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Novel Targeted Therapies for Esophagogastric Cancer

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Synopsis

Gastroesophageal cancer (GEC) remains a major cause of cancer-related mortality worldwide. Although the incidence of distal gastric adenocarcinoma (GC) is declining in the United States, proximal esophagogastric junction adenocarcinoma (EGJ) is rising in incidence. GEC, including GC and EGJ, is currently are treated with the same systemic regimens in the metastatic setting. Overall survival metastatic disease remains poor, with few molecular targeted approaches having been successfully incorporated into routine care to date – only first line anti-HER2 therapy for *ERBB2* amplification and second line anti-VEGFR2 therapy have succeeded in improving outcomes. Molecular characterization of GEC has identified other relatively frequent mutations and copy number variations in *EGFR*, *FGFR2*, *MET*, *PI3K*, and other oncogenes, candidate biomarkers, and immuno-oncologic checkpoints that may serve as actionable therapeutic targets. Here we review these key aberrations, their impact on protein expression, therapeutic implications, and potential future clinical directions within each pathway.

Keywords

Gastric cancer; esophagogastric junction cancer; gastroesophageal adenocarcinoma; HER2; VEGFR2; EGFR; MET; FGFR2; claudin 18.2

Background

Distal gastric adenocarcinoma (GC) is the fifth most common cancer globally and third most common cause of cancer-related mortality.^{1–3} Approximately twenty-five thousand new GC cases and eleven thousand deaths occurred in the United States in 2015.⁴ Esophagogastric junction adenocarcinoma (EGJ) continues to increase in incidence. For both diseases, the

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majority of patients present with either metastatic or locally advanced disease, and even patients with earlier stage disease have a high risk of recurrence despite aggressive perioperative therapy. In the metastatic setting, the median overall survival is approximately 11 months with optimal palliative chemotherapy. Over the past decade, molecular subtyping of GEC has highlighted the inter-patient heterogeneity of GEC and uncovered potentially actionable molecular pathways.⁵ Routine next generation sequencing identified that at least 37% of GC patients harbor genetic alterations in receptor tyrosine kinases (RTKs), including *ERBB2*, *MET*, *EGFR*, *KRAS*, and *FGFR2*.^{6–8} These genomic events, as well as recently derived key subsets of the disease, namely microsatellite instability-high (MSI-high), EBV-associated (EBV), chromosomal instability (CIN), and genomically stable (GS), provide for more specific molecularly targeted therapeutic possibilities.⁹

ERBB2

ERBB2, or HER2, is a transmembrane RTK within the epidermal growth factor receptor (EGFR) family, encoded on chromosome 17q21. HER2 regulates proliferation, adhesion, differentiation, and migration via activation of the RAS-MAPK and PI3K-AKT pathways. HER2 lacks an exogenous ligand and is transactivated via heterodimerization with other HER family members leading to downstream kinase activation. Significant and therapeutically relevant over-expression results predominantly from gene amplification. HER2 IHC expression localizes to the cell membrane in well-differentiated adenocarcinoma and to the cytoplasm in poorly-differentiated adenocarcinomas, which may affect treatment response.¹⁰ HER2 expressing tumors are more common with EGJ (15–20%) compared with the distal GC (10–15%), and the prognostic impact of HER2 expression remains controversial.^{11–18}

Effective targeting of HER2 in gastric cancer was initially demonstrated using trastuzumab, a humanized monoclonal anti-HER2 antibody against the HER2 ectodomain (Table 1). The phase III Trastuzumab for Gastric Cancer (ToGA) trial evaluated first line fluoropyrimidine/cisplatin chemotherapy doublet with or without trastuzumab in patients with HER-2 over-expressing (any IHC 3+ or FISH HER2:CEP17 ratio ≥ 2) unresectable or metastatic GEC. Patients receiving trastuzumab survived a median of 13.8 months versus 11.1 months with chemotherapy alone, and response rates were 47% and 35% respectively in the intention-to-treat (ITT) population. In a subset analysis, median survival was 16 vs 11.8 months in the combined IHC2+/FISH+ and IHC3+ groups, accounting for 77% of the patients. This trial therefore led to the approval of trastuzumab in HER2 over-expressing gastric cancer for the IHC2+/FISH+ and IHC3+ subsets of the trial.^{18,19}

