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REVIEW ARTICLE

Targeted therapies for advanced and metastatic adenocarcinoma of the gastroesophageal junction: is there something new?

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Abstract Despite improvements in systemic chemotherapy (CT), the prognosis of metastatic adenocarcinoma of the gastroesophageal junction remains poor. Over the years, new targeting agents have become available and were tested, with or without CT, in first or subsequent lines of therapy. The epidermal growth factor receptor family was targeted with monoclonal antibodies (MoAbs) (trastuzumab, cetuximab, panitumumab) and tyrosin kinase inhibitors (TKIs) (lapatinib, erlotinib, gefitinib). Only trastuzumab, in combination with cisplatin and fluoropyrimidines, significantly improved overall survival (OS) in first-line therapy (13.8 vs. 11.1 months). Angiogenesis also was targeted with MoAbs (bevacizumab and ramucirumab); ramucirumab, a vascular endothelial growth factor-receptor 2 antagonist, enhanced OS in two phase III studies in the first (9.6 vs. 7.4 months) and subsequent lines of treatment (5.2 vs. 3.8 months), while the bevacizumab study was negative. TKIs (sunitinib, sorafenib, regorafenib, apatinib) were tested in this setting in phase II studies in the second/third line, only showing modest antitumor activity. The hepatocyte growth factor receptor (MET) was targeted in untreated patients in a phase III trial with MoAb rilotumumab, with or without CT, but the study was stopped because of mortality excess in the rilotumumab arm. Mammalian target of rapamycin (MTOR) pathway inhibition with everolimus was tested in pretreated patients in a placebo-controlled phase III trial who failed to improve OS (5.4 vs. 4.3 months). In conclusion, considering the modest survival gain obtained overall, the high cost of these therapies and the quality of life issue must be primarily considered in treating these patients.

Keywords Gastroesophageal junction adenocarcinoma · Advanced disease · Targeted therapies

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Introduction

In metastatic adenocarcinoma of the gastroesophageal junction (GEJA) chemotherapy has long been considered the cornerstone treatment; nevertheless, studies devoted to this subset are lacking because these patients were enrolled in gastric cancer (GC) trials that were statistically unpowered to examine the two entities separately. In randomized clinical trials of GC, GEJA represented 13–29 % of the study population and the 2-year survival rate did not exceed 20 % [1]. Anyway, EJGA should be considered a distinct entity from non-cardia GC. The higher incidence of EJGA in Western countries confirms that GEJA and non-cardia GC are related to risk factors having different distributions across the world. Gastroesophageal reflux and Barret metaplasia are risk factors for EJGA [2], while gastric atrophia due to *Helicobacter pylori* infection is the main risk factor for non-cardia GC. From the clinicopathological point of view, GEJA demonstrated a higher aggressiveness compared to non-cardia GC, more advanced TNM stage, younger age, higher recurrence rate and lower survival rates [3–5].

Some studies report that mutations and copy number alterations differ between GEJA and non-cardia GC.

Tumors with chromosomal instability, marked aneuploidy and amplification of receptor tyrosine kinases showed elevated frequency in the gastroesophageal junction. TP53 and RAS mutations were also most frequent in GEJA, while tumors arising from the mid and distal stomach were more likely to have PIK3CA, RHOA and Wnt pathway mutations, microsatellite instability (MSI) and positivity for Epstein-Barr virus [5, 6]. Another strategy for molecular classification is based on the gene expression profile. One study used gene expression data and found different clinical outcomes in relation to four different patterns of molecular alterations. The mesenchymal-like type had the worst prognosis; the MSI group had the best overall prognosis, while the TP53-active and TP53-inactive groups presented an intermediate prognosis. The TP53-active subtype was most frequently found in GEJA [7]. Another study identified 511 genes with dysregulated expression in cardia or non-cardia GC; of these genes, about one-half were dysregulated in both cardia and non-cardia, one-fourth in cardia and one-fourth in non-cardia only. Some genes were associated with survival; the most significant *P* values were documented for ALDH3A1 and TRIP13 genes in GEJA, while ADA, ADH1, AKR1B10, ATP4B, LHFP, TFF2 and LIPF genes in non-cardia cancer [8]. Amplification of the HER2 gene is found in about 15–20 % of the patients and seems associated with a negative prognostic role; higher expression was documented in the GEJ (33.2 %) and proximal part compared to distal parts of the stomach [9].

A recent report from a German database on GEJA and GC for the years 2006–2009 showed that monotherapy, doublet and triplet chemotherapies were used in about 10, 60 and 30 % of the patients, respectively; older or less fit patients were more likely to receive monotherapy or doublets, while younger patients more commonly received triplets (40.2 vs. 20.8 %). Consistent with other reports, median age was 67 years with male preponderance (64 %). This analysis reflects the transfer of study data into clinical practice, although the impact on survival was not investigated [10]. Over the years, an increasing number of targeting agents has become available for many types of tumors, and these were also tested in GC and GEJA. In this review, we summarize the results of clinical studies testing targeted therapies in GEJA by separately analyzing targeted oncogenic pathways (Fig. 1).

