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REVIEW ARTICLE

# Targeting HER2 in Gastroesophageal Cancer: A New Appetite for an Old Plight

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## Abstract

The incidence of gastroesophageal cancers is rising, driven, in part, by an increasing burden of risk factors of obesity and gastroesophageal reflux. Despite efforts to address these risk factors, and a growing interest in methods of population screening, the bulk of these tumours are unresectable at diagnosis. In this setting, effective systemic treatments are paramount to improve survival and quality of life. Early and accurate identification of oncogenic drivers, such as human epidermal growth factor receptor 2 (HER2), present in 5–30% of gastroesophageal adenocarcinomas (GEAs), is integral to guide choice of therapies due to the clear predictive implications that arise from overexpression of this receptor. After trastuzumab, the first anti-HER2 agent with approved use in HER2-positive GEA, the addition of pembrolizumab to first-line trastuzumab-chemotherapy and trastuzumab deruxtecan in the refractory space have more recently changed practice. Yet, the response to these agents has been vastly different across patients with HER2-positive disease, underpinning the need for reliable biomarkers of response. Emergent data have suggested that levels of HER2 expression on tissue or liquid biopsies may predict response to first-generation HER2 therapies while HER2 heterogeneity, receptor changes, co-occurring molecular alterations and oncogenic genomic and metabolic reprogramming may be implicated in resistance. A robust knowledge of the mechanisms of resistance and response to HER2-directed therapies is necessary to inform novel strategies of HER2-targeting and guide choice combinations with other biomarker-directed therapies, to improve outcomes from a new generation of clinical trials in HER2-positive GEA. Understanding and close examination of previous failures in this space form an important part of this assessment, as does correlative biomarker and translational work pertaining to the role of HER2 and dynamic changes that result through treatment exposure. In this review, we aim to provide an overview of strategies for HER2 targeting, summarising both the successes and disappointments in this therapeutic landscape and discuss existing challenges and future perspectives on development in this highly morbid tumour type.

## 1 Introduction

The incidence of gastroesophageal cancers is estimated at 1.5 million cases per year [1], and holds the position as the 5th most common cancer and 4th leading cause of cancer death worldwide [2]. The burden of disease is greater for developing and Asian countries, and is higher in men than women [1, 2]. Given the association with risk factors of gastroesophageal reflux and obesity [3], incidence is rising and population modelling suggests a 62% growth in the number of cases should current rates continue [2].

Tumours located in the gastro-oesophageal region are classified by the Siewert criteria, which divides tumours anatomically based on the central point [4], and is supported by marked differences in intestinal metaplasia in the oesophagus, tumour grading, tumour growth, stage and lymphatic spread [5]. Type I tumours arise from intestinal metaplasia in the distal oesophagus, type II tumours from the epithelium of the gastric cardia or intestinal metaplasia at the gastrointestinal junction, and type III tumours arise below the gastric cardia [4]. Despite this classification assisting in determining the approach to surgery, the bulk of these malignancies are unresectable and 5-year overall survival

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**Key Points**

HER2 is a key driver of tumour growth and is overexpressed in up to 30 % of gastroesophageal adenocarcinomas (GEAs).

HER2-targeted therapies, such as trastuzumab in combination with chemotherapy, have become standard in metastatic GEA, with newer agents such as trastuzumab deruxtecan expanding options in early and advanced disease.

Resistance to HER2 therapies arises from factors such as heterogenous HER2 expression, receptor alterations and adaptive tumour mechanisms, although may be addressed through combination treatment with immunotherapy and other agents.

(OS) is limited. Even for those that are operable at diagnosis, the majority will still relapse and die from their disease, with an estimated median disease-free survival (DFS) after multimodality treatment around 26 months [6, 7].

The human epidermal growth factor receptor (HER) family, critically important for development, plays an integral role in oncogenesis. The HER2 is overexpressed in 5–30% of gastric and gastroesophageal cancers [8, 9]. When overexpressed, HER2 is an established predictor of benefit from anti-HER2 therapies, while its prognostic role in gastroesophageal tumours remains unclarified. Although a consistent literature body suggested associations with more aggressive biology and increased frequency of disease recurrence, the prognostic effect linked to HER2 overexpression seems to remain small in both earlier and advanced disease stages [8, 10–14]. In gastroesophageal cancer, HER2 positivity is determined by a result of 3+ on immunohistochemistry (IHC, [HercepTest]) or amplification on fluorescence in situ hybridization (FISH, [pharmDx tests]) in IHC 2+ cases [15].

Since the initial discovery of the role of HER2 in cancer, rapid development of methods of targeting this oncogene have ensued. However, until recently, the only effective anti-HER2 treatment for gastric and gastroesophageal junction (GEJ) adenocarcinoma has been trastuzumab, following a slew of failed combination and novel therapeutic strategies. Despite this, interest in targeting HER2 to improve the prognosis of patients with gastroesophageal adenocarcinomas (GEAs) remains robust, especially in light of the recent approval of trastuzumab deruxtecan (T-DXd) for second- and further-line treatment of HER2-positive locally advanced or metastatic gastric or gastroesophageal cancer [16].

Given the increasing complexity of HER2 targeting in GEA, the aim of this review is to provide an overview of strategies for HER2 targeting, inclusive of existing challenges and future perspectives on development in this area.

## 2 Biology of HER2-Positive Gastroesophageal Cancer

Human epidermal growth factor receptor 2 is a transmembrane glycoprotein belonging to a family of four closely related receptors (HER1, HER2, HER3 and HER4). While activated by a wide range of growth factors, none serve as a specific ligand for HER2, although these form various dimeric arrangements across tissues and harbour different degrees of tyrosine kinase activity, which is generally stronger for HER2-containing heterodimers. The HER2 is encoded by the *ERBB2* gene, which has oncogene properties and key roles in regulating epithelial cell growth and differentiation. When HER2 is constitutively activated in the absence of a ligand, signalling occurs through the phosphorylation of specific tyrosine residues with subsequent activation of the Rat sarcoma-mitogen-activated protein kinase (RAS–MAPK) and the phosphatidylinositol 3'-kinase (PI3K)-AKT–mammalian target of rapamycin (mTOR) pathways [17]. The HER2 aberrant expression has been associated with cancer transformation and progression among a variety of solid tumours, including GEA, where HER2 amplification or overexpression has been linked to junctional/proximal tumours and the intestinal subtype [18, 19].

Due to its therapeutic relevance in the advanced stages, HER2 testing guidelines, initially drawn up for breast cancer, have been adapted to account for the intrinsic differences that HER2 expression has in GEA, which encompasses a pattern of incomplete membranous staining and a higher degree of heterogeneity [20, 21]. Hoffman and colleagues proposed a four-tier HER2 scoring system (0: absent; 1: weak; 2: moderate; and 3: strong expression) assessed on an area of at least 10% immunoreactive tumour cells for surgical specimens and a small single cluster of cells (or at least five cells) for biopsy specimens [15]. Testing for HER2 expression currently requires IHC evaluation on pre-treatment tumour tissue, followed by FISH for equivocal cases (IHC 2+). Cases with IHC 3+ and 2+ with positive FISH are scored as HER2-positive [22, 23].

Although not identifying a distinct biological entity across various studies that attempted a molecular classification of gastric cancer, HER2 amplifications, together with receptor tyrosine kinase (RTK) aberrations, have been reported more frequently in The Cancer Genome Atlas (TCGA) chromosomal unstable (CIN) subtype [24, 25]. Of note, these features apply also to oesophageal adenocarcinoma, which

shares many similarities with the gastric CIN subtype at a molecular level, justifying the off-label use of trastuzumab in HER2-positive cases [26].

A distinctive feature of CIN tumours includes a vastly heterogeneous tumour immune microenvironment (TIME) with only peripheral infiltration of CD8+ T cells at the invasive margins [27]. This makes most of these tumours intrinsically cold and poorly responsive to immunotherapies. However, whether these features apply to HER2-positive GEA remains unclear. In breast cancer, the HER2 oncogenic signalling has been found to regulate the recruitment and activation of tumour-infiltrating immune cells, resulting in the association of the HER2-positive subtype with a denser lymphocytic infiltrate [28]. In GEA, fluoropyrimidine-platinum chemotherapy was shown to induce early on-treatment TIME remodelling, with upregulation of the programmed death-(ligand)1 (PD-(L)1) pathway, increased natural killer (NK) and effector T cell infiltration, and a shift from M2 to M1 polarised macrophages, particularly in responders. Of note, Kim and colleagues found that both baseline and on-treatment favourable TIME features were more pronounced in HER2-positive tumours treated with chemotherapy-trastuzumab, possibly suggesting both intrinsic biological differences and distinct trastuzumab-mediated immunomodulatory mechanisms in this subset [29]. Remodelling of the TIME appeared magnified by the sequential administration of an anti-PD-1 agent after chemotherapy, which led to the organisation of pro-immune multicellular hubs with substantial T cell expansion, primarily in patients with durable benefit and regardless of HER2 expression [30]. Combining chemoimmunotherapy with antibodies targeting tumour antigens, such as HER2, can promote cross-priming of the TIME, backing the establishment of early adaptive immune-permissive phenotypes [31].

Pre-existent immune-permissive TIME features have been demonstrated as crucial drivers of response to immune checkpoint inhibitors (ICIs) across solid tumours [32]. PD-1 and its ligand PD-L1 and cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), which are among the main targeted pathways by ICIs, are essential negative regulators of the T cell function, which ultimately restricts tumour cell recognition and killing [33–38]. However, the use of anti-PD-(L)1 agents, either with or without anti-CTLA-4 blockade, in an unselected population with GEA has resulted in worse survival outcomes [39, 40]. In contrast, when added to chemotherapy, ICIs have shown therapeutic synergy across various cancers including gastroesophageal tumours [41, 42]. Chemoimmunotherapy is an approved regimen for the frontline treatment of HER2-negative GEA, with greater benefit in PD-L1-expressing tumours [22, 23]. Prevalence of PD-L1 ranged from 35 to 60% of the cases in recent biomarker-unselected Phase 3 studies [43–46], and co-expression of PD-L1 (combined positive score [CPS] ≥ 1) has been particularly frequent in advanced HER2-positive GEA, notably 85% of the population in KEYNOTE-811 [47].

Higher levels of PD-L1 have revealed a positive correlation with intra-tumoral T cell enrichment, an essential feature of response to immunotherapy across different tumours [48]. In GEA, up-regulation of PD-L1 expression has been reported to occur under the pressure of systemic treatment and has been associated with tumour response, broadening the scope of using chemotherapy beyond its direct cytotoxic effect. Through its immunomodulatory properties, chemotherapy can indeed prime the immune system, altering favourably the baseline TIME composition and ultimately rescuing immune-depleted tumours.

Anti-HER2 agents were initially proven to exert their anti-tumour effect by interfering with the HER2 oncogenic signalling pathway and increasing susceptibility to chemotherapy-induced apoptosis [49–51]. In vitro studies reported that antibody-dependant (ADCC) and complement-dependant cytotoxicity (CDC) of HER2-overexpressing cells are additional mechanisms of trastuzumab-mediated tumour lysis exploited via the stimulation of the innate host immune response. Moreover, the processing of HER2-derived peptides as tumour-associated antigens can also induce adaptive immune responses, as reported using both animal and patient-derived models [52]. Co-administration with immunotherapy further enhanced the intra-tumoral infiltration of both innate and adaptive immune cells, ultimately producing increased tumour eradication in a murine study [53]. Results were consistent in clinical studies, where anti-HER2 biological agents were proven to mount specific HER2-mediated T cell responses [54, 55].

Collectively, these data support clinical testing of pembrolizumab plus trastuzumab-chemotherapy in a large Phase 3 study and may help an understanding of the success of this combinatorial approach [47].

## 3 Trials of Anti-HER2 Agents in Gastroesophageal Cancer

### 3.1 First-Line Treatment

For more than a decade, the front-line treatment of HER2-positive advanced GEA has consisted of trastuzumab, a monoclonal antibody directed at HER2, in combination with a platinum-fluoropyrimidine chemotherapy backbone. The global, open-label, randomised Phase 3 Trastuzumab for Gastric Cancer (ToGA) trial validated the use of the anti-HER2 agent (8 mg/kg loading dose, 6 mg/kg tri-weekly [Q3W] thereafter) added to cisplatin and 5-fluorouracil (5-FU) or capecitabine in a population of 594 patients with HER2 IHC 3+ or FISH-positive (HER2:chromosome 17 centromere [CEP17] ratio ≥2) disease [13]. The trial also

validated the use of modified histopathological scoring criteria for HER2 in gastric cancer, which accounted for the specific pattern of staining observed in this disease [15, 21]. The primary endpoint of the study, OS, was significantly improved with trastuzumab (13.8 vs 11.1 months, hazard ratio [HR] 0.74; 95% confidence interval [CI], 0.60–0.91; $p = 0.0046$). A pre-planned exploratory analysis demonstrated a greater survival benefit (HR 0.65, 95% CI 0.51–0.83) for patients with high HER2 expression (IHC 3+ or IHC 2+/FISH-positive), restricting regulatory approval to this population. Also, progression-free survival (PFS) (unstratified HR 0.71, 95% CI 0.59–0.85; $p = 0.0002$), duration of response (DOR) (unstratified HR 0.54, 95% CI 0.40–0.73, $p < 0.0001$), and tumour response rate (OR 1.70, 95% CI 1.22–2.38, $p = 0.0017$) all significantly favoured the trastuzumab arm. The addition of trastuzumab significantly prolonged time to deterioration of health-related quality of life and quality-adjusted survival [56]. Subsequent post hoc analyses and smaller Phase 2 studies suggested consistent trastuzumab efficacy across different subgroups and chemotherapy doublet backbones [57–60]. Pairing with triplet chemotherapy regimens or bevacizumab showed no additional benefit, while combination with oxaliplatin-based doublets instead of cisplatin emerged as possibly more effective and better tolerated than the ToGA regimen in a meta-analysis, becoming a recommended regimen worldwide [61–63].

The release of pharmacokinetic data from the ToGA trial, showing that trastuzumab serum concentrations in patients with GEA were lower than in patients with metastatic breast cancer and outcomes poorer for those in the lowest quartile, prompted the evaluation of different dose levels of trastuzumab. However, the use of higher doses of trastuzumab (10 mg/kg instead of 6 mg/kg in the maintenance phase after standard loading dose) failed to improve survival in GEA [64, 65].

Given that the additional benefit of trastuzumab over chemotherapy was relatively modest suggesting high rates of trastuzumab primary and secondary resistance, a variety of alternative HER2-targeted treatments were tested. In the global Phase 3 TRIO-013/LOGiC trial, 487 patients with advanced GEA and HER2-amplification or overexpression (IHC 3+) were randomised to receive either lapatinib (1250 mg once daily [OD]), a small molecule tyrosine kinase inhibitor (TKI) of the epidermal growth factor receptor (EGFR) and HER2, with capecitabine-oxaliplatin (CapeOx) or CapeOx alone. The addition of lapatinib improved the overall response rate (ORR: [53% vs 39%, $p = 0.0031$]), but did not meet the primary endpoint (OS: HR, 0.91; 95% CI 0.73–1.12; $p = 0.3492$) in the overall study population [14]. Of note, the OS benefit from lapatinib did not correlate with the IHC status (0–1+ vs 2+/3+).

Following evidence of greater efficacy in breast cancer and pre-clinical gastric cancer models [66], the global Phase 3 JACOB trial investigated dual anti-HER2 blockade with trastuzumab plus pertuzumab in advanced HER2-positive (IHC 3+ or 2+/FISH-positive) GEA. While both induce ADCC, trastuzumab and pertuzumab bind to non-overlapping HER2 epitopes. As a result, trastuzumab mostly inhibits HER2 homodimerisation and pertuzumab HER2 heterodimerisation with other receptors of the HER family. In the JACOB trial, 780 patients were randomised 1:1 to trastuzumab and platinum doublet chemotherapy with or without pertuzumab. Most of the enrolled population had gastric cancer, intestinal histology, and HER2 IHC 3+ disease. Overall survival, the primary endpoint of the study, was not significantly prolonged (HR 0.84, 95% CI 0.71–1.00, $p = 0.057$), despite being numerically longer in the experimental arm (17.5 vs 14.2 months). Similarly, PFS and ORR tended to favour the pertuzumab arm, but these analyses remained descriptive.