Though HER-2 over-expression/*ERBB2* amplification predicts benefit from the anti-HER2 antibody trastuzumab in the first line setting,¹⁸ the definition of positivity and trial inclusion criteria within trials has evolved over time. Current clinical diagnostic testing requires evaluation by a combination of IHC (membranous reactivity in $\geq 10\%$ of cancer cells in a surgical specimen or a cluster of at least 5 cells in a biopsy specimen), and fluorescence in-situ hybridization (FISH with HER2:CEP17 ratio ≥ 2). IHC 0/1 is considered negative, and IHC3+ is considered positive without the need for FISH testing, while IHC2+ requires FISH assessment. Higher throughput assays, including mass spectrometry and next-generation

sequencing (NGS), have emerged with the potential to refine diagnostic accuracy as well as possessing multiplexing capability to assess for other relevant aberrations.^{5,20,21} Assessment of *ERBB2* amplification by cell free DNA (cfDNA) is also emerging as a potential non-invasive strategy, potentially for serial assessment of ERBB2 status over time in a non-invasive manner,²² given reports supporting the concept of tumor evolution including the potential loss of ERBB2 expression over time.^{21,23–25}

Lapatinib, a selective intracellular tyrosine kinase inhibitor (TKI) of ERBB1 and EERBB2 was also studied in first and second line GEC (Table 1). The phase III TRIO-013/LOGiC (Lapatinib in Combination With Capecitabine Plus Oxaliplatin in Human Epidermal Growth Factor Receptor 2–Positive Advanced or Metastatic Gastric, Esophageal, or Gastroesophageal Adenocarcinoma) trial randomized 545 untreated HER2 positive (HER2:CEP17 ratio 2 by FISH or IHC 3+ if FISH not available) GEC patients to receive capecitabine and oxaliplatin in addition to either lapatinib or placebo. Lapatinib increased objective response from 39% to 53%, and modestly increased median PFS from 5.4 to 6 months, but failed to confer an overall survival benefit in the ITT population.²⁶ Younger and Asian patients appeared to derive the most benefit in subset analyses. The absolute level of amplification positively correlated with outcome, as previously described,^{27,28} signifying heterogeneity of benefit within the current HER2 positive classification. Recently, the degree of amplification has been shown to correlate closely with absolute protein expression level, again closely associated with clinical benefit.^{20,29} The variations in absolute amplification/ expression across various trials, as well as lack of antibody-dependent cell-mediated cytotoxicity (ADCC) with lapatinib as compared to trastuzumab, serve as two of many potential explanations when contrasting outcomes of ToGA and LOGiC. In the second line, the phase III Asian TyTAN trial enrolled patients regardless of HER2 expression (FISH 2 were eligible), where 31% of patients enrolled were FISH+ and IHC 0/1+.³⁰ Patients received paclitaxel alone or in combination with lapatinib. Despite response rates of 27% versus 9%, no significant PFS or OS benefit was demonstrated in the ITT population. Of note, when limiting the evaluation to only those patients with 3+ HER2 expression by IHC, median survival improved to 14 months from 7.6 months in this subgroup ($p=0.0176$), and progression-free survival 5.6 versus 4.2 months ($p=0.0101$). This highlights the need to improve patient selection for targeted therapies.

Trastuzumab emtansine (T-DM1), an antibody-drug conjugate that is approved in HER2 positive metastatic breast cancer, was studied in the second line GATSBY trial (Table 1), but this failed to support a response or survival benefit versus paclitaxel monotherapy.³¹ Possible explanations for this negative trial include intra-patient tumor heterogeneity recognized to be more frequent than observed in breast cancer, with HER2-negative clones not controlled by targeted cytotoxic therapy. There is now recognition of possible conversion to a HER2 negative status after first line therapy, making archived samples, as used in GATSBY (and TyTAN), inadequate for selecting appropriate HER2+ patients in second line.^{21,23–25}

Whereas trastuzumab binds domain IV of HER2, the HER2- targeted agent pertuzumab binds domain II and thereby prevents dimerization. The CLEOPATRA trial revealed progression-free and overall survival benefits with the addition of pertuzumab to trastuzumab and chemotherapy in breast cancer,³² and initial results from the JACOB trial,

evaluating pertuzumab in combination with trastuzumab and chemotherapy in the first line treatment of HER positive GEJ cancer, are eagerly awaited.

