# Evolving Landscape of Targeted Treatment Options for HER2-Positive Gastric/ Gastroesophageal Adenocarcinomas

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**Abstract:** Gastric and gastroesophageal adenocarcinomas are aggressive malignancies despite current standard-of-care treatments. For patients whose tumors express human epidermal growth factor receptor 2 (HER2), HER2-targeted treatments have been shown to improve outcomes. This review summarizes key trials that have guided contemporary use of these agents in both the localized and advanced settings. It also discusses limitations to current approaches in testing HER2 status and methods to better identify good candidates for these treatments. Finally, the review highlights notable ongoing studies investigating novel combinations and HER2-directed agents.

Keywords
Gastric cancer, gastroesophageal adenocarcinoma, gastroesophageal cancer, HER2

## Introduction

Stomach cancer has the fifth highest incidence and fourth highest mortality of all cancers globally, with more than 1 million new cases and 769,000 deaths annually; esophageal cancer ranks seventh in incidence and sixth in mortality, with 604,000 new cases and 544,000 deaths annually.[1] Adenocarcinoma accounts for 80% to 95% of gastric cancers and 67% of esophageal cancers in high-income countries.[1-3] Although the rates of gastric adenocarcinoma have been declining, the rates of esophageal adenocarcinomas have been increasing owing to risk factors such as excess body weight and gastroesophageal reflux disease.[1,4]

The global cost of treating gastric and gastroesophageal junction (GEJ) cancers is estimated to be at least $20.6 billion per year.[3] Despite this expenditure, prognosis is poor, with a 5-year survival rate of 28.8% among all patients diagnosed in the United States.[4] The prognosis is especially poor for patients with metastatic disease, who have a median 5-year survival of 5% to 10%.[3]

Human epidermal growth factor receptor 2 (HER2)-targeted treatments have emerged as useful tools for treating these aggressive malignancies. This review covers the evolution of HER2-targeted

therapies for both local and advanced gastric and GEJ adenocarcinomas.

## HER2 Assessment and Epidemiology

*HER2*, also known as *ERBB2,* is a proto-oncogene that encodes a tyrosine kinase receptor of the epidermal growth factor receptor family. The signaling pathways of HER2 lead to cell division, cell proliferation, and antiapoptosis. HER2 overexpression in gastric and gastroesophageal adenocarcinomas ranges from 12% to 23%, varying with histology and tumor grade.[5-9] Rates of high HER2 expression are similar in European (23.6%) and Asian (23.5%) populations.[9]

HER2 testing is typically performed on formalin-fixed, paraffin-embedded (FFPE) biopsy or tumor tissue samples, with initial HER2 expression scoring criteria based on earlier breast cancer models. For example, of the 3883 patients with advanced gastric cancer screened for the seminal ToGA trial, 22.1% were found to be HER2-positive using parallel immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) testing using a modified IHC scoring criteria.[9] The IHC scoring criteria needed to be modified from those used in breast cancer, given tumor heterogeneity and differences in basolateral staining in gastric and gastroesophageal cancers. Nevertheless, this scoring system showed an overall IHC-FISH concordance of 87.5% in the ToGA trial. Concordance between an IHC result of 3+ and ISH positivity has been reported to be greater than 90%, with concordance between an IHC result of 2+ and ISH positivity ranging from 30% to 50%.[5] Current guidelines from the National Comprehensive Cancer Network (NCCN) recommend IHC testing first, followed by ISH methods only in equivocal samples defined as IHC expression of 2+; positive (IHC 3+) and negative (IHC 0-1+) samples do not require testing.[10] The NCCN defines ISH positivity as a HER2:CEP17 ratio of at least 2:1 or an average HER2 copy number of at least 6.0 signals/cell.

Subsequent studies have shown increased rates of HER2 positivity according to histologic type, with increased rates of HER2 positivity among patients with intestinal-type histology (19%-33%) vs diffuse-type histology (6%-8%).[6,8] In a multicenter retrospective analysis of 381 patients with metastatic gastric cancer, HER2 positivity vs negativity was associated with longer overall survival (OS; 13.9 vs 11.4 months, respectively; *P*=.047), particularly among patients with intestinal-type histology (15.0 vs 12.4 months, respectively; *P*=.067), although HER2 status was not an independent prognostic factor in multivariate analysis (hazard ratio [HR], 0.79; 0.44-1.14; *P*=.194).[7]