As discussed in greater detail in Sect. 6, heterogeneity of HER2 expression, reliance on additional oncogene-driven pathways and co-occurring genomic alterations were proposed as possible reasons for the failure of these agents in GEA.

After more than a decade of trastuzumab as the only anti-HER2 agent approved in this context, evidence of synergistic activity of ICIs and trastuzumab in preclinical models of gastric cancer and encouraging activity of ICIs in advanced GEA, supported the evaluation of this combination in the clinical scenario. The global, randomised Phase 3 KEYNOTE-811 tested the addition of pembrolizumab, a monoclonal anti-PD-L1 antibody, to trastuzumab and platinum-based chemotherapy as first-line treatment for HER2-positive advanced GEA. A total of 698 patients were allocated 1:1 to receive trastuzumab-chemotherapy (fluoropyrimidine plus cisplatin or capecitabine plus oxaliplatin at investigator's discretion) plus pembrolizumab (200 mg Q3W) or placebo. Most of the patients had tumours with HER2 overexpression (IHC 3+) (78%) and PD-L1 CPS≥1 (85%). The combination arm with pembrolizumab yielded significantly higher ORR (74.4% vs 51.9%, 95% CI 11.2–33.7, $p = 0.00006$) and longer median PFS (10.0 vs 8.1 months, HR 0.73, 95% CI 0.61–0.87), particularly in the subgroup with PD-L1 CPS≥1 (HR 0.71, 95% CI 0.59–0.86). Overall survival, the second primary endpoint, was also significantly improved in the final analysis, whereas interim analyses showed benefit only in the PD-L1 CPS≥1 subgroup (20.0 vs 15.7 months, HR 0.81, 95% CI 0.67–0.98), reserving early regulatory approvals and guideline recommendations to these patients [23, 47, 67, 68].

### 3.2 Second- and Further-Lines of Treatment

The value of targeting HER2 beyond the first line of treatment in GEA had remained poorly clarified until recently. A small Phase 2 study showed compelling outcomes with trastuzumab-paclitaxel in the second line for trastuzumab-naïve patients (median PFS 5.1 months, 95% CI 3.8–6.5, and median OS 17.1 months, 95% CI 13.5–18.6) [69]. However, continuation of trastuzumab beyond progression with second-line paclitaxel did not improve outcomes in the Phase 2 T-ACT trial, where enrolled patients had been previously exposed to the anti-HER2 monoclonal antibody [70, 71]. In keeping with prior retrospective evidence, more than two-thirds (69%) of the evaluable patients in the T-ACT trial lost HER2 overexpression/amplification after their first line of treatment, partly explaining the failure of such a strategy. Also, quantification of HER2 amplification and HER2 extracellular domain in pre-treatment liquid biopsies did not correlate with outcomes in this study. A subsequent meta-analysis including both the T-ACT trial and cohort studies reinforced the evidence of a lack of OS benefit from the use of trastuzumab beyond progression [72].

The investigation of TKIs as alternative anti-HER2 strategies also had limited success in this setting. The Asian Phase 3 TyTan study failed to demonstrate superior OS (HR 0.84, 95% CI 0.64–1.11, $p = 0.1044$) or PFS (HR 0.85, 95% CI 0.63–1.13, $p = 0.2441$) by the addition of lapatinib (1500 mg OD) to second-line paclitaxel in patients with HER2-amplified GEA, despite showing a significant ORR benefit in favour of the experimental arm (OR 3.85, $p < 0.001$). In contrast to the TRIO-013/LOGiC trial conducted in first-line, a greater effect of lapatinib on survival outcomes was seen in patients with HER2 IHC 3+ (OS: HR 0.59, 95% CI 0.37–0.93, $p = 0.0176$ and PFS: HR 0.54, 95% CI 0.33–0.90, $p = 0.0101$) in the TyTan study, although the analyses remained explorative and affected by the small sample size [73]. Similarly, a small Phase 2 study conducted in Europe closed early for futility after failing to show any ORR improvement, the primary outcome of the trial, from lapatinib (1250 mg OD) either with or without capecitabine in patients with HER2-amplified refractory disease [74]. Finally, afatinib, an irreversible pan HER inhibitor, proved limited activity as monotherapy or in combination with trastuzumab in a Phase 2 study enrolling patients with pre-treated HER2-amplified GEA. Co-occurring genomic alterations were postulated as predictors of response (EGFR co-amplification) or resistance (mesenchymal epithelial transition [MET] co-amplification or mutations in the RAS or PI3K pathways) to afatinib in a correlative biomarker study, similar to prior findings with trastuzumab [75].

The exploration of antibody-drug conjugates (ADCs) held more promise despite initial failure. The Phase 2/3 GATSBY trial investigating trastuzumab-emtansine ([T-DM1] Phase 3 dose: 2.4 mg/kq weekly), an ADC comprising trastuzumab linked to the tubulin inhibitor emtansine with a drug-to-antibody ratio of 3.5, versus standard second-line taxane did not prove any OS (HR 1.15, 95% CI 0.87–1.51, $p = 0.86$) or PFS (HR 1.13 95% CI 0.89–1.43, $p = 0.31$) advantage in patients with refractory HER2-positive GEA [76]. Also, there was no evidence of differential benefit according to prior exposure to anti-HER2 agents or levels of HER2 IHC expression. However, in 2020, the Phase 2 DESTINY-Gastric01 study finally changed practice [77]. The study randomised 187 Japanese or Korean patients with refractory HER2-expressing GEA 2:1 to receive T-DXd (6.4 mg/kg Q3W) or standard chemotherapy (either paclitaxel or irinotecan at investigator's choice). The T-DXd is an ADC composed of a humanised anti-HER2 monoclonal antibody with the same amino acid sequence as trastuzumab, covalently linked via a cleavable linker to DXd, a topoisomerase I inhibitor, and has a higher antibody-to-drug ratio of 1:8 compared to T-DM1. Based on the favourable activity observed in the Phase 1 dose-expansion gastric cancer cohort and the demonstration of dose-level equivalent pharmacokinetics in GEA at a higher dose compared to that used in breast and lung cancer (5.4 mg/kg Q3W), T-DXd was further developed and subsequently approved at a dose of 6.4 mg/kg Q3W [78, 79]. In the subsequent DESTINY-Gastric01 study, enrolled patients had either high (IHC 3+ or 2+/FISH-positive) or low (HER2 IHC 2+/FISH-negative, or IHC 1+) HER2 expression on the most recent archival tissue and had received at least two prior lines of treatment including trastuzumab if HER2-high. Most patients had high HER2 expression (of which IHC 3+: 77%) and were included in the primary analysis, whereas patients with low HER2 expression were enrolled in two separate exploratory cohorts.

The ORR, the primary endpoint of the study, was significantly improved with the ADC (51% vs 14%, $p < 0.001$) among patients with HER2-high disease, including 9% of complete responses versus none in the comparator group. Of note, the response rate was almost doubled in patients with HER2 IHC 3+ (58%) compared to those with HER2 IHC 2+/FISH-positive (29%). Moreover, median OS (12.5 vs 8.4 months, HR 0.59, 95% CI 0.39–0.88, $p = 0.01$) and PFS (5.6 vs 3.5 months, HR 0.47, 95% CI 0.31–0.71) were both significantly improved with T-DXd [77].

The analysis of the exploratory cohorts with HER2-low expression ($n = 45$) reported some activity of T-DXd in this population with a confirmed ORR of 26.3% and 9.5% in patients with HER2 2+/FISH-negative (cohort 1, $n = 21$) and IHC 1+ (cohort 2, $n = 24$), respectively [80]. These

results provided preliminary evidence that T-DXd may be active for a broader population with HER2-expressing disease due to the ability of the payload to penetrate neighbouring cells regardless of HER2 expression levels (i.e., bystander effect). The parallel, single-arm, Phase 2 DESTINY-Gastric02 trial conducted in the USA and Europe confirmed the role of T-DXd in HER2-positive refractory GEA, independent of geography or ethnic group [81]. Confirmed ORR was 42%, including 4 complete responses (5%), among 79 patients with HER2 positivity confirmed on a post-progression biopsy and disease progression after a trastuzumab-containing first-line regimen. Median DOR was 8.1 months (95% CI 5.9–NE), PFS 5.6 months (95% CI 4.2–8.3) and OS 12.1 months (95% CI 9.4–15.4). Survival and efficacy outcomes were similar in the two DESTINY-Gastric studies, acknowledging baseline differences between the Western and the Asian patient cohorts. Compared to the Western population, the Asian population of DESTINY-Gastric01, while more extensively pre-treated, had fewer gastroesophageal junction tumours (14% vs 66%) and a lower disease burden (50% with sum of target lesions <5 cm vs 6% with <2 metastatic sites). Based on these findings, T-DXd has obtained regulatory approval in the USA, Europe, and Japan for HER2-positive GEA after exposure to trastuzumab [16, 82, 83]. Of note, a post-progression biopsy was not mandated by the ESMO guidelines but remains recommended whenever feasible [23]. While T-DXd is being further developed in the refractory setting in the DESTINY-Gastric06 (NCT04989816) in China and DESTINY-Gastric04 (NCT04704934) as second-line against paclitaxel-ramucirumab, the DESTINY-Gastric03 trial (NCT04379596) faced the task of testing T-DXd in combination with chemotherapy or immunotherapy as first-line treatment. Adding a chemotherapy partner to the ADC has proved feasible but expectedly challenging due to the narrow therapeutic window of T-DXd and anticipated overlapping toxicities [84]. Preliminary results from the dose-expansion phase of DESTINY-Gastric03 demonstrated the activity of T-DXd (6.4 mg/kg) in the first-line setting, achieving a confirmed ORR of 49%, a median PFS of 9 months, and a median OS of 18 months as a single agent [85]. When combined with full-dose fluoropyrimidine (ORR 78%), pembrolizumab (ORR 63%), or both (ORR 58%), T-DXd activity was further confirmed. However, the 6.4 mg/kg dose was associated with high rates of severe adverse events (AEs) when combined with full-dose chemotherapy (G≥3 AEs 76%) or with both chemotherapy and pembrolizumab (G≥3 AEs 91%). In contrast, the combination of T-DXd (5.4 mg/kg) and 5-FU (750 mg/m$^2$) at a reduced dose with pembrolizumab showed an improved safety profile (G≥3 AEs 34%), without compromising the activity (ORR 59%) and is now being developed further. Key trials in first- and later-lines of advanced GEA are presented in Table 1.

### 3.3 Use of Anti-HER2 Therapy in the Operable Space

Oesophago-gastric cancer is locoregional in 24–32% of patients at time of diagnosis [1]. For these patients, multimodality therapy is the pathway of choice, comprising combinations of systemic treatment with or without radiotherapy and surgery.

The use of perioperative chemotherapy has already been shown to improve OS, DFS and the rate of R0 resections [6]. However, disease relapse generally occurs within 2 years and OS remains modest; thus, the emergence of molecularly targeted agents has generated considerable interest in whether outcomes in this setting can be further improved.

The addition of trastuzumab to FLOT (fluorouracil, leucovorin, oxaliplatin, docetaxel) chemotherapy was investigated in the single-arm Phase 2 HER-FLOT trial. In this trial, trastuzumab was administered with FLOT for 8 biweekly cycles (4 before and 4 after surgery, at 4 mg/kg maintenance after a 6- mg/kg loading dose) followed by 9 consolidation cycles without chemotherapy. From the 56 evaluable patients, the pathological complete response (pCR) rate was 21%, R0 rate 93% and median DFS was 42 months, comparing favourably to FLOT alone in a retrospective analysis [86].

Alternative chemotherapy backbones have been evaluated with trastuzumab in the Phase 2 NEOHX and JCOG Trigger trials, which used XELOX and S-1 plus cisplatin, respectively, in combination with 3-weekly dosing of trastuzumab, as peri-operative treatment followed by maintenance treatment for up to 1 year [87, 88]. Despite JCOG Trigger terminating early due to poor accrual, both trials suggested improved pathological and radiological outcomes through the addition of trastuzumab.

Overall outcomes were no different with other anti-HER2 regimens, such as lapatinib or pertuzumab plus trastuzumab [7, 89, 90]. Investigated in Phase 2 studies and with different chemotherapy combinations (ECX for lapatinib and either FLOT or a choice of cisplatin plus capecitabine/5FU or CAPOX/FOLFOX for trastuzumab-pertuzumab), these agents showed improved pathological responses at the price of a quite low tolerability profile. In fact, rates of diarrhoea were consistently high when used in combination with cytotoxic drugs, which limited their further development. Also, patient accrual was generally slow, hampered by risks of misalignment between turnaround times for biomarker testing and access to downstaging treatment and potentially curative surgery.

The negative results of dual HER2 targeting in advanced disease from the JACOB study caused the premature closure of the PETRARCA study testing the regimen with FLOT in the perioperative space [91]. Despite this, there was a significant difference in pCR rates between the two arms (12% for FLOT alone vs 35% for combination, $p = 0.019$). Neither the median OS or DFS were mature at the time of publication,

**Table 1** Key trials in first and later lines of treatment for advanced gastroesophageal cancer

| Trial | First author | Phase | Number | HER-2 criteria | Line | Experimental | Comparison | Primary endpoint | Key secondary and exploratory endpoints | Primary outcome[^] |
|---|---|---|---|---|---|---|---|---|---|---|
| DESTINY-Gastric01 | Shitara | II | 187 | HER-2 IHC 3+ or 2+ and (F)ISH positive | 3 | Trastuzumab deruxtecan[◊] | Chemotherapy (irinotecan or paclitaxel) | ORR | DOR, PFS, DCR, TTR, safety | 51% vs 41%, $p<0.001$ |
| DESTINY-Gastric02 | Van Cutsem | II | 79 | HER-2 IHC 3+ or 2+ and (F)ISH positive | 2 | Trastuzumab deruxtecan[°] | – | ORR | PFS, OS, ORR, DOR, safety | 38% (95% CI 27.3–49.6) |
| GATSBY | Thuss-Patience | II/III | 415 | HER-2 IHC 3+ or 2+ and (F)ISH positive | 2 | Trastuzumab emtansine[∞] | Chemotherapy (docetaxel or paclitaxel) | OS | PFS, ORR, DOR, safety, PROs, pharmacokinetics | 1.15 (95% CI 0.87–1.51), $p=0.86$ |
| JACOB | Tabernero | III | 780 | HER-2 IHC 3+ or 2+ and ISH positive | 1 | Pertuzumab[§] + Trastuzumab* + chemotherapy | Trastuzumab + chemotherapy (cisplatin + 5FU/capecitabine) | OS | PFS, ORR, CBR, safety, QoL | 0.84 (95% CI 0.71–1.00), $p=0.057$ |
| KEYNOTE-811 | Janjigian | III | 698 | HER-2 IHC 3+ or 2+ and (F)ISH positive | 1 | Pembrolizumab + Trastuzumab* + chemotherapy | Trastuzumab* + chemotherapy (cisplatin + 5FU/capecitabine) | PFS, OS | ORR, DOR, QoL, safety | 0.72 (95% CI 0.60–0.87), $p=0.0002$ |
| T-ACT | Makiyama | II | 91 | HER-2 IHC 3+ or 2+ and HER2:CEP17 ≥2 | 2 | Trastuzumab* + chemotherapy | Chemotherapy (paclitaxel) | PFS | OS, ORR, safety | 0.91 (95% CI 0.67–1.22) $p=0.33$ |
| ToGA | Bang | III | 594 | HER-2 IHC 3+ or HER2:CEP17 ≥2 | 1 | Trastuzumab* + chemotherapy | Chemotherapy (cisplatin + 5FU/capecitabine) | OS | PFS, TTP, ORR, DOR, QoL, safety | 0.74 (95% CI 0.60–0.91), $p=0.0046$ |
| TRIO-013/LOGiC | Hecht | III | 487 | HER-2 IHC 3+ or HER2 amplification | 1 | Lapatinib[†] + chemotherapy | Chemotherapy (capecitabine + oxaliplatin) | OS | PFS, ORR, DOR, safety | 0.91 (95% CI 0.73–1.12), $p=0.3252$ |
| TyTan | Satoh | III | 261 | HER-2 IHC 3+ or 2+ and HER2:CEP17 ≥2 | 2 | Lapatinib + chemotherapy | Chemotherapy (paclitaxel) | OS | PFS, TTP, ORR, time to response, DOR, safety | 0.84 (95% CI 0.64–1.11), $p=0.1044$ |

Key trials of anti-HER-2 agents in advanced gastroesophageal cancer discussed in Sect. 3.1 and 3.2

*CEP17* chromosome 17 centromere, *DOR* duration of response, *HER-2* human epidermal growth factor receptor 2, *IHC* immunohistochemistry, *IV* intravenous, *OD* once daily, *ORR* overall response rate, *OS* overall survival, *PFS* progression-free survival, *TTP* time to progression

[*]8 mg/kg loading, followed by 6 mg/kg q3w, [†]1250 mg OD, [§]840 mg IV, [‡]1500 mg OD, [∞]3.6 mg/kg q3w or 2.4 mg/kg q1w, [◊]5.4 mg/kg or 6.4 mg/kg q3w, 6.4 mg/kg q3w, [^]primary outcome is reported as rates for objective response and hazard ratios for survival

but HRs were 0.56 (95% CI 0.21–1.47, $p = 0.228$) and 0.58 (95% CI 0.28–1.19, $p = 0.130$), respectively [7].

