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Current and Emerging Treatment Options for HER2-Positive Gastroesophageal Cancer

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Gastroesophageal Cancer and HER2 Biology:

Gastroesophageal cancer (GEC) is the fifth most common cancer and the second most common cause of cancer-related mortality, with 1.3 million annual deaths worldwide.[1,2] The global incidence is increasing, particularly among younger patients.[3] GEC can be classified into subtypes based on anatomic location, histology, molecular characteristics, or tumour biology and genomics.[4] In approximately 20% of all GECs overexpression of HER2 is identified.[5] The landscape of treatment options in this patient population is evolving rapidly. This review summarizes the progress of HER2-directed therapies for advanced disease and highlights future directions in targeting the disease.

The epidermal growth factor receptor (EGFR) family of transmembrane tyrosine kinase receptors, EGFR/HER1, HER2/neu, HER3, and HER4, all have an extracellular ligand-binding domain, lipophilic transmembrane domain, and an intracellular domain with tyrosine kinase activity[6], binding to these receptors results in activation of downstream RAS/MAPK and PI3K/AKT pathways.[6-8] In turn, this induces cell proliferation, differentiation, migration, and survival. The phase III Trastuzumab for Gastric Cancer (ToGA) trial reported the incidence of HER2-positive gastric cancer to be 22%.[9] Therefore, targeting HER2 and its downstream signaling pathways holds important potential as a therapeutic strategy. **Figure 1** illustrates potential targeting mechanisms that will be discussed in this review.

In GEC, HER2 positivity is distinct from that in other tumour types, such as breast cancer, as it demonstrates more heterogeneous HER2 immunohistochemistry (IHC) staining patterns and lower HER2 expression.[10] In HER2-positive breast cancer, combination blockade and sequential HER2 targeting at progression has revolutionized the treatment.[11] However, similar methods with the same therapies have not shown to have the same benefit in GEC.[12]

HER2-targeted Therapy in Metastatic Disease; The Current Landscape and Future Directions

Trastuzumab, a monoclonal anti-HER2 antibody, binds to the extracellular domain of HER2, inhibits its downstream signaling, and promotes antibody-dependent cellular cytotoxicity (ADCC).[9] In 2010, the ToGA study established trastuzumab as the standard treatment for first-line, metastatic GEC. It was a landmark study and was the first to demonstrate an improvement in overall survival (OS) (13.8 vs. 11.1 months).[9] In a preplanned exploratory analysis of patients with high HER2 expression in the tumours, defined as IHC 3+ or IHC 2+/FISH-positive—which has subsequently become the diagnostic criteria—the survival benefit was higher (16.0 vs. 11.8 months).[9]

Emerging preclinical and clinical evidence have confirmed the efficacy of dual anti-PD-1 and HER2-blockade, and phase II studies investigating these therapies have demonstrated an impressive objective response rate (ORR) of 91%.[13,14] The ToGA study, as a historical control, had an ORR of 47%[9]. Furthermore, the combination therapy showed a median progression-free survival (PFS) and OS of 13.0 and 27.0 months, respectively.[14] The mechanism of action of the interaction between HER2 and PD-1 inhibitors is not fully understood. It is thought to be a consequence of trastuzumab enhancing HER2 internalization and cross-presentation by dendritic cells, stimulating HER2-specific T-cell responses.[15] The stimulation of T cell responses results in the upregulation of PD-1 expression on tumour-infiltrating lymphocytes and expression