Targeting the epidermal growth factor family

The epidermal growth factor receptor (EGFR) family is composed of four members: HER1 (also known as EGFR/ErbB1), HER2, HER3 (also named ErbB-3) and HER4 (also termed ErbB-4). These receptors share the same molecular structure with an extracellular ligand-binding domain, a short transmembrane domain and an intracellular domain with tyrosin kinase (TK) activity (except the HER3). The binding of different ligands to the extracellular domain triggers a signal transduction cascade that can influence many aspects of tumor cell biology, including cell proliferation, apoptosis, adhesion, migration and differentiation. Ligand binding induces EGFR homodimerization as well as heterodimerization with other types of HER proteins. GFR signaling can be deregulated in cancer by various mechanisms (i.e., increased receptor expression, autocrine or paracrine ligand secretion and somatic mutations). In contrast to colorectal and lung cancer, KRAS mutation status and EGFR mutations do not seem to play a relevant role.

Clinical strategies have been developed to target GFR in gastrointestinal cancers such as:

1. Monoclonal antibody (moAb) binding epitopes of the extracellular domain of GFR;
2. MoAbs devoted to neutralizing ligands [i.e., vascular endothelial growth factor (VEGF)];
3. Small molecules that cross the cell membrane and interfere with the enzymatic function of TK receptor or intracellular signaling molecules able to inhibit aberrant signal transduction.

(**a**) The EGFR (HER1/EGFR/ErbB1) is a cell surface protein that binds to epidermal growth factor. Binding of the protein to the ligand induces receptor dimerization and tyrosine autophosphorylation leading to cell proliferation. EGFR is approximately expressed by immunohistochemistry (IHC) in 30–70 % of esophageal adenocarcinomas (ADs) and may correlate with a dismal survival. EGFR inhibition was attempted using moAbs cetuximab, panitumumab, matuzumab and nimotuzumab, and the results were reported in several phase I–II studies (Table 1) [11–22].

The AGITG ATTAX3 study [21], a randomized phase II study, compared chemotherapy (weekly docetaxel, cisplatin and fluoropyrimidine) with and without panitumumab. The addition of panitumumab to docetaxel-based chemotherapy did not improve efficacy, but increased some G3/4 toxicities. A safety alert from the REAL-3 study [23] prompted an unplanned review of the data; although no evidence of adverse outcomes was detected in the experimental arm, the study was stopped after enrolling 77 patients (38 with panitumumab).

A randomized phase II trial [22] evaluated nimotuzumab in association with irinotecan versus irinotecan in second-line therapy; the primary end point (PFS) was not met, but the combination showed potential outcome improvement in the EGFR 2+/3+ subset. On the whole, data from phase II showed modest survival gain; nevertheless panitumumab