In the 3-arm INNOVATION study, rates of major pathological response (MPR) were 23.3% for chemotherapy alone, 37.0% for chemotherapy-trastuzumab and 26.4% for chemotherapy-trastuzumab plus pertuzumab, acknowledging some differences following an amendment which allowed for use of FLOT rather than the previously allocated regimens of cisplatin plus 5FU/capecitabine or CAPOX/FOLFOX. The study did not meet its primary endpoint, as MPR was not significantly different between chemotherapy and the dual anti-HER2 combination [90]. Of note, tolerability may have substantially affected the outcomes of this study as toxicity represented the major reason for treatment discontinuation (70%) with a 7-fold increase in grade ≥3 diarrhoea noted after the addition of pertuzumab to the trastuzumab-chemotherapy combination and an overall reduced dose intensity of FLOT in this arm.

Importantly, the addition of HER2-targeted agents in these studies did not appear to affect progression to surgery or surgical outcomes beyond chemotherapy alone [6, 7, 87].

Preoperative chemoradiation is an alternative to perioperative chemotherapy in oesophageal and gastroesophageal junction tumours, and here the addition of HER2-targeted agents has also been investigated. The Phase 3 RTOG1010 trial randomised 203 patients to receive neoadjuvant chemoradiotherapy for 6 weeks with weekly carboplatin plus paclitaxel [92] with or without trastuzumab (4 mg/kg loading dose then 2 mg/kg) followed by surgery and further trastuzumab. This trial revealed no benefit from the addition of trastuzumab to chemoradiation in either pCR rate (27% vs 29%) or DFS (19.6 vs 14.2 months, $p = 0.97$).

The Phase 2 TRAP feasibility trial included pertuzumab together with neoadjuvant carboplatin/paclitaxel chemoradiotherapy and trastuzumab, at accepted doses [92]. The rate of pCR was 34% and the 3-year PFS and OS rates were 56.8% and 71.3%, respectively, in the 40-patient ITT population, concluding promising activity compared to historical controls and a need for further assessment.

Alternatively, the TOXAG study assessed purely adjuvant therapy with the addition of trastuzumab to adjuvant chemotherapy with three cycles of CAPOX and subsequent adjuvant capecitabine chemoradiation [93]. Trastuzumab was continued for one year of treatment and 12- and 24-month DFS was 65.7% and 55.0%, respectively.

These trials showed an absence of increased toxicity by the addition of HER2-targeted agents, and particularly no increased toxicity from the further inclusion of pertuzumab [94, 95].

Currently, there are no recommendations for the addition of anti-HER2 therapy in the operable space; however, multiple trials are ongoing to test novel anti-HER2 agents and combinations of these with chemotherapy (Table 2).

### 3.4 Investigational Anti-HER2 Agents in Gastroesophageal Cancer

Treatment modalities to target oncogenic pathways have expanded substantially in recent years, and HER2 targeting in gastroesophageal cancer is no different. Apart from the monoclonal antibodies of trastuzumab and pertuzumab and TKIs of lapatinib, neratinib, and tucatinib, the HER2 armamentarium now includes ADCs, bispecific antibodies, cellular therapies, and cancer vaccines, among others. While ADCs are currently the most promising [81], multiple trials are ongoing to test these novel methods of HER2 targeting or combinations of these in GEA (Table 2).

Following the benefit observed with trastuzumab in combination with chemotherapy as first-line treatment of metastatic gastroesophageal cancer [13], several alternative monoclonal antibodies have emerged. These included margetuximab, a monoclonal antibody Fc-engineered for increased affinity to CD16A and effective in HER2-positive breast cancer [96]. Before being discontinued, this agent had been tested in combination with anti-PD1 therapy in the Phase 2/3 MAHOGANY study [97]. In the enrolled population, all with HER2 IHC 3+ and CPS ≥1 tumours, the combination demonstrated an ORR of 53%, a DOR of 10.3 months (95% CI 4.6–NE) and 6-month PFS of 62%, all quite remarkable outcomes for a chemotherapy-free approach.

Bispecific antibodies extend targeting from one antigen or epitope, to two or—in the setting of trispecific antibodies—three. While many bispecific antibodies serve to activate cytoxic lymphocytes, so-named BiTEs or Bispecific T-cell Engagers, others target cytokines, checkpoints and oncogenic signalling pathways such as HER2 [98]. Zanidatamab is a HER2/HER2-bispecific antibody, engineered to target two non-overlapping HER2 domains [99]. Early results suggested tolerability with an encouraging ORR of 37% (95% CI 27.0–48.7) as monotherapy in a treatment-refractory population and of 79% (95% CI 63–90) in combination with standard doublet chemotherapy when used in the front line [99, 100]. The agent is currently undergoing assessment in the Phase 3 HERIZON-GEA-01 trial in combination with chemotherapy and tislelizumab. Also targeting HER2/HER2 is KN26, assessed in a Phase 2 trial of 46 patients with HER2-positive gastric and gastroesophageal cancer. Patients were divided into two cohorts by HER2 expression, with a reported ORR of 56% for HER2-high and 14% for HER2-low patients [101]. Further assessment, including in combination with the CTLA-4/PD-1 bispecific KN046, is currently ongoing following favourable results in a non-GEA cohort [102].

Additional target combinations for bispecific antibodies in GEA include HER2/HER3 (MM-111, MCLA-128), HER2/Trop2 (YH012), HER2/4-1BB (YH32367), HER2/

**Table 2** Ongoing studies of novel HER2 agents or targeted combinations based on a search of the clinicaltrials.gov database, using search terms "(gastric cancer OR oesophago-gastric OR esophagogastric OR gastroesophageal) AND (HER2 OR HER-2)"

| Group | Stage/agent | Mechanism of anti-HER2 | NCT number | Phase | Combination |
|---|---|---|---|---|---|
| Novel combinations with trastuzumab | Early/perioperative | Mab | NCT05218148 | II | SOX + trastuzumab + sintilimab |
| | | | NCT06123338 | II | Pembrolizumab + trastuzumab + chemotherapy |
| | | | NCT04819971 | II | Tirelizumab + trastuzumab + chemotherapy |
| | | | NCT05504720 | II | Pembrolizumab + trastuzumab + chemotherapy |
| | | | NCT05975749 | II | Serplulimab + trastuzumab + chemotherapy |
| | | | NCT05715931 | II | Toripalimab + trastuzumab + chemotherapy |
| | Advanced | Mab | NCT05583383 | – | Camrelizumab + trastuzumab + chemotherapy |
| | | | NCT06098898 | I | NK510 + trastuzumab |
| | | | NCT05187182 | I | CA-4948 + FOLFOX/PD1 + trastuzumab |
| | | | NCT05143970 | I | IPH5301 + trastuzumab + chemotherapy |
| | | | NCT05162755 | I | S095029 + Sym021 + Futuximab |
| | | | NCT05640830 | I/II | Trastuzumab + bevacizumab + chemotherapy |
| | | | NCT05555251 | I/II | BI-1607 + trastuzumab |
| | | | NCT05311189 | II | HLX10 + trastuzumab + chemotherapy |
| | | | NCT04150640 | II | NALIRIFOX + trastuzumab |
| | | | NCT05002127 | II/III | AXL148 + trastuzumab + ramucirumab + paclitaxel |
| Other HER2 monoclonal antibodies | HLX22 | Mab | NCT04908813 | II | HLX22 + trastuzumab + chemotherapy |
| HER2 bispecific antibodies | IBI-315 | HER2/PD1 | NCT05608785 | I/II | IBI-315 + CAPOX |
| | Zanidatamab | HER2/HER2 | NCT05270889 | II | Zanidatamab + tislelizumab |
| | | | NCT03929666 | II | Zanidatamab + chemotherapy |
| | | | NCT05152147 | III | Zanidatamab + chemotherapy + tislelizumab |
| | IMM-2902 | HER2/CD47 | NCT05076591 | I | IMM-2902 |
| | | | NCT05805956 | I/II | IMM-2902 |
| | KN-026 | HER2/HER2 | NCT06023758 | II | KN-026 + KN-046 + XELOX |
| | | | NCT05427383 | II/III | KN-026 + chemotherapy |
| | YH32367 | HER2/4-1BB | NCT05523947 | I/II | YH32367 |
| HER2 tri-specific antibodies | SAR443216 | HER2/CD3/CD28 | NCT05013554 | I | SAR443216 |

**Table 2** (continued)

| Group | Stage/agent | Mechanism of anti-HER2 | NCT number | Phase | Combination |
|---|---|---|---|---|---|
| HER2 anti-body drug conjugates | Trastuzumab deruxtecan | HER2 ADC MMAE payload | NCT04704661 | I | T-DXd + celerasertib |
| | | | NCT06085755 | I/II | T-DXd + afatinib |
| | | | NCT05894824 | I/II | T-DXd + ramicirumab |
| | | | NCT05965479 | II | T-DXd |
| | | | NCT05993234 | II | T-DXd |
| | | | NCT05034887 | II | T-DXd |
| | | | NCT04379596 | II | T-DXd + chemotherapy/PDL1 |
| | | | NCT04704934 | III | T-DXd |
| | Disitamab vedotin (RC48) | HER2 ADC MMAE payload | NCT06078982 | I | RC48 + toripalimab |
| | | | NCT05514158 | I | RC48 + RC98 |
| | | | NCT06157892 | I/II | RC48 + tucatinib |
| | | | NCT05982834 | I/II | RC48 + fruquintinib + tislelizumab |
| | | | NCT05313906 | II | RC48 + AK105 + cisplatin |
| | | | NCT05720533 | II | RC48 + sintilimab |
| | | | NCT05627414 | II | RC48 + sintilimab + S-1 |
| | | | NCT05113459 | II | RC48 + PD1 + capecitabine |
| | | | NCT05928897 | II | RC48 + sintilimab |
| | | | NCT05586061 | II | RC48 + tislelizumab + S-1 |
| | | | NCT06227325 | II | RC48 + sintilimab + XELOX |
| | | | NCT05241899 | II | RC48 + fruquintinib |
| | | | NCT06155383 | II | RC48 + toripalimab + chemotherapy |
| | | | NCT06221748 | II/III | RC48 + cadonilimab + paclitaxel |
| | | | NCT05980481 | II/III | RC48 + toripalimab + chemotherapy/trastuzumab |
| | | | NCT04714190 | III | RC48 + chemotherapy |
| | DP303c | HER2 ADC MMAE payload | NCT04826107 | II | DP303c |
| | DB-1303 | HER2 ADC TopoI payload | NCT05150691 | I/II | DB-1303 |
| | MRG002 | HER2 ADC MMAE payload | NCT04492488 | I/II | MRG002 |
| | | | NCT05141747 | II | MRG002 |
| | SHR-A1811 | HER2 ADC TopoI payload | NCT04513223 | I | SHR-A1811 |
| | | | NCT05671822 | II | SHR-A1811 |
| | | | NCT06123494 | III | SHR-A1811 |
| | IKS014 | HER2 ADC MMAF payload | NCT05872295 | I | IKS014 |
| Immune stimulating anti-body conjugate | BDC-1001 | Trastuzumab biosimilar TLR7/8 agonist payload | NCT04278144 | I/II | BDC-1001 |

**Table 2** (continued)

| Group | Stage/agent | Mechanism of anti-HER2 | NCT number | Phase | Combination |
|---|---|---|---|---|---|
| Tyrosine kinase inhibitors targeting HER2 | Afatinib | TKI | NCT06085755 | I/II | T-DXd + afatinib |
| | Tucatinib | TKI | NCT06157892 | I/II | RC48 + tucatinib |
| | | | NCT04430738 | I/II | Tucatinib + trastuzumab + chemotherapy/PD1 |
| | | | NCT04499924 | II/III | Tucatinib + trastuzumab |
| | Pyrotinib | TKI | NCT05111444 | II | Pyrotinib + camrelizumab + chemotherapy |
| | | | NCT05070598 | II | Pyrotinib + camrelizumab + chemotherapy |
| | Neratinib | TKI | NCT06109467 | II | Neratinib + trastuzumab + chemotherapy + PD1 |
| Cellular therapies | AB-201 | CAR-NK | NCT05678205 | I/II | AB-201 |
| | | Macrophage | NCT06224738 | I | HER-2 targeted macrophages |
| | | CAR-T | NCT03740256 | I | HER2 specific CAR-T + CAdVEC |
| | CCT303-406 | CAR-T | NCT04511871 | I | CCT303-406 |
| | TAC01-HER2 | TAC-T | NCT04727151 | I/II | TAC01-HER2 |
| | ACE1702 | ACC-NK | NCT04319757 | I | ACE1702 |
| | CT-0508 | CAR-macrophage | NCT04660929 | I | CT-0508 |
| Cancer vaccines | | B-cell epitope | NCT05315830 | I | HER2 tumour vaccine |
| | AST-301 | pNGVL3-hICD, plasmid DNA-based encoding HER2 ICD | NCT05771584 | II | AST-301 |
| | IMU-131 | B-cell peptide | NCT05311176 | II | IMU-131 + chemotherapy/PD1 |

Observational studies, studies of biosimilars, studies of imaging techniques or pathological assessment and studies of non–oesophago-gastric cancer were eliminated. Studies were included if they had a status of 'recruiting', 'active not recruiting' or 'not yet recruiting' and if gastroesophageal cancer was included in the cohorts

*ACC* antibody-cell conjugation, *ADC* antibody-drug conjugate, *CAR* chimeric antigen receptor, *HER-2* human epidermal growth factor receptor 2, *ICD* International Classification of Diseases, *Mab* monoclonal antibody, *MMAE* monomethyl auristatin E, *NK* natural killer, *SOX* S-1 plus oxaliplatin, *TAC* T-cell antigen coupler, *TDX* trastuzumab deruxtecan, *TKI* tyrosine kinase inhibitor, *TopoI* topoisomerase I

CLDN18 (HC-2G4S), HER2/CD47 (IMM-2902) and HER2/PD1 (IBI-315).

Antibody-drug conjugates provide a targeted method of chemotherapy delivery through the specificity of monoclonal antibodies for their corresponding target [103]. Trastuzumab is a common antibody backbone, being the basis for T-DXd and T-DM1, which have been previously discussed, and trastuzumab duocarmazine, a HER2-targeting ADC where trastuzumab covalently binds to the DNA-alkylating agent duocarmazine, at a drug-antibody ratio of 2.8. Its use in a Phase 1 trial led to an ORR of 6% among the 16 patients with refractory gastric cancer enrolled [104]. Disitamab vedotin (RC48) is an ADC consisting of a monoclonal antibody against HER2 (hertuzumab), cleavable linker and cytotoxic agent monomethyl auristatin E (MMAE) with a drug-antibody ratio of 4 [105]. The Phase 1 open-label Chinese trial enrolled 30 patients with GEA who were treated with RC48 and toripalimab following failure of, or intolerance to, prior treatment. Following a reported ORR of 48% across the dose levels, first-line treatment with RC48 (2.5 mg/kg), toripalimab, and S-1 yielded an impressive ORR of 95% in a small single-arm Phase 2 Chinese study [106, 107]. This agent remains under investigation in multiple trials, as various combinations with anti-PD1 or chemotherapy.