Thus, to date, no standard anti-HER2 directed approaches are recognized in trastuzumab refractory HER2+ GEC. However, standard chemotherapy with irinotecan or taxane based regimens are recommended. Notably, while second line ramucirumab trials, discussed below, included HER2 positive and trastuzumab-treated patients, this accounted for only ~6% of patients enrolled in RAINBOW (Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma) and <1% of REGARD (Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma).^{33,34} Other strategies under evaluation in second and later lines of therapy include novel TKIs like apatinib,³⁵ trastuzumab beyond progression,^{23,25} novel HER2 antibodies,³⁶ and combination therapy with immune checkpoint inhibitors (Table 5).³⁷

VEGF

Vascular endothelial growth factor (VEGF) induces angiogenesis and neovascularization. Over-expression is found in up to 58% of resected gastric cancer patients,³⁸ and 7% of the Cancer Genome Atlas (TCGA) gastric cancer patients have VEGF-A amplification.⁹ Ramucirumab, a human IgG1 monoclonal antibody directly binding to VEGFR2 thus inhibiting VEGF ligand binding, was evaluated in the second line setting in the phase III REGARD trial (Table 2).³⁴ Compared to supportive care, ramucirumab demonstrated an overall survival of 5.2 vs 3.8 months ($p=0.047$), despite a response rate of only 3 percent – the same as the placebo control.³⁴ The phase III RAINBOW trial subsequently compared paclitaxel with or without ramucirumab in the second line setting (Table 2). Patients had a significant overall survival benefit of 9.6 vs 7.4 months ($p=0.017$) as well as statistically significant PFS and ORR benefits.³³ In the third line setting, apatinib, a multi-TKI, including VEGFR kinases, demonstrated an absolute 0.8 month PFS advantage (2.6 vs 1.8mo) as well as a nearly 2 month overall survival benefit when compared with placebo in a Chinese population.³⁹

Unfortunately, evaluation of anti-angiogenesis in the first line setting of GEC has been disappointing to date. The AVAGAST (Avastin in Gastric Cancer) trial evaluated chemotherapy (cisplatin and capecitabine) with or without bevacizumab, a humanized IgG1 VEGFA monoclonal antibody. Despite PFS (6.7 vs 5.3 months, $p=0.0037$) and ORR (46% vs 37.4%, $p=0.0315$) benefits, the improved median OS of 12.1 over 10.1 months observed in the control was not statistically significant.⁴⁰ An Asian trial, AVATAR, confirmed these negative findings.⁴¹ A phase II trial of first line Ziv-aflibercept with FOLFOX recently did not meet its primary endpoint of 6 month PFS compared to FOLFOX alone.⁴² Additionally, a phase II trial in first line GEC comparing FOLFOX with or without ramucirumab was negative.⁴³ Despite this, the phase III RAINFALL (**Ramucirumab in Combination With Capecitabine and Cisplatin in Participants With Stomach Cancer**) trial is currently evaluating first line ramucirumab/placebo in combination with capecitabine and cisplatin in metastatic gastric cancer, with results eagerly awaited (NCT02314117).

Potential predictive biomarkers of response to anti-angiogenesis agents, to incorporate into routine practice have remained elusive.⁴⁴ The AVAGAST trial suggested that patients with high plasma VEGF-A levels had increased overall survival compared with those expressing low VEGF-A levels,¹² and hypertension as a biomarker has been noted.⁴² Further biomarker development may help identify a subset of patients that derive the most benefit from targeting this axis. However, biomarkers of response may remain undefined, potentially due to a marginal benefit realized by most patients.

EGFR

Epidermal growth factor receptor (EGFR) or ErbB1 is a transmembrane receptor and a well-recognized mediator of oncogenic phenotype that is 'overexpressed' in approximately 30% of GEC^{45,46}. EGFR-overexpressing tumors are associated with higher stage, more poorly differentiated histology, increased vascular invasion, and potentially shorter survival.^{14,47} *EGFR* amplification is found in only ~5% of patients.^{9,48,49}

EGFR-directed therapies evaluated in GEC include monoclonal antibodies such as cetuximab and panitumumab, which antagonize the extracellular binding domain. Pre-clinical data also suggested that cetuximab, a recombinant human-murine chimeric monoclonal antibody of a murine Fv region and a human IgG1 heavy and k light chain Fc region, induces ADCC.⁵⁰ Small molecule TKIs, such as gefitinib, erlotinib, lapatinib, and afatinib competitively bind intracellularly to the tyrosine kinase domain. Early phase II trials combining cetuximab, panitumumab, or erlotinib with cytotoxic chemotherapy in GEC reported first line therapy response rates ranging from 41–65%.^{51–54} Second line phase II evaluation of gefitinib or erlotinib monotherapy led to more modest responses of ~9–11%, and responses appeared limited to proximal EGJ cancers rather than distal GC.^{55,56}

Subsequent phase III GEC trials targeting EGFR included EXPAND ((cetuximab, first line), REAL-2 (panitumumab, first line), and COG (gefitinib, second line) (Table 3).^{15,57,58} Each trial was negative, and panitumumab actually resulted in worse survival when combined with chemotherapy compared to chemotherapy alone. Notably, each of these trials enrolled all-comers without biomarker selection of any kind.

