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Update on Gastroesophageal Adenocarcinoma Targeted Therapies

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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) incidence is rising. GC and EGJ, together, are treated uniformly in the metastatic setting as GEC. Overall survival in the metastatic setting 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. Here we review aberrations in EGFR, MET, and ERBB2, their therapeutic implications, and future directions in targeting these pathways.

Keywords

Gastroesophageal; gastric; MET; EGFR; HER2; ERBB2; treatment; targeted

Background

Distal gastric adenocarcinoma (GC) incidence remains the fifth most common cancer globally, and the third highest for cancer-related mortality.[1–3] Approximately twenty-five

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thousand new GC cases and eleven thousand deaths were predicted in the United States in 2015.[4] Further, esophagogastric junction adenocarcinoma (EGJ) incidence is increasing. When assessing GC and EGJ cancers, together known as gastroesophageal cancer (GEC), the majority of patients present with metastatic or locally advanced disease with a high risk of recurrence despite aggressive perioperative therapy. In the metastatic/recurrent setting, median overall survival remains approximately 11 months with optimal palliative chemotherapy in *ERRB2* non-amplified patients. 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, namely amplifications, in receptor tyrosine kinases (RTKs), including *ERBB2, MET, EGFR, KRAS,* and *FGFR2.*[6–8] Clinical trials of agents targeting these pathways have had mixed results. However, interpretation of these results requires understanding both the agents used as well as the study population. 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 molecularly targeted therapeutic possibilities.[9]

ERBB2

ERBB2, or HER2, is a transmembrane RTK within the epidermal growth factor receptor (EGFR) family, encoded at chromosome17q21. HER2 regulates proliferation, adhesion, differentiation, and migration via activation of the RAS-MAPK and PI3K-AKT pathways (Figure 1). HER2 lacks an exogenous ligand and is transactivated via heterodimerization with other HER family members leading to downstream kinase activation. Significant and therapeutically relevant protein over-expression results predominantly from gene amplification; less commonly, other genomic events may include activating mutation. 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* amplified tumors are more common with EGJ (15–32%) compared with the distal GC (10–15%), and the prognostic impact of *HER2* amplification remains controversial (Table 1).[11–18]

Effective targeting of HER2 in GEC was initially demonstrated using trastuzumab, a humanized monoclonal anti-HER2 antibody against the HER2 ectodomain (Table 2). The phase III ToGA trial evaluated a 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.[18] Patients receiving trastuzumab survived a median of 13.8 months versus 11.1 months with chemotherapy alone (HR 0.74, p=0.0046), 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 enrolled, whereas IHC0-1+/FISH+ patients appeared to derive no benefit. 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]

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Finally, whereas trastuzumab binds domain IV of HER2, pertuzumab binds domain II, and thereby prevents dimerization with other RTKS, namely HER3. The CLEOPATRA trial in breast cancer revealed progression-free and overall survival benefits with the addition of pertuzumab to trastuzumab and chemotherapy as first line therapy,[20] and initial results from the counter-part JACOB trial for GEC evaluating pertuzumab in combination with trastuzumab and chemotherapy are pending.[21] A large trial with appropriate HER2 selection (ie not allowing IHC0-1+/FISH+ patients), and without the concern of later line evolution (ie not second or later line of therapy) nor lack of ADCC (ie like the lapatinib trials) will likely allow JACOB to adequately test the hypothesis whether there is benefit of adding pertuzumab to standard cytotoxic plus trastuzumab therapy for these patients. However, intratumoral and spatial HER2 heterogeneity (at higher rates than compared to breast cancer) may still have implications on the overall trial results. The results of this trial remain eagerly awaited. Lapatinib, a selective intracellular tyrosine kinase inhibitor (TKI) of ERBB1 and ERBB2 was also studied in first and second line GEC (Table 2). The phase III TRIO-013/LOGiC trial randomized 545 untreated first line 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.[22] 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,[23,24] signifying heterogeneity of benefit within the current ‘HER2 positive’ classification. *HER2* amplification varies depending on the report, ranging from 4 to 20% of GEC patients (Table 1). Recently, the degree of amplification has been shown to correlate closely with both absolute protein expression level and clinical benefit.[25] The inter-trial variations in absolute amplification/expression and lapatinib’s lack of antibody-dependent cell-mediated cytotoxicity (ADCC) 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 ratio ≥2 were eligible), where 31% of patients enrolled were IHC 0-1+/FISH+.[26] Patients received paclitaxel alone or in combination with lapatinib. Despite response rates of 27% versus 9%, no statistically 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), with progression-free survival of 5.6 versus 4.2 months, respectively (p=0.0101).