## First-line Therapy

Trastuzumab is a monoclonal antibody that targets the HER2 receptor. The ToGA trial was the first phase 3 trial to show OS improvement with the addition of trastuzumab to chemotherapy in the first-line setting among patients with HER2-positive inoperable locally advanced, recurrent, or metastatic adenocarcinoma of the stomach or GEJ.[11] This study established the addition of trastuzumab to chemotherapy in patients with HER2 overexpression. Patients were randomized to receive cisplatin plus capecitabine or cisplatin plus 5-fluorouracil (5-FU) with (n=298) or without (n=296) trastuzumab. Median OS was significantly longer in the trastuzumab arm than in the chemotherapy-only arm, at 13.8 vs 11.1 months, respectively (HR, 0.74; *P*=.0046). A post-hoc exploratory analysis suggested improved outcomes in patients with high HER2 expression, (defined as IHC 2+ and FISH positive, or IHC 3+) with a median OS of 16.0 months (95% CI, 15-19) in the trastuzumab arm vs 11.8 months (95% CI, 10-13; HR, 0.65; 95% CI, 0.51-0.83) in the chemotherapy-only arm. This trend toward improved outcomes with trastuzumab was not seen in the group with low HER2 expression (IHC 0 and FISH positive, or IHC 1+ and FISH positive), with a median OS of 10.0 months in the trastuzumab arm vs 8.7 months in the chemotherapy-only arm (HR, 1.07; 95% CI, 0.70-1.62).

The phase 3 HELOISE trial sought to clarify the optimal dosing of trastuzumab in the first-line setting by comparing standard-dose trastuzumab (n=124) vs high-dose trastuzumab (n=124) in combination with capecitabine + cisplatin chemotherapy among patients with metastatic gastric and GEJ adenocarcinoma.[12] The study found no significant differences between standard-dose trastuzumab and high-dose trastuzumab in the primary outcome of OS (12.5 vs 10.6 months, respectively; HR, 1.24; *P*=.2401). There were also no differences in the secondary outcomes of progression-free survival (PFS; 5.7 months for standard dose vs 5.6 months for high dose; HR, 1.04; *P*=.8222) or overall response rates (ORR; 56.9% for high dose vs 58.9% for standard dose, HR, 0.92; 95% CI, 0.56-1.53]). Given the lack of clinical benefit of high-dose over standard-dose trastuzumab, the standard of care remains a loading dose of 8 mg/kg followed by a maintenance dose of 6 mg/kg every 3 weeks.

Following the ToGA trial, cisplatin was the most-studied platinum agent used in combination with anti-HER2 therapy in the first-line setting for advanced gastric and GEJ adenocarcinoma. An early retrospective study by Soularue and colleagues reported on the efficacy of trastuzumab with oxaliplatin-based chemotherapy given in combination with capecitabine (CAPOX) or 5-FU (modified FOLFOX)[13] in the first- and second-line settings.

**Table 1.** Summary of Clinical Trials for HER2-Positive Gastric/Gastroesophageal Adenocarcinoma in the First-Line and Nonmetastatic Setting

| Trial | Patient population | Region | Phase | Study arms | Results |
|---|---|---|---|---|---|
| ToGA | Inoperable locally advanced, recurrent, or metastatic gastric or GEJ adenocarcinoma | Global | 3 | Chemotherapy (capecitabine + cisplatin or 5-FU + cisplatin) with trastuzumab vs chemotherapy alone | Improved median OS with trastuzumab (13.8 vs 11.1 mo; *P*=.0046) |
| HELOISE | Metastatic gastric and GEJ adenocarcinoma | Global | 3 | Chemotherapy (capecitabine + cisplatin) with high-dose (8 mg/kg loading + 10 mg/kg maintenance) vs standard-dose (8 mg/kg loading + 6 mg/kg maintenance) trastuzumab | No improvement in OS with high-dose trastuzumab (12.5 vs 10.6 mo; *P*=.2401) |
| KEYNOTE-811 | Unresectable or metastatic gastric or GEJ adenocarcinoma | Global | 3 | Trastuzumab + chemotherapy (5-FU/cisplatin or CAPOX) with vs without pembrolizumab | Improved ORR with pembrolizumab (74.4% vs 51.9%; *P*=.00006), OS data pending |
| LOGiC | Advanced or metastatic esophageal, gastric, or GEJ adenocarcinoma | Global | 3 | Lapatinib plus chemotherapy (CAPOX) vs placebo plus chemotherapy | No improvement in OS with lapatinib (12.2 vs 10.5 mo) |
| JACOB | Metastatic gastric and GEJ adenocarcinoma | Global | 3 | Trastuzumab plus chemotherapy (cisplatin + capecitabine or cisplatin + 5-FU) with vs without pertuzumab | No improvement in OS with pertuzumab (17.5 vs 14.2 mo; *P*=.057) |
| PETRARCA | Node-positive and high-risk node negative resectable gastric and GEJ adenocarcinoma | Germany | 2 | Perioperative FLOT plus trastuzumab + pertuzumab vs FLOT alone | Improved rates of pathologic CR (35% vs 12%; *P*=.02) |
| RTOG 1010 | Locally advanced resectable esophageal adenocarcinoma | United States | 3 | Neoadjuvant chemoradiation (paclitaxel + carboplatin) with perioperative trastuzumab vs neoadjuvant chemoradiation alone | No significant benefit in DFS (19.6 vs 14.2 mo; *P*=.97) |

