (similar to breast cancer) overexpress Her2/neu.[16–18] This variability is presumably related to the differences in Her2/neu testing based on immunohistochemistry (IHC) or fluorescent in-situ hybridization (FISH) and different stages of disease. Her2 positivity is more common in the intestinal type and EGC rather than the diffuse type and pure GC.[19–21] Her2 amplification on FISH is an independent prognostic factor which correlates with the depth of invasion, nodal/distant metastasis, and poor survival.[21–23] There is high concordance observed between HER2 results obtained by both IHC and FISH on primary tumors and corresponding metastases.[24]

Anti-Her2/neu monoclonal antibody (trastuzumab)

Trastuzumab (Herceptin®, Genentech, South San Francisco, CA) is a humanized IgG1 monoclonal antibody targeting the Her2/neu receptor. It acts through several mechanisms, including inhibition of receptor dimerization, increasing receptor endocytosis and degradation, and inducing antibody dependent cytotoxicity.[25] Trastuzumab is approved by the United States Food and Drug Administration (FDA) for the treatment of breast cancer, both in the adjuvant and metastatic settings.[26–29]

Safran et al[30] did a Phase I/II study (n = 19) of trastuzumab in combination with cisplatin and paclitaxel in locally advanced, HER2 overexpressing, esophageal adenocarcinoma. The ORR was 43%, with an OS of 24 months. The 2-year survival was 50%. There was no significant cardiotoxicity related to trastuzumab.

Recently, Bang et al[31] published the results of the Phase III ToGA (Trastuzumab for GC) trial of capecitabine/5-fluorouracil (5-FU) and cispaltin with or without trastuzumab. This was an open-label, international, Phase III, randomized controlled trial and included patients with Her2 overexpressing (by IHC or FISH) GC or GEJ tumors. Participants were randomly allocated in a 1:1 ratio to receive a chemotherapy regimen (capecitabine/5-FU plus cisplatin given every 3 weeks for six cycles) or the same chemotherapy in combination with intravenous trastuzumab. Out of a total of 3807 patients whose tumors were assessed for Her2 positivity, 22.1% were Her2 positive and 594 were randomized. Median follow-up was 18.6 months in the trastuzumab plus chemotherapy group and 17.1 months in the chemotherapy alone group. There was a statistically significant increase in ORR in the trastuzumab-containing arm compared with the chemotherapy alone arm (47.3% versus 34.5%; $P = 0.0017$). The median progression-free survival (PFS) (6.7 versus 5.5 months, hazard ratio [HR] 0.71, 95% confidence interval [CI] 0.59–0.85; $P = 0.0002$) and OS (13.8 months versus 11.1 months $P = 0.0046$, HR = 0.74, 95% CI 0.60–0.91) were also in favor of the trastuzumab-containing arm compared with the chemotherapy alone arm.

In an exploratory post-hoc analysis, the OS was longer in patients with high expression of Her2 compared with those with low Her2 expression.[31] This analysis suggested that in patients with the highest levels of HER2 protein expression (HER2 2+ and FISH positive, HER2 3+ and FISH positive), trastuzumab conferred an even greater survival benefit than that observed for the intention-to-treat population (16.0 versus 11.8 months; HR 0.65). This treatment combination is the first to result in a median survival beyond 1 year and will change the standard of care for HER2-positive GC. Based on these data, trastuzumab has been approved for the treatment of HER2-positive advanced GC in combination with chemotherapy in several countries, including in Australia where it is approved (but not yet subsidized) for first-line HER2-positive advanced GC/GEJ cancers in combination with cisplatin, and either 5-FU or capecitabine. The data suggests that trastuzumab is more effective in the subgroup of patients with IHC 3+ tumors (HR 0.66, 95% CI 0.50–0.87) compared with patients with IHC 2+ tumors (HR 0.78, 95% CI 0.55–1.10). There was also no unexpected toxicity in the trastuzumab arm including symptomatic heart failure; however, there was an increased incidence of asymptomatic decrease in ejection fraction (4.6% versus 1.1%). The quality of life was not compromised in the trastuzumab arm in a recent analysis.[32] Future research should focus on evaluating the role of trastuzumab beyond progression and locally advanced (neo-adjuvant/adjuvant) settings. The pattern of HER2 amplification/overexpression in GC tissue (heterogeneous and frequently focal), and the scoring system used to assess it, differ from that in breast cancer, and consequently, HER2 testing protocols used for breast cancer specimens require modification to be used for GC specimens.[33,34]

Anti-Her2/neu tyrosine kinase inhibitor (lapatinib)

Lapatinib (Tykerb®, GlaxoSmithKline, London, UK) is an orally active, dual TK inhibitor (TKI) with activity against both EGFR (ERBB1) and Her2 (ERBB2). Two Phase II trials have evaluated the role of lapatinib in EGC, but the results have been disappointing. The Southwest Oncology Group (SWOG) performed a Phase II study evaluating the role of lapatinib as monotherapy in the first-line setting in advanced GC patients (n = 47).[35] The partial response rate was only 7%, with a median time to treatment failure and OS of 2 and 5 months respectively. In the second Phase II study, 25 patients with pretreated Her2-positive EGC (through IHC or FISH) were evaluated.[36] The ORR was 0% in 21 evaluable patients, with two patients having stable disease for 5 and 9 months.

Despite the poor ORR from Phase II studies, two Phase III studies are evaluating the role of lapatinib in conjunction with chemotherapy: LOGIC Trial (lapatinib in combination with capecitabine and oxaliplatin as first line) and TYTAN trial (lapatinib in combination with weekly paclitaxel as second line). The clinical trials of anti-Her2/neu agents in EGC are summarized in Table 1.

EGFR

EGFR (or ERBB1) is a member of the ERBB TK receptors. Ligand binding to the extracellular domain of the TK receptor leads to its activation and subsequent homo-dimerization, followed by auto-phosphorylation of the intracellular signaling cascade including RAS/RAF/MAP kinase pathway. These pathways play an important role in angiogenesis, cell survival and proliferation, apoptosis, and metastasis.

Abnormal expression and activating mutations of EGFR have been reported in EGC, eg, EGFR overexpression by IHC/SISH occurs in 50%–63% of patients with GC.[37] Overexpression of EGFR is a poor prognostic indicator in EGC with poorly differentiated histology, depth of invasion, and shorter survival.[38] EGFR overexpression is more commonly associated with SCC histology than AC.

Table 1 Clinical trials of anti-Her2/neu agents in EGC

Author	Phase	Histology	Stage	Treatment	No of patients	ORR or pCR rate	TTP/PFS (months)	OS (months)
Bang et al[31]	III	AC	LA (20) Met (584)	5-FU/capecitabine + cisplatin versus 5-FU/capecitabine + cisplatin + trastuzumab	290 versus 294	34.5% versus 47.3%	5.5 versus 6.7	11.1 versus 13.8
Safran et al[30]	I/II	AC	LA	Trastuzumab + cisplatin/paclitaxel/RT	19	43%	NS	24
Iqbal et al[35]	II	AC	Met	Lapatinib	47	7%	2	5
Hecht et al[36]	II	AC	Met	Lapatinib	25	0%	NS	NS

Abbreviations: 5-FU, 5-fluorouracil; EGC, esophagogastric cancer; NS, not stated; ORR, overall response rate; TTP, time to progression; PFS, progression-free survival; OS, overall survival; pCR, pathological complete response; AC, adenocarcinoma; LA, locally advanced; Met, metastatic; RT, radiotherapy.

