Update on Gastroesophageal Adenocarcinoma Targeted Therapies

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KEYWORDS

• Gastroesophageal • Gastric • MET • Epidermal growth factor receptor • HER2 • ERBB2 • Treatment • Targeted

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-epidermal growth factor receptor 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.

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 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

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with optimal palliative chemotherapy in Erb-B2 receptor tyrosine kinase 2 (ERBB2) 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,* epidermal growth factor receptor (*EGFR*), kirsten rat sarcoma 2 viral oncogene homolog (KRAS), and fibroblast growth factor receptor 2 (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 EGFR family, encoded at chromosome 17q21. HER2 regulates proliferation, adhesion, differentiation, and migration via activation of the RAS-MAPK and PI3K-AKT pathways (**Fig. 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 overexpression results predominantly from gene amplification; less commonly, other genomic events may include activating mutation. HER2 immunohistochemistry (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

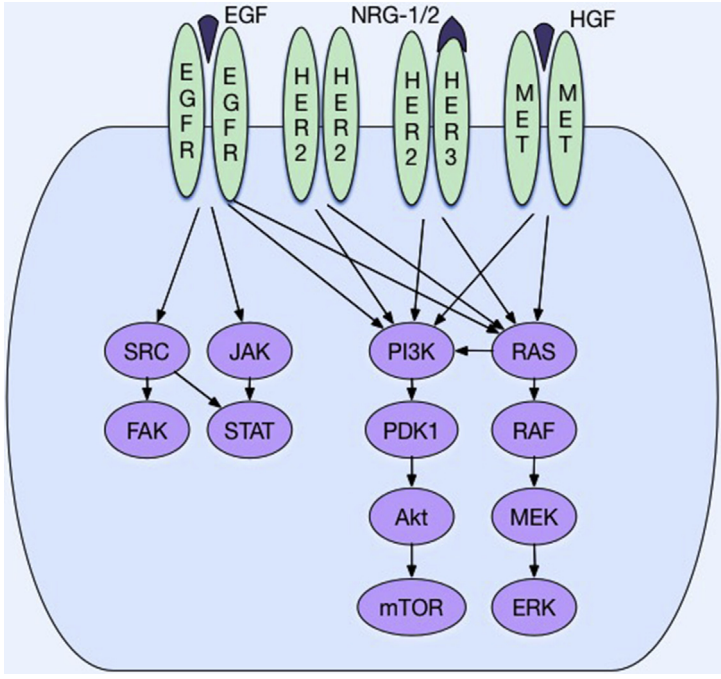

Fig. 1. EGFR, HER2, and c-MET kinase cascade.