5-FU, 5-fluorouracil; CAPOX, capecitabine and oxaliplatin; CR, complete response; DFS, disease-free survival; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; GEJ, gastroesophageal junction; HER2, human epidermal growth factors receptor 2; mo, months; ORR, overall response rate; OS, overall survival.

Investigators reported a median PFS of 9.0 months and a median OS of 17.3 months, with an ORR of 41%, similar to the ToGA trial. Grade 3 or 4 events occurred in 32% of patients, which was lower than the 68% reported in the ToGA trial. Prospective data from the phase 2 HERXO trial, which assessed the safety and efficacy of trastuzumab plus oxaliplatin-containing chemotherapy, reported similar efficacy and tolerability findings, establishing modified FOLFOX and CAPOX as effective regimens with acceptable safety profiles.[14]

The benefit of adding the anti–programmed death 1 (PD-1) monoclonal antibody pembrolizumab (Keytruda, Merck) to trastuzumab and chemotherapy in unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma was studied in KEYNOTE-811, after preclinical studies suggested that anti–PD-1 agents may improve the activity of anti-HER2 monoclonal antibodies.[15,16] Patients were randomized to receive trastuzumab plus chemotherapy (5-FU/cisplatin or CAPOX) with (n=217) or without (n=217) pembrolizumab. The first interim analysis showed than patients in the pembrolizumab group vs the control group had a significantly higher ORR (74.4% vs 51.9%, respectively; *P*=.00006) and a trend toward deeper responses, with 32.3% vs 14.8% achieving an 80% decrease from baseline, and 11.3% vs 3.1% achieving a complete response (CR). Results for the primary endpoint of OS are pending. However, with these promising ORR data, the US Food and Drug Administration (FDA) has approved the addition of pembrolizumab to trastuzumab and fluoropyrimidine/platinum chemotherapy in the first-line setting for advanced, unresectable, or metastatic HER2-positive gastric or GEJ adenocarcinoma. Notably, 84.1% of the participants in this study had a programmed death ligand 1 (PD-L1) combined positive score (CPS)

of 1 or greater, with investigators noting a trend toward improved ORR in patients with a CPS of 1 or greater.

Other anti-HER2 agents have yet to demonstrate benefits in HER2-positive gastroesophageal malignancies in the first-line setting. Lapatinib is an oral small-molecule tyrosine kinase inhibitor (TKI) of epidermal growth factor receptor (EGFR) and HER2. In the LOGiC trial, the addition of lapatinib to CAPOX chemotherapy did not demonstrate an OS benefit vs placebo plus CAPOX (HR, 0.91; *P*=.3492) and was associated with increased toxicity.[17] Interestingly, this study reported significant differences between lapatinib and placebo for PFS (6.0 vs 5.4 months, respectively; HR, 0.82, *P*=.0381) and ORR (53% vs 39%, respectively; *P*=.0031), although given the lack of OS benefit, the clinical relevance of this is unclear. A larger proportion of patients experienced grade 3 or higher toxicity, with 58% of lapatinib patients reporting grade 3 or higher diarrhea vs 29% of placebo patients.

The JACOB trial examined the efficacy of the anti-HER2 humanized monoclonal antibody pertuzumab (Perjeta, Genentech) in combination with trastuzumab and chemotherapy for HER2-positive metastatic gastric and GEJ adenocarcinoma in the first-line setting. Although pertuzumab has demonstrated enhanced antitumor effects when combined with trastuzumab in preclinical gastric cancer studies and in the breast cancer literature, JACOB did not meet its primary outcome of OS (HR, 0.84; *P*=.057).[18,19] Given these negative results, lapatinib and pertuzumab are not routinely used for first-line treatment of advanced gastroesophageal cancer outside of clinical trials.