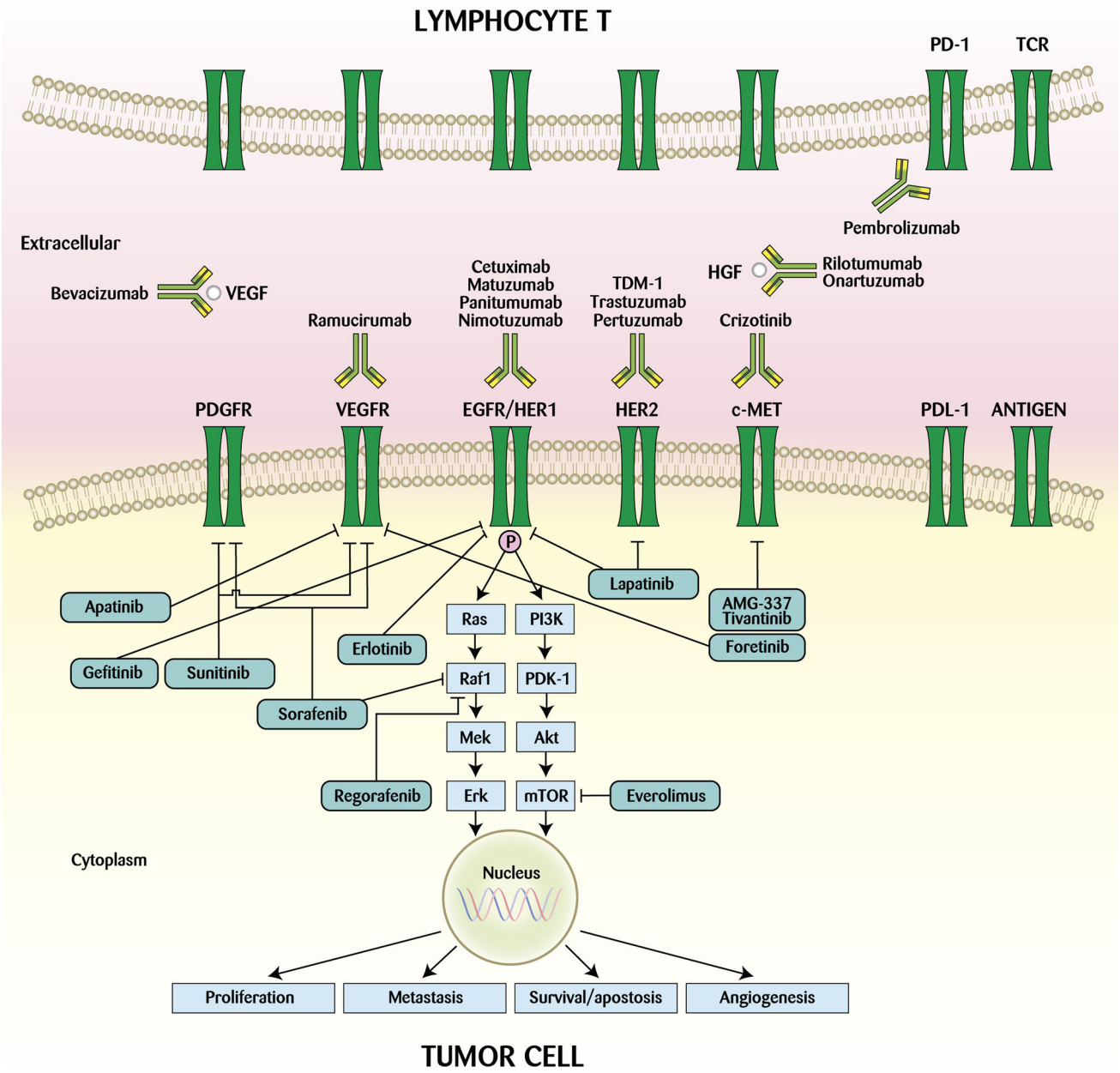

Fig. 1 Targeted oncogenic pathways in advanced gastroesophageal adenocarcinoma

and cetuximab underwent evaluation in the REAL-3 [23] and EXPAND [24] phase III randomized clinical trials (Table 2). A nimotuzumab phase III study is ongoing in recurrent Asian patients overexpressing EGFR 2+/3+ in IHC. The REAL-3 trial [23] compared a standard EOX regimen (epirubicin, oxaliplatin, capecitabine) with a modified EOX (mEOX) associated with panitumumab; indeed, the panitumumab arm was detrimental in terms of OS, which was the primary end point.

In an exploratory analysis of 276 patients receiving panitumumab, the development of any grade of rash (79 % of the patients) was associated with significantly longer OS and PFS: median OS was 10.3 vs. 4.3 months and median PFS was 6.8 vs. 3.7 months in patients with or without rash, respectively ($p < 0.0001$). Negative results were also obtained in the EXPAND trial [24], which tested the combination of capecitabine and cisplatin with or without cetuximab. The addition of cetuximab failed to improve the PFS (the primary end point), OS and response rate (RR). In a predefined subset analysis, irrespective of the treatment arm, patients with HER2-negative tumor (535 patients) showed increased risk of death (HR 1.55, 95 % CI 1.24–1.94) and reduced RR (HR 0.47, 95 % CI 0.31–0.72) compared with patients with HER2-positive tumors (144

Table 1 Phase I–II studies with anti-EGFR moAbs

Ref.	Patients	Setting	Population	Therapy	Outcome
Pinto et al. [11]	72	Metastatic 1st line	Gastric and GEJ AD (18 %)	Cetuximab + Cisplatin and docetaxel	RR = 41 % mTTP = 5 mo mOS = 9 mo
Pinto et al. [12]	38	Metastatic 1st line	Gastric and GEJ AD (10.5 %)	Cetuximab + FOLFIRI	RR = 44 % mTTP = 8 mo mOS = 16 mo
Gold et al. [13]	63	Metastatic 2nd line	Esophageal AD	Cetuximab	RR = 5 % mPFS = 1.8 mo mOS = 4 mo
Chan et al. [14]	35	Metastatic 2nd line	Gastric, Esophageal AD (34 %), GEJ AD (23 %)	Cetuximab	RR = 3 % mPFS = 1.6 mo mOS = 3
Kim et al. [15]	44	Metastatic 1st line	Gastric and GEJ AD	Cetuximab + XELOX	RR = 52 % mPFS = 6.5 mo mOS = 11.8 mo
Lordick et al. [16]	52	Metastatic 1st line	Gastric and GEJ AD (48 %)	Cetuximab + FUFOX	RR = 65 % mTTP = 7.6 mo mOS = 9.5 mo
Moehler et al. [17]	49	Metastatic 1st line	Gastric and GEJ AD (29 %)	Cetuximab + FI	RR = 46 % mPFS = 9 mo mOS = 16.5 mo
Rao et al. [18]	35	Metastatic 1st line randomized Phase II	Gastric and GEJ AD (60 %)	Matuzumab + ECX	RR = 31 % mPFS = 4.8 mo mOS = 9.4 mo
Trarbach et al. [19]	15	Metastatic/ recurrent	Gastric and GEJ AD (27 %)	Matuzumab + PLF	RR = 27 %
Schoennemann et al. [20]	50	Metastatic/ recurrent	Gastric and GEJ AD (86 %)	Cetuximab + irinotecan	RR = 14 % mPFS = 3.3 mo mOS = 5.5 mo
Tebbutt et al. [21]	38	Metastatic 1st line randomized Phase II	Gastric and GEJ AD (% not reported) 10 % SCC	Panitumumab + docetaxel, cisplatin, fluoropyrimidine	RR = 58 % mPFS = 6.0 mo mOS = 10.0 mo
Satoh et al. [22]	83	Metastatic 2nd line randomized Phase II	Gastric and GEJ AD (10.4 %)	Irinotecan + nimotuzumab	RR = 18.4 % mPFS = 2.4 mo mOS = 8.3 mo