Another oncogene downstream of EGFR is KRAS. The predictive value of KRAS status to anti-EGFR therapy has been well validated in metastatic colorectal cancer.[39,40] At present, none of the trials evaluating the EGFR-targeted therapies are restricted to patients with wild-type KRAS tumors, as the frequency of KRAS mutations in GC is expected to be low (around 5%),[41] and there are currently no data to suggest that KRAS gene mutation is predictive of lack of response to EGFR-targeted monoclonal antibody therapy in this tumor type.

Anti-EGFR monoclonal antibodies

Cetuximab

Cetuximab (Erbitux®, ImClone Systems, New York, NY) is a partially humanized murine IgG1 monoclonal antibody that blocks the binding of protein ligands to the EGFR and its activation.[42] Various other proposed mechanisms of action of cetuximab include receptor internalization through endocytosis and immune-mediated mechanisms including antibody-dependent cytotoxicity, complement-dependent cytotoxicity, and complement-dependent cell-mediated cytotoxicity.[43,44] It is currently FDA approved in the management of metastatic colorectal cancer as monotherapy or combination therapy and in conjunction with radiotherapy (RT) in the management of head and neck SCC.[45,46]

Cetuximab is the most extensively studied anti-EGFR monoclonal antibody in the management of EGC, both in the locally advanced and metastatic settings as first- or second-line therapy. Cetuximab has been evaluated in the locally advanced setting in six clinical trials. It has been used in combination with various cytotoxic regimens and RT preoperatively (4/6),[47–50] monotherapy with RT preoperatively (1/6),[51] and in combination with cytotoxic therapy and RT both preoperatively and postoperatively (1/6).[52] The results from these trials should be interpreted with caution as the findings are preliminary and time to progression (TTP) and OS data are awaited. The ORR/pathological complete response (pCR) rates range from 13%–40% across these trials. The results have been summarized in Table 2. With the exception of the trial by Ma et al[52] (100% grade 3/4 serious adverse event rate and lower pCR), the toxicity profile in these trials have been consistent with other combined chemoradiotherapy trials.

Cetuximab has been evaluated in the first-line metastatic setting in combination with other cytotoxic therapies in numerous trials. The chemotherapy backbone used in these trials includes FOLFIRI (two weekly bolus 5-FU/leucovorin/irinotecan and infusional 5-FU),[53] 5-FU/cisplatin,[54] continuous infusion high-dose 5-FU/leucovorin/cisplatin,[55] capecitabine/cisplatin,[56] cisplatin/docetaxel,[57] oxaliplatin/irinotecan,[58] FUFOX (weekly oxaliplatin/leucovorin/infusional 5-FU),[59] FUFIRI regimen (weekly irinotecan/infusional 5-FU/leucovorin),[60] and mFOLFOX.[61] The results of these trials are summarized in Table 3. These results are promising, with ORR of 40%–69%, TTP 5.0–8.5 months, and OS of 9.5–17.0 months across these eight trials. The toxicity in these trials has been consistent with known side-effect profiles of the chemotherapy backbone used, along with additive toxicity from cetuximab (grade 3/4: diarrhea 4%–33%, skin toxicity 6%–24%, infusion reactions/anaphylaxis $< 5\%$).

Tumor overexpression of EGFR has been associated with a poorer prognosis in GC.[62] Overexpression of EGFR by IHC/SISH was not a prerequisite for most of these trials, except the trial by Pinto et al.[53] Therefore, the impact of EGFR positivity on response remains unclear. Even in the study by Pinto et al,[53] evaluating the combination of FOLFIRI and cetuximab, there was no correlation between the degree of EGFR positivity and treatment response. Similar results were also noted by Lordick et al[59] when they evaluated a combination of cetuximab with 5-FU/leucovorin/oxaliplatin (FUFOX). In contrast, Han et al[61] in their trial of cetuximab in combination with modified 5-FU/leucovorin/oxaliplatin (mFOLFOX-6), noted that patients with EGFR-positive tumors and low EGF/TGF alpha levels (n = 11) had an ORR of 100% compared with only 37% in the remaining patients (n = 27) with EGFR-negative tumors ($P \leq 0.001$).

The studies evaluating combination of cetuximab with other chemotherapeutic agents in previously treated EGC have been disappointing, with the best ORR of only 11% in the SWOG study.[63–65] These studies are summarized in Table 3. Currently, cetuximab is being evaluated in an open-label Phase III study in combination with capecitabine and cisplatin versus capecitabine/cisplatin alone (EXPAND-NCT00678535; Phase III; CX +/− cetuximab) as a first-line therapy in the management of advanced GC/GEJ AC.

Panitumumab

Panitumumab (Vectibix®, Amgen, Thousand Oaks, CA) is a fully humanized IgG2 anti-EGFR monoclonal antibody. It is currently FDA approved for the management of metastatic colorectal cancer.[66] It has not been evaluated as extensively as cetuximab in the management of EGC; however, a Phase III study is being conducted in the UK to determine whether adding panitumumab to epirubicin, oxalipaltin, and capecitabine (EOX) prolongs OS (REAL3 – NCT00824785; Phase III; EOX +/− panitumumab). Another study currently open

Table 2 Clinical trials of cetuximab in EGC

Author	Phase	Histology	Stage	Treatment	No of patients	ORR or pCR rate	TTP/PFS (months)	OS (months)
Enzinger et al[47]	II	AC	LA	Cetuximab + cisplatin/irinotecan/RT	17	13%	NS	NS
Safran et al[48]	II	AC/SCC	LA	Cetuximab + carbolatin/paclitaxel/RT	60	27%	NS	NS
Ruhstaller et al[50]	II	AC/SCC	LA	Cetuximab + cisplatin/docetaxel/RT	28	32%	NS	NS
De Vita et al[49]	II	AC/SCC	LA	Cetuximab + FOLFOX/RT	27	40%	NS	NS
Agrawala et al[51]	II	AC/SCC	LA	Cetuximab + RT	40	36%	NS	NS
Ma et al[52]	II	AC	LA	Cetuximab + cisplatin/irinotecan + surgery → Cetuximab + 5-FU/LV/RT	20	0%	NS	NS
Lordick et al[59]	II	AC	Met	Cetuximab + FUFOX	52	65 (of 46)	7.6	9.5
Pinto et al[57]	II	AC	Met	Cetuximab + cisplatin/docetaxel	48	41 (of 42)	NS	NS
Zhang et al[56]	II	AC	Met	Cetuximab + cisplatin/capecitabine	49	48 (of 47)	5.2	NS
Han et al[61]	II	AC	Met	Cetuximab + FOLFOX	40	50	5.5	9.9
Yeh et al[55]	II	AC	Met	Cetuximab + high dose 5-FU/LV/cisplatin	35	69	11	14
Woell et al[58]	II	AC	Met	Cetuximab + oxaliplatin/irinotecan	51	63% (of 35)	6.2	9.5
Lorenzen et al[54]	II	SCC	Met	Cetuximab + 5-FU/cisplatin versus 5-FU/cisplatin	32 versus 30	19% versus 13%	5.7 versus 3.6	9.5 versus 5.5
Pinto et al[53]	II	AC	Met/UR	Cetuximab + FOLFIRI (FOLCETUX)	38	44% (of 34)	8	16
Kanzler et al[60]	II	AC	Met	Cetuximab + FUFIRI	49	42% (of 48)	8.5	16.6