Other novel HER2-targeting ADCs comprise tubulin inhibitors MMAE (DP303c, MRG002, ZW49) or monomethyl auristatin F (MMAF) (ARX788, IKS014) as payloads, topoisomerase inhibitors (DB1303, SHR-A1811) and Aur0101 (PF-06804103), with cleavable linkers. Phase 1 data are available for PF-06804103, which demonstrated an ORR of 52.4% at doses of ≥3 mg/kg in a pre-treated breast and gastric cancer population [108]; MRG002 with an ORR of 50% in a mixed population, which included two gastric cancer patients [109]; ARX788, which reported an ORR of 37.9% in the gastric cancer dose-expansion cohort [110]; and ZW49, a bispecific anti-HER2 antibody (zanidatamab)

conjugated to a microtubule inhibitor auristatin payload (ZD02044), which showed anti-tumour activity in gastric cancer preclinical models and led to an ORR of 28% in a Phase 1 tumour-agnostic dose-escalation study [68, 111].

An additional therapeutic class that involves use of a HER2-targeted antibody is the immune-stimulating antibody conjugates (ISAC), wherein the antibody is conjugated to an immune-stimulating toll-like receptor agonist with the aim of generating a tumour-targeted adaptive immune response. The BDC-1001 is an ISAC incorporating a trastuzumab biosimilar conjugated to a TLR7/8 agonist, assessed in a Phase 1/2 trial of 118 patients alone or in combination with nivolumab with reported good tolerance [112]. Four partial responses (PRs) were reported in a patient population that also included HER2-low (IHC 2+, non-amplified) tumours [112].

Despite a lack of benefit with lapatinib [14], small molecule inhibitors remain of interest. More often than not, these possess activity that is not specific for HER2. This includes pan-ErbB inhibitors pyrotinib [113], afatinib and neratinib [114]. The exception to this is tucatinib, a highly selective HER2 inhibitor initially under investigation in combination with trastuzumab, paclitaxel and ramucirumab in the Phase 2/3 MOUNTAINEER-02 study [115]. After having reported an ORR of 76.5% in the Phase 2 dose optimisation part, the study was terminated early by the Sponsor, perhaps with some contribution by tolerability issues with the quadruplet regimen and the approval of T-DXd in this space. Phase 1 data are available for pyrotinib from the multicentre PHOEBE study, where it was administered together the PD-1 inhibitor camrelizumab and first-line chemotherapy for GEA. In 48.8% of patients, a grade ≥3 treatment-related AE (TRAE) was experienced, and reported ORR was a promising 77.8% (95% CI 57.7–91.4) with 2 complete responses [113].

Cellular therapies, while slower to break into solid tumours than their liquid counterparts, are under investigation in HER2 gastroesophageal cancer in the form of HER2-targeted CAR-T cells (AB-201, CCT303-406, CT-0508), macrophages and NK cells (ACE1702). One Phase 1 trial has reported on the safety of HER2-targeted CAR-T, CT-0508, in a small population of seven patients, which did not include either gastric or oesophageal adenocarcinoma [116]. An alternative to CAR-T is TAC-T, co-opting the natural T cell receptor with a reportedly lower risk of toxicity, investigated in a Phase 1/2 trial with a safety endpoint, which also noted a PR in 1 patient with gastric cancer [117].

Several trials of HER2 cancer vaccines are in progress, as monotherapy or in combination with chemotherapy. Support for a combination strategy could be gleaned from the Phase 2 HER-Vaxx trial, wherein 36 HER2-naïve patients with GEA were randomised to either chemotherapy alone or in combination with the HER2 IMU-131 vaccine. A HR of 0.58 (95% CI 0.36–0.93) was observed in favour of the vaccine combination, with median OS 13.9 months (9.5% CI 7.5–14.3) compared to 8.3 (95% CI 6.0–9.6) for chemotherapy alone [118].

As technology evolves in line with improved understanding of the biology of HER2-positive GEA, it is to be hoped that these improvements can overcome previous challenges with targeting HER2 in GEA and provide robust survival benefits for this patient population.

## 4 Safety Profile of HER2-Directed Agents

Outside of its role in oncogenesis, HER2 is involved in a wide range of cellular functions and development [119]. It is found expressed in human tissue of the brain, skin, muscles, lung and gastrointestinal tract [119], and consequently targeting normal tissues with HER2 expression can mediate on-target, off-tumour toxicity.

Trastuzumab is the only monoclonal antibody approved for use in gastric/GEJ cancer [13]. Trials of this agent administer it exclusively in combination with chemotherapy, with resultant AEs mainly reflecting the toxicities of the chemotherapeutic partner, as evidenced in reported rates of myelosuppression, peripheral neuropathy, and palmar plantar erythema. The Phase 3 ToGA trial concluded no difference in the rate of AEs with trastuzumab and chemotherapy compared to chemotherapy alone with the exception of diarrhoea, occurring at 37% for all grades of severity with the combination, as opposed to 28% with chemotherapy alone [13]. Slightly higher rates of stomatitis, anaemia, thrombocytopenia, fatigue, pyrexia, weight loss, and mucosal inflammation were also seen in the trastuzumab group but did not reach significance [13]. Similar results were reported for other trials of chemotherapy and trastuzumab, and with dual anti-HER2 blockade with pertuzumab. When checkpoint inhibition is added to the combination of chemotherapy and trastuzumab, a slightly higher rate of AEs of special interest (AESI) is observed, at 38% compared to 24%. Despite this, overall TRAEs and grade 5 events were no different to the combination of chemotherapy and trastuzumab alone [47, 120].

Cardiac toxicity from anti-HER2 agents is of particular interest, reportedly occurring in approximately 10% of patients receiving these treatments [121]. The mechanism of this is poorly understood and, at least in breast cancer, thought to be related to upregulation of myocyte HER2 expression by anthracyclines [122]. In ToGA, there

was no difference in the rate of cardiac adverse events in the trastuzumab group, although a slightly higher rate of left-ventricular ejection fraction (LVEF) dysfunction was noted (5% vs 1%) [13]. Rates of LVEF dysfunction in other anti-HER2 trials of monoclonal antibodies vary widely between 0 and 16% [61, 62, 64, 70, 91, 123].

Despite a theoretical reduction in toxicity from selective delivery of cytotoxic payloads, ADCs generate side effects through on-target and off-target toxicity, as well as traditional chemotherapeutic toxicities related to the characteristics of the ADC payload and linker [124].

So far, the only ADC approved for GEA is T-DXd. Besides side effects from the topoisomerase DXd payload of nausea, vomiting, cytopenia and alopecia, notable toxicities of this agent also include interstitial lung disease (ILD)/pneumonitis. In the Phase 2 DESTINY-Gastric02 trial, this occurred in eight patients (10%) with two deaths as a consequence of the same [81]. The earlier DESTINY-Gastric01 trial reported similar rates, although only one death occurred as a result of pneumonia [77]. It is noted by the authors that DESTINY-Gastric02 enrolled and treated patients throughout the COVID-19 pandemic, although the two episodes of grade 5 ILD were ruled secondary to drug by the investigators [81]. The mechanism of alveolar damage from this agent is incompletely understood. Since lung *ERBB2* is limited to bronchial epithelium, it is thought that a target-independent origin is likely and may involve the uptake of T-DXd into alveolar macrophages [125, 126].

Small molecule inhibitors of HER2 act through binding to the HER2 intracellular domain and often to other RTKs to prevent autophosphorylation and downstream signalling [73]. While common AEs with these agents include diarrhoea, nausea and anorexia, their different spectrum of activity may explain nuances in their safety profiles. Of note, as lapatinib binds to HER2 and EGFR at similar inhibitory concentration $(IC)_{50}$, trials of this agent have reported increased rates of diarrhoea, often implicated in dose discontinuation and grade 5 events [73, 74]. For instance, in the TRIO-013/LOGiC trial, rates of grade 3 diarrhoea were 12% with lapatinib compared to 3% with chemotherapy (58% vs 29% any grade) [14].

Besides optimising supportive medications to improve tolerance and mitigate toxicity of small molecule inhibitors, improving linker technology and payload delivery for ADCs are further challenges facing HER2 targeting. Another challenge is the use of newer technologies such as cellular therapies, which introduce specific toxicities such as cytokine release syndrome and ICANS, which are outside of the scope of this review.

Table 3 summarises common AEs and AESIs across the different anti-HER2 classes of agents tested in gastric and gastroesophageal tumours.

## 5 Biomarkers of Response and Determinants of Resistance in HER2-Positive Disease

The HER2 protein overexpression or *ERBB2* gene amplification in IHC 2+ cases represent the only current validated predictive biomarkers of response to anti-HER2 therapies in GEA.

Although either a moderate (2+) or strong (3+) HER2 expression determines eligibility for approved anti-HER2 treatments in GEA, higher levels of protein expression (IHC 3+) have been almost consistently associated with a higher benefit. This notion is held with regard to both monoclonal antibodies and T-DXd, regardless of the line of treatment, suggesting that high target engagement is key for the therapeutic success of molecules that bond to the extracellular portion of the HER2 receptor [13, 77, 81, 127, 128]. Trastuzumab showed no survival improvements among the FISH-positive but IHC-negative (0 or 1+) cases in the ToGA study. Alternatively, differential benefit by IHC categories was not proven for lapatinib, which links to the intracellular ATP-binding site of the receptor [14]. Although HER2 expression is still relevant for ADCs, their activity can be retained at lower target levels due to their bystander effect. This paradigm has marked the success of T-DXd in patients with HER2-low breast cancer [129]. In keeping with these results, T-DXd has been proven active, despite less than across IHC 3+ cases, for HER2-low (IHC 2+/FISH-negative and IHC 1+) gastroesophageal tumours [80], prompting its further evaluation in dedicated studies (NCT06078982, NCT05894824, NCT06085755).

Potential surrogates of protein overexpression, such as the *ERBB2* gene amplification and *ERRB2* copy numbers (CNs), may also predict response to anti-HER2 therapies. Concordance between protein overexpression and gene amplification is generally fairly high in GEA, and patients with both features achieved the highest magnitude of benefit from trastuzumab in the ToGA trial [13]. Baseline high *ERBB2* CNs were correlated with longer PFS in HER2 IHC-positive patients treated with trastuzumab with or without pertuzumab [130, 131]. Again, patients with concordant high *ERBB2* CN variations and IHC 3+ HER2 expression derived the highest survival benefit from dual anti-HER2 blockade.

As well as tissue biomarkers, both *ERBB2* CNs and gene amplification, detected on circulating tumour DNA (ctDNA), have potential as novel non-invasive biomarkers of response. HER2 was found on ctDNA in about 50–94% of HER2-positive cases by standard tissue analysis, with a study suggesting higher sensitivity rates in cases scored on more recent (<6 months) tissue specimens [132–135]. Circulating *ERBB2* CN correlated with disease burden and both

**Table 3** Table of key adverse events in published data of anti-HER2 agents in gastric cancer

| Adverse event | | Overall (N=3433) | | Monoclonal antibodies (N=2312) | | Antibody drug conjugates (N=479) | | Small molecule inhibitors (N=642) | |
|---|---|---|---|---|---|---|---|---|---|
| | | All [N (%)] | Grade ≥3 [N (%)] | All [N (%)] | Grade ≥3 [N (%)] | All [N (%)] | Grade ≥3 [N (%)] | All [N (%)] | Grade ≥3 [N (%)] |
| Cardiovascular | Cardiotoxicity | 13 (0.4) | 6 (0.2) | 6 (0.3) | 4 (0.2) | 1 (0.2) | 0 (0.0) | 6 (0.9) | 2 (0.3) |
| Constitutional | Anorexia | 1032 (30.1) | 176 (5.1) | 666 (28.8) | 118 (5.1) | 112 (23.4) | 30 (6.3) | 254 (39.6) | 28 (4.4) |
| | Fatigue | 848 (24.7) | 132 (3.8) | 570 (24.7) | 82 (3.5) | 79 (16.5) | 25 (5.2) | 199 (31.0) | 25 (3.9) |
| | Asthenia | 422 (12.3) | 88 (2.6) | 285 (12.3) | 63 (2.7) | 46 (9.6) | 8 (1.7) | 91 (14.2) | 17 (2.6) |
| | Weight loss | 385 (11.2) | 29 (0.8) | 293 (12.7) | 23 (1.0) | 34 (7.1) | 3 (0.6) | 58 (9.0) | 3 (0.5) |
| Dermatological | Palmar plantar erythema | 436 (12.7) | 36 (1.0) | 431 (18.6) | 36 (1.6) | 1 (0.2) | 0 (0.0) | 4 (0.6) | 0 (0.0) |
| Endocrine | Hypothyroid | 52 (1.5) | 1 (0.0) | 52 (2.2) | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Gastrointestinal | Nausea | 1441 (42.1) | 156 (4.5) | 1063 (46.0) | 119 (5.1) | 141 (29.4) | 13 (2.7) | 242 (37.7) | 24 (3.7) |
| | Diarrhoea | 1312 (38.2) | 252 (7.3) | 855 (37.0) | 176 (7.6) | 72 (15.0) | 5 (1.0) | 385 (60.0) | 71 (11.1) |
| | Constipation | 358 (10.4) | 5 (0.1) | 272 (11.8) | 4 (0.2) | 57 (11.9) | 0 (0.0) | 29 (4.5) | 1 (0.2) |
| | Dysphagia | 49 (1.4) | 16 (0.5) | 35 (1.5) | 10 (0.4) | 6 (1.3) | 3 (0.6) | 8 (1.2) | 3 (0.5) |
| | Stomatitis | 282 (8.2) | 46 (1.3) | 214 (9.3) | 44 (1.9) | 5 (1.0) | 0 (0.0) | 63 (9.8) | 2 (0.3) |
| | Colitis | 28 (0.8) | 17 (0.5) | 27 (1.2) | 16 (0.7) | 1 (0.2) | 1 (0.2) | 0 (0.0) | 0 (0.0) |
| | Hepatitis | 50 (1.5) | 14 (0.4) | 6 (0.3) | 4 (0.2) | 2 (0.4) | 1 (0.2) | 42 (6.5) | 9 (1.4) |
| Haematological | Neutropaenia | 892 (26.0) | 578 (16.8) | 652 (28.2) | 407 (17.6) | 110 (23.0) | 86 (18.0) | 130 (20.2) | 85 (13.2) |
| | Anaemia | 867 (25.3) | 401 (11.7) | 655 (28.3) | 243 (10.5) | 116 (24.2) | 120 (25.1) | 96 (15.0) | 38 (5.9) |
| | Thrombocytopenia | 407 (11.9) | 135 (3.9) | 367 (15.9) | 91 (3.9) | 38 (7.9) | 44 (9.2) | 2 (0.3) | 0 (0.0) |
| Immunologic | Infusion reaction | 185 (5.4) | 15 (0.4) | 185 (8.0) | 15 (0.6) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Metabolic | Hyponatraemia | 34 (1.0) | 38 (1.1) | 27 (1.2) | 36 (1.6) | 0 (0.0) | 0 (0.0) | 7 (1.1) | 2 (0.3) |
| | Hypokalaemia | 138 (4.0) | 96 (2.8) | 106 (4.6) | 82 (3.5) | 14 (2.9) | 8 (1.7) | 18 (2.8) | 6 (0.9) |
| | Hyperglycaemia | 24 (0.7) | 16 (0.5) | 4 (0.2) | 2 (0.1) | 2 (0.4) | 1 (0.2) | 18 (2.8) | 13 (2.0) |
| Neurological | Peripheral neuropathy | 279 (8.1) | 36 (1.0) | 162 (7.0) | 20 (0.9) | 6 (1.3) | 11 (2.3) | 111 (17.3) | 5 (0.8) |
| Renal | Creatinine rise | 129 (3.8) | 20 (0.6) | 114 (4.9) | 17 (0.7) | 7 (1.5) | 2 (0.4) | 8 (1.2) | 1 (0.2) |
| | Nephritis | 0 (0) | 1 (0.0) | 0 (0.0) | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Respiratory | Pneumonitis | 43 (1.3) | 9 (0.3) | 28 (1.2) | 7 (0.3) | 12 (2.5) | 1 (0.2) | 3 (0.5) | 1 (0.2) |
| | Dyspnoea | 34 (1.0) | 14 (0.4) | 21 (0.9) | 4 (0.2) | 7 (1.5) | 1 (0.2) | 6 (0.9) | 9 (1.4) |

Data from 3433 patients across 26 trials, including combinations of trastuzumab [UMIN000005603, NCT01359397], trastuzumab + chemotherapy [NCT01041404, NCT01450696, NCT03615326, NCT01774786, UMIN000009297, NCT01774851], trastuzumab + pembrolizumab + chemotherapy [NCT03615326], trastuzumab + pertuzumab + chemotherapy [NCT01774786, NCT01461057], lapatinib [NCT01145404, NCT00447226], lapatinib + chemotherapy [NCT01145404, NCT00680901, NCT00486954, NCT01145404, NCT00526669, NCT01769508], afatinib [NCT01649271], afatinib + paclitaxel [NCT01522768], TDM-1 [NCT01641939, NCT02465060], margetuximab + pembrolizumab [NCT02689284], TDXd [NCT03329690, NCT04014075, NCT03368196], AZD8931 + chemotherapy [NCT01579578], SBT6050 + TDXd [NCT05091528], MM-111 + trastuzumab + chemotherapy [NCT01774851], SBT6050 + tucatinib + trastuzumab [NCT05091528], CUDC-101[NCT01384799]

pre-treatment and on-treatment levels were associated with higher responses to anti-HER2 agents, including T-DXd, with greater sensitivity compared to serum tumour markers [128, 133–135]. In a separate analysis, post-treatment higher than baseline *ERBB2* CNs were associated with innate trastuzumab resistance [136].