Trastuzumab emtansine (T-DM1), an antibody-drug conjugate that is approved in HER2 positive metastatic breast cancer, was also studied in the second line GATSBY trial for ‘HER2+’ GEC (Table 2), but this failed to support a response or survival benefit versus paclitaxel monotherapy.[27] Possible explanations for this negative trial include intra-patient HER2 tumor heterogeneity, which is more frequent in GEC than observed in breast cancer.[28] With clonal heterogeneity, it has been hypothesized that HER2-negative (or low expressing) clones are not controlled by HER2-targeted cytotoxic therapy. Furthermore, HER2

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expression/amplification has been demonstrated to 'convert' after first line therapy. Archived specimen testing, as used in both second line trials (GATSBY and TyTAN), may therefore lead to inadequate HER2+ patient selection in subsequent line trials.[29–32] Specifically, a recent phase II randomized study of paclitaxel plus trastuzumab versus paclitaxel, trastuzumab plus MM-111 (a bivalent antibody towards HER2 and HER3) was conducted in the second line setting after failure of first line cytotoxic therapy for HER2+ cancers. Eligibility for trial enrollment was determined by archived original diagnostic samples, and correlative studies demonstrated this *HER2* amplification molecular evolution concern. In this trial, the median overall survival of 44 patients receiving trastuzumab and paclitaxel was 14 months versus 8 months in the 44 patients receiving MM-111, trastuzumab and paclitaxel (HR 2.12, p = 0.045, 95% CI 1.0–4.5). Interestingly, central HER2 testing of the 66% of available original archived samples revealed that 30% of cases were actually considered IHC0/1 and 8% IHC2+/FISH-, demonstrating an overall 38% of cases that would never have been considered HER2 positive. This could be due to a combination of factors including intra-tumoral HER2 heterogeneity testing different regions spatially within a tumor, or technique/assay variability and subjective scoring. Importantly, of ~40 patients having matched archival and fresh biopsy prior to initiating second line therapy, ~15% of patients initially considered HER2+ (ratio ≥2) were later found to be HER2- prior to second line therapy initiation. Regardless, approximately 50% of patients enrolled into this 'HER2+' selection trial were considered HER2 negative in retrospect. Future trials evaluating the role of anti-HER2 therapy for GEC patients after failure of prior anti-HER2 therapy should therefore mandate fresh biopsy (and/or possibly cfDNA assessment) to confirm the presence of HER2 positivity at the time of enrollment and thereby ensure proper treatment arm stratification by HER2 status.

As alluded to above, though HER-2 over-expression/*ERBB2* amplification predict benefit from the anti-HER2 antibody trastuzumab in the first line setting,[18,33] the definitions of positivity and trial inclusion criteria have evolved over time. Current clinical diagnostic testing requires evaluation by a combination of IHC (membranous reactivity in ≥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 now considered negative, and IHC3+ is considered positive, while IHC2+ requires reflex to FISH assessment. Higher throughput assays, including mass spectrometry and next-generation sequencing (NGS), have emerged with the potential to refine diagnostic accuracy and allow multiplexing capability to assess for other relevant aberrations with limited tissue samples.[5,25,32] Similarly, circulating cell-free DNA (cfDNA) is emerging as a potential non-invasive method, particularly for serial *ERBB2* amplification,[34] which may provide further insight into tumor genetic evolution.[29–32]

Nevertheless, to date, no standard anti-HER2 directed approaches are recognized in trastuzumab refractory HER2+ GEC using any available diagnostic testing. Standard chemotherapy with irinotecan or taxane based regimens are recommended. Notably, while second line ramucirumab trials included HER2 positive and trastuzumab-treated patients, this accounted for only ~6% of patients enrolled in the RAINBOW trial and <1% of patients enrolled to the REGARD trial (Medical Letter).[35,36] Other strategies under evaluation in the second and later lines include novel TKIs like apatinib,[37] trastuzumab beyond progression

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(and ensuring persisting HER2 positivity),[29,30] novel HER2 antibodies,[38] and combination therapy with immune checkpoint inhibitors (NCT02689284).