Abbreviations: EGC, esophagogastric cancer; 5-FU, 5-fluorouracil; FOLFIRI, two weekly bolus 5-FU/leucovorin, irinotecan, infusional 5-FU; FUFIRI, weekly irinotecan/leucovorin/infusional; 5-FU FUFOX, weekly oxaliplatin/leucovorin/infusional 5-FU; LV, leucovorin; RT, radiation therapy; NS, not stated; ORR, overall response rate; TTP, time to progression; PFS, progression-free survival; OS, overall survival; pCR, pathological complete response; AC, adenocarcinoma; SCC, squamous cell carcinoma; LA, locally advanced; Met, metastatic; UR, unresectable.

Table 3 Clinical trials of anti-VEGF agents

Author	Phase	Histology	Stage	Treatment	No of patients	ORR or pCR rate	TTP/PFS (months)	OS (months)
Ohtsu et al[88]	III	AC	Met/UR	5-FU/capecitabine + cisplatin + placebo versus 5-FU/capecitabine + cisplatin + bevacizumab	387 versus 387	29.5% versus 38%	5.3 versus 6.7	10.1 versus 12.1
Shah et al[84]	I/II	AC	Met	Bevacizumab + cisplatin/irinotecan	47	65%	8.3	12.3
Kelsen et al[86]	II	AC	Met	Bevacizumab + docetaxel/cisplatin/5-FU	44	67% (of 37)	12	16.2
Enzinger et al[87]	II	AC/SCC	Met	Bevacizumab + docetaxel/cisplatin/irinotecan	32	63% (of 30)	NS	NS
Bang et al[91]	II	AC	Met	Sunitinib	42	2.6%	2.3	6.8
Sun et al[95]	II	AC	Met/UR	Sorafenib + docetaxel/cisplatin	44	38.5%	5.8	14.9

Abbreviations: 5-FU, 5-fluorouracil; NS, no stated; ORR, overall response rate; TTP, time to progression; PFS, progression-free survival; OS, overall survival; pCR, pathological complete response; AC, adenocarcinoma; SCC, squamous cell carcinoma; LA, locally advanced; Met, metastatic; UR, unresectable; VEGF, vascular endothelial derived growth factor.

to recruitment (NEOPECX) is an open-label randomized controlled Phase II trial of panitumumabin in combination with epirubicin, cisplatin, and capecitabine (ECX) versus chemotherapy alone in patients with locally advanced GC/GEJ tumors.

Matuzumab

Matuzumab (EMD 72000, Merck) is a humanized monoclonal antibody targeting the EGFR. It has been evaluated in a Phase I study in combination with epirubicin, cisplatin, and capecitabine (ECX) as a first-line therapy for patients with EGFR-positive EGC.[67] The response to different doses of matuzumab was 57% (four partial responses and two stable disease) with 400 mg and 43% (three partial responses and two stable disease) with 800 mg. The major dose limiting toxicity was grade 3 fatigue. A Phase II study looking at a combination of matuzumab and ECX has recently completed recruitment (MATRIX EG).

Anti- EGFR tyrosine kinase inhibitors

Erlotinib

Erlotinib (Tarceva®, Genentech) is an oral small molecule TKI. It inhibits the binding of adenosine triphosphate to the TK domain of the EGFR, leading to cessation of downstream autophosphorylation and signal transduction. It is currently FDA approved for the management of advanced non-small cell lung cancer and pancreatic cancer.[68,69]

A Phase II study conducted by the SWOG evaluated erlotinib in the first-line setting in the management of GC (n = 26) and GEJ tumors (n = 44).[70] There were no responses in the GC patients, and the ORR was only 9% (one complete response and two partial responses) in the GEJ tumors. The reason for the apparent differential sensitivity of GEJ and GC to EGFR blockade using erlotinib is unclear.

The TTF and OS were 2 months and 6.7 months respectively in the GEJ tumor group. No EGFR gene mutation was detected in the 54 samples analyzed in this trial.

Gefitinib

Gefitinib (Iressa®, AstraZeneca Pharmaceuticals, London, UK) is another oral small molecule TKI. It is currently approved in the management of advanced non-small cell lung cancer.[71]

Rodriguez et al[84] assessed the efficacy of gefitinib in combination with cisplatin/5-FU and RT (n = 80) to chemo-RT alone (n = 93) in a Phase II trial of patients with EGC. There was a trend towards improved 3-year OS rates in favor of gefitinib arm (40% versus 28%; $P = 0.07$). Toxicity profiles were similar in both the arms.

In another Phase II study, gefitinib was evaluated in the second-line setting in 28 patients.[72] The partial response rate was 3% and stable disease in 28%. The TTP and OS were 2.0 and 5.5 months respectively. There was a nonsignificant trend towards improved outcome in patients with high EGFR expression compared with low EGFR expression (TTP 5.1 months versus 1.8 months and OS 7.8 months versus 2.8 months).[73]

In all the trials of oral TKIs as monotherapy or combination therapy, there has been no significant additional toxicity associated with the use of TKIs. However, they have limited activity as monotherapy in both the first- and second-line setting in the management of EGC. From the available evidence, it seems that patients with squamous histology, high EGFR expression, and esophageal/GEJ tumors are more likely to have any meaningful response to TKIs, but these tumors are rarely of squamous type.

VEGFR

Our increasing understanding of the pathogenesis of tumor biology in most solid tumors has led us to believe that there is a strong link between tumor growth, distant metastasis, and angiogenesis.[74] VEGF is the most potent and specific pro-angiogenic factor regulating endothelial cell mitogenesis and migration, induction of proteinases, increased vascular permeability, and maintaining survival of newly formed blood vessels.[75] It exerts its angiogenic effect by binding to various transmembrane receptors, more specifically VEGFRs type 1 (VEGFR-1) and 2 (VEGFR-2).[76]

VEGF is overexpressed in 30%–60% of EGCs, and elevated levels of VEGF in the serum and tumor are associated with poor prognosis in EGCs.[77–81] There is also evidence to support in esophageal AC that higher VEGF expression correlates with transition from Barrett's esophagus to high grade dysplasia and from micro-invasive disease to locally advanced cancer.[82,83]

Anti-VEGF monoclonal antibodies

Bevacizumab

Bevacizumab (Avastin®, Genentech) is a humanized IgG1 monoclonal antibody-targeting VEGF. It is currently FDA approved for the management of advanced colorectal cancer, non-small cell lung cancer, glioblastoma multiforme, and metastatic renal cell carcinoma.

Multiple Phase II studies have looked at the role of bevacizumab in combination with chemotherapy as the initial treatment for patients with advanced GC/GEJ tumors. The early results from these studies have been encouraging.