Among patients treated with approved agents, about half did not achieve an objective response to targeted treatments

and nearly 15% showed primary refractoriness in registration trials [13, 77]. Multiple and often co-occurrent biological events have been found to hamper benefit in this molecularly selected population. The high degree of tumour heterogeneity, a recognised hallmark of GEA, has been proposed as a leading mechanism of innate and acquired resistance, resulting in the heterogenous distribution of HER2-positive clones and different levels of protein overexpression across these.

Human epidermal growth factor receptor2 intratumor spatial heterogeneity has been frequently reported in multiple tissue studies and in more recent analyses using HER2 PET to assess changes in HER2 expression [137–141]. In the ToGA trial, variability in HER2 staining (≤30% stained cells) was observed in almost half of the cases, with higher rates in lower IHC classes [20]. Even for HER2 IHC 3+ tumours, heterogeneous protein expression has been found in around 30% of the cases [142]. Despite all qualifying for trastuzumab, patients with HER2 heterogeneous disease were found to have significantly reduced survival benefit compared to those with HER2 homogeneous expression [143–145]. Similarly, using quantitative proteomics, HER2 protein expression was found to be largely different (115-fold range) among cases identified as HER2-positive by standard methods and a protein level cut-off of 1825 amol/μg was proposed as predictive of benefit from trastuzumab chemotherapy (median OS: 35.0 vs 17.5 months, $p = 0.011$) [146]. Recently, a digital pathology method for quantitative continuous scoring of HER2 tried to bridge the gap between qualitative and quantitative assessment of HER2 expression. By incorporating information on target density and spatial distribution, the algorithm performed better than conventional IHC criteria in the prognostic stratification of patients with breast cancers treated with T-DXd and is planned for further assessment in gastroesophageal tumours [147].

Temporal heterogeneity of HER2 expression has also been encountered repeatedly. Among patients with HER2-positive disease, loss of HER2 on a post-trastuzumab tumour specimen has been reported in up to 70% of the cases, a finding that may have impacted post-trastuzumab trials where HER2 status was confirmed on archival tissue [70, 71, 148]. Alternatively, some degree of heterogeneity may result from interobserver variability, particularly for weak-to-moderate expression. Reassessment of HER2 on repeat biopsies, which rescued only about 4–9% of the cases initially classified as HER2-negative overall, was shown to upgrade around 25% of the tumours that were scored as HER2 IHC 2+ at their first evaluation [149, 150]. Further discordance of HER2 expression has been described between primary and metastatic sites, particularly at a genomic level (around 60% of the cases) [149, 151–155]. The study by Ye and colleagues required the assessment of up to 6 biopsies per patient to reduce the false negative risk of misclassification to 0 [153]. A variety of pre-analytical (time to formalin fixation), analytical (single vs multiple samples assessment, tumour microarray vs whole-specimen analysis, use of different antibody assays), and post-analytical factors (central vs local assessment, adoption of different scoring criteria) have been considered substantial contributors to the variable reporting of HER2 heterogeneity across different studies, prompting a call for a rigorous assessment according to shared validated guidelines on multiple biopsy specimens if a resection sample is not available [21, 22, 156].

The vast heterogeneity of gastroesophageal tumours not only affects tumour response to targeted therapies due to reduced HER2 availability but also because of the high genetic diversity with implications for resistance to anti-HER2 agents. Several preclinical studies have reported HER2-receptor modifications, including protein mutations, internalisation, and glycosylation among the mechanisms of primary and acquired resistance to trastuzumab, as these changes will ultimately prevent effective receptor binding [157–160]. Upregulation of alternative receptors including HER3/HER4, FGFR, MET, and EGFR or presence of molecular co-aberrations, such as PTEN loss or *PIK3CA* mutations, have also been implicated in trastuzumab resistance by sustaining the reactivation of the downstream PI3K/AKT and MAPK signalling pathways. The *PIK3CA* mutations and *ERBB2/4* gene mutations were enriched in about one-third of the patients with innate and acquired resistance to trastuzumab, respectively, and, when identified in the baseline plasma, were associated with significantly worse PFS [136]. In trastuzumab-resistant patients, afatinib restored sensitivity to HER2 inhibition in cases with co-occurrent HER2 and EGFR alterations but not in those with MET amplifications, suggesting a role for personalised approaches based upon the specific molecular drivers of resistance [75]. Targeted sequencing of candidate genomic alterations (AMNESIA panel), including EGFR/MET/PI3K/PTEN mutations and EGFR/MET amplifications, were able to capture patients with reduced benefit from trastuzumab, but less so from trastuzumab-pertuzumab, which remains an investigational tool [131, 161]. A more recent work suggested that RTK co-alterations are also implicated in reduced response to T-DXd, while the impact of downstream signal alterations (e.g., KRAS/NRAS and PIK3CA) is unclear [162].

Epithelial-to-mesenchymal transition (EMT) with the acquirement of stem cell-like properties [163], alterations in cell cycle regulatory pathways [164, 165], and induction of specific metabolic signatures have also been described as possible mediators of resistance to anti-HER2 treatments in gastroesophageal tumours [166–168]. Upon trastuzumab exposure, Transforming growth factor-β (TGF-β)/WNT-induced EMT, co-amplification of several cell cycle regulators (c-Myc, CCNE1, CCND1, and CDK6 among others), selective selection of tumour clones with phosphorylated (inactive) retinoblastoma protein, and dysregulation of the

DNA repair machinery promote proliferative signalling and ultimately disease progression. Finally, GATA-6-mediated metabolic reprogramming, PI3K/AKT-associated autophagy activation, and certain DNA metabolites, were found to contribute to trastuzumab resistance. A summary of the most relevant mediators of response and resistance is provided in Fig. 1.

## 6 Conclusions and Future Perspectives

The use of trastuzumab for HER2-positive GEA has revolutionised the treatment algorithm of this disease, introducing gastroesophageal tumours in the previously uncharted territory of precision oncology. A decade later, the approvals of T-DXd in the refractory setting and trastuzumab-pembrolizumab-chemotherapy in the front-line space have reignited the value of targeting this oncogenic pathway. A clear testimony of this is in the large number of clinical trials with different novel HER2-directed agents that are under development in both the advanced and operable settings (Table 2).

The traditionally target-devoid context of advanced gastroesophageal cancer is now studded with new therapeutic targets, such as PD-L1, CLDN18.2, and FGFR2b [43–46, 169–171]. Phase 3 evidence of superiority of chemotherapy combinations with anti-PD-(L)1 or anti-CLDN18.2 monoclonal antibodies poses new challenges of biomarker testing prioritisation and ultimately treatment allocation. However, with these trials being restricted to patients with HER2-negative disease, HER2 testing seems to retain its leading position in the biomarker testing flowchart.

The development of blood-based biomarker quantifying methods may help overcome shortage of tissue to allow minimally invasive concurrent testing for multiple biomarkers and possibly repeated assessment at disease progression since the expression of therapeutic targets in GEA has been found to be dynamic under the pressure of systemic

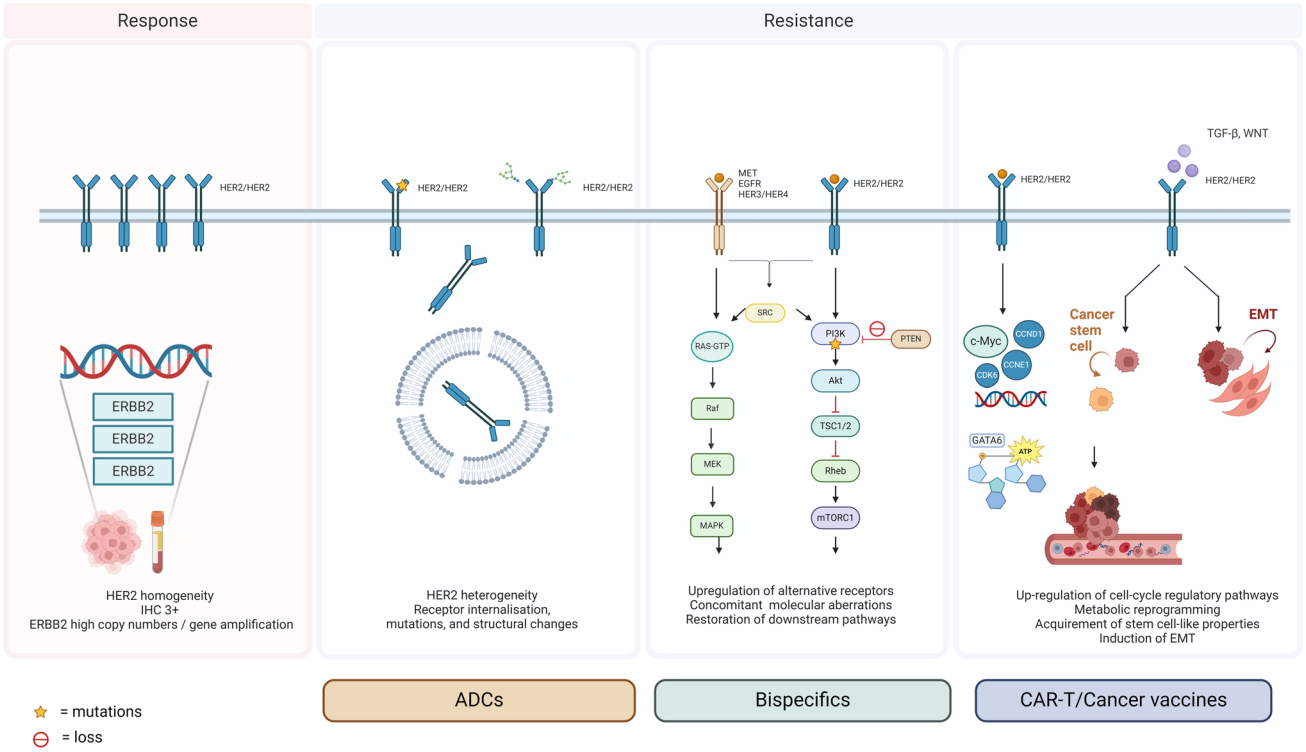


**Fig. 1** Main mechanisms of response and resistance to anti-HER2 therapies in gastroesophageal cancers. The figure illustrates the main mechanisms of response and resistance to anti-HER2 treatments in gastroesophageal cancers. The boxes underneath the figure indicate the classes of novel therapeutic agents that could potentially overcome the specific areas of resistance depicted above them. Created with Biorender.com. *ADCs* antibody-drug conjugates, *Akt (also known as PKB)* protein kinase B, *ATP* adenosine triphosphate, *CAR-T* chimeric antigen receptor T cell therapy, *CCND1* cyclin D, *CCNE1* cyclin E, *CDK6* cyclin-dependent kinase 6, *c-Myc* cellular Myc, *EGFR* epithelial growth factor receptor, *EMT* epithelial-to-mesenchymal transition, *ERBB2* v-erb-b2 avian erythroblastic leukaemia viral oncogene homolog 2, *GATA6* GATA-binding factor 6, *HER2/3/4* human epidermal growth factor receptor 2/3/4, *IHC* immunohistochemistry, *MEK* (also known as *MAPKK*), mitogen-activated protein kinase, *MET* mesenchymal epithelial transition [receptor], *mTORC1* mammalian target of rapamycin complex 1, *PI-3K* phosphoinositide 3-kinase, *PTEN* phosphatase and tensin homolog, *Raf* rapidly accelerated fibrosarcoma, *RAS-GPT* rat sarcoma-guanosine-5'-triphosphate, *Rheb* Ras homolog enriched in brain, *Src* steroid receptor coactivator, *TGF-β* transforming growth factor-β, *TSC1/2* tuberous sclerosis 1/2, *WNT* wingless-related integration site

treatment [172], and HER2-loss has been largely reported after trastuzumab exposure [71, 148].

The introduction of ADCs in the treatment of GEA, with demonstrated activity outside of the boundaries of conventionally defined HER2-positive disease [80], gives rise to additional questions. If further validated, these results may lead to necessary revisions of present scoring criteria to add more granularity as to what falls under the umbrella of HER2-negative disease. With both PD-L1 and CLDN18.2 being fairly prevalent targets at currently studied cut-offs, the question of treatment sequencing or combination in the setting of overlapping actionable alterations will become increasingly pertinent.

While for HER2-positive (IHC 3+ and 2+/FISH-positive) tumours with concomitant PD-L1 expression, the dual targeted approach of trastuzumab-pembrolizumab will be the first recommended option [22, 156], the value of targeting different levels of HER2 expression in the context of other targets remains to be explored. Furthermore, in keeping with trastuzumab and other anti-HER2 targeted agents, where lower levels of HER2 expression were generally associated with reduced therapeutic activity [13, 77, 81, 127], as a potential indirect measure of a more heterogenous disease landscape, T-DXd showed doubled tumour response rates in HER2 IHC 3+.

With the pool of anti-HER2 therapies for GEA evolving at a fast pace and moving forward into earlier disease settings, including operable stages, novel studies will need to address whether the mechanisms of resistance identified for trastuzumab apply to other classes of HER2-directed drugs. As part of this assessment, correlative biomarker studies will be needed to investigate implications of the development of resistance to the immunotherapy partner of trastuzumab or the chemotherapy payload of ADCs on HER2 oncogenic signalling.

Integrating preclinical data with clinical validation of emergent putative tissue and liquid biomarkers and improving understanding of pharmacogenomic factors influencing drug response, will be key to improving patient selection at each stage and address the current therapeutic puzzle in GEA in a highly anticipated, personalised approach.

In summary, HER2 remains a critical therapeutic target in gastroesophageal cancer, with well-established roles in cancer proliferation and survival. Despite notable challenges in moving antagonists of this pathway from bench to bedside, recent strategies of combination therapy and novel agents hold promise. However, further research is required to refine biomarker selection and to understand resistance mechanisms and pharmacogenomics to improve outcomes across both advanced and earlier stages of disease.

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**Ethics Approval** Ethics approval was not required for the formulation of this review.

**Consent to Participate** Not applicable.

**Consent for Publication** Consent for publication was not required for this review.

**Availability of Data and Material** All data used in this review are available online through the given references.

**Code Availability** No coding was used in the formulation of this review.

**Author Contributions** All authors have contributed to the design, data collection and interpretation, drafting and critical review of the manuscript, and have approved its final version.