Neoadjuvant HER2-directed therapy has been integrated into routine breast cancer therapy based upon the phase III NeOAdjuvant Herceptin (NOAH) trial, which identified an improved 5 year event-free survival and overall survival with the addition of trastuzumab to neoadjuvant chemotherapy.[39] Similarly, the GeparQuattro trial demonstrated increased pathologic complete remission with neoadjuvant trastuzumab in HER2-positive breast cancer patients,[40] which was further increased by combining trastuzumab and lapatinib with chemotherapy in the NeoALTTO trial.[41] Based on these results and the ToGA trial,[18] RTOG1010 explores neoadjuvant chemoradiation in EGJ with carboplatin and paclitaxel with or without trastuzumab. Accrual has completed, and results are awaited (NCT01196390). Similarly, the neoadjuvant INNOVATION trial is evaluating the addition of trastuzumab and pertuzumab to cisplatin and fluoropyrimidine doublet therapy in GEC.[42] The phase II HER-FLOT trial identified an R0 resection rate of 93.3% and pathologic complete remission in 22.2% of patients when trastuzumab was added to peri-operative 5-FU, oxaliplatin, leucovorin, and docetaxel (FLOT).[43] A similar phase II study combining FOLFIRINOX and trastuzumab in the peri-operative setting remains underway (NCT02581462). These findings will be further explored in the phase III PETRARCA study, which randomizes patients to receive peri-operative FLOT with or without trastuzumab and pertuzumab (NCT02581462). However, until these results from these trials are available, HER2-targeted therapy is not considered standard-of-care for GEC in the neoadjuvant setting.

EGFR

Epidermal growth factor receptor (EGFR) or ERBB1 is a transmembrane receptor and a well-recognized mediator of oncogenic phenotype that is expressed in approximately 30% of GEC.[44,45] EGFR-overexpressing tumors are associated with higher stage, more poorly differentiated histology, increased vascular invasion, and potentially shorter survival.[14,46] *EGFR* amplification and consequent overexpression is found in only 2–6% of GEC patients, and mutations in less than 2%, though the functional and therapeutic implications of these aberrations are yet to be clearly defined (Table 1).[9,47,48]

EGFR-directed therapies include monoclonal antibodies such as cetuximab and panitumumab, which antagonize the extracellular binding domain. Pre-clinical data also suggests 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, also induces ADCC similar to trastuzumab.[49] Small molecule TKIs, such as gefitinib, erlotinib, lapatinib, and afatinib competitively bind intracellular to the tyrosine kinase domain at varying potencies and specificities. Early phase II trials combining cetuximab, panitumumab, or erlotinib with cytotoxic chemotherapy in unselected GEC patients identified first line therapy response rates from 41–65%.[50–53] Second line phase II evaluations of gefitinib or erlotinib monotherapy led to more modest responses of ~9-11%, and responses appeared higher in proximal EGJ cancers rather than distal GC.[54,55]

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Subsequent phase III GEC trials targeting EGFR included EXPAND (cetuximab plus Capecitabin/Cisplatin, first line), REAL-3 (panitumumab plus Epirubicin/Oxaliplatin/Capecitabine, first line), and COG (gefitinib monotherapy, second line) (Table 3).[15,56,57] Disappointingly, each trial was resoundingly negative, and panitumumab actually resulted in worse survival compared to the control. Notably, each of these trials enrolled all-comers without biomarker selection of any kind.

Preclinically, 20% of patient-derived xenografts responded to cetuximab, and of these responders, half were later found to harbor *EGFR* amplification [58] In the phase II study combining FOLFOX with cetuximab, 22% of patients had greater than 4 *EGFR* copies, which correlated with increased overall survival.[59] Similarly, in TRANS-COG, the preplanned translational correlative study of COG, 15.6% of patients had increased gene copy number (GCN) including true *EGFR* amplification (ratio *EGFR/CEP7* ≥2) (~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).[60] 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] Thus, 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] A Phase III trial of second line nimotuzumab with irinotecan (NCT01813253) is also currently recruiting patients deemed to harbor EGFR overexpressing (IHC 2/3+) tumors.