EGFR epidermal growth factor receptor, *moAbs* monoclonal antibodies, *AD* adenocarcinoma, *GEJ* gastroesophageal junction, *SCC* squamous cell carcinoma, *RR* response rate, *mTTP* median time to progression, *mOS* median overall survival, *mPFS* median progression-free survival, *FOLFIRI* leucovorin, fluorouracil, irinotecan, *XELOX* capecitabine and oxaliplatin, *FUFOX* leucovorin, fluorouracil and oxaliplatin, *FI* irinotecan, folinic acid and fluorouracile, *ECX* epirubicin, cisplatin and capecitabine, *PLF* fluorouracil, leucovorin and cisplatin, *mo* months

patients). Tumor EGFR expression was generally low; however, using a series of cutoff points from an IHC score, there was a tendency for improved OS, PFS and RR when adding cetuximab to CT in patients with high tumor EGFR IHC scores. This finding suggests a benefit from adding cetuximab to CT in a small proportion of patients with high EGFR tumor expression [25].

(b) The clinical role of HER2 overexpression was been first evaluated in the ToGA trial [26]. The study enrolled 594 patients (about 18 % with GEJA) and compared cisplatin-fluoropyrimidine chemotherapy alone or with trastuzumab with OS as the primary endpoint. All patients had immunohistochemical overexpression of HER2 or gene amplification by FISH. Among the screened tumors, HER2

Table 2 Phase III randomized clinical trials targeting EGFR

Ref.	Patients	Setting	Primary end point	Population	Therapy	Outcome
Waddel et al. [23]	553	Metastatic 1st line	OS	Gastric and GEJ AD (34 %)	Panitumumab + mEOX vs. standard EOX	RR = 42 vs. 46 % mPFS = 6 vs. 7.4 mo ($p = 0.068$) mOS = 8.8 vs. 11 mo ($p = 0.01$)
Lordick et al. [24]	904	Metastatic 1st line	PFS	Gastric and GEJ AD (16 %)	Cetuximab ± capecitabine and cisplatin	RR = 30 vs. 29 % mPFS = 4.4 vs. 5.9 mo mOS = 9.4 vs. 10.7 mo

EOX epirubicin, oxaliplatin and capecitabine, *mo* months, *mEOX* modified epirubicin, oxaliplatin and capecitabine

Table 3 Phase III randomized clinical trials targeting HER2

Ref.	Patients	Setting	Primary end point	Population	Therapy	Outcome
Bang et al. [26]	594	Metastatic 1st line	OS	Gastric and GEJ AD (18 %)	Trastuzumab ± fluoropyrimidine and cisplatin	RR = 47 vs. 35 % mPFS = 6.7 vs. 5.5 mo mOS = 13.8 vs. 11.1 mo
Hecht et al. [27]	545	Metastatic 1st line	OS	Gastric, Esophageal (5 %) and GEJ AD (9 %)	Lapatinib ± capeOx	RR = 53 vs. 40 % mPFS = 6 vs. 5.4 mo mOS = 12.2 vs. 10.5 mo
Satoh et al. [28]	261	Metastatic 2nd line phase II-III	OS	Gastric	Lapatinib ± paclitaxel	RR = 27 vs. 9 % mPFS = 5.4 vs. 4.4 mo mOS = 11 vs. 8.9 mo
Kang [29]	415	Metastatic 2nd line	OS	Gastric and GEJ AD (% NR)	TDM-1 vs. paclitaxel	RR = 21 vs. 20 % mPFS = 2.7 vs. 2.9 mo mOS = 7.9 vs. 8.6 mo

CapeOx capecitabine and oxaliplatin, *mo* months, *NR* not reported

overexpression was positive in 21 % of gastric carcinomas and in 33 % of GEJA. The cohort receiving trastuzumab had a significant improvement in OS (13.8 vs. 11.1 months, HR 0.74, 95 % CI 0.6–0.91, $p = 0.0046$), PFS (6.7 vs. 5.5 months) and RR (47 vs. 35 %) ($p = 0.0017$). In an explorative analysis, patients with strongly HER2-positive tumors derived the greatest OS benefit with the addition of trastuzumab (16.0 vs. 11.8 months, HR 0.68, 95 % CI 0.5–0.83). Based on these data, trastuzumab was approved, in combination with cisplatin and a fluoropyrimidine, for first-line treatment of metastatic HER2-overexpressing gastric or GEJA (Table 3).

