Novel Targeted Therapies for Esophagogastric Cancer

Steven B. Maron, MD, Daniel V.T. Catenacci, MD*

KEYWORDS

- Gastric cancer • Esophagogastric junction cancer
- Gastroesophageal adenocarcinoma • HER2 • VEGFR2 • EGFR • MET • FGFR2

KEY POINTS

- Anti-human epidermal growth factor receptor 2 (HER2) trastuzumab therapy is standard for HER2 amplified/overexpressed gastroesophageal adenocarcinoma, whereas second/later lines of anti-HER2–directed therapy have not shown definitive benefit to date.
- Anti–vascular endothelial growth factor receptor 2 (VEGFR2) ramucirumab modestly improves survival as monotherapy and in combination with paclitaxel in second-line treatment of patients with gastroesophageal adenocarcinoma.
- Anti–epidermal growth factor receptor (EFGR) therapy has not shown benefit in unselected gastroesophageal patients in any line of therapy, although gene amplification/overexpression warrants further investigation.
- Anti-MET therapy has not shown benefit in overexpressing gastroesophageal patients in any line of therapy, although gene amplification/overexpression may merit further investigation.
- Other promising predictive biomarkers and targeted therapies, including fibroblast growth factor type 2 and claudin 18.2, require further investigation in larger trials to confirm therapeutic benefits for patients with gastroesophageal adenocarcinoma.

BACKGROUND

Distal gastric adenocarcinoma (GC) incidence ranks fifth globally and third for cancer-related mortality of all malignancies.[1–3] Approximately 25,000 new GC cases and 11,000 deaths occurred in the United States in 2015.[4] In contrast,

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Section of Hematology/Oncology, University of Chicago Comprehensive Cancer Center, 900 E 57th St, Suite 7128, Chicago, IL 60637, USA
* Corresponding author.
E-mail address: dcatenac@medicine.bsd.uchicago.edu

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esophagogastric junction adenocarcinoma (EGJ), is increasing in incidence. For both (gastroesophageal cancer [GEC]), most patients present with metastatic disease, or locally advanced disease with a high risk of recurrence despite aggressive perioperative therapy. In the metastatic setting, median overall survival (OS) remains approximately 11 months with optimal palliative chemotherapy in *ERRB2*-nonamplified patients. Over the past decade, molecular subtyping of GEC has highlighted the interpatient heterogeneity of GEC and uncovered potentially actionable molecular pathways.[5] Routine next-generation sequencing identified that at least 37% of patients with GC 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), Epstein-Barr virus (EBV) associated, chromosomal instability (CIN), and genomically stable (GS), provide more molecularly targeted therapeutic possibilities.[9]

Erb-B2 Receptor Tyrosine Kinase 2

Erb-B2 receptor tyrosine kinase 2 (Erb-B2), or HER2, is a transmembrane RTK within the epidermal growth factor receptor (EGFR) family, encoded at chromosome 17q21. HER2 regulates proliferation, adhesion, differentiation, and migration via activation of the Ras and Mitogen-activated protein kinases (RAS-MAPK) and phosphatidylinositol-3-kinase and AKT (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 overexpression 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 distal GC (10%–15%), and the prognostic impact of HER2 expression remains controversial.[11–16]

Effective targeting of HER2 in GEC was initially shown using trastuzumab, a humanized monoclonal anti-HER2 antibody against the HER2 ectodomain (**Table 1**). The phase III ToGA trial evaluated first-line fluoropyrimidine/cisplatin chemotherapy doublet with or without trastuzumab in patients with HER-2 over-expressing (any IHC 3+ or fluorescence in-situ hybridization [FISH] HER2/CEP17 ratio $\geq$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 versus 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 overexpressing GEC for the IHC2+/FISH+ and IHC3+ subsets of the trial.[16,17]

Although HER-2 overexpression/*ERBB2* amplification predicts benefit from the anti-HER2 antibody trastuzumab in the first-line setting,[16] 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 FISH (with HER2/CEP17 ratio $\geq$2). IHC 0/1 is considered negative, and IHC3+ is considered positive, whereas IHC2+ requires reflex FISH assessment. Higher throughput assays, including mass spectrometry and next-generation sequencing, have emerged with potential to refine diagnostic accuracy as well as possessing multiplexing capability to assess for other relevant aberrations.[5,18,19] Assessment of ERBB2 amplification by cell-free DNA is also emerging as a potential noninvasive strategy for serial assessment of HER2 status that can monitor intrapatient tumoral evolution.[19–23]