## Second-line Therapy and Beyond

Unlike HER2-positive breast cancers, studies on subsequent HER2-directed therapies for gastroesophageal cancers after progression on a prior trastuzumab-based regimen have yielded mostly negative results until recently. Trastuzumab deruxtecan, also known as T-DXd (Enhertu, Daiichi-Sankyo/AstraZeneca), is currently the only FDA-approved targeted therapy for this indication. T-DXd is an antibody-drug conjugate consisting of a humanized, monoclonal anti-HER2 antibody bound to a cleavable cytotoxic topoisomerase I inhibitor. DESTINY-Gastric01 was a phase 2 randomized, open-label trial comparing trastuzumab deruxtecan (n=125) with physician's choice of chemotherapy (n=62) in the third-line and beyond setting for patients with advanced HER2-positive gastric and GEJ adenocarcinoma in Japan and Korea.[20] All patients had progressed on fluoropyrimidine plus platinum chemotherapy and trastuzumab. In this study, the majority of patients in the chemotherapy group received irinotecan (n=55), with a minority receiving paclitaxel (n=7). All patients submitted archival tissue samples to a central laboratory confirming HER2-positive cancer, defined as an IHC result of 3+, or 2+ with ISH positivity. Fresh biopsy samples were only submitted if archival tissue was inadequate. Given its reliance on archival tissue samples, HER2 loss after first-line therapy was not captured. This study met its primary endpoint of ORR, which was 51% in the T-DXd group vs 14% in the chemotherapy group (*P*<.001). Ten patients (8%) were able to achieve a CR with T-DXd, compared with none in the chemotherapy arm. Responses were durable, with a median duration of response of 11.3 months. Secondary endpoints also favored T-DXd over chemotherapy, including median OS (12.5 vs 8.4 months, respectively; HR, 0.59; *P*=.01) and PFS (5.6 vs 3.5 months, respectively; HR, 0.47; 95% CI, 0.31-0.71). Treatment-related adverse events are an important consideration with T-DXd. The most common grade 3 or higher adverse events with T-DXd vs chemotherapy were neutropenia (51% vs 24%, respectively), anemia (38% vs 23%, respectively), and decreased white blood cell count (21% vs 11%, respectively). Twelve patients (10%) in the T-DXd arm developed interstitial lung disease or pneumonitis.

DESTINY-Gastric02 is an ongoing, single-arm, phase 2 study examining the efficacy of T-DXd in the second-line and beyond setting in Western populations (ie, the United States and the European Union) with unresectable or metastatic gastric and GEJ cancers.[21] An updated analysis with a median follow-up of 10.2 months showed an ORR of 41.8%, with 4 CRs, 29 partial responses, and 10 (12.7%) patients remaining on T-DXd.

In addition to ongoing research establishing safety and efficacy in Western populations, there is interest in determining if T-DXd has activity in patients with low-intermediate levels of HER2 expression, as has been demonstrated in breast cancer.[22] Given its high drug-to-antibody ratio, T-DXd does not require high HER2 expression in preclinical models of antitumor activity, as the released topoisomerase payload can easily diffuse across membranes to neighboring tumor cells. A small phase 2 trial focusing on the exploratory cohort of DESTINY-Gastric01 examined the effectiveness of T-DXd in the third-line and beyond setting among patients with HER2-low, locally advanced or metastatic gastric/GEJ adenocarcinoma. Patients had not received any anti-HER2 therapy before enrollment. HER2-low disease was defined as IHC 2+/ISH– (cohort 1, n=19) and IHC 1+ (cohort 2, n=21).[23] The study reported an ORR of 26.3% in cohort 1 and 9.5% in cohort 2, with a disease control rate of 89.5% and 71.4%, respectively. The median OS was 7.8 months in cohort 1 and 8.5 months in cohort 2, with a median PFS of 4.4 months and 2.8 months, respectively. These promising results suggest potential clinical utility of T-DXd in this subset of patients, although more studies are needed.