Xenograft models evaluating anti-EGFR therapy for *EGFR*-amplified tumors have reported potential benefit.⁵⁹ In the phase II study combining FOLFOX with cetuximab, 22% of patients had greater than 4 *EGFR* copies, which correlated with increased overall survival.⁶⁰ Similarly, in TRANS-COG, 15.6% of patients had increased gene copy number (GCN) including true *EGFR* amplification (~5%); this latter small subset of *EGFR* amplified patients derived a statistically significant survival benefit with the addition of gefitinib (HR 0.19, p=0.007). The EXPAND trial also demonstrated survival benefit in the small subset with extremely high EGFR expression by IHC H-Score (likely representing EGFR amplified tumors, but yet to be confirmed).⁶¹ With these recent promising subset analyses of *EGFR* amplification and consequent overexpression, future studies assessing the benefits of anti-EGFR therapy in these patients are being pursued.⁶² Also, a Phase III trial of second line nimotuzumab with irinotecan (NCT01813253) is currently recruiting patients deemed to harbor EGFR overexpressing (IHC 2/3+) tumors (Table 5).

MET

The MET proto-oncogene encodes the c-MET receptor tyrosine kinase, which is involved in cell proliferation, angiogenesis, and migration. MET over-expression, as well as the subset with *MET* amplification, are each associated with worse survival in most reports.^{47,48,63–71} Canonical MET activation occurs via binding of its ligand, hepatocyte growth factor (HGF), but MET activation can also occur in an HGF-independent manner through RTK cross-talk.^{72,73} *MET* amplification leads to constitutive receptor activation independent of ligand, and is reported in ~4–10% of GEC cases,^{48,74–76} but over-expression ranges from 23.7–70% in GEC, depending on the cohort evaluated and method of analysis used.^{66–68,77–79}

As a predictive biomarker, early phase reports and trials initially suggested that GEC patients with MET-expressing tumors may benefit from MET-directed therapy.^{71,77} However, a subsequent phase II,⁸⁰ and two Phase III MET-directed trials in GEC have been reported with overall negative results (Table 4).^{80,81} The MetGastric study evaluated onartuzumab, a humanized IgG1 antibody against the extracellular domain of c-MET, in combination with mFOLFOX6, in patients with c-MET-expressing tumors (1+, 50% cells).⁸² However, METGastric was terminated prematurely (70% of planned accrual) due to negative results (in any MET expression group) in the prior/parallel YO28252 phase II biomarker evaluation trial of onartuzumab in unselected GEC patients.⁸⁰ With this in mind, no benefit was seen in the ITT nor in the MET IHC 2/3+ subgroup analysis (~38% of enrolled patients, HR 0.64, p=0.06), which had less power to identify a benefit due to early termination of the trial.⁸² Similarly, RILOMET-1, which evaluated epirubicin, cisplatin, and capecitabine (ECX) with or without the addition of rilotumumab, a fully human IgG2 antibody against HGF ligand, was terminated due to an increased risk of death from the study drug.⁸¹ Ultimately, no improvement in any outcome was observed for the combination of rilotumumab and chemotherapy compared to chemotherapy alone.

One pitfall of these phase III trials is the loose definition of MET expression. In RILOMET-1, patients selection was defined as 1+ MET expression by IHC in ≥25% of tumor cells to be eligible, and of all patients enrolled ~90% were at the lowest 1+ intensity of any extensity. Similarly, only 38% of METGastric were IHC 2/3+, yet as above, these patients demonstrated a near-significant benefit, in an under-accrued trial. Even with the large phase III MET inhibitor trials, one could argue that the selection for ‘MET-dependent’ cancers was too lenient and inadequate, and the highest expressing tumors under-represented.^{48,74–76} Another negative trial in second line with the multi-targeted-TKI foretinib was observed, again without selecting patients by any biomarker.⁸³