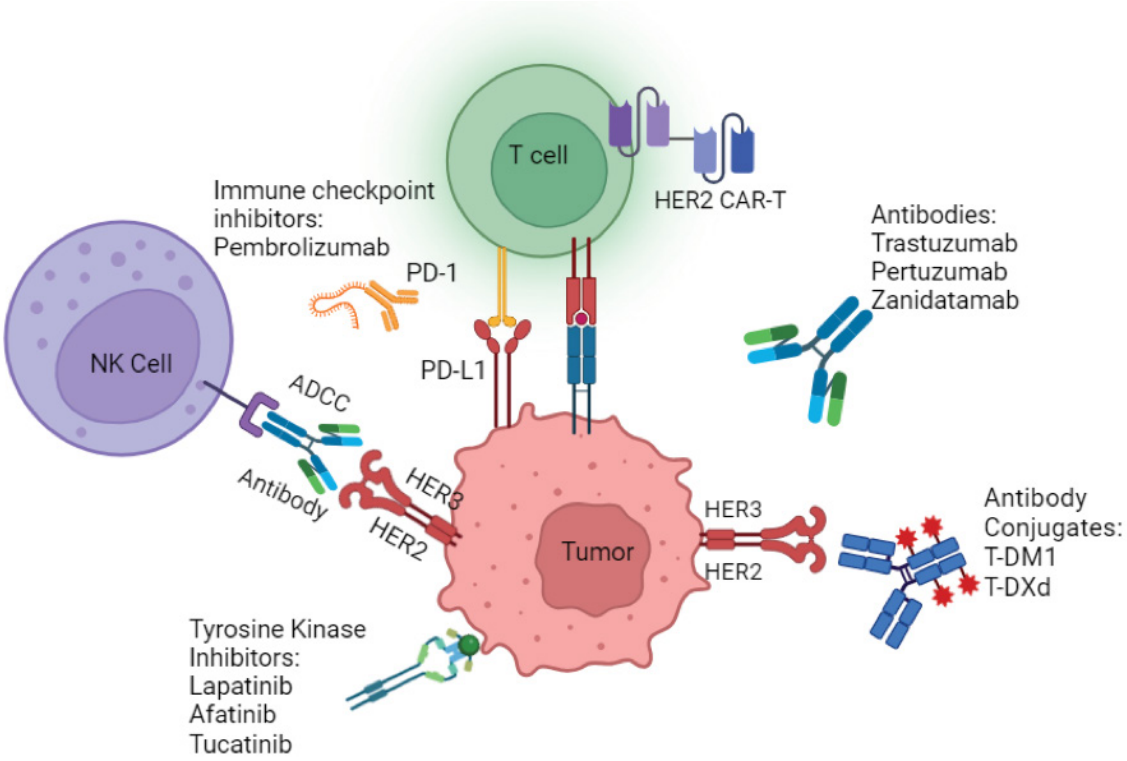

Figure 1. Strategies for targeting HER2 positive; *courtesy of Ronan Andrew McLaughlin, MD and Elena Elimova, MD*

Anti-HER2 antibodies include trastuzumab, pertuzumab, and zanidatamab. Antibody-drug conjugates include T-DM1 and T-DXd. Tyrosine kinase inhibitors include lapatinib, afatinib, and tucatinib. Receptors on NK cells bind to the anti-HER2 antibodies bound to HER2 on tumour cells and trigger an anti-tumour immune response via ADCC. Immune checkpoint inhibitors, including pembrolizumab, target co-inhibitory signals for T cell antigen receptor signalling (e.g PD-1 or PD-L1) to enhance T cell anti-tumour immunity. CAR-T cells expressing HER2-specific CARs may serve as a future treatment option for HER2-positive GEC. **Abbreviations: ADCC:** antibody-dependent cellular cytotoxicity; **CAR:** chimeric antigen receptor; **GEC:** gastroesophageal cancer; **NK:** natural killer; **PD-1:** programmed cell death protein 1; **PD-L1:** programmed cell death ligand 1; **T-DXd:** trastuzumab deruxtecan; **T-DM1:** ado-trastuzumab emtansine.

of PD-L1 in the tumour microenvironment, and by blocking PD-1, pembrolizumab can increase the efficacy of the therapy.[15] In the subsequent, randomised, global phase III KEYNOTE-811 trial, the addition of pembrolizumab to trastuzumab and chemotherapy led to a 23% improvement in ORR (74.4% vs. 51.9%).[16] It must be noted that there was a significant difference in the inclusion of patients with IHC 3+ disease in KEYNOTE 811 versus ToGA, (82% vs. 48% in the treatment arm with similar differences in the control), which may explain the significant differences observed in ORR. The PFS was longer in the pembrolizumab group than in the placebo group at the third interim analysis (median 10.0 months vs. 8.1 months; HR: 0.73). In the subgroup of patients with tumours with a PD-L1 combined positive score (CPS) of ≥1, the PFS was 10.9 months in response to treatment (vs. 7.3 months for placebo; HR: 0.71), but did not differ in the population with a PD-L1 CPS of <1 (median 9.5 months vs. 9.5 months; HR 1·03). PFS was consistently improved with pembrolizumab versus placebo irrespective of disease burden, number of metastatic sites, or patient performance status, with the exception of patients with tumours with a PD-L1 CPS of <1.[17]

Trial	Setting	Design	Outcomes
ToGA	First-Line Metastatic	Chemotherapy +/- Trastuzumab	Median OS 13.8 vs. 11.1 months
KEYNOTE-811	First-Line Metastatic	Trastuzumab + Chemotherapy +/- Pembrolizumab	ORR 74% vs. 52% CR 11% vs. 3%
DESTINY-Gastric 01	Third-Line Metastatic (Asian patients)	T-DXd vs. physicians' choice of taxane or irinotecan	ORR 51% vs. 14% Median PFS: 5.6 vs. 3.5 months Median OS: 12.5 vs. 6.4 months
DESTINY-Gastric 02	Second-Line Metastatic (Western patients)	T-DXd	ORR: 42% Median PFS: 5.6 months Median OS: 12.1 months

Table 1. Landmark studies that have changed the landscape of metastatic HER2 positive GEC treatment; *courtesy of Ronan Andrew McLaughlin, MD and Elena Elimova, MD*

Abbreviations: CR: complete response; **ORR:** objective response rate; **OS:** overall survival; **PFS:** progression-free survival; **T-DXd:** trastuzumab deruxtecan.