**Table 2.** Summary of Clinical Trials for HER2-Positive Gastric/Gastroesophageal Adenocarcinoma in the Second-Line and Beyond Setting

| Trial | Patient population | HER2 status assessment | Region | Phase | Study arms | Results |
|---|---|---|---|---|---|---|
| DESTINY-Gastric01 | Locally advanced or metastatic gastric or GEJ junction cancer that has progressed ≥2 regimens (including a fluoropyrimidine, a platinum agent, and trastuzumab) | Archival | Japan, Korea | 2 | Trastuzumab deruxtecan vs physician's choice of chemotherapy | Improved ORR (51% vs 14%; *P*<.001) |
| DESTINY-Gastric02 | Unresectable or metastatic gastric and GEJ cancers that have progressed on ≥1 prior line of therapy | Archival | United States, European Union | 2 | Single-arm trastuzumab deruxtecan | ORR 41.8%, median OS 12.1 mo (95% CI, 9.4-15.4) |
| TYTAN | Advanced gastric cancer that had progressed on 1 prior line of therapy | Archival samples | Asia | 3 | Lapatinib plus paclitaxel vs paclitaxel alone | No improvement in OS (11.0 vs 8.9 mo; *P*=.1044) |
| GATSBY | Locally advanced or metastatic gastric or GEJ adeno-carcinoma that has progressed during or after first-line platinum + a fluoropyrimidine +/- trastuzumab therapy | Archival tissue samples | Global | 2/3 | T-DM1 vs physician's choice of paclitaxel or docetaxel chemotherapy | No improvement in OS (7.9 vs 8.6 mo; *P*=.86) |
| T-ACT | Advanced gastric or GEJ cancer refractory to first-line chemotherapy with trastuzumab in combination with fluoropyrimidine and platinum | Predominantly archival, with some post-progression samples | Japan | 2 | Paclitaxel plus trastuzumab vs paclitaxel alone | No improvement in PFS (3.7 vs 3.2 mo; *P*=.33) |

GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; mo, months; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

## Negative Studies

TYTAN was an early phase 3 study investigating the role of second-line lapatinib among Asian patients with HER2-positive advanced gastric cancer.[24] When comparing second-line paclitaxel with or without lapatinib, the primary endpoint of OS was not met, with median OS of 11.0 months in the lapatinib group vs 8.9 months in the paclitaxel-only group (*P*=.1044). Interestingly, the study showed a higher ORR in the lapatinib group (27% vs 9%; odds ratio, 3.85; *P*<.001). A subgroup analysis showed better efficacy in patients with IHC 3+, with a decreased risk of death (HR, 0.59; *P*=.0176) and PFS (5.6 vs 4.2 months; HR, 0.54; *P*=.0101). However, no significant differences in deaths and PFS were seen in patients with IHC0-1+ and IHC 2+ in subgroup analyses. These ORR findings suggest that there may be a subgroup of patients that could benefit from second-line lapatinib, although more investigation is needed to better elucidate which groups derive benefit. There was no treatment difference in OS or PFS in the subgroup analyses of patients who had previously received trastuzumab, although few patients in this study had received first-line trastuzumab (just 6% in the lapatinib group and 5% in the paclitaxel-only group). Given these results, lapatinib is not routinely used in the second-line setting.

T-DM1 (Kadcyla, Genentech) is an antibody-drug conjugate consisting of trastuzumab linked to emtansine, a cytotoxic tubulin inhibitor that is approved for use in advanced breast cancers in both the adjuvant and metastatic settings.[25] The GATSBY study evaluated the efficacy of T-DM1 in gastric cancer, with patients receiving either T-DM1 (n=228) or physician's choice of taxane chemotherapy (n=117)[19] after progression on first-line platinum plus fluoropyrimidine chemotherapy.[26] The majority of both groups received first-line trastuzumab. This study did not meet its primary endpoint, with a median OS of 7.9 vs 8.6 months in the T-DM1 and taxane groups, respectively (HR, 1.15; *P*=.86). Subgroup analyses did not identify any clinical or biomarker subgroups with OS

**Table 3.** Summary of HER2-Directed Agents and Mechanism of Action

| Name | Mechanism of action |
|---|---|
| Trastuzumab | Monoclonal antibody targeting the extracellular domain of the HER2 receptor |
| Lapatinib | Oral small-molecule tyrosine kinase inhibitor of epidermal growth factor receptor and HER2 |
| Pertuzumab | Monoclonal antibody targeting extracellular HER2 dimerization domain |
| Trastuzumab deruxtecan | Antibody-drug conjugate, consisting of a monoclonal anti-HER2 antibody bound to a cleavable cytotoxic topoisomerase I inhibitor |
| T-DM1 | Antibody-drug conjugate consisting of trastuzumab linked to emtansine, a cytotoxic tubulin inhibitor |
| Tucatinib | Tyrosine kinase inhibitor selective for HER2 kinase domain, with minimal inhibition of EGFR |
| Neratinib | Irreversible tyrosine kinase inhibitor of EGFR, HER2, and HER4 |
| Margetuximab | Chimeric Fc-engineered IgG1 kappa anti-HER2 monoclonal antibody |
| Zanidatamab (ZW25) | Bispecific, IgG1-like monoclonal antibody binding to extracellular and dimerization domains of HER2 |

EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; IgG1, immunoglobulin G isotype 1.

benefit. Importantly, enrolled patients were considered HER2-positive based on archival biopsy samples, and the authors suggested that loss or alteration of HER2 expression after first-line therapy, as well as the higher incidence of heterogeneous expression of HER2 in gastric vs breast cancers, may explain the lack of efficacy of T-DM1.

The question of whether trastuzumab should be continued beyond progression after first-line therapy was examined in the T-ACT study.[27] This approach has shown clinical and survival benefits in HER2-positive breast cancers, and investigators sought to examine if similar benefits would be seen in gastroesophageal cancers.[28] Patients were randomized to receive paclitaxel with (n=46) or without (n=45) trastuzumab. This study did not meet its primary endpoint, reporting a median PFS of 3.2 in the paclitaxel arm (HR, 0.91; *P*=.33). There was no significant difference in OS between the groups (HR, 1.23; *P*=.20). It should be noted that HER2 positivity for inclusion was determined based on histologic assessment before first-line chemotherapy. Available FFPE tumor samples following first-line treatment were collected and tested for HER2 expression. Of the 16 samples suitable for FISH testing, HER2 positivity (IHC 3+ or IHC2+/FISH positive) was redemonstrated in only 5 (31%) patients, suggesting that reduced HER2 expression may be a mechanism underlying the lack of efficacy of trastuzumab used beyond progression.

## Nonmetastatic Disease

Based on the finding that dual anti-HER2 treatment improved disease-free survival (DFS) in the adjuvant setting for node-positive and high-risk node-negative HER2-positive breast cancers, the PETRARCA trial sought to investigate this strategy in early esophagogastric adenocarcinomas.[29,30] PETRARCA was a phase 2/3 trial examining the efficacy of 5-FU, leucovorin, oxaliplatin, and docetaxel (FLOT) alone (n=41) vs FLOT in combination with trastuzumab/pertuzumab (n=40) followed by maintenance trastuzumab/pertuzumab for 8 cycles. Notably, after the results of JACOB showed no survival benefit of adding pertuzumab to trastuzumab and chemotherapy, PETRARCA did not transition into the phase 3 portion of the trial. The study met its primary outcome of pathologic CR, reporting rates of 12% in the FLOT-only arm and 35% (*P*=.02) in the FLOT + trastuzumab/pertuzumab arms. Although secondary outcomes, including DFS (22 months vs not reached), trended toward better results when trastuzumab/pertuzumab was added to FLOT, the differences at the time of reporting were not significant (*P*=.14). Median OS was not yet reached (HR, 0.56; *P*=.24), although the OS rate at 24 months was higher in the trastuzumab/pertuzumab group (84%) vs the FLOT-only arm (77%). These results suggest that anti-HER2 treatment may be beneficial in the perioperative setting, although more research is needed before it is employed as standard of care.

The phase 3 RTOG 1010 trial explored the efficacy of adding trastuzumab in the neoadjuvant setting for esophageal adenocarcinoma.[31] Patients with HER2-positive locally advanced esophageal adenocarcinoma were randomized to neoadjuvant chemoradiation with and without perioperative trastuzumab. HER2 positivity was defined as an IHC result of 3+ or a FISH ratio greater than 2:1, regardless of the IHC score. This differed from standard-of-care HER2 testing as put forth by the NCCN, given the lower rates of concordance between IHC and ISH at IHC scores of 0 to 2. There was no significant benefit in DFS (HR, 0.99; *P*=.97) or pathologic CR. Given these negative results, perioperative trastuzumab is not routinely given for HER2-positive esophageal adenocarcinomas.