More promising results have been reported in smaller trials of MET inhibitors for *MET* amplified patients (4–5% of GEC),^{48,67,74,76} with consequent over-expression.⁷⁴ AMG-337, a relatively highly selective MET TKI, demonstrated clinical responses in *MET*-amplified advanced GEC patients (ORR 50%), but the phase II study has been on hold after the expansion phase of the trial (results not publically available).⁸⁴ Similarly, half of *MET*-amplified patients treated with crizotinib in a phase I expansion cohort experienced response,⁴⁸ and 75% of MET amplified patients receiving ABT-700 monoclonal antibody monotherapy demonstrated an objective response.⁸⁵ The challenge of molecular heterogeneity,^{23,86} particularly in the CIN subset of GEC,⁹ may account for lack of response

and relative quickly developed resistance to MET-directed therapy of *MET* amplified GEC. Any future therapeutic attempts with MET inhibitors will likely be directed towards the small subset of *MET* amplified patients (Table 5).⁸⁷

FGFR2

Fibroblast growth factor type 2 (*FGFR2*) encodes a RTK that regulates cell angiogenesis and proliferation, and when highly expressed, portends a poor prognosis in both Western and Asian populations.⁸⁸ *FGFR2* expression in GEC is primarily driven by gene copy number, with 4–10% of GEC demonstrating *FGFR2* amplification.^{6,88,89} *FGFR2* amplification is associated with diffuse type GC. Dovitinib, a TKI targeting FGFR 1-3, VEGF 1-3, PDGFR, and c-KIT, had promising results in in vitro studies.⁶ The SHINE trial compared paclitaxel with AZD4547, an *FGFR2* TKI, in advanced GC in Asia, but the paclitaxel arm had superior survival – even in the *FGFR2*-amplified patient subset.⁹⁰ On the other hand, another small phase IIa trial demonstrated response in 3/9 (33%) with promising durability in *FGFR2* amplified patients, and also observed that higher and homogenous gene amplification may better predict therapeutic benefit.⁹¹ These early phase trials suggest safety from this class of inhibitors, with mainly hypophosphatemia and ocular toxicities reported.⁹⁰ Phase II trials are ongoing in combination with cytotoxic therapies and may be a more promising approach than monotherapy. Recently, 2/6 (33%) *FGFR2* over-expressing gastric cancer patients responded to FPA144, a novel humanized monoclonal IgG1 antibody against *FGFR2b*, in a chemotherapy-refractory phase I evaluation.⁹² Another 3/6 (50%) had stable disease, resulting in a 5/6 (83%) disease control rate in this early assessment. Phase I expansion accrual remains ongoing in this patient population, with specific interest in *FGFR2* amplified GEC patients (Table 5).

PI3K-AKT-mTOR

The PI3K-AKT-mTOR pathway is commonly altered in GEC leading to increased proliferation and apoptotic resistance, and this pathway is downstream from transmembrane receptors including HER2, EGFR, VEGFR, and FGFR. *PIK3CA* activating mutations, loss of *PTEN*, *RICTOR* amplification or *AKT* amplification have all been described.^{5,9,49} *PIK3CA* activating mutation alone is observed in ~15% of GEC.

Attempted inhibition of mTOR with everolimus demonstrated a median PFS of 2.7 months and OS of 10.1 months in an early study, but the subsequent phase III GRANITE-1 trial comparing everolimus with placebo in an unselected patient population as 2nd or 3rd line therapy failed to demonstrate an overall survival benefit.^{93,94} Results from a phase III trial of paclitaxel with or without everolimus are still awaited (NCT01248403). Numerous PI3K inhibitors have shown benefit in preclinical studies including BEZ235 and BKM120 as monotherapy, or in combination with HSP90 or hedgehog inhibitors, but the as yet uncertain clinical benefit in patients suggests a disconnect between preclinical models and treated GEC patients.^{95,96} Second line AKT inhibition trials are ongoing with AZD5363 in combination with paclitaxel (NCT02451956/NCT02449655), as well as the first line JAGUAR trial combining FOLFOX with or without AKT inhibition using ipatasertib (NCT01896531). Strategies selecting for only those with tumors having a genomically

activated PI3K-AKT-mTOR pathway may enrich for clinical benefit with these targeted therapies (Table 5).