Lapatinib ditosylate is a dual anti-EGFR and anti-HER2 TK. This oral drug was investigated in the LOGIC [27] and TyTAN [28] trials. In the LOGIC study, the primary efficacy population (PEP) comprised all subjects with centrally confirmed tumor FISH amplification. Patients were randomized to CapeOx with or without lapatinib. The study failed to meet its primary endpoint (i.e., OS of PEP); mOS and mPFS were 12.2 vs. 10.5 months, 6.0 vs. 5.4 months in the experimental arm and control arm, respectively. Prespecified subset analyses showed significant OS improvements in patients who were Asian (HR = 0.68) and under 60 years (HR = 0.69). There was no association between IHC and OS. In patients treated with lapatinib, the toxicity profile showed increased skin toxicity and grade 3+ diarrhea (12 vs. 3 %). Based on these negative results, lapatinib is not recommended outside clinical trials. The TyTAN study [28] was conducted in Asian HER2 FISH-amplified patients comparing lapatinib in association with paclitaxel or not in second-line treatment; OS was not different in the two arms. However, lapatinib produced OS and PFS improvement in the small subsets of Chinese patients and those with IHC3+.

T-DM1 is a conjugate of the MoAb trastuzumab and a chemotherapy drug, called emtansine; after binding to

Table 4 Phase II studies with TKI (erlotinib, gefitinib)

Ref.	Patients	Setting	Population	Therapy	Outcome
Wainberg et al. [31]	33	Metastatic 1st line	Gastric and esophageal AD	Erlotinib + FOLFOX 6	RR = 51.5 % mPFS = 5.5 mo mOS = 11 mo
Dragovich et al. [32]	70	Metastatic 1st line	Gastric and GEJ AD	Erlotinib	RR = 9 %
Ilson et al. [33]	30	Metastatic 2nd line	Esophageal and GEJ AD and SCC	Erlotinib	RR = 8 %
Adelstein et al [34]	58	Metastatic 1st/2nd line	Esophageal and GEJ AD and SCC	Gefitinib	RR = 7 % mOS = 5.5 mo
Ferry et al. [35]	27	Inoperable 1st line	Esophageal AD	Gefitinib	RR = 11 % mOS = 4.5 mo mPFS = 1.9 mo

FOLFOX 5-fluorouracil, leucovorin and oxaliplatin, *mo* months

HER2 receptor on the tumor cell membrane, it delivers the drug to the cytoplasm. The GATSBY study [29] compared TDM-1 vs. paclitaxel single agent in second-line therapy; the primary end point, i.e., OS, was not met, although grade 3 adverse events were lower in the experimental arm (70 vs. 60 %). Dual HER2 inhibition is currently under investigation in the JACOB phase III study randomizing cisplatin fluoropyrimidine chemotherapy combined with trastuzumab with or without pertuzumab [30].

(c) The small-molecule tyrosine kinase inhibitors (TKI), erlotinib and gefitinib, were also tested as single agent or in combination with chemotherapy (Table 4). Gefitinib and erlotinib specifically target the EGFR tyrosine kinase by binding in a reversible fashion to the adenosine triphosphate (ATP) binding site of the receptor to form a homodimer. By inhibiting the ATP, formation of phosphotyrosine residues in EGFR is not possible, and the signal cascades are not initiated.

Stable disease and RR generally were in the magnitude of 10 %, except in one trial [31]. One trial suggested that GEJAs were more likely to respond to erlotinib than gastric cancers [32]; in another trial, responses were seen almost exclusively in SCC as compared to AD [33]. A possible explanation is that KRAS and EGFR mutations are uncommon [31–35] and thus not predictive of response to TKI in esophageal cancer. In conclusion, the results were very modest at best for these agents in a metastatic setting.

Targeting angiogenesis

Aberrant tumor angiogenesis has been considered a potential target in cancer therapy. Currently, there are no validated biomarkers to select patients for antiangiogenic therapy, although some candidate surrogate markers of bevacizumab response have been described. Tumor VEGF expression was identified as a poor prognosis marker in esophageal cancer [36]. Strategies developed to modulate angiogenic signaling were: (1) targeting proangiogenic factors with moAbs (i.e., the anti-VEGF moAb bevacizumab); (2) targeting angiogenic receptors with moAbs (i.e., the moAb ramucirumab); (3) targeting angiogenic receptors with TKI (i.e., sunitinib, sorafenib) Table 5.