## References

1. Lambert R, Hainaut P. Epidemiology of oesophagogastric cancer. Best Pract Res Clin Gastroenterol. 2007;21(6):921–45.
2. Morgan E, Arnold M, Camargo MC, Gini A, Kunzmann AT, Matsuda T, et al. The current and future incidence and mortality of gastric cancer in 185 countries, 2020–40: a population-based modelling study. eClinicalMedicine. 2022;47: 101404.
3. Balakrishnan M, George R, Sharma A, Graham DY. Changing trends in stomach cancer throughout the world. Curr Gastroenterol Rep. 2017;19(8):36.
4. Siewert JR, Stein HJ. Classification of adenocarcinoma of the oesophagogastric junction. Br J Surg. 2003;85(11):1457–9.
5. Siewert JR, Stein HJ, Feith M. Adenocarcinoma of the Esophago-Gastric junction. Scandinavian J Surg. 2006;95(4):260–9.
6. Al-Batran SE, Pauligk C, Homann N, Schmalenberg H, Kopp HG, Haag GM, et al. Docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) for resectable esophagogastric cancer: updated results from multicenter, randomized Phase 3 FLOT4-AIO trial (German Gastric Group at AIO). Ann Oncol. 2017;28: v616.
7. Hofheinz RD, Merx K, Haag GM, Springfeld C, Ettrich T, Borchert K, et al. FLOT versus FLOT/Trastuzumab/Pertuzumab perioperative therapy of human epidermal growth factor receptor 2-positive resectable esophagogastric adenocarcinoma: a

randomized phase II trial of the AIO EGA study group. J Clin Oncol. 2022;40(32):3750–61.
8. Abrahao-Machado LF, Scapulatempo-Neto C. HER2 testing in gastric cancer: an update. World J Gastroenterol. 2016;22(19):4619–25.
9. Torre LA, Siegel RL, Ward EM, Jemal A. Global cancer incidence and mortality rates and trends–an update. Cancer Epidemiol Biomark Prevent. 2016;25(1):16–27.
10. Kurokawa Y, Matsuura N, Kimura Y, Adachi S, Fujita J, Imamura H, et al. Multicenter large-scale study of prognostic impact of HER2 expression in patients with resectable gastric cancer. Gastric Cancer. 2015;18(4):691–7.
11. Jørgensen JT, Hersom M. HER2 as a prognostic marker in gastric cancer—a systematic analysis of data from the literature. J Cancer. 2012;3:137–44.
12. Terashima M, Kitada K, Ochiai A, Ichikawa W, Kurahashi I, Sakuramoto S, et al. Impact of expression of human epidermal growth factor receptors EGFR and ERBB2 on survival in stage II/III gastric cancer. Clin Cancer Res. 2012;18(21):5992–6000.
13. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a Phase 3, open-label, randomised controlled trial. Lancet. 2010;376(9742):687–97.
14. Hecht JR, Bang YJ, Qin SK, Chung HC, Xu JM, Park JO, et al. Lapatinib in combination with capecitabine plus oxaliplatin in human epidermal growth factor receptor 2-positive advanced or metastatic gastric, esophageal, or gastroesophageal adenocarcinoma: TRIO-013/LOGiC–a randomized phase III trial. J Clin Oncol. 2016;34(5):443–51.
15. Hofmann M, Stoss O, Shi D, Büttner R, van de Vijver M, Kim W, et al. Assessment of a HER2 scoring system for gastric cancer: results from a validation study. Histopathology. 2008;52(7):797–805.
16. FDA approves fam-trastuzumab deruxtecan-nxki for HER2-positive gastric adenocarcinomas [press release]. 01/15/2021.
17. Rubin I, Yarden Y. The basic biology of HER2. Ann Oncol. 2001;12(Suppl 1):S3–8.
18. Klapper LN, Glathe S, Vaisman N, Hynes NE, Andrews GC, Sela M, Yarden Y. The ErbB-2/HER2 oncoprotein of human carcinomas may function solely as a shared coreceptor for multiple stroma-derived growth factors. Proc Natl Acad Sci USA. 1999;96(9):4995–5000.
19. Gravalos C, Jimeno A. HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target. Ann Oncol. 2008;19(9):1523–9.
20. Van Cutsem E, Bang YJ, Feng-Yi F, Xu JM, Lee KW, Jiao SC, et al. HER2 screening data from ToGA: targeting HER2 in gastric and gastroesophageal junction cancer. Gastric Cancer. 2015;18(3):476–84.
21. Bartley AN, Washington MK, Colasacco C, Ventura CB, Ismaila N, Benson AB 3rd, et al. HER2 testing and clinical decision making in gastroesophageal adenocarcinoma: guideline from the College of American Pathologists, American Society for Clinical Pathology, and the American Society of Clinical Oncology. J Clin Oncol. 2017;35(4):446–64.
22. Ajani JA, D'Amico TA, Bentrem DJ, Cooke D, Corvera C, Das P, et al. Esophageal and esophagogastric junction cancers, version 2.2023, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2023;21(4):393–422.
23. Lordick F, Carneiro F, Cascinu S, Fleitas T, Haustermans K, Piessen G, et al. Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. ESMO Gastric Cancer Living Guideline, v1.4 September 2024. Ann Oncol. 2022;33(10):1005–20.
24. Bass AJ, Thorsson V, Shmulevich I, Reynolds SM, Miller M, Bernard B, et al. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014;513(7517):202–9.
25. Cristescu R, Lee J, Nebozhyn M, Kim KM, Ting JC, Wong SS, et al. Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes. Nat Med. 2015;21(5):449–56.
26. Cancer_Genome_Atlas_Research_Network. Integrated genomic characterization of oesophageal carcinoma. Nature. 2017;541(7636):169-75.
27. Derks S, de Klerk LK, Xu X, Fleitas T, Liu KX, Liu Y, et al. Characterizing diversity in the tumour-immune microenvironment of distinct subclasses of gastroesophageal adenocarcinomas. Ann Oncol. 2020;31(8):1011–20.
28. Denkert C, von Minckwitz G, Darb-Esfahani S, Lederer B, Heppner BI, Weber KE, et al. Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvant therapy. Lancet Oncol. 2018;19(1):40–50.
29. Kim R, An M, Lee H, Mehta A, Heo YJ, Kim KM, et al. Early tumor-immune microenvironmental remodeling and response to first-line fluoropyrimidine and platinum chemotherapy in advanced gastric cancer. Cancer Discov. 2022;12(4):984–1001.
30. An M, Mehta A, Min BH, Heo YJ, Wright SJ, Parikh M, et al. Early immune remodeling steers clinical response to frontline chemoimmunotherapy in advanced gastric cancer. Cancer Discov. 2024.
31. Kiessling R, Wei WZ, Herrmann F, Lindencrona JA, Choudhury A, Kono K, Seliger B. Cellular immunity to the Her-2/neu protooncogene. Adv Cancer Res. 2002;85:101–44.
32. Bagaev A, Kotlov N, Nomie K, Svekolkin V, Gafurov A, Isaeva O, et al. Conserved pan-cancer microenvironment subtypes predict response to immunotherapy. Cancer Cell. 2021;39(6):845-65.e7.
33. Park JJ, Omiya R, Matsumura Y, Sakoda Y, Kuramasu A, Augustine MM, et al. B7–H1/CD80 interaction is required for the induction and maintenance of peripheral T-cell tolerance. Blood. 2010;116(8):1291–8.
34. Yang J, Riella LV, Chock S, Liu T, Zhao X, Yuan X, et al. The novel costimulatory programmed death ligand 1/B7.1 pathway is functional in inhibiting alloimmune responses in vivo. J Immunol (Baltimore, Md: 1950). 2011;187(3):1113–9.
35. Paterson AM, Brown KE, Keir ME, Vanguri VK, Riella LV, Chandraker A, et al. The programmed death-1 ligand 1:B7–1 pathway restrains diabetogenic effector T cells in vivo. J Immunol (Baltimore, Md: 1950). 2011;187(3):1097–105.
36. Butte MJ, Keir ME, Phamduy TB, Sharpe AH, Freeman GJ. Programmed death-1 ligand 1 interacts specifically with the B7–1 costimulatory molecule to inhibit T cell responses. Immunity. 2007;27(1):111–22.
37. Dong H, Zhu G, Tamada K, Chen L. B7–H1, a third member of the B7 family, co-stimulates T-cell proliferation and interleukin-10 secretion. Nat Med. 1999;5(12):1365–9.
38. Walker LS, Sansom DM. The emerging role of CTLA4 as a cell-extrinsic regulator of T cell responses. Nat Rev Immunol. 2011;11(12):852–63.
39. Shitara K, Van Cutsem E, Bang YJ, Fuchs C, Wyrwicz L, Lee KW, et al. Efficacy and safety of pembrolizumab or pembrolizumab plus chemotherapy vs chemotherapy alone for patients with first-line, advanced gastric cancer: the KEYNOTE-062 phase 3 randomized clinical trial. JAMA Oncol. 2020;6(10):1571–80.
40. Shitara K, Ajani JA, Moehler M, Garrido M, Gallardo C, Shen L, et al. Nivolumab plus chemotherapy or ipilimumab in gastro-oesophageal cancer. Nature. 2022;603(7903):942–8.

41. Heinhuis KM, Ros W, Kok M, Steeghs N, Beijnen JH, Schellens JHM. Enhancing antitumor response by combining immune checkpoint inhibitors with chemotherapy in solid tumours. Ann Oncol. 2019;30(2):219–35.
42. Lake RA, Robinson BW. Immunotherapy and chemotherapy—a practical partnership. Nat Rev Cancer. 2005;5(5):397–405.
43. Janjigian YY, Shitara K, Moehler M, Garrido M, Salman P, Shen L, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, Phase 3 trial. Lancet (London, England). 2021;398(10294):27–40.
44. Kato K, Shah MA, Enzinger P, Bennouna J, Shen L, Adenis A, et al. KEYNOTE-590: phase III study of first-line chemotherapy with or without pembrolizumab for advanced esophageal cancer. Future Oncol. 2019;15(10):1057–66.
45. Xu RH, Oh DY, Kato K, Arkenau HT, Tabernero J, Cruz-Correa M, et al. 139MO Tislelizumab (TIS) plus chemotherapy (Chemo) vs placebo (PBO) plus chemo as first-line (1L) treatment of advanced gastric or gastroesophageal junction adenocarcinoma (GC/GEJC): final analysis results of the RATIONALE-305 study. Ann Oncol. 2023;34:S1526–7.
46. Rha SY, Oh DY, Yañez P, Bai Y, Ryu MH, Lee J, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol. 2023;24(11):1181–95.
47. Janjigian YY, Kawazoe A, Bai Y, Xu J, Lonardi S, Metges JP, et al. Pembrolizumab plus trastuzumab and chemotherapy for HER2-positive gastric or gastro-oesophageal junction adenocarcinoma: interim analyses from the phase 3 KEYNOTE-811 randomised placebo-controlled trial. The Lancet. 2023;402(10418):2197–208.
48. Zito Marino F, Ascierto PA, Rossi G, Staibano S, Montella M, Russo D, et al. Are tumour-infiltrating lymphocytes protagonists or background actors in patient selection for cancer immunotherapy? Expert Opin Biol Ther. 2017;17(6):735–46.
49. Baselga J, Albanell J. Mechanism of action of anti-HER2 monoclonal antibodies. Ann Oncol. 2001;12(Suppl 1):S35-41.
50. Hudis CA. Trastuzumab–mechanism of action and use in clinical practice. N Engl J Med. 2007;357(1):39–51.
51. Mittendorf EA, Liu Y, Tucker SL, McKenzie T, Qiao N, Akli S, et al. A novel interaction between HER2/neu and cyclin E in breast cancer. Oncogene. 2010;29(27):3896–907.
52. zum Büschenfelde CM, Hermann C, Schmidt B, Peschel C, Bernhard H. Antihuman epidermal growth factor receptor 2 (HER2) monoclonal antibody trastuzumab enhances cytolytic activity of class I-restricted HER2-specific T lymphocytes against HER2-overexpressing tumour cells. Cancer Res. 2002;62(8):2244–7.
53. Park S, Jiang Z, Mortenson ED, Deng L, Radkevich-Brown O, Yang X, et al. The therapeutic effect of anti-HER2/neu antibody depends on both innate and adaptive immunity. Cancer Cell. 2010;18(2):160–70.
54. Taylor C, Hershman D, Shah N, Suciu-Foca N, Petrylak DP, Taub R, et al. Augmented HER-2 specific immunity during treatment with trastuzumab and chemotherapy. Clin Cancer Res. 2007;13(17):5133–43.
55. Montgomery RB, Makary E, Schiffman K, Goodell V, Disis ML. Endogenous anti-HER2 antibodies block HER2 phosphorylation and signaling through extracellular signal-regulated kinase. Cancer Res. 2005;65(2):650–6.
56. Satoh T, Bang YJ, Gotovkin EA, Hamamoto Y, Kang YK, Moiseyenko VM, et al. Quality of life in the trastuzumab for gastric cancer trial. Oncologist. 2014;19(7):712–9.
57. Kimura Y, Fujii M, Masuishi T, Nishikawa K, Kunisaki C, Matsusaka S, et al. Multicenter phase II study of trastuzumab plus S-1 alone in elderly patients with HER2-positive advanced gastric cancer (JACCRO GC-06). Gastric Cancer. 2018;21(3):421–7.
58. Sawaki A, Ohashi Y, Omuro Y, Satoh T, Hamamoto Y, Boku N, et al. Efficacy of trastuzumab in Japanese patients with HER2-positive advanced gastric or gastroesophageal junction cancer: a subgroup analysis of the Trastuzumab for Gastric Cancer (ToGA) study. Gastric Cancer. 2012;15(3):313–22.
59. Ryu MH, Yoo C, Kim JG, Ryoo BY, Park YS, Park SR, et al. Multicenter phase II study of trastuzumab in combination with capecitabine and oxaliplatin for advanced gastric cancer. Eur J Cancer (Oxford, England: 1990). 2015;51(4):482–8.
60. Gong J, Liu T, Fan Q, Bai L, Bi F, Qin S, et al. Optimal regimen of trastuzumab in combination with oxaliplatin/capecitabine in first-line treatment of HER2-positive advanced gastric cancer (CGOG1001): a multicenter, phase II trial. BMC Cancer. 2016;16:68.
61. Meulendijks D, Beerepoot LV, Boot H, de Groot JW, Los M, Boers JE, et al. Trastuzumab and bevacizumab combined with docetaxel, oxaliplatin and capecitabine as first-line treatment of advanced HER2-positive gastric cancer: a multicenter phase II study. Invest New Drugs. 2016;34(1):119–28.
62. Mitsui Y, Sato Y, Miyamoto H, Fujino Y, Takaoka T, Miyoshi J, et al. Trastuzumab in combination with docetaxel/cisplatin/S-1 (DCS) for patients with HER2-positive metastatic gastric cancer: feasibility and preliminary efficacy. Cancer Chemother Pharmacol. 2015;76(2):375–82.
63. Ter Veer E, Creemers A, de Waal L, van Oijen MGH, van Laarhoven HWM. Comparing cytotoxic backbones for first-line trastuzumab-containing regimens in human epidermal growth factor receptor 2-positive advanced oesophagogastric cancer: a meta-analysis. Int J Cancer. 2018;143(2):438–48.
64. Shah MA, Xu RH, Bang YJ, Hoff PM, Liu T, Herráez-Baranda LA, et al. HELOISE: phase IIIb randomized multicenter study comparing standard-of-care and higher-dose trastuzumab regimens combined with chemotherapy as first-line therapy in patients with human epidermal growth factor receptor 2-positive metastatic gastric or gastroesophageal junction adenocarcinoma. J Clin Oncol. 2017;35(22):2558–67.
65. Cosson VF, Ng VW, Lehle M, Lum BL. Population pharmacokinetics and exposure-response analyses of trastuzumab in patients with advanced gastric or gastroesophageal junction cancer. Cancer Chemother Pharmacol. 2014;73(4):737–47.
66. Yamashita-Kashima Y, Iijima S, Yorozu K, Furugaki K, Kurasawa M, Ohta M, Fujimoto-Ouchi K. Pertuzumab in combination with trastuzumab shows significantly enhanced antitumor activity in HER2-positive human gastric cancer xenograft models. Clin Cancer Res. 2011;17(15):5060–70.
67. FDA amends pembrolizumab's gastric cancer indication [press release]. 11/08/2023 2023.
68. https://www.merck.com/news/merck-announces-phase-3-keynote-811-trial-met-dual-primary-endpoint-of-overall-survival-os-as-first-line-treatment-in-patients-with-her2-positive-advanced-gastric-or-gastroesophageal-junction-gej/ [press release]. 2024.
69. Nishikawa K, Takahashi T, Takaishi H, Miki A, Noshiro H, Yoshikawa T, et al. Phase II study of the effectiveness and safety of trastuzumab and paclitaxel for taxane- and trastuzumab-naïve patients with HER2-positive, previously treated, advanced, or recurrent gastric cancer (JFMC45-1102). Int J Cancer. 2017;140(1):188–96.
70. Makiyama A, Sukawa Y, Kashiwada T, Kawada J, Hosokawa A, Horie Y, et al. Randomized, phase II study of trastuzumab beyond progression in patients with HER2-positive advanced gastric or gastroesophageal junction cancer: WJOG7112G (T-ACT Study). J Clin Oncol. 2020;38(17):1919–27.
71. Pietrantonio F, Caporale M, Morano F, Scartozzi M, Gloghini A, De Vita F, et al. HER2 loss in HER2-positive gastric or