CLDN18.2

Claudins are structural components of tight junctions that seal the intercellular space, and are over-expressed in numerous cancers. *CLDN18* gene amplification is found in 3% of TCGA gastric cancer patients and 3% of patients also harbor oncogenic gene fusions between *CLDN18* and *ARHGAP26*, a RHOA inhibitor.⁹⁷ These fusions impair cell-extracellular membrane adhesion, and in doing so promote migration. Claudiximab (IMAB362) is a chimeric IgG1 monoclonal antibody against CLDN18.2 that is intended to enhance T-cell infiltration and ADCC.⁹⁸ Claudiximab was developed from high throughput screening of malignancy-specific cell surface molecules that identified gastric specificity of the claudin 18 splice variant 2.⁹⁹ Phase II evaluation in combination with EOX first line cytotoxic therapy demonstrated a 39% ORR along with benefits in PFS and OS, most pronounced in high expressers of CLDN18.2 (Table 5).¹⁰⁰ Further evaluation is planned in a phase III study.

PD-L1

Immune checkpoint inhibition with programmed-death 1 (PD-1) and programmed-death ligand 1 (PD-L1) inhibitors are under evaluation in many cancers, including GEC. PD-L1 normally binds to receptors on T-lymphocytes thereby inhibiting T-cell proliferation and inducing apoptosis, which impairs the cytotoxic immune response. EBV-associated GEC over-expresses PD-L1 and PD-L2 due to amplification of 9p24,¹⁰¹ and MSI-High tumors are also associated with intense immune infiltration and overexpression of checkpoint inhibitor targets.^{9,102} Keynote-012 evaluated pembrolizumab, a PD-1 inhibitor, in PDL1+ (~30–40% of patients screened) advanced GC, and demonstrated a 22% objective response rate.¹⁰³ Of note, although PD-L1 over-expression correlated with a higher response rate, PD-L1 expression remains a poor predictive biomarker – patients without PD-L1 expression can still respond, and often those with expression do not derive benefit.¹⁰³ Similarly, in the CheckMate-032 trial, objective response to nivolumab, another PD-1 inhibitor, was 18% and 12% in PD-L1 positive and negative patients, respectively in chemotherapy refractory GEC patients.¹⁰⁴ Second line response rates, stratified by PD-L1 status, were similar in the Javelin GEC trial with avelumab, a PD-L1 antagonist (18.2% vs 9.1%), and less in later therapy lines (10% vs 3.1%).¹⁰⁵ RNA expression signatures reflecting interferon gamma activity and T-cell activity, which may identify patients more response to immune checkpoint inhibition, are currently under development to improve patient selection.¹⁰⁶ Phase III evaluation of pembrolizumab (KEYNOTE-062, KEYNOTE-061) in the first line and second line metastatic settings respectively, and nivolumab (CheckMate-577) in the adjuvant setting are ongoing, with various other approaches in all lines of therapy being assessed with the various available checkpoint inhibitors.¹⁰⁷

CTLA-4

Cytotoxic T lymphocyte antigen 4 (CTLA4) is constitutively expressed on the surface of T-regulatory cells and expression can be inducible on activated T lymphocytes and monocytes. Up-regulation leads to IL-2 production and IL-2R expression, with subsequent priming of

the T-cell response¹⁰⁸. Mutations and copy number variation of CTLA4 occur rarely in only 2.5% of TCGA gastric cancer patients. Tremelimumab is a fully humanized IgG2 anti-CTLA4 monoclonal antibody that has undergone evaluation in numerous other malignancies. Of the 18 metastatic GC patients enrolled in a second line phase II trial, no objective responses were seen after cycle 1. However, 12-month survival was 33%, and one patient later derived a partial response after 25.4 months of therapy and was alive at 32.7 months at the time of publication¹⁰⁹. Ipilimumab, another CTLA-4 antagonist, was evaluated as maintenance therapy after receiving a platinum fluoropyrimidine doublet, but failed to prolong PFS or OS.¹¹⁰ Evaluation remains underway in combination with PD-1/PD-L1 antagonists as discussed above.¹⁰⁷

Summary

Despite trials evaluating targeted therapies for GEC, only trastuzumab and ramucirumab have demonstrated benefit and been approved in the first and second line settings, respectively. Subset analyses have successively identified patients with *MET*, *EGFR* and *FGFR2* genomic aberrations that may benefit from matched targeted therapies, yet designing traditional trials for such infrequent aberrations and inter-patient heterogeneity continues to remain extremely challenging. Tumor molecular heterogeneity within patients and over time and serial lines of therapy, are also hurdles to successful implementation of these targeted agents. Novel trial designs such as the PANGEA type II expansion platform may better identify and treat these uncommon actionable aberrations as a way forward by testing a treatment strategy.^{23,62,111} Immune checkpoint inhibitors are being evaluated and hold promise, with investigations ongoing to determine subsets likely to derive benefit. Future directions should focus on improving diagnostic assays and validating predictive biomarkers for benefit from immuno-oncologic therapies.