MET

The MET protooncogene encodes the c-MET receptor tyrosine kinase, which is involved in cell proliferation, angiogenesis, and migration. MET over-expressing and *MET* amplified tumors are each associated with worse survival.[46,47,63–71] 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 (Figure 1).[72,73] *MET* amplification leads to constitutive receptor activation independent of ligand, and is reported in ~4-10% of GEC cases,[47,74–76] but over-expression ranges from 25–70% by IHC in GEC (Table 1).[66–68,77–79]

Early phase reports and trials suggested that MET-expression may serve as a predictive biomarker for MET-directed therapeutic response in GEC patients.[71,77] However, a subsequent phase II,[80] and two Phase III MET-directed trials in GEC have all reported overall negative results (Table 4).[80,81] The first line MetGastric phase III 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 predefined MET expression subgroup) reported from the prior/parallel YO28252 phase II biomarker evaluation trial of onartuzumab enrolling unselected GEC patients.[80] With this in mind, no benefit was seen in the METGastric ITT, nor in the MET IHC 2/3+ pre-planned subgroup analysis (which accounted for ~38% of enrolled patients, HR 0.64, p=0.06); this subgroup notably now possessed less power to identify a

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true benefit due to early termination of the trial.[82] Similarly, RILOMET-1, which evaluated first line epirubicin, cisplatin, and capecitabine (ECX) with or without the addition of rilotumomab, a fully human IgG2 antibody against HGF ligand, for 'MET expressing' GEC was terminated due to an increased risk of death from the study drug.[81]

One pitfall of these phase III trials was their loose definition of MET expression. In RILOMET-1, patient selection was defined as ≥1+ MET expression by IHC in ≥25% of tumor cells to be eligible, accounting for 81% of patients screened, and of all patients enrolled only 21% of tumors had high expression (≥2+, ≥50% cells). Similarly, only 38% of METGastric were IHC 2/3+ in ≥50% of cells, yet as above, these patients demonstrated a near-significant benefit, in an under-accrued trial. Thus, 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 clearly under-represented, particularly in RILOMET-1.[47,74–76]

However, more promising results have been reported in smaller earlier phase trials of MET inhibitors in *MET* amplified patients (4–5% of GEC),[47,67,74,76] 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 expansion phase of the trial has been on hold (results not publically available).[83] Similarly, half of *MET*-amplified patients treated with crizotinib in a phase I expansion cohort experienced response,[47] and 75% of MET amplified patients receiving ABT-700 monoclonal antibody monotherapy demonstrated an objective response.[84] The challenge of molecular heterogeneity,[29,85] particularly in the CIN subset of GEC,[9] may account for lack of response and/or rapid development of resistance to MET-directed monotherapy of *MET* amplified GEC. Any future therapeutic attempts of the MET pathway will likely be directed towards the small *MET* amplified subset of patients,[86] in conjunction with cytotoxic agents,[55] other targeted therapies, and/or immune checkpoint inhibitors either in combination or in sequential fashion to achieve optimal benefit.

Summary

Development of molecularly targeted therapies in GEC has been hindered by inadequate predictive biomarkers. With respect to HER2, despite the breast cancer and ToGA experiences, patients with *HER2* FISH+ but IHC negative disease were included in the Tytan (36% of patients) and LOGiC (17% of patients) trials,[26] Moreover, 10.4% of patients in the GATSBY trial harbored IHC3+/FISH- tumors compared to the ToGA trial's 2.3%, raising the question as to whether this molecular subset IHC3+/FISH- should be considered similar or dissimilar to genomic driver subset IHC3+/FISH+. Furthermore, nearly one third of cases in the second line trastuzumab with/without MM-111 were later reclassified as *HER2* negative and another 15% were no longer HER2+ upon repeat biopsy after first line progression, suggesting that updated HER2 testing prior to each line might be necessary for optimal patient selection.[30] For MET, although early trials suggested MET expression as a predictive biomarker for anti-MET therapies, the RILOMET-1 trial MET expression requirements may have been too loose, and the power for METGastric to identify a more likely HR of ~0.7–0.8 was low given that the trial was under-accrued due to early

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termination.[81] Finally, in the phase III EGFR trials, no biomarkers of selection were utilized. All of the evidence suggests that targeted therapies may have a role, but in more targeted select patient populations. Finally, using alternative diagnostic platforms, including DNA amplification and mass spectroscopy, it may be feasible to better select the appropriate patient population in future studies.[62]