gastroesophageal cancer after trastuzumab therapy: implication for further clinical research. Int J Cancer. 2016;139(12):2859–64.
72. Ter Veer E, van den Ende T, Creemers A, de Waal L, van Oijen MGH, van Laarhoven HWM. Continuation of trastuzumab beyond progression in HER2-positive advanced esophagogastric cancer: a meta-analysis. Acta Oncologica (Stockholm, Sweden). 2018;57(12):1599–604.
73. Satoh T, Xu RH, Chung HC, Sun GP, Doi T, Xu JM, et al. Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of HER2-amplified advanced gastric cancer in Asian populations: TyTAN–a randomized, phase III study. J Clin Oncol. 2014;32(19):2039–49.
74. Lorenzen S, Riera Knorrenschild J, Haag GM, Pohl M, Thuss-Patience P, Bassermann F, et al. Lapatinib versus lapatinib plus capecitabine as second-line treatment in human epidermal growth factor receptor 2-amplified metastatic gastro-oesophageal cancer: a randomised phase II trial of the Arbeitsgemeinschaft Internistische Onkologie. Eur J Cancer (Oxford, England: 1990). 2015;51(5):569–76.
75. Sanchez-Vega F, Hechtman JF, Castel P, Ku GY, Tuvy Y, Won H, et al. EGFR and MET amplifications determine response to HER2 inhibition in ERBB2-amplified Esophagogastric cancer. Cancer Discov. 2019;9(2):199–209.
76. Thuss-Patience PC, Shah MA, Ohtsu A, Van Cutsem E, Ajani JA, Castro H, et al. Trastuzumab emtansine versus taxane use for previously treated HER2-positive locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma (GATSBY): an international randomised, open-label, adaptive, phase 2/3 study. Lancet Oncol. 2017;18(5):640–53.
77. Shitara K, Bang YJ, Iwasa S, Sugimoto N, Ryu MH, Sakai D, et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. N Engl J Med. 2020;382(25):2419–30.
78. Yoshihara K, Kobayashi Y, Endo S, Fukae M, Hennig S, Kastrissios H, et al. Trastuzumab deruxtecan dosing in human epidermal growth factor receptor 2-positive gastric cancer: population pharmacokinetic modeling and exposure-response analysis. J Clin Pharmacol. 2023;63(11):1232–43.
79. Shitara K, Iwata H, Takahashi S, Tamura K, Park H, Modi S, et al. Trastuzumab deruxtecan (DS-8201a) in patients with advanced HER2-positive gastric cancer: a dose-expansion, phase 1 study. Lancet Oncol. 2019;20(6):827–36.
80. Yamaguchi K, Bang YJ, Iwasa S, Sugimoto N, Ryu MH, Sakai D, et al. Trastuzumab deruxtecan in anti-human epidermal growth factor receptor 2 treatment-naive patients with human epidermal growth factor receptor 2-low gastric or gastroesophageal junction adenocarcinoma: exploratory cohort results in a phase II trial. J Clin Oncol. 2023;41(4):816–25.
81. Van Cutsem E, di Bartolomeo M, Smyth E, Chau I, Park H, Siena S, et al. Trastuzumab deruxtecan in patients in the USA and Europe with HER2-positive advanced gastric or gastroesophageal junction cancer with disease progression on or after a trastuzumab-containing regimen (DESTINY-Gastric02): primary and updated analyses from a single-arm, phase 2 study. Lancet Oncol. 2023;24(7):744–56.
82. ENHERTU® Approved in Japan for Treatment of Patients with HER2 Positive Unresectable or Metastatic Breast Cancer [press release]. 2020.
83. EMA. Enhertu. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/enhertu#:~:text=Trastuzumab%20also%20stops%20HER2%20from,HER2%20mutation%2C%20HER2%20is%20overactive.
84. Janjigian YY, Oh D-Y, Rha SY, Lee KW, Steeghs N, Chao Y, et al. Dose-escalation and dose-expansion study of trastuzumab deruxtecan (T-DXd) monotherapy and combinations in patients (pts) with advanced/metastatic HER2+ gastric cancer (GC)/gastroesophageal junction adenocarcinoma (GEJA): DESTINY-Gastric03. J Clin Oncol. 2022;40(4_suppl):295.
85. Janjigian YY, van Laarhoven HWM, Rha SY, Kozlov V, Oh DY, Gravina A, et al. 1401O Trastuzumab deruxtecan (T-DXd) monotherapy and combinations in patients (pts) with advanced/metastatic HER2-positive (HER2+) esophageal, gastric or gastroesophageal junction adenocarcinoma (GEJA): DESTINY-Gastric03 (DG-03). Ann Oncol. 2024;35:S878.
86. Hofheinz R-D, Hegewisch-Becker S, Kunzmann V, Thuss-Patience P, Fuchs M, Homann N, et al. Trastuzumab in combination with 5-fluorouracil, leucovorin, oxaliplatin and docetaxel as perioperative treatment for patients with human epidermal growth factor receptor 2-positive locally advanced esophagogastric adenocarcinoma: A phase II trial of the Arbeitsgemeinschaft Internistische Onkologie Gastric Cancer Study Group. Int J Cancer. 2021;149(6):1322–31.
87. Rivera F, Izquierdo-Manuel M, García-Alfonso P, Martínez de Castro E, Gallego J, Limón ML, et al. Perioperative trastuzumab, capecitabine and oxaliplatin in patients with HER2-positive resectable gastric or gastro-oesophageal junction adenocarcinoma: NEOHX phase II trial. Eur J Cancer (Oxford, England: 1990). 2021;145:158–67.
88. Kataoka K, Tokunaga M, Mizusawa J, Machida N, Katayama H, Shitara K, et al. A randomized Phase II trial of systemic chemotherapy with and without trastuzumab followed by surgery in HER2-positive advanced gastric or esophagogastric junction adenocarcinoma with extensive lymph node metastasis: Japan Clinical Oncology Group study JCOG1301 (Trigger Study). Jpn J Clin Oncol. 2015;45(11):1082–6.
89. Smyth EC, Rowley S, Cafferty FH, Allum W, Grabsch HI, Stenning S, et al. Safety and efficacy of the addition of lapatinib to perioperative chemotherapy for resectable HER2-positive gastroesophageal adenocarcinoma: a randomized phase 2 clinical trial. JAMA Oncol. 2019;5(8):1181–7.
90. Wagner AD, Grabsch HI, Mauer M, Romario UF, Kang Y-K, Bouche O, et al. Integration of trastuzumab (T), with or without pertuzumab (P), into perioperative chemotherapy (CT) of HER-2 positive gastric (GC) and esophagogastric junction cancer (EGJC): first results of the EORTC 1203 INNOVATION study, in collaboration with the Korean Cancer Study Group, and the Dutch Upper GI Cancer group. J Clin Oncol. 2023;41(16_suppl):4057.
91. Tabernero J, Hoff PM, Shen L, Ohtsu A, Shah MA, Cheng K, et al. Pertuzumab plus trastuzumab and chemotherapy for HER2-positive metastatic gastric or gastro-oesophageal junction cancer (JACOB): final analysis of a double-blind, randomised, placebo-controlled phase 3 study. Lancet Oncol. 2018;19(10):1372–84.
92. Eyck BM, van Lanschot JJB, Hulshof M, van der Wilk BJ, Shapiro J, van Hagen P, et al. Ten-year outcome of neoadjuvant chemoradiotherapy plus surgery for esophageal cancer: the randomized controlled CROSS trial. J Clin Oncol. 2021;39(18):1995–2004.
93. Abali H, Yalcin S, Onal HC, Dane F, Oksuzoglu B, Ozdemir N, et al. A phase II study of the combination of oxaliplatin, capecitabine, and trastuzumab and chemoradiotherapy in the adjuvant setting in operated patients with HER2-positive Gastric or Gastroesophageal Junction Cancer (TOXAG Study): a Turkish Oncology Group Study. Am J Clin Oncol. 2021;44(7):301–7.
94. Safran HP, Winter K, Ilson DH, Wigle D, DiPetrillo T, Haddock MG, et al. Trastuzumab with trimodality treatment for oesophageal adenocarcinoma with HER2 overexpression (NRG Oncology/RTOG 1010): a multicentre, randomised, phase 3 trial. Lancet Oncol. 2022;23(2):259–69.
95. Stroes CI, Schokker S, Creemers A, Molenaar RJ, Hulshof M, van der Woude SO, et al. Phase II feasibility and biomarker study of neoadjuvant trastuzumab and pertuzumab with

chemoradiotherapy for resectable human epidermal growth factor receptor 2-positive esophageal adenocarcinoma: TRAP study. J Clin Oncol. 2020;38(5):462–71.
96. Rugo HS, Im SA, Cardoso F, Cortes J, Curigliano G, Musolino A, et al. Margetuximab versus trastuzumab in patients with previously treated HER2-positive advanced breast cancer (SOPHIA): final overall survival results from a randomized phase 3 trial. J Clin Oncol. 2023;41(2):198–205.
97. Catenacci DVT, Kang YK, Yoon HH, Shim BY, Kim ST, Oh DY, et al. Margetuximab with retifanlimab as first-line therapy in HER2+/PD-L1+ unresectable or metastatic gastroesophageal adenocarcinoma: MAHOGANY cohort A. ESMO Open. 2022;7(5): 100563.
98. Esfandiari A, Cassidy S, Webster RM. Bispecific antibodies in oncology. Nat Rev Drug Discov. 2022;21(6):411–2.
99. Meric-Bernstam F, Beeram M, Hamilton E, Oh D-Y, Hanna DL, Kang Y-K, et al. Zanidatamab, a novel bispecific antibody, for the treatment of locally advanced or metastatic HER2-expressing or *HER2*-amplified cancers: a phase 1, dose-escalation and expansion study. Lancet Oncol. 2022;23(12):1558–70.
100. Elimova E, Ajani JA, Burris III HA, Denlinger CS, Iqbal S, Kang Y-K, et al. Zanidatamab + chemotherapy as first-line treatment for HER2-expressing metastatic gastroesophageal adenocarcinoma (mGEA). J Clin Oncol. 2023;41(4_suppl):347.
101. Xu J, Ying J, Liu R, Wu J, Ye F, Xu N, et al. KN026 (anti-HER2 bispecific antibody) in patients with previously treated, advanced HER2-expressing gastric or gastroesophageal junction cancer. Eur J Cancer (Oxford, England: 1990). 2023;178:1–12.
102. Gong J, Chen L, Sun M, Ni M, Zhao R, Wang X, et al. Efficacy and safety of KN026 in combination with KN046 in patients with locally advanced unresectable or metastatic HER2-positive other solid tumours. J Clin Oncol. 2023;41(16_suppl):3621.
103. Dumontet C, Reichert JM, Senter PD, Lambert JM, Beck A. Antibody–drug conjugates come of age in oncology. Nat Rev Drug Discovery. 2023;22(8):641–61.
104. Banerji U, van Herpen CML, Saura C, Thistlethwaite F, Lord S, Moreno V, et al. Trastuzumab duocarmazine in locally advanced and metastatic solid tumours and HER2-expressing breast cancer: a phase 1 dose-escalation and dose-expansion study. Lancet Oncol. 2019;20(8):1124–35.
105. Shi F, Liu Y, Zhou X, Shen P, Xue R, Zhang M. Disitamab vedotin: a novel antibody-drug conjugates for cancer therapy. Drug Delivery. 2022;29(1):1335–44.
106. Wang Y, Gong J, Wang A, Wei J, Peng Z, Wang X, et al. Disitamab vedotin (RC48) plus toripalimab for HER2-expressing advanced gastric or gastroesophageal junction and other solid tumours: a multicentre, open label, dose escalation and expansion phase 1 trial. eClinicalMedicine. 2024;68: 102415.
107. Li S, Liu Z, Liu Y, Li K, Cong L, Cao F, et al. Efficacy of disitamab vedotin (RC48) plus tislelizumab and S-1 as first-line therapy for HER2-overexpressing advanced stomach or gastroesophageal junction adenocarcinoma: a multicenter, single-arm, phase II trial (RCTS). J Clin Oncol. 2024;42(16_suppl):4009.
108. Meric-Bernstam F, Calvo E, Moreno V, Chung HC, Park YH, Bang Y-J, et al. A phase I dose escalation study evaluating the safety and tolerability of a novel anti-HER2 antibody-drug conjugate (PF-06804103) in patients with HER2-positive solid tumours. J Clin Oncol. 2020;38(15_suppl):1039.
109. Guo Y, Xue J, Peng W, Xue L, Ge X, Zhao W, et al. 271P First-in-human, phase I dose escalation and expansion study of anti-HER2 ADC MRG002 in patients with HER2 positive solid tumours. Ann Oncol. 2021;32:S480–1.
110. Zhang Y, Qiu MZ, Wang JF, Zhang YQ, Shen A, Yuan XL, et al. Phase 1 multicenter, dose-expansion study of ARX788 as monotherapy in HER2-positive advanced gastric and gastroesophageal junction adenocarcinoma. Cell Rep Med. 2022;3(11): 100814.
111. Jhaveri K, Han H, Dotan E, Oh DY, Ferrario C, Tolcher A, et al. 460MO Preliminary results from a phase I study using the bispecific, human epidermal growth factor 2 (HER2)-targeting antibody-drug conjugate (ADC) zanidatamab zovodotin (ZW49) in solid cancers. Ann Oncol. 2022;33:S749–50.
112. Li BT, Pegram MD, Lee K-W, Sharma M, Lee J, Spira AI, et al. A phase 1/2 study of a first-in-human immune-stimulating antibody conjugate (ISAC) BDC-1001 in patients with advanced HER2-expressing solid tumours. J Clin Oncol. 2023;41(16_suppl):2538.
113. Li S, Bao J, Li X, Yang Q, Xu J, Chen S, et al. Multicenter phase I dose escalation and expansion study of pyrotinib in combination with camrelizumab and chemotherapy as first-line treatment for HER2-positive advanced gastric and gastroesophageal junction adenocarcinoma. eClinicalMedicine. 2023;66: 102314.
114. Hamzehlou S, Momeny M, Zandi Z, Kashani B, Yousefi H, Dehpour AR, et al. Anti-tumour activity of neratinib, a pan-HER inhibitor, in gastric adenocarcinoma cells. Eur J Pharmacol. 2019;863: 172705.
115. Tehfe M, Lee J, Rha SY, Nakamura Y, Tabernero J, Shitara K, et al. 1523P Phase II dose optimization results from MOUNTAINEER-02: a study of tucatinib, trastuzumab, ramucirumab, and paclitaxel for HER2+ gastroesophageal cancer (GEC). Ann Oncol. 2023;34:S857–8.
116. Reiss KA, Yuan Y, Ueno NT, Johnson ML, Gill S, Dees EC, et al. A phase 1, first-in-human (FIH) study of the anti-HER2 CAR macrophage CT-0508 in subjects with HER2 overexpressing solid tumours. J Clin Oncol. 2022;40(16_suppl):2533.
117. Schlechter BL, Olson D, George MA, Saibil S, Giordano A, Bouvier R, et al. A phase I/II trial investigating safety and efficacy of autologous TAC01-HER2 in relapsed or refractory solid tumours. J Clin Oncol. 2023;41(16_suppl):2519.
118. Maglakelidze M, Ryspayeva DE, Andric Z, Petrovic Z, Bulat I, Nikolic I, et al. HERIZON: a phase 2 study of HER-Vaxx (IMU-131), a HER2-targeting peptide vaccine, plus standard of care chemotherapy in patients with HER2-overexpressing metastatic or advanced gastric/GEJ adenocarcinoma—overall survival analysis. J Clin Oncol. 2023;41(4_suppl):289.
119. Moasser MM. The oncogene HER2: its signaling and transforming functions and its role in human cancer pathogenesis. Oncogene. 2007;26(45):6469–87.
120. Janjigian YY, Kawazoe A, Yañez P, Li N, Lonardi S, Kolesnik O, et al. The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer. Nature. 2021;600(7890):727–30.
121. Brown LJ, Meredith T, Yu J, Patel A, Neal B, Arnott C, Lim E. Heart failure therapies for the prevention of HER2-monoclonal antibody-mediated cardiotoxicity: a systematic review and meta-analysis of randomized trials. Cancers. 2021;13(21):5527.
122. de Korte MA, de Vries EG, Lub-de Hooge MN, Jager PL, Gietema JA, van der Graaf WT, et al. 111Indium-trastuzumab visualises myocardial human epidermal growth factor receptor 2 expression shortly after anthracycline treatment but not during heart failure: a clue to uncover the mechanisms of trastuzumab-related cardiotoxicity. Eur J Cancer (Oxford, England: 1990). 2007;43(14):2046–51.
123. Kang YK, Rha SY, Tassone P, Barriuso J, Yu R, Szado T, et al. A phase IIa dose-finding and safety study of first-line pertuzumab in combination with trastuzumab, capecitabine and cisplatin in patients with HER2-positive advanced gastric cancer. Br J Cancer. 2014;111(4):660–6.
124. Tarantino P, Ricciuti B, Pradhan SM, Tolaney SM. Optimizing the safety of antibody–drug conjugates for patients with solid tumours. Nat Rev Clin Oncol. 2023;20(8):558–76.
125. Tarantino P, Modi S, Tolaney SM, Cortés J, Hamilton EP, Kim S-B, et al. Interstitial lung disease induced by

