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Review Article

Targeted and Immunotherapy Approaches in HER2-Positive Gastric and Gastroesophageal Junction Adenocarcinoma: A New Era

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ABSTRACT

HER2-targeted therapy with the *HER2* monoclonal antibody trastuzumab has achieved impressive outcomes in the first-line settings of patients with advanced gastric and gastroesophageal junction (GEJ) adenocarcinoma overexpressing *HER2*. However, considering that a substantial proportion of those patients eventually relapses, as well as the relatively limited performance of those agents in second-line settings, a deeper understanding of resistance mechanisms is needed for enhanced guidance for patients' therapeutic selection in the second-line setting and beyond. In this review, we highlight trastuzumab's (*HER2*-targeting agent) performance in patients with gastric or GEJ cancer, with insight into mechanisms of resistance. We also discuss the new integration of *PD-1* inhibitor pembrolizumab into the trastuzumab for gastric cancer frontline regimen, the latest addition of trastuzumab deruxtecan to the treatment armamentarium, and the potential of pipeline *HER2*-targeting approaches and combinations in patients with gastric or GEJ adenocarcinoma.

Keywords: gastric cancer, gastroesophageal junction, *HER2*, trastuzumab

INTRODUCTION

Approximately 15–20% of advanced gastric and gastroesophageal junction (GEJ) adenocarcinomas overexpress the tyrosine kinase *HER2* (human epithelial growth factor receptor 2),[1] which portends a poor prognosis. Although the *HER2*-targeted monoclonal antibody trastuzumab has seen most of its success in breast cancer, research involving gastric or GEJ cancer has faced several challenges. These include the heterogeneity of *HER2* expression in gastric cancer as well as the high frequency of co-occurrence of additional oncogenic drivers, which lend themselves to multiple mechanisms of resistance to targeted therapies.[2] Over the last decade, research has elucidated some of these challenges and attempted to find alternative targeted therapies beyond trastuzumab. In this article, we will review the successes of trastuzumab in the treatment of advanced gastric or GEJ cancer as well as the less successful second-line trials and mechanisms of trastuzumab resistance. We will then highlight the most recent novel therapies beyond trastuzumab that are targeting advanced *HER2*-expressing gastric or GEJ cancer.

Gastric cancer is the third leading cause of cancer-associated deaths.[3] The 5-year survival rate for advanced or metastatic disease is between 5 and 20% and the median overall survival (OS) is less than a year.[4] Combination chemotherapy was standard of care until it was established that in patients with *HER2*-expressing (*HER2*+) gastric or GEJ cancer, *HER2*-directed therapy could provide a survival benefit in advanced cases,

which was demonstrated by the Trastuzumab for Gastric Cancer (ToGA) trial in 2010.[5] The phase III international randomized control trial assigned treatment-naïve patients with inoperable locally advanced, recurrent, or metastatic gastric or GEJ adenocarcinoma to trastuzumab in combination with chemotherapy or chemotherapy alone. Significant improvements were seen in OS, progression-free survival (PFS), and overall response rate (ORR) in the experimental group, with the highest OS rates being seen in patients with high HER2 expression. This landmark study led to US Food and Drug Administration (FDA) approval of the combination of trastuzumab + chemotherapy for patients with metastatic or unresectable, high *HER2*-expressing gastric or GEJ adenocarcinoma as first-line therapy. Subsequently, current guidelines from the College of American Pathologists, American Society for Clinical Pathology, and the American Society of Clinical Oncology recommend that all patients with advanced gastroesophageal adenocarcinoma who are candidates for *HER2*-targeting therapy undergo *HER2* assessment prior to therapy initiation.[6]

Additionally, the TRIO-013/LOGiC phase 3 trial compared capecitabine and oxaliplatin (CapeOx) plus lapatinib (*HER2* inhibitor) with CapeOx and placebo in untreated *HER2*-amplified advanced gastroesophageal adenocarcinoma and found no increase in OS with increased diarrhea adverse events in the lapatinib arm.[7] These findings could be due to the inferior performance of lapatinib to trastuzumab as demonstrated in breast cancer studies.[8] Also, the relatively lower ability of patients with gastroesophageal cancer to tolerate gastrointestinal toxicities like diarrhea contributes to the reduced efficacy and compliance. Furthermore, the addition of pertuzumab to trastuzumab and chemotherapy was found to improve survival in *HER2*-positive breast cancer, yet this benefit did not translate to patients with metastatic gastric or GEJ cancer as reported in the JACOB phase 3 trial, which failed to detect improvement in OS.[9]