Although approximately one-third to half of patients with GEC harbor potentially actionable alterations, patient population selection with varying scoring, heterogeneity, and/or infrequent incidence has stifled clinical trial success. As of 2016, only trastuzumab has been approved for first line GEC patients in a select HER2 positive population. Subset analyses have identified patients with *MET* and *EGFR* amplifications that are more likely to benefit from respective targeted therapies, albeit for a finite period of time before various developed resistance mechanisms emerge - molecular evolution over time. Intra-patient molecular heterogeneity is also emerging as a considerable hurdle for targeted therapies.[29] However, designing traditional trials for such infrequent genomic aberrations remains difficult. One solution may be further development of novel trial designs such as the PANGEA type II expansion platform trial (particularly with serial assessment and ‘re-targeting’ over time) that may better identify and treat these uncommon actionable aberrations by testing an overall treatment strategy composed of various biomarker/drug pairings, and compare this personalized treatment strategy outcome to a treatment control arm.[62]

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Key Points

- Trastuzumab is a treatment standard for HER2 amplified/overexpressed gastroesophageal adenocarcinoma, yet benefit has not been demonstrated in second and later lines of therapy, or beyond progression in first line therapy.
- Anti-EGFR therapy warrants further investigation for gene amplification/over-expression despite lack of benefit demonstrated in unselected gastroesophageal patients to date.
- Anti-MET therapy has not demonstrated benefit in ‘over-expressing’ gastroesophageal patients in any line of therapy, but evidence supports further investigation in patients with gene amplification/overexpression.

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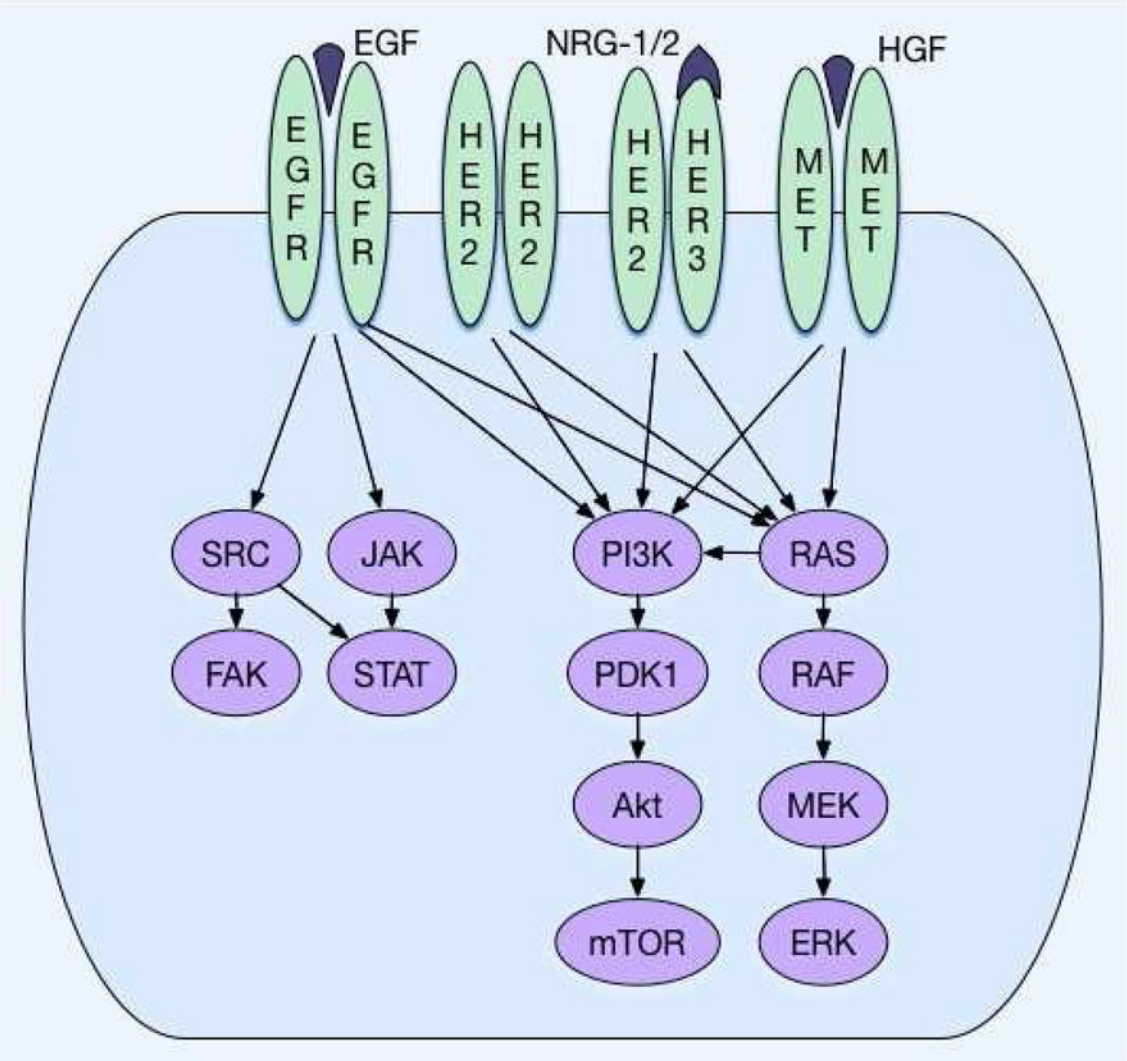

Figure 1.
EGFR, HER2, and c-MET kinase cascade.