## Tumor Heterogeneity Testing and Genomics

The Cancer Genome Atlas (TCGA) described the prevalence of *ERBB2* expression in gastric and esophageal cancers.[32] By assessing patterns of somatic genetic alterations, TCGA developed a molecular classification of gastroesophageal adenocarcinomas, which was divided into 4 subtypes: Epstein-Barr virus (EBV)-positive, microsatellite instability–high (MSI-high), genomically stable (GS), and with chromosomal instability (CIN). *ERBB2* amplifications were noted in 17% of samples across all molecular subtypes, with the CIN subtype having the highest frequency, followed by the EBV and GS subtypes. No amplifications were noted in the MSI-high group. The molecular alterations in esophageal squamous cancers were distinct from those for esophageal adenocarcinomas. Specifically, esophageal adenocarcinomas closely resembled CIN gastric adenocarcinomas, with *ERBB2* expression seen in 32%. In contrast, only 3% of squamous cell carcinomas expressed *ERBB2*.[27] Given these findings, future studies on anti-HER2 therapy in CIN gastric adenocarcinomas and esophageal adenocarcinomas may be helpful in identifying subsets of patients who may benefit from this targeted approach.

Co-occurring alterations and levels of *ERBB2* amplifications may affect the response to HER2-directed therapy. In a study by Kim and colleagues, the assessment of next-generation sequencing (NGS) and response to first-line lapatinib with CAPOX for metastatic or recurrent gastric cancer found that *CCNE1* amplification was the most common co-occurring alteration, being found in 40% of tumors.[33] The presence of this amplification may be associated with a lack of response to HER2-directed therapy (found in 66.7% of nonresponders vs 22.2% responders; $P$=.08). Additionally, high levels of *ERBB2* amplifications on NGS were more likely to respond to therapy compared with those with low levels ($P$=.02), with detectable *ERBB2* copy number amplifications predictive of response rates (100% of responders). The authors suggest that even among patients considered HER2-positive by traditional IHC/FISH methods, additional biomarkers may better help identify responders to HER2-directed therapy, such as lapatinib.

A single-center prospective study done at Memorial Sloan Kettering Cancer Center paired NGS analysis with tumor and normal samples of 295 patients with stage IV esophagogastric cancer.[34] A total of 68 of the 295 patients were found to be HER2-positive by IHC or FISH. Of this group, 4 patients had discordant *ERBB2* amplification by NGS and FISH/IHC HER2 positivity results. These patients had significantly shorter PFS on first-line trastuzumab/chemotherapy compared with those patients with *ERBB2*-amplified tumors (5.8 vs 14.0 months; $P$=10-6). Additionally, higher levels of *ERBB2* amplification were correlated with increased PFS following first-line trastuzumab, with patients in the top quartile of expression reporting a significantly longer median PFS compared with patients without amplification ($P$<.001). An analysis of 44 patients who had progressed after trastuzumab revealed that 16% of patients had become ERBB2-negative by NGS; IHC testing of post-progression tumor samples showed lack of or significantly decreased HER2 expression among all patients. *ERBB2*-nonamplified clones could be a mechanism of resistance to HER2-targeted agents. Furthermore, these findings suggest that cell-free genomic techniques such as NGS may be useful tools in identifying which patients may benefit from anti-HER2 therapy, particularly given the high genomic heterogeneity among GEJ carcinomas, and mechanisms of resistance.

## Future Directions: Novel Agents and Ongoing Research

Ongoing research includes investigations into novel combination regimens and novel anti-HER2 therapies. Currently, more than 40 ongoing clinical trials are evaluating therapeutic strategies in HER2-positive gastroesophageal cancers. Selected studies of interest are highlighted below.

The quadruplet combination of tucatinib (Tukysa, Seagen), trastuzumab, ramucirumab (Cyramza, Lilly), and paclitaxel is being examined for second-line treatment in the ongoing phase 2/3 MOUNTAINEER-02 trial for patients with HER2-positive locally advanced or metastatic gastric or GEJ adenocarcinoma. Tucatinib is a highly selective HER2-directed oral TKI that has shown efficacy in combination with trastuzumab and chemotherapy in metastatic breast cancer.[35]

Given the promising interim results of KEYNOTE-811, the safety and efficacy of combination HER2-directed therapy and PD-1 inhibition with chemotherapy is an anticipated area of research. A phase 2, single-arm multicenter study is evaluating the combination of pembrolizumab, neratinib (Nerlynx, Puma), and paclitaxel in the second-line setting for recurrent or advanced HER2-positive gastric cancers.[36] Neratinib is an irreversible pan-HER TKI that has been shown to improve outcomes in advanced breast cancers.[37]

Expanded indications for T-DXd use in the second-line treatment for unresectable or metastatic gastric and GEJ adenocarcinomas are an area of interest. DESTINY-Gastric03 is evaluating T-DXd in combination with 5-FU or capecitabine, and DESTINY-Gastric04 is investigating the efficacy of T-DXd monotherapy vs the current standard of care, which is ramucirumab plus paclitaxel.[38,39] Results of these studies are pending at the time of this writing.