Depletion of proangiogenic factors

Bevacizumab is a moAb anti-VEGF-A, a protein playing a significant role in angiogenesis. The drug was tested in the AVAGAST phase III trial [37], which enrolled 774 patients (14 % GEJA) and compared the combination of cisplatin fluoropyrimidine with and without bevacizumab in first-line treatment. The trial failed to meet the primary endpoint (OS); subgroup analysis for GEJA was also consistent with the overall result of the study.

Median OS was 10.1 and 12.1 months in the control and bevacizumab subsets, respectively (HR 0.87, $p = 0.1$); on the other hand, there was a significant improvement in PFS (5.3 vs. 6.7 mo) and RR (37 vs. 46 %) in the experimental arm. The bevacizumab safety profile was as expected, with increased rates of hypertension (6.2 vs. 0.5 %) and gastrointestinal perforation (2.3 vs. 0.3 %). Traslational research [38] evaluated the efficacy of bevacizumab with a comprehensive prospective biomarker analysis. High plasma VEGF-A levels and low neuroplin-1 expression were negative prognostic factors, although these patients were more likely to respond to bevacizumab. Consequently, plasma VEGF-A and tumor neuropilin-1 seem potential biomarker candidates for predicting clinical outcome; however, the finding needs confirmation in prospective studies. In a recent phase II study, 39 patients

Table 5 Phase II studies targeting angiogenesis with TKI (sunitinib, sorafenib, regorafenib, apatinib)

Ref.	Patients	Setting	Population	Therapy	Outcome
Moehler MH et al. [49]	91 (45 sunitinib) Randomized phase II	Metastatic 2nd/3rd line	Gastric and GEJ AD (50 %)	Sunitinib ± FOLFIRI	RR = 20 % mPFS = 3.6 mo mOS = 10.5 mo
Bang et al. [50]	78	Metastatic 2nd line	Gastric and GEJ AD (6.4 %)	Sunitinib	RR = 2.6 % mPFS = 2.3 mo mOS = 6.8 mo
Moehler M et al. [51]	51	Metastatic 2nd line	Gastric and GEJ AD (22 %)	Sunitinib	RR = 3.9 % mPFS = 1.3 mo mOS = 5.8 mo
Martin-Richard et al. [52]	40	Metastatic 2nd line	Gastric and GEJ AD (27.5 %)	Sorafenib + oxaliplatin	RR = 2.5 % mPFS = 3 mo mOS = 6.5 mo
Sun et al. [53]	44	Metastatic 1st line	Gastric and GEJ AD (% not reported)	Sorafenib + docetaxel/cisplatin	RR = 41 % mPFS = 5.8 mo mOS = 13.6 mo
Pavlakis et al. [54]	152 Randomized phase II	Metastatic 2nd–3rd line	Gastric and GEJ AD (37 %)	Regorafenib vs. placebo	RR = NR vs. NR mPFS = 11.1 vs. 3.9 wks mOS = 25 vs. 19.4 wks
Li et al. [56]	273 Randomized phase III	Metastatic after 2nd line	Gastric and GEJ AD (22 %)	Apatinib vs. placebo	RR = 2.8 vs. 0 % mPFS = 2.6 vs. 1.8 mo mOS = 6.5 vs. 4.7 mo

mo months, *NR* not reported, *wks* weeks

(66 % distal esophageal and GEJ adenocarcinoma) received bevacizumab with a modified FOLFOX regimen. RR was 56 %, mTTP 8.2 months and mOS 15.2 months; 12.8 % of deep venous thromboembolism and pulmonary embolism was reported [39]. A phase Ib/II study, testing weekly docetaxel and cisplatin together with capecitabine and bevacizumab, was closed early, after the accrual of 22 patients because of the accumulation of toxicity-related deaths [40].

Targeting angiogenic receptors with moAbs

Ramucirumab is a human IgG1 moAb VEGF-receptor 2 antagonist. The REGARD [41] and RAINBOW [42] randomized phase III clinical trials tested the efficacy of ramucirumab in advanced/metastatic pretreated gastric or GEJA patients with ECOG PS = 0–1; OS, the primary end point, was met in both studies. In the REGARD trial [41], 355 patients (25 % GEJA) were randomized (2:1) to receive ramucirumab or placebo. In the ramucirumab arm, median OS was 5.2 vs. 3.8 months (HR 0.78, 95 % CI, 0.60–0.99; $p = 0.047$), median PFS was 2.1 vs. 1.3 months (HR 0.48, $p < 0.0001$), and the disease control rate was 49 vs. 23 % ($p < 0.0001$). In the subgroup analysis for GEJA, significance was maintained only for PFS (HR 0.39, 95 % CI 0.23–0.65) and not for OS. While rates of adverse events were mostly similar between groups, rates of hypertension were higher in ramucirumab-treated patients (16 vs. 8 %). Outcome and toxicity profiles were similar in patients ≤65 years or older [43]. Ramucirumab has been approved by FDA as a single agent for the treatment of patients with advanced or metastatic, gastric or GEJA progressing on or after prior fluoropyrimidine-or platinum containing chemotherapy Table 6.