Shah et al[85] from Memorial Sloan-Kettering Cancer Centre (MSKCC) looked at a combination of bevacizumab with cisplatin and irinotecan in the first-line management of advanced GC/GEJ AC (n = 47). The results were encouraging, with an ORR 65%, TTP 8.3 months (compared with TTP in historical controls of 5 months) and OS of 12.3 months. Toxicities related to the use of bevacizumab were: gastric perforation/near perforation 6%, myocardial infarction 2%, grade 3/4 thromboembolic events 25.5%.[86] The same group from MSKCC also evaluated bevacizumab in combination with a modified regimen of docetaxel/cisplatin/5-FU (mDCF) in chemo-naïve patients (n = 44) and reported ORR of 67%, PFS of 12 months, and OS of 16.2 months in 39 patients with measurable disease.[87] The toxicity profile of the mDCF was better than the original DCF,[13] with febrile neutropenia rates of 4% versus 29% respectively. The side effects attributed to bevacizumab included: grade 3/4 thromboembolism 31% and gastric perforation/bleeding 2%. The studies evaluating bevacizumab in the first-line setting in combination with chemotherapy are summarized in Table 3.

Bevacizumab has also been tested in the second-line setting in a small study by Enzinger et al[88] in combination with docetaxel. The ORR was 24% (17 patients evaluated). Bevacizumab-attributed grade 3/4 serious adverse events (SAEs) included: gastrointestinal bleeding (12%) and arterial thrombosis (8%).

Due to the encouraging results with bevacizumab in conjunction with chemotherapy, both in the first- and second-line settings, a confirmatory Phase III trial (AVAGAST) was conducted.[89] The AVAGAST trial was a multinational, randomized, placebo-controlled trial designed to evaluate the efficacy of bevacizumab in combination with capecitabine/cisplatin in the first-line treatment of advanced GC/GEJ tumors (n = 774). The OS (primary end point) was 12.1 months with bevacizumab plus capecitabine/5-FU-cisplatin and 10.1 months with placebo plus capecitabine/5-FU-cisplatin (HR 0.87; 95% CI, 0.73–1.03; $P = 0.1002$). Although the primary endpoint (OS) was not met, both ORR (46.0% versus 37.4%; $P = 0.0315$) and median PFS (6.7 versus 5.3 months; HR 0.80; 95% CI, 0.68–0.93; $P = 0.0037$) were significantly improved with bevacizumab versus placebo. The incidence of venous and arterial thrombosis did not differ between the two groups. Although the rates of hypertension and bleeding were slightly higher in the bevacizumab arm, most of the bleeding was grade 1 nasal bleeding.

There were significant regional differences in the outcome in an unplanned subset analysis. The Asian population had the longest OS (12.1 months), but the smallest impact from addition of bevacizumab (HR, 0.97; 95% CI, 0.75–1.25) compared with the Pan-American population (which contributed only one-fifth of patients to the whole group) who had the shortest OS (6.8 months) but the greatest impact from addition of bevacizumab (median, 11.5 versus 6.8 months for placebo-chemotherapy; HR, 0.63; 95% CI, 0.43–0.94). The potential explanations forwarded for these differences were that the Asian population had low incidence of junctional tumors, low frequency of liver metastases, and a higher proportion of them received second-line chemotherapy compared with the American group (66% versus 21%).

In the UK, another Phase III study [Medical Research Council Adjuvant Gastric Infusional Chemotherapy trial (MAGIC)-B] is currently recruiting patients to determine the efficacy of adding bevacizumab to chemotherapy (ECX) in the peri-operative setting.

Ramucirumab

Ramucirumab (IMC-1121B, ImClone Systems Corporation) is a fully humanized, IgG1 monoclonal antibody targeting VEGFR-2. It is currently being tested in a randomized, double-blind placebo-controlled trial in patients with metastatic GC/GEJ AC who have failed first-line chemotherapy with a platinum agent or fluoropyrimidine.

Anti-VEGF TKIs

Three anti-VEGF TKIs have been evaluated in EGC: sunitinib, sorafenib, telatinib.

Sunitinib

Sunitinib (Sutent®, Pfizer, New York, NY) is an oral multi-targeted TKI with activity against VEGFR, platelet derived growth factor (PDGFR), RET, c-kit, and Flt-3. It is currently FDA approved for the treatment of metastatic renal cell carcinoma and gastrointestinal stromal tumors.[90,91]

Sunitinib has been tested in two Phase II trials. Bang et al[92] evaluated sunitinib as a second-line therapy in advanced GC/GEJ AC. Two patients had a partial response, and 25 had stable disease with PFS and OS of 2.3 and 6.8 months respectively. Moehler et al[93] also examined sunitinib in previously treated GC and reported disease control in 5/14 patients. The toxicity with sunitinib was manageable in both these studies, with the common SAEs being thrombocytopenia, anorexia, nausea, and fatigue.

Sorafenib

Sorafenib (Nexavar®, Bayer, Leverkusen, Germany) is another oral multikinase inhibitor, with activity against both intracellular RAF-kinases (CRAF, BRAF) and cell surface kinase receptors (VEGFR-1 to 3, PDGFR-beta, RET, Flt-3, and c-kit). It is currently FDA approved for advanced renal cell carcinoma and hepato-cellular carcinoma.[94,95]

Sorafenib has been tested by the Eastern Cooperative Oncology group (ECOG) in a Phase II study in combination with cisplatin/docetaxel (n = 44) in the management of metastatic/unresectable GC/GEJ AC.[96] The results were encouraging, with an ORR of 38.5%, TTP of 5.8 months, and OS of 14.9 months. Grade 3 or 4 neutropenia occurred in 49% of patients.

Telatinib

Telatinib is also an oral small molecule TKI with selective inhibitory effect against VEGFR and PDGFR. It is not currently FDA approved. Ko et al[97] conducted a Phase II study of telatinib in combination with capecitabine/cisplatin as first-line treatment in patients with advanced GC/GEJ tumors. The best response in the seven patients evaluated included two with partial response and four with stable disease. One patient progressed while on treatment. Grade 3 SAEs that have been reported so far include hand-foot syndrome, fatigue, hypertension, anorexia, febrile neutropenia, and pulmonary embolism. No grade 4 SAEs have been recorded so far.

The clinical trials of anti-VEGF agents are summarized in Table 3.

Mammalian target of rapamycin (mTOR)

Mammalian target of rapamycin (mTOR) serine-threonine kinase is a downstream component of the phosphatidylinositol 3-kinase/Aktkinase signaling pathway. This pathway regulates cellular metabolism and growth by acting as a cellular sensor for nutrients and growth factors. Upregulation of this pathway has been associated with worse prognosis in GC[98] and also in squamous cell esophageal cancer.[99] It has been postulated to contribute to chemotherapy resistance.[100]

Everolimus (Afinitor®, Novartis, Basel, Switzerland) blocks the mTOR pathway by forming a complex with the immunophilin FK506-binding protein-12. It is currently FDA approved for use in progressive neuroendocrine tumors of pancreatic origin and advanced renal cell carcinoma after failure of first-line sunitinib or sorafenib. Phase I data exist showing marked tumor response to everolimus in esophageal carcinoma;[101] however, as yet no Phase II data are available investigating its use in esophageal cancer.