At the same third interim analysis, median OS was 20.0 months in the pembrolizumab group versus 16.8 months in the placebo group (HR: 0.84), and 20.0 months versus 15.7 months (HR: 0.81) in the population with a PD-L1 CPS of ≥1.[17] These results led to the FDA approval of pembrolizumab with trastuzumab and chemotherapy as a new standard-of-care in the first-line setting, initially approved in all patients, but this was later updated to patients with a CPS ≥1 (**Table 1**), subsequently leading to Health Canada and European Medicines Agency approvals.[17]

Several other first-line studies in metastatic HER2-positive GEC have not resulted in better outcomes. The TyTAN and LOGiC trials investigated lapatinib, a reversible TKI that binds to the intracellular ATP-binding domains of HER2 and EGFR, with disappointing results.[18,19] Additionally, the JACOB trial of dual HER2 blockade, in which trastuzumab and chemotherapy were combined with pertuzumab, a monoclonal anti-HER2 antibody, was also unsuccessful in showing survival benefits.[12] Archival tissue HER2 assessment for assessing eligibility was permitted in all three studies, and the TyTAN and LOGIC studies permitted local HER2 status assessments.[18,19] This may have influenced the results based on research results on the development of resistance to HER2. While TKI have not yet been successful in HER2-positive GEC, tucatinib, a reversible HER2-targeted small-molecule TKI, is currently under investigation. Tucatinib plus trastuzumab has shown tumour growth inhibition in HER2-positive gastric cancer (GC) xenograft models and a phase Ib/II trial in which tucatinib is combined with trastuzumab and chemotherapy for untreated advanced GC is ongoing (NCT04430738). The phase II/III MOUNTAINEER 02 study, which was designed to test the efficacy of tucatinib when combined with trastuzumab, paclitaxel, and ramucirumab in the second-line of treatment, has stopped enrolling patients (NCT04499924).[20] The reasons for this are unclear.

Although the therapies assessed by ToGA and KEYNOTE 811 have improved outcomes through several mechanisms, most patients ultimately develop resistance.[9,17] Due to the heterogeneity of GEC, if HER2-positive clones are successfully eradicated with HER2 inhibition,

HER2-negative clones can drive resistance.[21] HER2 loss is one of the primary causes of acquired resistance to trastuzumab.[22] In patients with HER2-positive gastric cancer receiving trastuzumab, 29%–64% developed loss of HER2 expression during treatment (IHC score <3+ and absence of ISH amplification) and/or loss of HER2 overexpression (IHC "down scoring" from 2+/3+ to 0/1+).[23] At the same time, the heterogeneity of HER2 gene expression increased. This phenomenon was found more frequent in tumours with an initial IHC score of 2+, suggesting that HER2 status needs to be reassessed before starting second-line anti-HER2 therapy.[23] In the event a repeat tissue biopsy is not easily obtained, there is evidence to support the use of liquid biopsy to confirm HER2 status. Studies have determined the HER2 amplification status from circulating DNA fragments in blood using a HER2 Copy Number Variation assay to establish a minimally invasive approach. Furthermore and most importantly, changes in HER2 status during therapy have been confirmed in liquid biopsies, indicating that it reflects the changes in HER2 status and may aid in assessing therapy efficiency and uncovering treatment resistance.[24] Unfortunately, several second-line studies allowed for inclusion based on archival tissue, which may have impacted their results.