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Table 1

Rates of key receptor tyrosine kinase overexpression and gene amplification in gastroesophageal cancer

	ERBB2		EGFR		MET			
Study	**Amp (%)**	**Exp (%)**	**Amp (%)**	**Exp (%)**	**Amp (%)**	**Exp (%)**	**Population**	**Site**
Nagatsuma[46]	9	11.8	2.4	24.9	1.3	24.9	950	Gastric, resected
Nakajima[66]	11.7	16.4			10.2	46.1	128	Gastric, resected
Lennerz[47]	8.9		4.7		2		489	Gastroesophageal, all comers
Terashima[14]	13.3	13.6		9			829	Gastric, resected
Van Cutsem[87]	4.1	21.4/32.2 (G/EGJ)					3280	Gastric/EGJ,advanced
Kim[44]			2.3	27.4			511	Gastric, resected
Luber[59]			3				39	Gastric/EGJ, advanced
Petty[60]			6.1				450	Esophageal/EGJ, advanced
Catenacci[63]					5.2	35.2	394	Gastroesophageal,resected
Graziano[68]					10		216	Gastric, resected
Lee[67]					3.4	62.3	439	Gastric, resected
Jardim[75]					6		77	Gastroesophageal, all comers

Amp: Amplification, Exp: Over-expression

Hematol Oncol Clin North Am. Author manuscript; available in PMC 2018 June 01.

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Table 2

HER2-directed phase III clinical trials for gastroesophageal cancer

Line	Trial	N	Treatment	Primary Endpoint (Met?)	mOS (mo)	HR	mPFS (mo)	HR	RR
1L	**Bang et al**[18] TOGA	584	Cis/FP Cis/FP + Trastuzumab	OS (Yes)	11.8* 16*	0.74 0.65* P<0.05*	5.5 6.7	0.71 P<0.001	35% 47%
1L	**Hecht et al**[22] LOGiC	545 (487)	Cis/FP 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	**Satoh et al**[26] TYTAN	261	Paclitaxel 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 et al**[27] GATSBY	345 (1:2)	Pac38% / 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

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Table 3

EGFR-directed phase III clinical trials for gastroesophageal cancer

Line	Trial	N	Treatment	1° Endpt (Met?)	mos (mo)	HR	mPFS(mo)	HR	RR
1L	**Lordick et al** [15] EXPAND	904	Cis/Cape/Placebo Cis/Cape/Cetuximab	PFS (No)	10.7 9.4	1.00	5.6 4.4	1.09 p=0.32	29% 30%
1L	**Waddell et al**[16] REAL-3	553	Epi/Oxali/Cape-Pl 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 et al**[57] COG	450	Placebo Gefitinib	OS (No)	3.67 3.73	0.9	1.17 1.57	0.8	~1% ~4%

Cis/Cape: Cisplatin/Capecitabine; Epi/Oxali/Cape:

Epirubicin/Oxaliplatin/Capecitabine; Pl: Placebo; P: Panitumumab

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Table 4

MET-directed phase II/III clinical trials for gastroesophageal cancer

Line	Trial	N	Treatment	1° Endpoint (Met?)	mOS (mo)	HR	mPFS (mo)	HR	RR (%)
1L	**Cunningham et al** [88] RILOMET-1	609	Epi/Cis/5FU/Placebo Epi/Cis/5FU/Rilotumumab	OS (No)	11.5 9.6	1.37 p=0.016	5.7 5.7	1.3	39 30
1L	**Shah et at** [82] 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
1L	**Shah et al** [80] Y028252	123	FOLFOX6/Placebo FOLFOX6-Onartuzumab	PFS (No)	11.27 10.61	1.06 p=0.83	6.97 6.77	1.08 0.71	57.1 60.5

Epi/Cis/5FU: Epirubicin/Cisplatin/5-fluorouracil