More progress has been made investigating the use of everolimus in metastatic gastric cancer. Doi et al[102] reported a Phase II study of everolimus in this population with promising results. Fifty-three patients who had previously received chemotherapy for metastatic GC received everolimus. There were no complete or partial responses in this trial; however, 45% of patients had a reduction in tumor size from baseline. Furthermore, OS was 10.1 months, which compares favorably with other single-agent trials,[103,104] where OS ranges from 3.5 to 7.2 months and combination trials,[105,106] where OS ranges from 6.0 to 10.7 months. Recently, the results of the Phase III GRANITE-1study evaluating the role of everolimus in previously treated advanced GC patients were released at the ASCO GI 2012 meeting, concluding that everolimus monotherapy does not significantly improve the OS and PFS.[107] A total of 656 patients with advanced GC were randomized in 2:1 fashion to everolimus/best supportive care compared with placebo/best supportive care. The OS was 5.39 months with everolimus compared with 4.34 months in the placebo arm (HR, 0.90; 95% CI, 0.75–1.08; $P = 0.1244$). Median PFS per local investigator assessment was 1.68 and 1.41 months with everolimus and placebo respectively (HR, 0.66; 95% CI, 0.56–0.78; $P < 0.0001$). The ORR was also not very encouraging (4.5% with everolimus versus 2.1% with placebo).

Novel targets

Marimastat

Marimastat is an MMP inhibitor and has been tested in a Phase III study (compared with placebo) including 369 patients with inoperable/metastatic GC/GEJ AC.[108] There was a small but statistically significant improvement in OS (160 versus 138 days; $P = 0.02$) and 2-year survival (9% versus 3%), favoring the marimastat arm. However, this drug's further development has stopped.

Foretinib

Another novel target, c-MET, which is a receptor for hepatocyte growth factor is currently under evaluation.[109] The c-MET oncogene is amplified in 10%–15% of GC, and its overexpression has been associated with poor prognosis.[110,111] Foretinib is an oral TKI with activity against VEGFR-2 and c-MET. It was evaluated at two different doses in a Phase II study (n = 64) involving previously treated patients with EGC.[108] The ORR was 0%, with stable disease in 21% and 25% of patients in each dose cohort. Amplification of c-MET was lower than expected (5%) in this study, and future studies are planned limiting the use of foretinib in patients with c-MET amplification only.

Bryostatin

Bryostatin-1 is an inhibitor of protein kinase C, which plays a role in mediation of anti-apoptotic signals.[112] Two Phase II studies have evaluated sequential taxol and bryostatin in EGC. Grade 3/4 myalgias occurred in about half of the patients, leading to cessation of further development of this drug.[113,114]

Cyclo-oxygenase-2 inhibitors

Cyclo-oxygenase-2 (COX-2) is an enzyme involved in the prostaglandin synthesis and malignant transformation of Barrett's esophagus. The use of aspirin and other nonsteroidal agents have been associated with lower esophageal cancer rates. In a meta-analysis including nine studies with more than 1800 patients, there was 43% risk reduction of developing esophageal cancer with these agents.[115] However, the chemoprevention for Barrett's esophagus trial did not find any difference in the primary outcome – change from baseline to 48 weeks of therapy in the proportion of biopsy specimens with dysplasia in the celecoxib and placebo arms.[116] The criticism of this study was the short treatment duration and follow up, but the negative results in conjunction with the known cardiotoxicity of COX-2 inhibitors[117] makes routine use of these agents as chemoprevention inappropriate.

Other novel agents

Studies are ongoing with other novel agents targeting insulin-like growth factor receptor (IGF), its ligand IGF-1, and telomerase enzyme.[118]

Conclusion

In conclusion, the prognosis associated with advanced EGC remains poor. Various molecular targeted therapies have been evaluated in clinical trials with trastuzumab now becoming a standard treatment option for patients with Her2-positive EGC. Further research in this field is urgently needed to improve outcomes for patients.

Disclosure

The authors have no conflicts of interest to declare.

References

1. Blot WJ, Devesa SS, Kneller RW, Fraumeni JF Jr. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. *JAMA.* 1991;265(10):1287–1289.
2. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin.* 2009;59(4):225–249.
3. Bollschweiler E, Wolfgarten E, Gutschow C, Holscher AH. Demographic variations in the rising incidence of esophageal adenocarcinoma in white males. *Cancer.* 2001;92(3):549–555.
4. Brown LM, Devesa SS. Epidemiologic trends in esophageal and gastric cancer in the United States. *Surg Oncol Clin N Am.* 2002;11(2):235–256.
5. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin.* 2011;61(2):69–90.
6. Orringer MB, Marshall B, Iannettoni MD. Transhiatal esophagectomy: clinical experience and refinements. *Ann Surg.* 1999;230(3):392–400; discussion 400–403.
7. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med.* 2006;355(1):11–20.
8. Tepper J, Krasna MJ, Niedzwiecki D, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. *J Clin Oncol.* 2008;26(7):1086–1092.
9. Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TP. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. *N Engl J Med.* 1996;335(7):462–467.
10. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med.* 2001;345(10): 725–730.
11. Enzinger PC, Mayer RJ. Esophageal cancer. *N Engl J Med.* 2003;349(23): 2241–2252.
12. Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med.* 2008;358(1): 36–46.
13. Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol.* 2006;24(31):4991–4997.
14. al-Kasspooles M, Moore JH, Orringer MB, Beer DG. Amplification and over-expression of the EGFR and erbB-2 genes in human esophageal adenocarcinomas. *Int J Cancer.* 1993;54(2):213–219.
15. Ross JS, Sheehan CE, Fletcher JA. Her-2/neu oncogene amplification determined by fluorescence in situ hybridization. *Methods Mol Med.* 2001;49:93–104.
16. Liang Z, Zeng X, Gao J, et al. Analysis of EGFR, HER2, and TOP2A gene status and chromosomal polysomy in gastric adenocarcinoma from Chinese patients. *BMC Cancer.* 2008;8:363.
17. Bang Y, Chung H, Xu J, et al. Pathological features of advanced gastric cancer (GC): relationship to human epidermal growth factor receptor 2 (HER2) positivity in the global screening programme of the ToGA trial. *J Clin Oncol.* 2009;27:15s.
18. León-Chong J, Lordick F, Kang YK, et al. HER2 positivity in advanced gastric cancer is comparable to breast cancer. *J Clin Oncol.* 2007;25: 15057.
19. Gravalos C, Màrquez A, Garcia-Carbonero R, et al. Correlation between Her2/neu over-expression/amplification and clinicopathological parameters in advanced gastric cancer patients: a prospective study. *Gastrointestinal Cancer Symposium.* 2007;120:A89.
20. Kang Y, Bang Y, Lordick F, et al. Incidence of gastric and gastroesophageal cancer in the ToGa trial: correlation with HER2 positivity. *Gatrointestinal Cancers Symposium.* 2008;75:A11.
21. Tanner M, Hollmen M, Junttila TT, et al. Amplification of HER-2 in gastric carcinoma: association with Topoisomerase IIalpha gene amplification, intestinal type, poor prognosis and sensitivity to trastuzumab. *Ann Oncol.* 2005;16(2):273–278.
22. Park DI, Yun JW, Park JH, et al. HER-2/neu amplification is an independent prognostic factor in gastric cancer. *Dig Dis Sci.* 2006;51(8): 1371–1379.
23. Brien TP, Odze RD, Sheehan CE, McKenna BJ, Ross JS. HER-2/neu gene amplification by FISH predicts poor survival in Barrett's esophagus-associated adenocarcinoma. *Hum Pathol.* 2000;31(1): 35–39.
24. Bozzetti C, Negri FV, Lagrasta CA, et al. Comparison of HER2 status in primary and paired metastatic sites of gastric carcinoma. *Br J Cancer.* 2011;104(9):1372–1376.