Unfortunately, the progression of disease while on trastuzumab combined therapy is inevitable for those with advanced or metastatic gastric or GEJ cancer, and targeted treatment options for second-line therapy have yielded less than promising results. With the knowledge that trastuzumab after tumor progression provided clinical benefit in the *HER2*+ breast cancer population,[10] the phase II T-ACT study in Japan investigated if trastuzumab plus paclitaxel improved outcomes when compared with chemotherapy alone for gastric or GEJ tumors that progressed on chemotherapy plus trastuzumab.[11] Results from this trial showed no significant improvement in OS, PFS, or ORR. It is important to mention that eligibility criteria included high *HER2* expression before first-line treatments, but only a small number of samples were assessed for *HER2* status after first-line therapy. Of these samples, 69% lost *HER2* positivity. Loss of *HER2* positivity after anti–*HER2*-directed therapy is a well-known occurrence in this disease population; recent analyses have shown that up to 60% of tumors lose *HER2* positivity and up to 22% demonstrate a change from *HER2* genetic homogeneity to heterogeneity.[12,13] *HER2* heterogeneity can loosely be defined as differing expression levels according to fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC) of separate biopsies within the same tumor. Hence, progression on *HER2*-targting agents warrants reassessment of *HER2* status to ensure optimal treatment. Possible explanation for such phenomenon includes the differential effect of *HER2*-targeting agents on clonal subsets, inducing the expansion of *HER2*-negative subsets.[14] In addition, those dynamic changes could be attributed to chemotherapy regardless of the addition of *HER2* agents. A meta-analysis of the T-ACT randomized control trial as well as four other non-randomized cohort studies led to the conclusion that OS and ORR did not significantly improve with trastuzumab therapy compared with chemotherapy alone but did have improved PFS and no significant differences in adverse effects between treatment groups.[15] These findings showed that trastuzumab beyond progression had some limited clinical benefit but did not have a marked effect on prognosis. The variability in response to treatment depending on *HER2* expression pre and post treatment is one of the major challenges in *HER2*+ gastric or GEJ cancer.

Included studies in this literature review were retrieved through the PubMed search engine. Studies pertaining to *HER2* agents in gastric or GEJ cancer were included; there were no limitations regarding study design or sample size.

MECHANISMS OF RESISTANCE

HER2 expression in gastric or GEJ cancer has more heterogeneity than breast at the intralesional and interlesional level[14]: the incidence of *HER2* heterogeneity can range from 39.0 to 75.4% within tumor samples.[16] A retrospective study comparing biopsy specimens and therapeutic response in patients with advanced gastric or GEJ cancer treated with trastuzumab-based therapy revealed that tumors with *HER2* homogeneity (positive *HER2* staining by IHC in all samples from the tumor) were associated with significantly better ORR, median survival time, and PFS than the heterogenous group.[17] Within this study, multivariate analysis revealed *HER2* heterogeneity as an independent prognostic factor, and other analyses have confirmed these findings of poor prognosis and decreased trastuzumab efficacy.[16,18] Notably, the percentage of *HER2* heterogeneity across previous studies seems to vary from 5 to 75.4%, which in part is attributed to the lack of a generally acceptable definition of heterogeneity that accounts for both intratumoral and intertumoral heterogeneity.[19–21]