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Key Points

- Anti-HER2 trastuzumab therapy is standard for HER2 amplified/overexpressed gastroesophageal adenocarcinoma, while second/later lines of anti-HER2 directed therapy have not demonstrated definitive benefit to date.
- Anti-VEGFR2 ramucirumab therapy has demonstrated modest survival benefit as monotherapy and in combination with paclitaxel in second line gastroesophageal adenocarcinoma patients.
- Anti-EGFR therapy has not demonstrated benefit in unselected gastroesophageal patients in any line of therapy, while gene amplification/overexpression has some evidence to support further investigation.
- Anti-MET therapy has not demonstrated benefit in ‘over-expressing’ gastroesophageal patients in any line of therapy, while gene amplification/overexpression has some evidence to support further investigation.
- Other promising predictive biomarkers and targeted therapies, including FGFR2 and claudin18.2, require further investigation in larger trials to confirm therapeutic benefits for gastroesophageal adenocarcinoma patients.

Table 1

Phase III trials evaluating HER2-targeted therapies.

Line	Trial	N	Treatment	Primary Endpoint (Met?)	mOS (mo)	HR	mPFS (mo)	HR	RR
1L	Bang <i>et al</i> ¹⁸ TOGA	584	Cis/FP + Placebo Cis/FP + Trastuzumab	OS (Yes)	11.1 13.8	0.74 P<0.0046	5.5 6.7	0.71 P<0.001	35% 47%
1L	Hecht <i>et al</i> ²⁶ LOGIC	545 (487)	Cis/FP + Placebo Cis/FP + Lapatinib	OS (No)	10.5 12.2	0.91 p=N.S.	5.4 6	0.82 P=0.03	39% 53%
2L	Sato <i>et al</i> ³⁰ TYTAN	261	Paclitaxel + Placebo Paclitaxel + Lapatinib	OS (No)	8.9 11	0.84 p=N.S.	4.4 5.5	0.84 p<0.001	9% 27%
2L	Kang <i>et al</i> ³¹ GATSBY	345 (1:2)	Pac (38%)/ Doc (62%) T-DM1	OS (No)	8.6 7.9	1.15 p=N.S.	2.9 2.7	1.13 p=N.S.	20% 21%

Cis/FP: Cisplatin+Fluoropyrimidine, Pac: Paclitaxel, Doc: Docetaxel

Table 2

Phase III trials of VEGF-targeted therapies in GEC

Line	Trial	N	Treatment	Primary Endpoint (Met?)	mOS (mo)	HR	mPFS (mo)	HR	RR
2L	Fuchs <i>et al</i> ³⁴ REGARD	335	Placebo Ram	OS	3.5 5.2	0.78 p=0.047	1.3 2.1	0.48	3% 3%
2L	Wilke <i>et al</i> ³³ RAINBOW	665	Paclitaxel + Placebo Paclitaxel + Ram	OS	7.4 9.6	0.8 p=0.017	2.9 4.4	0.64	16% 27%
3L	Li <i>et al</i> ³⁹	267	Placebo Apatinib	OS/PFS	4.7 6.5	0.71 p=0.015	1.8 2.6	0.44	0 3%
1L	Ohtsu <i>et al</i> ⁴⁰ VAGAST	774	Cis/5FU + Placebo Cis/5FU + Bev	OS (No)	10.1 12.1	0.87 N.S.	5.3 6.7	0.8 p=0.004	37.4 46
1L	Shen <i>et al</i> ⁴¹ AVATAR	202	Cis/Cape + Placebo Cis/Cape + Bev	OS (No)	11.4 10.5	1.11 N.S.	6 6.3	0.89 N.S.	34 41
1L	Yoon <i>et al</i> ⁴³	168	FOLFOX + Placebo FOLFOX + Ram	PFS (No)	11.7 11.5	1.08 N.S.	6.7 6.4	0.98 N.S.	46 45
1L	Enzinger <i>et al</i> ⁴²	64 1:02	FOLFOX + Placebo FOLFOX + Afibercept	6m PFS (No)	18.7 13.7	0.7 N.S.	7.3 9.9	0.88 N.S.	75 61