25. Hudis CA. Trastuzumab – mechanism of action and use in clinical practice. *N Engl J Med.* 2007;357(1):39–51.
26. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med.* 2005;353(16):1659–1672.
27. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med.* 2005;353(16):1673–1684.
28. Cobleigh MA, Vogel CL, Tripathy D, et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. *J Clin Oncol.* 1999;17(9):2639–2648.
29. Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. *J Clin Oncol.* 2002;20(3):719–726.
30. Safran H, Dipetrillo T, Akerman P, et al. Phase I/II study of trastuzumab, paclitaxel, cisplatin and radiation for locally advanced, HER2 overexpressing, esophageal adenocarcinoma. *Int J Radiat Oncol Biol Phys.* 2007;67(2):405–409.
31. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet.* 2010;376(9742):687–697.
32. Satoh T, Leon J, Lopez RI, et al. Quality of life results from a Phase III trial of trastuzumab plus chemotherapy in first-line HER2-positive advanced gastric and GE junction cancer. Proceedings of the Gastrointestinal Cancer Symposium; 2010:A7.
33. Albarello L, Pecciarini L, Doglioni C. HER2 testing in gastric cancer. *Adv Anat Pathol.* 2011;18(1):53–59.
34. Bilous M, Osamura RY, Ruschoff J, et al. HER-2 amplification is highly homogenous in gastric cancer. *Hum Pathol.* 2010;41(2):304–305; author reply 305–306.
35. Iqbal S GB, Lenz H, et al. S0413: a Phase II SWOG study of GW572016 (lapatinib) as first line therapy in patients with advanced or metastatic gastric cancer. *J Clin Oncol.* 2007:25.
36. Hecht JR, Urba SG, Koehler M, et al. Lapatinib monotherapy in recurrent upper gastrointestinal malignancy: Phase II efficacy and biomarker analyses. Proceedings of the Gastrointestinal Cancer Symposium; 2008:A43.
37. Rojo F Albanell J, Sauleda S, et al. Characterization of epidermal growth factor (EGF) receptor and transforming growth factor (TGF) alpha expression in gastric cancer and its association with activation of mitogen-activated protein kinase (MAPK). *Proc Am Soc Clin Oncol.* 2001;20(abstr 1717).
38. Gamboa-Dominguez A, Dominguez-Fonseca C, Quintanilla-Martinez L, et al. Epidermal growth factor receptor expression correlates with poor survival in gastric adenocarcinoma from Mexican patients: a multivariate analysis using a standardized immunohistochemical detection system. *Mod Pathol.* 2004;17(5):579–587.
39. Amado RG, Wolf M, Peeters M, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol.* 2008;26(10):1626–1634.
40. Van Cutsem E, Kohne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med.* 2009;360(14):1408–1417.
41. Liu Z, Liu L, Li M, et al. Epidermal growth factor receptor mutation in gastric cancer. *Pathology.* 2011;43(3):234–238.
42. Goldstein NI, Prewett M, Zuklys K, Rockwell P, Mendelsohn J. Biological efficacy of a chimeric antibody to the epidermal growth factor receptor in a human tumor xenograft model. *Clin Cancer Res.* 1995;1(11):1311–1318.
43. Kawaguchi Y, Kono K, Mimura K, Sugai H, Akaike H, Fujii H. Cetuximab induce antibody-dependent cellular cytotoxicity against EGFR-expressing esophageal squamous cell carcinoma. *Int J Cancer.* 2007;120(4):781–787.
44. Imai K, Takaoka A. Comparing antibody and small-molecule therapies for cancer. *Nat Rev Cancer.* 2006;6(9):714–727.
45. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med.* 2004;351(4):337–345.
46. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med.* 2006;354(6):567–578.
47. Enzinger PC, Yock T, Suh W, et al. Phase II cisplatin, irinotecan, cetuximab and concurrent radiation therapy followed by surgery for locally advanced esophageal cancer. *J Clin Oncol.* 2006;24(Suppl 18):4064.
48. Safran H, Suntharalingam M, Dipetrillo T, et al. Cetuximab with concurrent chemoradiation for esophagogastric cancer: assessment of toxicity. *Int J Radiat Oncol Biol Phys.* 2008;70(2):391–395.
49. De Vita F, Orditura M, Innocente R, et al. Induction primary CT with Folfox-4 and cetuximab followed by RT and cetuximab in locally advanced esophageal cancer (LAEC): analysis of preliminary data from B152 Trial. *J Clin Oncol.* 2008;26(Suppl):Abstr 15524.
50. Ruhstaller T, Pless M, Schuller J, et al. Cetuximab in combination with chemoradiotherapy prior to surgery in patients with resectable, locally advanced esophageal carcinoma: a prospective, multicenter Phase lb-ll trial of the Swiss Group for Clinical Cancer Research (SAKK 75/06). *J Clin Oncol.* 2009;27(Suppl 15):Abstr 4570.
51. Agarwala A, Hanna N, McCollum A, et al. Preoperative cetuximab and radiation (XRT) for patients (pts) with surgically resectable esophageal and gastroesophageal junction (GEJ) carcinomas: a pilot study from the Hoosier Oncology Group and the University of Texas Southwestern. *J Clin Oncol.* 2009;27(Suppl 15):Abstr 4557.
52. Ma HY, Ryan T, Newman E, et al. Neoadjuvant therapy of gastric cancer with irinotecan, cisplatin, and cetuximab followed by surgical resection and adjuvant chemoradiation. Proceedings of the Gastrointestinal Cancer Symposium; 2009:A58.
53. Pinto C, Di Fabio F, Siena S, et al. Phase II study of cetuximab in combination with FOLFIRI in patients with untreated advanced gastric or gastroesophageal junction adenocarcinoma (FOLCETUX study). *Ann Oncol.* 2007;18(3):510–517.
54. Lorenzen S, Schuster T, Porschen R, et al. Cetuximab plus cisplatin-5-fluorouracil versus cisplatin-5-fluorouracil alone in first-line metastatic squamous cell carcinoma of the esophagus: a randomized Phase II study of the Arbeitsgemeinschaft Internistische Onkologie. *Ann Oncol.* 2009;20(10):1667–1673.
55. Yeh K, Hsu C, Hsu C, et al. Phase II study of cetuximab plus weekly cisplatin and 24-hour infusion of high-dose 5-fluorouracil and leucovorin for the first-line treatment of advanced gastric cancer. *J Clin Oncol.* 2009;27(15 Suppl):Abstr 4567.
56. Zhang X, Xu J, Shen L, et al. A phase II study of cetuximab with cisplatin and capecitabine as first-line treatment in advanced gastric cancer. Proceedings of the Gastrointestinal Cancer Symposium; 2009:Abstr LBA39.
57. Pinto C Di Fabio F, Barone C, et al. Cetuximab in combination with cisplatin and docetaxel as first-line treatment in patients with locally advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma (Italian phase II DOCETUX study). *J Clin Oncol.* 2008;26(Suppl):Abstr 4575.
58. Woell E, Greil R, Eisterer W, et al. Oxaliplatin, irinotecan, and cetuximab in advanced gastric cancer. First efficacy results of a multicenter phase II trial (AGMT Gastric-2) of the arbeitsgemeinschaft medikamentoese tumortherapie (AGMT). *J Clin Oncol.* 2009;27(Suppl 15):Abstr 4538.
59. Lordick F, Lorenzen S, Hegewisch-Becker S, et al. Cetuximab plus weekly oxaliplatin/5FU/FA (FUFOX) in 1st line metastatic gastric cancer. Final results from a multicenter phase II study of the AIO upper GI study group. *J Clin Oncol.* 2007;25(Suppl 18):Abstr 4526.
60. Kanzler S, Trarbach T, Seufferlein T, et al. Cetuximab with irinotecan/folinic acid/5-FU as first-line treatment in advanced gastric cancer: a nonrandomized multicenter AIO phase II study. *J Clin Oncol.* 2009;27(Suppl 15):Abstr 4534.