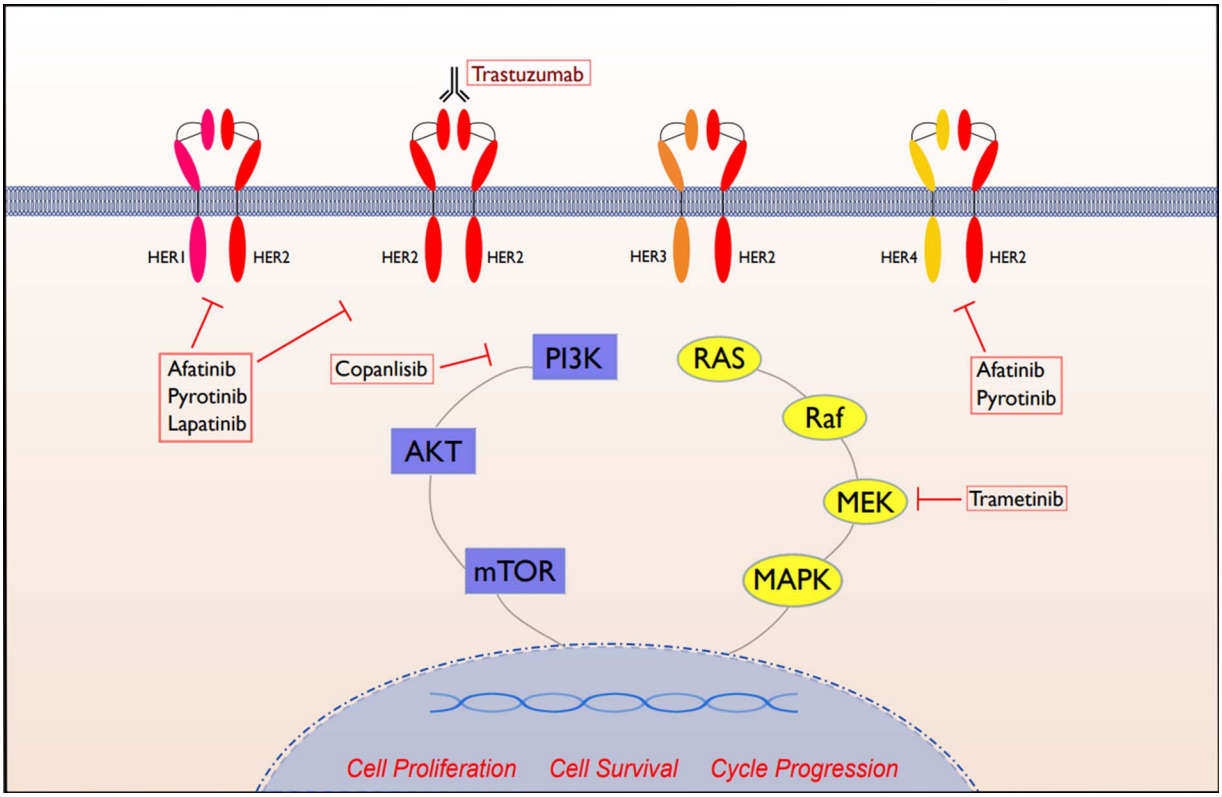

Figure 1. Overcoming trastuzumab resistance. In the setting of *HER2* expression, tumor cells promote cell proliferation, cell survival, and cycle progression through formation of dimers and activation of the *RAS* and *PI3K* pathways. Trastuzumab inhibits *HER2* homodimerization; however, resistance can develop. The use of afatinib and pyrotinib (pan-*HER* inhibitors), lapatinib (dual *HER1/2* inhibitor), copanlisib (*PI3K* inhibitor), trametinib (*MEK* inhibitor) attempts to overcome these mechanisms of resistance.

Therefore, it is important to thoroughly sample and evaluate the *HER2* status of *HER2*+ gastric or GEJ cancers to determine trastuzumab efficacy. Along with heterogeneity, loss of HER2 expression after trastuzumab treatment happens frequently, as previously stated.[2,22] In addition to *HER2* status, several coamplifications and mutations have been documented that may contribute to trastuzumab resistance. Through the AMNESIA biomarker study, *HER2*+ trastuzumab-resistant metastatic gastric or GEJ tumors were found to have *EGFR, MET, KRAS, PI3K, PTEN* mutations as well as *EGFR, MET, KRAS* amplifications.[23] In response to the amplification of *EGFR* (*HER1*), pan-*HER* inhibitors have been used in the treatment of trastuzumab-resistant cancer, but resistance to these inhibitors can occur. A phase II study analyzing the efficacy of pan-*HER* inhibitor afatinib found that tumors resistant to treatment were associated with a downregulation of *EGFR* and/or amplification of *MET*. The addition of a *MET* inhibitor to afatinib resulted in complete tumor regression in xenograft models.[24] Resistance to dual-*HER1/2* inhibitor lapatinib can be precipitated by the loss of function mutations of *CSK* and *PTEN*, increasing *PI3K* and *MAPK* signaling. This resistance may be overcome by using lapatinib in combination with therapies that inhibit *PI3K* and *MAPK* pathways such as copanlisib (*PI3K* inhibitor) or trametinib (*MEK* inhibitor).[25] Figure 1 illustrates possible approaches to overcoming trastuzumab resistance.