Trastuzumab deruxtecan (T-DXd), an antibody-drug conjugate (ADC) consisting of a monoclonal anti-HER2 antibody bound by a cleavable tetrapeptide-based linker to a cytotoxic topoisomerase I inhibitor payload, has transformed options in trastuzumab-refractory disease. With a drug-to-antibody ratio of 8-to-1, the released payload diffuses across cellular membranes, entering neighboring tumour cells. Given the biological heterogeneity of GEC, this high drug-to-antibody ratio and the membrane permeability of its payload have resulted in significant success.[25] The DESTINY-Gastric01 study evaluated T-DXd as third or later line treatment. This open-label phase II trial, which required repeat biopsy to confirm HER2-positivity, demonstrated superior efficacy of T-DXd compared with the physician's choice of paclitaxel or irinotecan, with an improved ORR (51% vs. 14%), median PFS (5.6 vs. 3.5 months), and OS (12.5 vs 8.4 months)[25]. DESTINY-Gastric02, a single-arm phase II trial of T-DXd after progression on trastuzumab also demonstrated significant success with a 42% ORR and median PFS and OS of 5.6 and 12.1 months, respectively.[26] This resulted in FDA approval and incorporation of T-DXd into the NCCN Clinical Practice Guidelines in Oncology (**Table 1**). T-DXd versus ramucirumab/paclitaxel as second-line treatment is currently being evaluated in the phase III DESTINY-Gastric04 study, and T-DXd is being evaluated in the first-line setting, both as monotherapy and in combination with chemotherapy and an anti-PD-(L)1 agent, in the ongoing phase I/II DESTINY-Gastric03 trial (NCT04704934 and NCT04379596). The ASPEN-06 study is currently recruiting patients with HER2-positive metastatic GEC who have progressed on prior HER2-directed therapy and are suitable for second or third-line therapy. This is a randomised phase II/III study of Evorpacept (ALX148), a CD47 blocker, in combination with trastuzumab, ramucirumab, and paclitaxel (NCT05002127).

A host of new bispecific antibodies are currently being investigated in the phase II and III settings. Zanidatamab, which simultaneously binds domains II and IV of the HER2 protein, has shown greater activity than the combination of pertuzumab and trastuzumab.[27] The ongoing phase II trial in which this therapy is combined with chemotherapy in the first-line setting reported a high disease control rate (DCR) of 92% (95% CI: 79-98%). The median duration of response (DOR) was 20.4 months (95% CI: 6.8-non-estimable [NE]), with 57% (17/30) having an ongoing response at the data cut-off. In all patients, the median PFS was 12.5 months (95% CI: 7.1-NE), and the median OS was not yet reached. The survival rate at 18 months was estimated to be 87.3%.[28,29] These findings support the use of zanidatamab in combination with chemotherapy as a potential new first-line standard-of-care treatment, which is being investigated in a phase III study with chemotherapy and the anti-PD-1 antibody tislelizumab (NCT05152147).[30]

HER2-Targeted Therapy; Novel Future Directions

Due to the recent success of T-DXd, several ADCs have been developed with the aim to improve the effects of T-DXd, often with enhanced antibody engineering. These include the bispecific ADC zanidatamab zovodotin and disitamab vedotin. Disitamab vedotin utilizes the anti-HER2 antibody hertuzumab, which induces more potent ADCC than trastuzumab.[31]

Cinrebafusp alfa, a first-in-class bispecific antibody-Anticalin® fusion protein that targets HER2 and the co-stimulatory immune receptor 4-1BB on T cells, showed deep and durable responses in a previous phase I study, and is currently being investigated in a two-arm phase II trial in patients with metastatic HER2-positive and HER2-low GEC (NCT05190445).[32]

Anti-HER2 vaccines are in development in early phase studies, such as IMU-131 (HER-Vaxx). A significant potential benefit of vaccination is that active immunization may be able to overcome resistance mechanisms.[33] HER-Vaxx is currently being evaluated in combination with chemotherapy and immune checkpoint blockade (NCT05311176).

In vitro studies of genetically modified T cells expressing a HER2-specific chimeric antigen receptor (CAR) demonstrate the ability to recognize and kill HER2-positive cancer cells.[34] These in vitro studies have resulted in the evaluation of HER2- specific CAR-T cells in early phase trials (NCT04650451). Another development is ^{89}Zr-trastuzumab PET, a HER2-labeled radiotracer, which is promising for distinguishing between HER2-positive and HER2-negative tumours and may have future ability to deliver cytotoxic therapy.[35]

Conclusion

After a plethora of negative studies and little progress in the area, many recent successful trials are altering the treatment landscape of metastatic HER2-positive GEC. For the up to 20% of GEC cases that are HER2-positive there is cause for optimism. With a greater understanding of the emergence of HER2 resistance, repeat biopsies to evaluate HER2 status after progression is of fundamental importance to determine and sequence subsequent therapies. Incorporating new agents into the perioperative environment and the numerous new mechanisms of HER2-targeting being evaluated in the metastatic setting, clinicians will have several treatment options for GEC, which was once believed to be “un-targetable”. To add further excitement to the field, HER2-low disease, previously regarded as “HER2-negative,” is being investigated to be treated with HER2-directed ADC. This may add a new subset of patients with GEC potentially responding to HER2-directed treatment.

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