61. Han SW, Oh DY, Im SA, et al. Phase II study and biomarker analysis of cetuximab combined with modified FOLFOX6 in advanced gastric cancer. *Br J Cancer.* 2009;100(2):298–304.
62. Kopp R, Ruge M, Rothbauer E, et al. Impact of epidermal growth factor (EGF) radioreceptor analysis on long-term survival of gastric cancer patients. *Anticancer Res.* 2002;22(2B):1161–1167.
63. Gold P, Goldman B, Iqbal S, et al. Cetuximab as second-line therapy in patients with metastatic esophageal cancer: a Phase II Southwest Oncology Group study. *Gastrointestinal Cancers Symposium.* 2008;26:Abstr 96.
64. Tebbutt N, Sourjina T, Strickland A, et al. ATTAX2 – docetaxel plus cetuximab as second-line treatment for docetaxel refractory oesophago-gastric cancer: final results of a multi-center phase II trial by the AGITG. Proceedings of the Gastrointestinal Cancer Symposium; 2008:Abstr 87.
65. Schønnemann KR, Bjerregaard JK, Jensen HA, et al. Biweekly cetuximab and irinotecan as second-line therapy to patients with platinium-resistant gastroesophageal cancer. Proceedings of the Gastrointestinal Cancer Symposium; 2009:Abstr 73.
66. Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. *J Clin Oncol.* 2007;25(13):1658–1664.
67. Rao S, Starling N, Cunningham D, et al. Phase I study of epirubicin, cisplatin and capecitabine plus matuzumab in previously untreated patients with advanced oesophagogastric cancer. *Br J Cancer.* 2008;99(6):868–874.
68. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med.* 2005;353(2):123–132.
69. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol.* 2007;25(15):1960–1966.
70. Dragovich T, McCoy S, Fenoglio-Preiser CM, et al. Phase II trial of erlotinib in gastroesophageal junction and gastric adenocarcinomas: SWOG 0127. *J Clin Oncol.* 2006;24(30):4922–4927.
71. Fukuoka M, Yano S, Giaccone G, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (The IDEAL 1 Trial) [corrected]. *J Clin Oncol.* 2003;21(12):2237–2246.
72. Janmaat ML, Gallegos-Ruiz MI, Rodriguez JA, et al. Predictive factors for outcome in a phase II study of gefitinib in second-line treatment of advanced esophageal cancer patients. *J Clin Oncol.* 2006;24(10):1612–1619.
73. Ferry DR, Anderson M, Beddard K, et al. A phase II study of gefitinib monotherapy in advanced esophageal adenocarcinoma: evidence of gene expression, cellular, and clinical response. *Clin Cancer Res.* 2007;13(19):5869–5875.
74. Carmeliet P. Angiogenesis in health and disease. *Nat Med.* 2003;9(6):653–660.
75. Ferrara N, Davis-Smyth T. The biology of vascular endothelial growth factor. *Endocr Rev.* 1997;18(1):4–25.
76. Eskens FA, Verweij J. The clinical toxicity profile of vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor (VEGFR) targeting angiogenesis inhibitors; a review. *Eur J Cancer.* 2006;42(18):3127–3139.
77. Inoue K, Ozeki Y, Suganuma T, Sugiura Y, Tanaka S. Vascular endothelial growth factor expression in primary esophageal squamous cell carcinoma. Association with angiogenesis and tumor progression. *Cancer.* 1997;79(2):206–213.
78. Kleespies A, Guba M, Jauch KW, Bruns CJ. Vascular endothelial growth factor in esophageal cancer. *J Surg Oncol.* 2004;87(2):95–104.
79. Shih CH, Ozawa S, Ando N, Ueda M, Kitajima M. Vascular endothelial growth factor expression predicts outcome and lymph node metastasis in squamous cell carcinoma of the esophagus. *Clin Cancer Res.* 2000;6(3):1161–1168.
80. Imdahl A, Bognar G, Schulte-Monting J, Schoffel U, Farthmann EH, Ihling C. Predictive factors for response to neoadjuvant therapy in patients with oesophageal cancer. *Eur J Cardiothorac Surg.* 2002;21(4):657–663.
81. Fondevila C, Metges JP, Fuster J, et al. p53 and VEGF expression are independent predictors of tumour recurrence and survival following curative resection of gastric cancer. *Br J Cancer.* 2004;90(1):206–215.
82. Mobius C, Stein HJ, Becker I, et al. The 'angiogenic switch' in the progression from Barrett's metaplasia to esophageal adenocarcinoma. *Eur J Surg Oncol.* 2003;29(10):890–894.
83. Vallbohmer D, Peters JH, Kuramochi H, et al. Molecular determinants in targeted therapy for esophageal adenocarcinoma. *Arch Surg.* 2006;141(5):476–481; discussion 481–482.
84. Rodriguez C, Adelstein D, Rybicki L, et al. A phase II trial of perioperative concurrent chemoradiotherapy (CCRT) and gefitinib (G) in locally advanced esophagus (E) and gastroesophageal junction (GEJ) cancer. *J Clin Oncol*. 2008;26:4547
85. Shah MA, Ramanathan RK, Ilson DH, et al. Multicenter phase II study of irinotecan, cisplatin, and bevacizumab in patients with metastatic gastric or gastroesophageal junction adenocarcinoma. *J Clin Oncol.* 2006;24(33):5201–5206.
86. Shah MA, Ilson D, Kelsen DP. Thromboembolic events in gastric cancer: high incidence in patients receiving irinotecan- and bevacizumab-based therapy. *J Clin Oncol.* 2005;23(11):2574–2576.
87. Kelsen D, Jhawer M, Ilson D, et al. Analysis of survival with modified docetaxel, cisplatin, fluorouracil (mDCF), and bevacizumab (BEV) in patients with metastatic gastroesophageal (GE) adenocarcinoma: results of a phase II clinical trial. *J Clin Oncol.* 2009;27(Suppl 15):abstr 4512.
88. Enzinger PC, Fidias P, Meyerhardt J, et al. Phase II study of bevacizumab and docetaxel in metastatic esophageal and gastric cancer. Proceedings of the Gastrointestinal Cancer Symposium; 2006: Abstr 68.
89. Ohtsu A, Shah MA, Van Cutsem E, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. *J Clin Oncol.* 2011;29(30):3968–3976.
90. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med.* 2007;356(2):115–124.
91. Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet.* 2006;368(9544):1329–1338.
92. Bang YJ, Kang YK, Kang WK, et al. Phase II study of sunitinib as second-line treatment for advanced gastric cancer. *Invest New Drugs.* 2011;29(6):1449–1458.
93. Moehler M, Hartmann JT, Lordick F, et al. Sunitinib in patients with chemorefractory metastatic gastric cancer: preliminary results of an open-label, prospective non-randomized multicentre AIO Phase II trial. *Proc GI ASCO.* 2009:61.
94. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med.* 2007;356(2):125–134.
95. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med.* 2008;359(4):378–390.
96. Sun W, Powell ME, O'Dwyer P, et al. A phase II study: combination of sorafenib with docetaxel and cisplatin in the treatment of metastatic or advanced unresectable gastric and gastroesophageal junction (GEJ) adenocarcinoma (ECOG 5203). *J Clin Oncol.* 2008;(Suppl 26): Abstr 4635.
97. Ko AH, Tabernero J, Garcia De Paredes M, et al. Phase II study of telatinib (T) in combination with capecitabine (X) and ciplatin (P) as first-line treatment in patients (pts) with advanced cancer of the stomach (G) or gastro-esophageal junction (GEJ). *J Clin Oncol.* 2010;28(Suppl): Abstr e14575.
98. Yu G, Wang J, Chen Y, et al. Overexpression of phosphorylated mammalian target of rapamycin predicts lymph node metastasis and prognosis of chinese patients with gastric cancer. *Clin Cancer Res.* 2009;15(5):1821–1829.