PI: Placebo, Ram: Ramucirumab, Cis/5FU: Cisplatin/5-fluorouracil, Bev: Bevacizumab, Cis/Cape: Cisplatin/Capecitabine

Table 3

Phase III trials evaluating EGFR-targeted therapies

Line	Trial	N	Treatment	1 ^o Endpt (Met?)	mOS (mo)	HR	mPFS (mo)	HR	RR
1L	Lordick <i>et al</i> ¹⁵ EXPAND	904	Cis/5FU +Placebo Cis/5FU +Cetuximab	PFS (No)	10.7 9.4	1.00	5.6 4.4	1.09 p=0.32	29% 30%
1L	Waddell <i>et al</i> ¹⁶ REAL-3	553	Epi/Oxali/Cape + PI Epi/Oxali/Cape + P	OS (No)	11.3 8.8	1.37 p=0.013	7.4 6.0	1.22	42% 46%
2L	Dutton <i>et al</i> ⁸ COG	450	Placebo Gefitinib	OS (No)	3.67 3.73	0.9	1.17 1.57	0.8	~1% ~4%

Cis/5FU; Cisplatin/5-fluorouracil;Epi/Oxali/Cape: Epirubicin/Oxaliplatin/Capecitabine, PI; Placebo, P; Panitumumab

Table 4

Phase III trials evaluating MET-targeted therapies in GEC

Line	Trial	N	Treatment	I ⁰ Endpoint (Met?)	mOS (mo)	HR	mPFS (mo)	HR	RR
1L	Cunningham <i>et al</i> ¹² RILOMET-1	609	Epi/Cis/5FU+ Placebo Epi/Cis/5FU + Rilo	OS (No)	11.5 9.6	1.37 p=0.016	5.7 5.7	1.3	39% 30%
1L	Shah <i>et al</i> ⁸⁰ MET-GASTRIC	562	FOLFOX + Placebo FOLFOX + Onartuzumab	OS (No)	11.3 11	0.82 p=0.24	6.8 6.7	0.9	41% 46%

Epi/Cis/5FU: Epirubicin/Cisplatin/5-fluorouracil; Rilo: Rilotumumab.

Table 5

Additional targeted therapy trials in GEC

Target	Line	Trial	Phase	Treatment	I ⁰ Endpoint	Outcome
HER2	2L HER2+	NCT02689284	I/II	Targetuximab+Pembro	MTD/ORR	Ongoing
HER2	1L	NCT01774786 JACOB	III	TP+/- Pertuzumab	OS	Ongoing
EGFR	1+, amplified	NCT02213289(BR)/PANGEA-IMBBP	I/II	Chemotherapy+ABT-806	OS	Ongoing
MET	2+L, MET-amplified	NCT02016534	II	AMG-337	ORR	Ongoing (HOLD)
EGFR	2, EGFR Exp 2/3+	NCT01813253	III	Irinotecan +/- Nimotuzumab	OS/PFS	Ongoing
FGFR2	3+L, amplified	NCT01719549	II	Dovitinib	RR/PFS	Ongoing
FGFR2	2+L, amplified	NCT01921673	I/II	Dovitinib+Docetaxel	MTD/PFS	Ongoing
FGFR2	2L, polysomy/amplified	<u>NCT01457846</u> SHINE ⁹⁰	II	AZD4547 vs Paclitaxel	PFS	Negative (amplified mPFS 1.5 vs 2.3 mo)
FGFR2	Any	NCT02318329 ⁹²	I	FPA144	MTD/DLT	Ongoing
PI3K	2+L 2-4L, PIK3CA	NCT01576666	IB	LDE225+BKM120	MTD/DLT	Ongoing
PI3K	mutated/amplified or HER2+	NCT01613950	IB	BYL719+AUY922	MTD/DLT	Ongoing
Akt	2L, PIK3CA mutated/amplified	NCT02451956	II	AZD5363+Paclitaxel	ORR	Ongoing
Akt/mTOR	2L	NCT02449655	II	Paclitaxel + AZD5363 or AZD2014	ORR	Ongoing
mTOR	2-3L	NCT00879333 GRANITE-1 ⁹⁴	III	Everolimus vs Placebo	OS	Negative (5.4 vs 4.3 mo, $p=0.124$)
CLDN18.2	1L, CLDN18.2 expressing	NCT01630083 FAST ¹⁰⁰	II	EOX + - IMAB362	PFS	Positive - improved PFS, OS