In the RAINBOW study [42], 665 patients were randomized (1:1) to paclitaxel with or without ramucirumab. In the ramucirumab arm median OS was 9.6 vs. 7.4 months (HR 0.81, 95 % CI 0.67–0.96; $p = 0.017$), median PFS was 4.4 vs. 2.9 months (HR 0.63, 95 % CI 0.54–0.75; $p < 0.0001$), and RR was 28 vs. 16 % ($p = 0.0001$). At multivariate analysis, factors significantly associated with OS were geographical region, ECOG PS, weight loss,

number of metastatic sites, presence of ascites, tumor differentiation and prior gastrectomy. The HR for OS improved after adjusting for these factors (HR 0.745, 95 % CI 0.62–0.88; $p = 0.001$) [44]. With the addition of ramucirumab, QoL was maintained for a longer time, and more patients reported stable or improved scores [45]. Outcome was similar in Western and Japanese populations, with a prolonged post-progression survival in Japanese patients (5.8 vs. 4.4 months), probably due to higher use of post-discontinuation treatment [46].

Preliminary pharmacokinetic data from patients enrolled in the REGARD and RAINBOW trials found an association of longer PFS, OS, improved HR and increased toxicity with higher ramucirumab exposures [47]. To validate this finding, a phase II randomized trial is investigating the pharmacokinetics and safety of different ramucirumab doses in second-line patients (ClinicalTrials.gov Identifier: NCT 02443883).

A randomized phase II study, enrolling 168 patients (84 in the ramucirumab arm), GEJA 31 %, compared modified FOLFOX6 plus ramucirumab vs. placebo; mPFS, the primary end point, was 6.4 vs. 6.7 months and OS 11.7 vs. 11.5 months in the experimental and control arm, respectively. PFS and OS were not influenced by the primary tumor location (esophageal vs. gastric/GEJ), and the disease control rate was higher in the ramucirumab arm (85 vs. 67 %, $p = 0.008$) [48]. The ongoing RAINFALL placebo-controlled phase III trial compares capecitabine and cisplatin with or without ramucirumab in first-line therapy in patients with metastatic gastric or GEJ AD with PFS as primary end point (ClinicalTrials.gov Identifier: NCT 02314117).

Targeting angiogenic receptors with TKI

Sorafenib, sunitinib and regorafenib are multitargeted TKIs that inhibit angiogenesis by targeting different signaling pathways. A randomized placebo-controlled multicentric AIO phase II trial compared FOLFIRI with or without sunitinib in pretreated patients. The study failed to meet the primary end point (PFS); biomarker analysis has been planned to identify subgroups potentially benefiting from the addition of sunitinib [49]. Other phase II studies have been conducted mostly in second line, showing modest activity: mPFS in the range of 1.3–3.6 months and OS of about 7 months [50–52]. In front-line therapy, sorafenib in combination with chemotherapy provided a 41 % RR (primary end point) [53]. The randomized phase II INTEGRATE trial documented a statistically improved PFS with regorafenib in respect to placebo, but only a trend for OS [54]. Regional differences were found in the magnitude of effect, but regorafenib was effective in all regions and subsets. High plasma levels of IL8, VEGF-A and sVEGFR-1 showed no convincing evidence of a relation with adverse prognosis [55]. A broader biomarker study including markers beyond the VEGF axis and tissue-based markers is ongoing (Clinical trial information: ACTRN12612000239864).

Apatinib, a novel vascular endothelial growth factor receptor 2 TKI, was tested vs. placebo in patients with advanced gastric or GEJ AD failing at least two lines of prior chemotherapy in the Chinese population. In this heavily pretreated but highly selected, subset, the study met both the co-primary end points (OS, PFS), without significant differences in QoL [56].

Targeting hepatocyte growth factor receptor (MET)

MET is a transmembrane TKR for which hepatocyte growth factor (HGF) is the only known ligand. MET activation induces complex cellular signaling mediated through a variety of transduction pathways. Under

Table 6 Studies targeting in mTOR complex

Ref.	Patients	Setting	Population	Therapy	Outcome
Doi T et al. [66]	53	Advanced/metastatic 2nd line Phase II	Gastric and GEJ AD (% not reported)	Everolimus	RR = 0 % DCR = 56 % mPFS = 2.7 mo mOS = 10.1 mo
Ohtsu et al. [67]	650	2nd–3rd line Phase III	Gastric and GEJ AD (27 %)	Everolimus ± BSC	RR = 5 % vs. 2 % DCR = 44 % vs. 22 % mPFS = 1.7 vs. 1.4 mo mOS = 5.4 vs. 4.3 mo

mo months, *BSC* best supportive care

physiological conditions, MET-driven invasive growth is tightly regulated and plays a key role in tissue growth and repair. Aberrant HGF/MET activation occurs in multiple types of malignancies, including GEJA, via several mechanisms including overexpression, focal gene amplification, gene copy number gain, activating mutations, TKR transactivation and autocrine or paracrine signaling.