99. Hirashima K, Baba Y, Watanabe M, et al. Phosphorylated mTOR expression is associated with poor prognosis for patients with esophageal squamous cell carcinoma. *Ann Surg Oncol.* 2010;17(9):2486–2493.
100. Yu HG, Ai YW, Yu LL, et al. Phosphoinositide 3-kinase/Akt pathway plays an important role in chemoresistance of gastric cancer cells against etoposide and doxorubicin induced cell death. *Int J Cancer.* 2008;122(2):433–443.
101. Okamoto I, Doi T, Ohtsu A, et al. Phase I clinical and pharmacokinetic study of RAD001 (everolimus) administered daily to Japanese patients with advanced solid tumors. *Jpn J Clin Oncol.* 2010;40(1):17–23.
102. Doi T, Muro K, Boku N, et al. Multicenter phase II study of everolimus in patients with previously treated metastatic gastric cancer. *J Clin Oncol.* 2010;28(11):1904–1910.
103. Graziano F, Catalano V, Baldelli AM, et al. A phase II study of weekly docetaxel as salvage chemotherapy for advanced gastric cancer. *Ann Oncol.* 2000;11(10):1263–1266.
104. Jo JC, Lee JL, Ryu MH, et al. Docetaxel monotherapy as a second-line treatment after failure of fluoropyrimidine and platinum in advanced gastric cancer: experience of 154 patients with prognostic factor analysis. *Jpn J Clin Oncol.* 2007;37(12):936–941.
105. Baek JH, Kim JG, Sohn SK, et al. Biweekly irinotecan and cisplatin as second-line chemotherapy in pretreated patients with advanced gastric cancer: a multicenter phase II study. *J Korean Med Sci.* 2005;20(6):966–970.
106. Takiuchi H, Goto M, Imamura H, et al. Multi-center phase II study for combination therapy with paclitaxel/doxifluridine to treat advanced/recurrent gastric cancer showing resistance to S-1 (OGSG 0302). *Jpn J Clin Oncol.* 2008;38(3):176–181.
107. Van Cutsem E, Yeh K, Bang Y, et al. Phase III trial of everolimus (EVE) in previously treated patients with advanced gastric cancer (AGC): GRANITE-1. *J Clin Oncol.* 2012;30(Suppl 4):Abstr LBA3.
108. Bramhall SR, Hallissey MT, Whiting J, et al. Marimastat as maintenance therapy for patients with advanced gastric cancer: a randomised trial. *Br J Cancer.* 2002;86(12):1864–1870.
109. Jhawer M, Kindler HL, Wainberg Z, et al. Assessment of two dosing schedules of GSK1363089 (GSK089), a dual MET/VEGFR2 inhibitor, in metastatic gastric cancer (GC): interim results of a multicenter phase II study. *J Clin Oncol.* 2009;27(15 Suppl):Abstr 4502.
110. Bachleitner-Hofmann T, Sun MY, Chen CT, et al. HER kinase activation confers resistance to MET tyrosine kinase inhibition in MET oncogene-addicted gastric cancer cells. *Mol Cancer Ther.* 2008;7(11):3499–3508.
111. Nakajima M, Sawada H, Yamada Y, et al. The prognostic significance of amplification and overexpression of c-met and c-erb B-2 in human gastric carcinomas. *Cancer.* 1999;85(9):1894–1902.
112. Philip PA, Harris AL. Potential for protein kinase C inhibitors in cancer therapy. *Cancer Treat Res.* 1995;78:3–27.
113. Ajani JA, Jiang Y, Faust J, et al. A multi-center phase II study of sequential paclitaxel and bryostatin-1 (NSC 339555) in patients with untreated, advanced gastric or gastroesophageal junction adenocarcinoma. *Invest New Drugs.* 2006;24(4):353–357.
114. Ku GY, Ilson DH, Schwartz LH, et al. Phase II trial of sequential paclitaxel and 1 h infusion of bryostatin-1 in patients with advanced esophageal cancer. *Cancer Chemother Pharmacol.* 2008;62(5):875–880.
115. Corley DA, Kerlikowske K, Verma R, Buffler P. Protective association of aspirin/NSAIDs and esophageal cancer: a systematic review and meta-analysis. *Gastroenterology.* 2003;124(1):47–56.
116. Heath EI, Canto MI, Piantadosi S, et al. Secondary chemoprevention of Barrett's esophagus with celecoxib: results of a randomized trial. *J Natl Cancer Inst.* 2007;99(7):545–557.
117. Bresalier RS, Sandler RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med.* 2005;352(11):1092–1102.
118. Turner NC, Reis-Filho JS, Russell AM, et al. BRCA1 dysfunction in sporadic basal-like breast cancer. *Oncogene.* 2007;26(14):2126–2132.