anti-ERBB2 antibody-drug conjugates: a review. JAMA Oncol. 2021;7(12):1873–81.
126. Kumagai K, Aida T, Tsuchiya Y, Kishino Y, Kai K, Mori K. Interstitial pneumonitis related to trastuzumab deruxtecan, a human epidermal growth factor receptor 2-targeting Ab–drug conjugate, in monkeys. Cancer Sci. 2020;111(12):4636–45.
127. Shah MA, Kang YK, Thuss-Patience PC, Ohtsu A, Ajani JA, Van Cutsem E, et al. Biomarker analysis of the GATSBY study of trastuzumab emtansine versus a taxane in previously treated HER2-positive advanced gastric/gastroesophageal junction cancer. Gastric Cancer. 2019;22(4):803–16.
128. Shitara K, Bang Y-J, Iwasa S, Sugimoto N, Ryu M-H, Sakai D, et al. Trastuzumab deruxtecan in HER2-positive advanced gastric cancer: exploratory biomarker analysis of the randomized, phase 2 DESTINY-Gastric01 trial. Nat Med. 2024;30:1933–42.
129. Modi S, Jacot W, Yamashita T, Sohn J, Vidal M, Tokunaga E, et al. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. N Engl J Med. 2022;387(1):9–20.
130. Zhang L, Hamdani O, Gjoerup O, Cho-Phan C, Snider J, Castellanos E, et al. ERBB2 copy number as a quantitative biomarker for real-world outcomes to anti-human epidermal growth factor receptor 2 therapy in advanced gastroesophageal adenocarcinoma. JCO Precis Oncol. 2022;6: e2100330.
131. Pietrantonio F, Manca P, Bellomo SE, Corso S, Raimondi A, Berrino E, et al. HER2 copy number and resistance mechanisms in patients with HER2-positive advanced gastric cancer receiving initial trastuzumab-based therapy in JACOB trial. Clin Cancer Res. 2023;29(3):571–80.
132. Shoda K, Ichikawa D, Fujita Y, Masuda K, Hiramoto H, Hamada J, et al. Monitoring the HER2 copy number status in circulating tumour DNA by droplet digital PCR in patients with gastric cancer. Gastric Cancer. 2017;20(1):126–35.
133. Catenacci DV, Kang YK, Uronis HE, Lee KW, Ng MC, Enzinger PC, et al. Circulating tumor DNA as a predictive biomarker for clinical outcomes with margetuximab and pembrolizumab in pretreated HER2-positive gastric/gastroesophageal adenocarcinoma. Oncology (Williston Park). 2023;37(4):176–83.
134. Wang H, Li B, Liu Z, Gong J, Shao L, Ren J, et al. HER2 copy number of circulating tumour DNA functions as a biomarker to predict and monitor trastuzumab efficacy in advanced gastric cancer. Eur J Cancer (Oxford, England: 1990). 2018;88:92–100.
135. Zhang C, Chen Z, Chong X, Chen Y, Wang Z, Yu R, et al. Clinical implications of plasma ctDNA features and dynamics in gastric cancer treated with HER2-targeted therapies. Clin Transl Med. 2020;10(8): e254.
136. De-Shen W, Ze-Xian L, Yun-Xin L, Hua B, Xue W, Zhao-Lei Z, et al. Liquid biopsies to track trastuzumab resistance in metastatic HER2-positive gastric cancer. Gut. 2019;68(7):1152.
137. Yang J, Luo H, Li Y, Li J, Cai Z, Su X, et al. Intratumoral heterogeneity determines discordant results of diagnostic tests for human epidermal growth factor receptor (HER) 2 in gastric cancer specimens. Cell Biochem Biophys. 2012;62(1):221–8.
138. Personeni N, Baretti M, Bozzarelli S, Spaggiari P, Rubino L, Tronconi MC, et al. Assessment of HER2 status in patients with gastroesophageal adenocarcinoma treated with epirubicin-based chemotherapy: heterogeneity-related issues and prognostic implications. Gastric Cancer. 2017;20(3):428–37.
139. Creemers A, Ebbing EA, Hooijer GKJ, Stap L, Jibodh-Mulder RA, Gisbertz SS, et al. The dynamics of HER2 status in esophageal adenocarcinoma. Oncotarget. 2018;9(42):26787–99.
140. Lumish MA, Maron SB, Paroder V, Chou JF, Capanu M, Philemond S, et al. Noninvasive assessment of human epidermal growth factor receptor 2 (HER2) in esophagogastric cancer using (89)Zr-Trastuzumab PET: a pilot study. J Nuclear Med. 2023;64(5):724–30.
141. Maron SB, Chatila W, Walch H, Chou JF, Ceglia N, Ptashkin R, et al. Determinants of survival with combined HER2 and PD-1 blockade in metastatic esophagogastric cancer. Clin Cancer Res. 2023;29(18):3633–40.
142. Grillo F, Fassan M, Sarocchi F, Fiocca R, Mastracci L. HER2 heterogeneity in gastric/gastroesophageal cancers: from benchside to practice. World J Gastroenterol. 2016;22(26):5879–87.
143. Wakatsuki T, Yamamoto N, Sano T, Chin K, Kawachi H, Takahari D, et al. Clinical impact of intratumoral HER2 heterogeneity on trastuzumab efficacy in patients with HER2-positive gastric cancer. J Gastroenterol. 2018;53(11):1186–95.
144. Yagi S, Wakatsuki T, Yamamoto N, Chin K, Takahari D, Ogura M, et al. Clinical significance of intratumoral HER2 heterogeneity on trastuzumab efficacy using endoscopic biopsy specimens in patients with advanced HER2 positive gastric cancer. Gastric Cancer. 2019;22(3):518–25.
145. Bang K, Cheon J, Park YS, Kim HD, Ryu MH, Park Y, et al. Association between HER2 heterogeneity and clinical outcomes of HER2-positive gastric cancer patients treated with trastuzumab. Gastric Cancer. 2022;25(4):794–803.
146. An E, Ock CY, Kim TY, Lee KH, Han SW, Im SA, et al. Quantitative proteomic analysis of HER2 expression in the selection of gastric cancer patients for trastuzumab treatment. Ann Oncol. 2017;28(1):110–5.
147. Kapil A, Spitzmüller A, Brieu N, Haneder S, Shumilov A, Meier A, et al. HER2 quantitative continuous scoring for accurate patient selection in HER2 negative trastuzumab deruxtecan treated breast cancer. Sci Rep. 2024;14(1):12129.
148. Saeki H, Oki E, Kashiwada T, Arigami T, Makiyama A, Iwatsuki M, et al. Re-evaluation of HER2 status in patients with HER2-positive advanced or recurrent gastric cancer refractory to trastuzumab (KSCC1604). Eur J Cancer (Oxford, England: 1990). 2018;105:41–9.
149. Park SR, Park YS, Ryu MH, Ryoo BY, Woo CG, Jung HY, et al. Extra-gain of HER2-positive cases through HER2 reassessment in primary and metastatic sites in advanced gastric cancer with initially HER2-negative primary tumours: Results of GASTric cancer HER2 reassessment study 1 (GASTHER1). Eur J Cancer (Oxford, England: 1990). 2016;53:42–50.
150. Hyung J, Kim HD, Ryu MH, Park YS, Moon M, Kang YK. GASTric cancer HER2 re-assessment study 2 (GASTHER2): HER2 re-assessment for initially HER2-negative advanced gastric cancer patients after progression on first-line treatment. Cancer Res Treat. 2024;56(1):199–207.
151. Amato M, Perrone G, Righi D, Pellegrini C, Rabitti C, Di Matteo F, et al. HER2 status in gastric cancer: comparison between primary and distant metastatic disease. Pathol Oncol Res. 2017;23(1):55–61.
152. Stahl P, Seeschaaf C, Lebok P, Kutup A, Bockhorn M, Izbicki JR, et al. Heterogeneity of amplification of HER2, EGFR, CCND1 and MYC in gastric cancer. BMC Gastroenterol. 2015;15:7.
153. Ye P, Zhang M, Fan S, Zhang T, Fu H, Su X, et al. Intra-tumoral heterogeneity of HER2, FGFR2, cMET and ATM in gastric cancer: optimizing personalized healthcare through innovative pathological and statistical analysis. PLoS One. 2015;10(11): e0143207.
154. Silva ANS, Coffa J, Menon V, Hewitt LC, Das K, Miyagi Y, et al. Frequent coamplification of receptor tyrosine kinase and downstream signaling genes in Japanese primary gastric cancer and conversion in matched lymph node metastasis. Ann Surg. 2018;267(1):114–21.
155. Pectasides E, Stachler MD, Derks S, Liu Y, Maron S, Islam M, et al. Genomic heterogeneity as a barrier to precision

medicine in gastroesophageal adenocarcinoma. Cancer Discov. 2018;8(1):37–48.
156. Lordick F, Carneiro F, Cascinu S, Fleitas T, Haustermans K, Piessen G, et al. Gastric cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022;33(10):1005–20.
157. Piro G, Carbone C, Cataldo I, Di Nicolantonio F, Giacopuzzi S, Aprile G, et al. An FGFR3 autocrine loop sustains acquired resistance to trastuzumab in gastric cancer patients. Clin Cancer Res. 2016;22(24):6164–75.
158. Ding X, Tong C, Chen R, Wang X, Gao D, Zhu L. Systematic molecular profiling of inhibitor response to the clinical missense mutations of ErbB family kinases in human gastric cancer. J Mol Graph Model. 2020;96: 107526.
159. Duarte HO, Rodrigues JG, Gomes C, Hensbergen PJ, Ederveen ALH, de Ru AH, et al. ST6Gal1 targets the ectodomain of ErbB2 in a site-specific manner and regulates gastric cancer cell sensitivity to trastuzumab. Oncogene. 2021;40(21):3719–33.
160. Liu N, Zhu M, Linhai Y, Song Y, Gui X, Tan G, et al. Increasing HER2 α2,6 sialylation facilitates gastric cancer progression and resistance via the Akt and ERK pathways. Oncol Rep. 2018;40(5):2997–3005.
161. Pietrantonio F, Fucà G, Morano F, Gloghini A, Corso S, Aprile G, et al. Biomarkers of primary resistance to trastuzumab in HER2-positive metastatic gastric cancer patients: the AMNESIA case-control study. Clin Cancer Res. 2018;24(5):1082–9.
162. Shitara K, Bang Y-J, Iwasa S, Sugimoto N, Ryu M-H, Sakai D, et al. Trastuzumab deruxtecan in HER2-positive advanced gastric cancer: exploratory biomarker analysis of the randomized, phase 2 DESTINY-Gastric01 trial. Nat Med. 2024;30(7):1933–42.
163. Ebbing EA, Steins A, Fessler E, Stathi P, Lesterhuis WJ, Krishnadath KK, et al. Esophageal adenocarcinoma cells and xenograft tumors exposed to Erb-b2 receptor tyrosine kinase 2 and 3 inhibitors activate transforming growth factor beta signaling, which induces epithelial to mesenchymal transition. Gastroenterology. 2017;153(1):63-76.e14.
164. Liu W, Chang J, Liu M, Yuan J, Zhang J, Qin J, et al. Quantitative proteomics profiling reveals activation of mTOR pathway in trastuzumab resistance. Oncotarget. 2017;8(28):45793–806.
165. Elyashiv O, Ledermann J, Parmar G, Farrelly L, Counsell N, Feeney A, et al. ICON 9-an international phase III randomized study to evaluate the efficacy of maintenance therapy with olaparib and cediranib or olaparib alone in patients with relapsed platinum-sensitive ovarian cancer following a response to platinum-based chemotherapy. Int J Gynecol Cancer. 2021;31(1):134–8.
166. Chang J, Wang Q, Bhetuwal A, Liu W. Metabolic pathways underlying GATA6 regulating Trastuzumab resistance in Gastric Cancer cells based on untargeted metabolomics. Int J Med Sci. 2020;17(18):3146–64.
167. Ye H, Chai X, Wang X, Zheng Q, Zheng D, Wu F, et al. Autophagy flux inhibition augments gastric cancer resistance to the anti-human epidermal growth factor receptor 2 antibody trastuzumab. Oncol Lett. 2018;15(4):4143–50.
168. Kunzke T, Hölzl FT, Prade VM, Buck A, Huber K, Feuchtinger A, et al. Metabolomic therapy response prediction in pretherapeutic tissue biopsies for trastuzumab in patients with HER2-positive advanced gastric cancer. Clin Transl Med. 2021;11(9): e547.
169. Shah MA, Shitara K, Ajani JA, Bang YJ, Enzinger P, Ilson D, et al. Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial. Nat Med. 2023;29(8):2133–41.
170. Shitara K, Lordick F, Bang YJ, Enzinger P, Ilson D, Shah MA, et al. Zolbetuximab plus mFOLFOX6 in patients with CLDN182-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial. Lancet (London, England). 2023;401(10389):1655–68.
171. Wainberg ZA, Enzinger PC, Kang Y-K, Qin S, Yamaguchi K, Kim I-H, et al. Bemarituzumab in patients with FGFR2b-selected gastric or gastro-oesophageal junction adenocarcinoma (FIGHT): a randomised, double-blind, placebo-controlled, phase 2 study. Lancet Oncol. 2022;23(11):1430–40.
172. Kim J, Bowlby R, Mungall AJ, Robertson AG, Odze RD, Cherniack AD, et al. Integrated genomic characterization of oesophageal carcinoma. Nature. 2017;541(7636):169–75.