Dysregulated HGF/MET signaling is commonly seen in GEJA. Approximately 0–10 % of gastric cancers exhibit MET amplification and up to 60 % MET overexpression; both amplification and overexpression have been associated with a more aggressive phenotype and poor prognosis [57–59]. However, quantification of MET overexpression is flawed by the different evaluation criteria used; pathologist training and inter-laboratory quality control are needed for standardization of the results. A phase II randomized study evaluated anti-HGF moAb rilotumumab with or without ECX chemotherapy in 121 non-MET selected naïve patients. Rilotumumab improved OS in MET-high tumors (11.1 vs. 5.7 months, HR 0.29, 95 % CI 0.11–0.76, $p = 0.012$). MET-high tumor (42 % of evaluable patients) was defined as weak (1+) or stronger MET IHC staining in >50 % of malignant cells [60]. The RILOMET-1 phase III study compared ECX with or without rilotumumab in 609 untreated patients with unresectable/advanced gastric/GEJ adenocarcinoma, tumor MET-positive by IHC, HER2 negative. The study was stopped early based on an imbalance in deaths; OS (the primary end point), PFS and ORR were statistically worse in the rilotumumab arm. No subgroups seemed to benefit from rilotumumab, including those with higher percentages of cells with = 1 + MET expression. Adverse events were higher with rilotumumab: peripheral edema, hypoalbuminemia, deep vein thrombosis and hypocalcemia [61]. The toxicity profile of rilotumumab in combination with cisplatin and capecitabine in Japanese patients with MET-positive gastric/GEJ cancer was consistent with that of Western patients [62]. Crizotinib, tivantinib and foretinib failed to demonstrate significant antitumor activity.

A placebo-controlled phase II study failed to demonstrate PFS improvement with onartuzumab and FOLFOX6 in first-line patients of whom about 33 % were MET positive, irrespective of different MET cutoffs [63]. Due to these negative findings, the phase III study was prematurely stopped after enrolling 562 patients out of the 800 foreseen. OS and PFS were similar in the control and experimental arms (about 11 and 7 months, respectively) [64].Preliminary data reported an encouraging response rate in a phase I study testing AMG 337, an investigational oral MET kinase inhibitor, in MET-amplified patients [65].

Targeting the mammalian target of rapamycin (MTOR) complex

mTOR is an intracellular serine/threonine kinase that acts in two protein complexes, TORC1 and TORC2 the mammalian target of rapamicin complex. mTOR is involved in multiple pathways regulating cell survival, motility, metabolism and protein synthesis. TORC1 is engaged by the PI3K/AKT signaling pathway, which is frequently deregulated in cancer. Everolimus is an oral drug inhibiting the mTOR pathway. A phase II study in chemotherapy-pretreated patients reported a disease control rate of 56 % [66] and mOS and mPFS of 10 and 2.7 months, respectively. Everolimus-related pneumonitis (G1–2) was observed in 15 % of the patients. Based on these data, the GRANITE-1, a placebo-controlled phase III study of everolimus in second-/third-line treatment of metastatic GEJA/GC, failed to prolong OS, the primary end point. In the intervention arm, the disease control rate was 43 %, and PFS and OS 1.7 and 5.4 months, respectively. Pneumonitis occurred in 3 % of the patients [67].

The ability of everolimus to enhance the activity of second-line treatment with paclitaxel is currently being investigated in another phase III trial, rad001-paclitaxel (RAD-PAC) (AIOSTO-0111, NCT01248403).

Targeting the immune check point pd-1 (programmed death 1)

Malignant cells may evade the immune system control favoring disease progression. Immune check points (such as CTLA-4 and PD-1 and its ligands) play a key role suppressing T-lymphocyte activity. Reversing the inhibition of adaptive immunity can lead to active stimulation of patient's immune system. Pembrolizumab is a selective MoAb against PD-1. Preliminary data from the phase I KEYNOTE012 study in heavily pretreated patients showed 31 % RR, with a significant association between the PD-L1 expression level and RR; 6-month OS rate was surprisingly high (69 %), however at the price of not negligible toxicity [68, 69]. Based on these results, two phase III studies are ongoing [ClinicalTrials.gov Identifier: NCT02494583 and NCT02370498].

Conclusions

In unresectable and metastatic GEJA chemotherapy has produced a modest impact on OS [1, 70]. The availability of targeted agents gives new hope to the patients on the difficult steep path to the cure of this aggressive tumor,

although to date only a small survival gain has been shown. Two other major points have to be primarily considered: clinical results must be balanced against the quality of life and quality-adjusted survival and the high cost of these drugs.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards This article does not contain any studies with human or animal subjects performed by any of the authors.

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