Resistance to anti-*HER2* agents is also mediated by positive crosstalk between *MET* and *HER2* pathway; suppression of transcription factor *FOXO1* allows for interplay between the two pathways and increased resistance to lapatinib.[26] Dysregulation of cell-cycle mediators is a response to anti-*HER2* treatment; resistance to pan-*HER* inhibitor pyrotinib has been associated with *CCND1* and *CDK4* upregulation, and subsequent tumor regression occurred with the addition of a *CDK4/6* inhibitor.[27] Bypassing *HER2* and activating the epithelial-to-mesenchymal transition in response to trastuzumab treatment through the *HER4-YAP1* axis, which upregulates the *PI3K-AFT* pathways, has also been documented.[28] Crosstalk between *HER2* and *VEGF* pathways is another major mechanism of resistance of trastuzumab resistance.[29] The standard of care for advanced gastric or GEJ cancer in the second-line setting, regardless of *HER2* status, has been ramucirumab, a *VEGF2* antagonist, plus paclitaxel, based on the significantly improved clinical outcomes demonstrated in the RAINBOW trial[30] as well as various other salvage chemotherapy regimens. Because of these primary and acquired mechanisms of resistance, it is imperative to develop personalized novel combinatorial therapies that will continue to provide

Table 1. Ongoing trials for advanced HER2+ gastric or gastroesophageal junction adenocarcinoma

Drug Class	Interventions	Setting	Phase	ClinicalTrials.gov Identifier
Monoclonal antibodies	HLX22 (mAb) + trastuzumab + chemotherapy	First-line	2	NCT04908813
	Zanidatamab (ZW25) ± chemotherapy	Second-line	1	NCT02892123
			1b/2	NCT04276493
			2	NCT03929666
	Margetuximab + chemotherapy + retifanlimab or tebotelimab	First-line	2/3	NCT04082364
	Cinrebafusp alfa (PRS-343) + ramucirumab and paclitaxel or tucatinib	Second-line	2	NCT05190445
	Atezolizumab + trastuzumab + capecitabine + oxaliplatin	(Neo)adjuvant	2	NCT04661150
	DKN-01 + tislelizumab ± chemotherapy	First- or second-line	2	NCT04363801
Antibody drug conjugates	MEDI4276	Second-line	1/2	NCT02576548
	SBT6050 + trastuzumab deruxtecan or tucatinib, trastuzumab, and capecitabine, or tucatinib and trastuzumab	Second-line	1/2	NCT05091528
	DP303C	Second-line	2	NCT04826107
	ZW49	Second-line	1	NCT03821233
	Trastuzumab duocarmazine (SYD985) + paclitaxel	Second-line	1	NCT04602117
	ARX788	Second-line	1	NCT03255070
Tyrosine kinase inhibitors	SHR6390 (CDK4/6 inhibitor) + pyrotinib	Second-line	1	NCT03480256
	Tucatinib + trastuzumab ± chemotherapy ± pembrolizumab	First-line	1/2	NCT04430738
	Tucatinib + trastuzumab + ramucirumab + paclitaxel	Second-line	2/3	NCT04499924
	Camrelizumab (PD-1 inhib) + pyrotinib + nab-paclitaxel + tegafur	First-line	2	NCT05070598
Other novel agents	CCT303-406 (CAR-T cells)	Second-line	1	NCT04511871
	BPX-603 (dual-switch CAR-T cells)	Second-line	1/2	NCT04650451
	CAdVEC (oncolytic adenovirus) + HER2-specific CAR-T cells	Second-line	1	NCT03740256
	BVAC-B (vaccine)	Second-line	1	NCT03425773
	TAEK-VAC-HerBy (vaccines) ± trastuzumab	Second-line	1	NCT04246671
	IMU-131(HER-Vaxx) + chemotherapy	First-line	1/2	NCT02795988

CAR: chimeric antigen receptor; mAb: monoclonal antibody; PD: programmed cell death protein.

clinical benefit after trastuzumab within this patient population. Table 1 summarizes ongoing trials on advanced *HER2*+ gastric or GEJ adenocarcinoma.

MONOCLONAL ANTIBODIES

Whereas trastuzumab binds to and blocks the extracellular domain IV of *HER2*, pertuzumab binds the extracellular domain II, which prevents heterodimerization and thus activation of the complex. The JACOB trial, which studied trastuzumab plus pertuzumab or placebo and chemotherapy, showed that adding pertuzumab did not significantly improve OS in patients with *HER2*-positive metastatic gastric or GEJ cancer.[9] One limitation of this and many other similar trials is the lack of mandatory *HER2* testing at the time of progression on trastuzumab frontline regimen because this may lead to unintentional enrichment of *HER2*-negative or low *HER2*-expression and associated low or no response to *HER2*-targeted approaches. Another *HER2*-targeted antibody, margetuximab, contains a modified Fc region that binds with more affinity to *CD16A* on NK cells, promoting antibody-dependent cell-mediated cytotoxicity. The SOPHIA trial in *HER2*+ breast cancer demonstrated significantly improved PFS (24% relative risk reduction) as well as a trend toward increased median OS with margetuximab versus trastuzumab plus chemotherapy.[31] In preclinical studies, the combination of margetuximab and pembrolizumab (anti–*PD-1*) had synergistic antitumor activity, which was confirmed with a single-arm, phase Ib/II trial (CP-MGAH22-05), in which patients with advanced trastuzumab-refractory *HER2*+ gastroesophageal cancer were treated with margetuximab + pembrolizumab. The study was found to have adequate safety and tolerability, as well as a favorable OS when compared with other second-line trials.[32] Unlike most of the other *HER2*-targeted therapy trials in this setting, this trial mandated *HER2* positivity as an integrated eligibility marker. The positive outcomes here highlight the importance of incorporating molecular retesting in targeted therapy trials to better test the efficacy of those novel agents. The ongoing MAHOGANY trial is further investigating the efficacy of margetuximab with anti-*PD-1* agent retifanlimab and anti–*LAG-3* agent tebotelimab.[33] Bispecific antibodies are an emerging form of monoclonals that can target two different epitopes of the antigen (*HER2*) through their two different arms. This leads to better