ASPEN-06 is an ongoing phase 2/3 study of evorpacept (ALX148), a high-affinity anti-CD47 protein, in combination with trastuzumab, ramucirumab, and paclitaxel.[40] CD47 interacts with signal regulatory protein α (SIRPα), a membrane glycoprotein expressed on macrophages to prevent phagocytosis. Inhibiting this interaction is thought to improve the immune system antitumor response when used in combination with therapeutic antibodies against tumor-specific antigens, such as trastuzumab.[41] The phase 3 study will compare the efficacy of this combination with ramucirumab and paclitaxel in the second-line and beyond setting for patients with advanced HER2-positive gastric and GEJ adenocarcinomas previously treated with HER2-directed therapy.

Margetuximab (Margenza, MacroGenics) is an Fc-optimized anti-HER2 monoclonal antibody with enhanced antibody-dependent cell-mediated cytotoxicity compared with trastuzumab in ex vivo analyses of peripheral blood samples.[42] MAHOGANY is an ongoing phase 2/3 trial examining the safety and efficacy of margetuximab plus the anti–PD-1 monoclonal antibody retifanlimab in the first-line setting for unresectable or metastatic HER2-positive, PD-L1–positive (defined as a CPS of >1%), microsatellite-stable gastric and GEJ adenocarcinomas.[43] A safety analysis of the phase 2 single-arm cohort (n=43) reported grade 3 adverse events in 18.6% of patients, with the most common adverse events being fatigue, infusion reaction, rash, diarrhea, and pruritis. The ORR was 53% (95% CI, 36.1-68.5), with similar response rates across CPS expression subgroups. Although margetuximab and retifanlimab is a nonchemotherapy-containing combination, the ORR reported is similar to the chemotherapy-containing regimens reported in ToGA, HELOISE, and JACOB. Whether this ORR signal correlates with an OS benefit is still under investigation. Other margetuximab combinations are also being examined, specifically margetuximab and retifanlimab with chemotherapy as well as margetuximab with tebotelimab, an anti–PD-1 dual-affinity retargeting [DART] molecule).[44]

Zanidatamab (ZW25) is a novel anti-HER2 bispecific antibody designed to bind 2 HER2 epitopes, ECD 4 (trastuzumab-binding domain) and ECD 2 (pertuzumab-binding domain). Phase 2 results of first-line ZW25 in combination with chemotherapy reported an ORR of 79% (n=38; 95% CI, 63%-90%), with 3 patients achieving a CR.[45] The secondary outcome of PFS was 12.5 months, with an 18-month survival rate of 87.3%, and median OS not yet reached at the time of reporting. The most common treatment-related adverse events included diarrhea, nausea, peripheral sensory neuropathy, decreased appetite, fatigue, vomiting, and hypokalemia. Investigation of ZW25 combinations continues, with the ongoing HORIZON-GEA-01 phase 3 trial comparing combination ZW25 and chemotherapy with vs without tislelizumab. Tislelizumab is a novel anti–PD-1 monoclonal antibody that is engineered to minimize FcγR binding on macrophages, which is a possible mechanism of acquired anti–PD-1 therapy resistance.[46]

## Conclusion

Although gastroesophageal cancers are aggressive malignancies with a generally poor prognosis, HER2-targeted therapies are useful tools in increasing survival among patients with HER2-positive adenocarcinomas. Trastuzumab plus chemotherapy has been shown to improve outcomes in first-line treatment of advanced disease, with ongoing studies investigating the role of anti–PD-1 agents in improving its efficacy. Other anti-HER2 agents have not been shown to improve outcomes in the first-line setting. In the second-line and beyond setting, T-DXd is the only anti-HER2 therapy shown to improve survival, with ongoing studies investigating if these findings extend beyond Asian populations. In the nonmetastatic setting, HER2-targeted therapy is not routinely employed. Beyond traditional IHC and ISH testing, new genomic classification schemas and cell-free genomic techniques are promising tools for better identifying optimal candidates for anti-HER2 therapy, particularly given the high inter- and intra-tumoral heterogeneity of this disease. Finally, ongoing investigations of novel HER2-directed agents and combinations search for even more efficacious treatments in this subset of gastroesophageal cancers.

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