clustering of *HER2* and tumor cell binding and improved receptor internalization. For instance, the bispecific antibody ZW25 has shown promising results as a single agent in previously treated *HER2*-expressing cancers, including gastric.[34]

ANTIBODY-DRUG CONJUGATES

Antibody-drug conjugates (ADCs) consist of a monoclonal antibody and a cytotoxic agent. *HER2*-targeted ADCs specifically inhibit *HER2*-mediated signaling and downstream effects while also causing antibody-dependent cellular cytotoxicity. In *HER2*+ breast cancer studies, continuing trastuzumab after progression through ADCs has had clinical success in the setting of advanced disease. Trastuzumab emtansine (T-DM1) is an ADC consisting of trastuzumab linked to the antimitotic microtubule drug emtansine. Both the EMILIA and TH3RESA trials showed that trastuzumab emtansine improved outcomes in patients with *HER2*+ breast cancer that progressed on trastuzumab therapy.[35,36] However, the GATSBY trial showed that T-DM1 was not superior to taxane for patients previously treated for advanced *HER2*+ gastric or GEJ cancer and provided no survival benefit.[37] Again, loss of *HER2* positivity may explain why T-DM1 did not perform better than taxane in the GATSBY trial. The GASTHER3 trial demonstrated that 29.1% of patients lost *HER2* positivity following treatment with trastuzumab-containing regimens including T-DM1.[13] Trastuzumab deruxtecan (DS-8201a), an ADC with a topoisomerase I inhibitor, has had much more promising results for gastric cancer. This agent has a drug to antibody ratio of approximately 8 and a bystander cytotoxic effect that showed efficacy in even *HER2*-low-expression breast cancer and patients previously treated with multiple lines of *HER2*-directed therapy, including T-DM1.[38] Subsequently, the DESTINY-Gastric01 trial demonstrated significantly improved OS in *HER2*+ gastric or GEJ cancer with trastuzumab deruxtecan compared with standard chemotherapy for those with *HER2*+ gastric or GEJ adenocarcinoma that had progressed while they were receiving at least two previous therapies, including trastuzumab.[39] Several other *HER2*-directed ADCs are being investigated in early clinical trials, including disitamab vedotin (RC48), which has shown promise as second-line therapy for *HER2*-overexpressing advanced gastric cancer in phase II clinical trials.[40] In preclinical trials, the new ADCs trastuzumab duocarmazine (SYD985), XMT-1522 (TAK-522), ARX788, and ZW49 were more potent than T-DM1 in cell line and xenograft models and are currently being investigated in phase I clinical trials. Furthermore, the novel third-generation ADC DP303c will be studied in several *HER2*+ cancer clinical trials, including advanced gastric cancer (NCT04826107).[41]

ANTI-*HER2* AND ANTI-PD1 COMBINATORIAL TRIALS

Immune checkpoint inhibitors have been investigated as a first-, second-, and third-line option for gastric cancer, regardless of *HER2* status. In the setting of *HER2*-negative disease, several trials (KEYNOTE-059, -061, -062, -590) have been conducted to investigate the clinical benefit of pembrolizumab monotherapy or in addition to standard chemotherapy regimens.[42,43] In *HER2*-positive disease, preclinical and clinical studies have shown that pembrolizumab and trastuzumab can be used in combination and may have synergistic activity.[44,45] The KEYNOTE-811 study investigated the use of pembrolizumab or placebo + trastuzumab + standard chemotherapy in the first-line setting of *HER2*+ gastric or GEJ cancer.[46] In the first interim analysis, the researchers found a 74.4% ORR with the addition of pembrolizumab, a 22.7% improvement compared with the trastuzumab and chemotherapy regimen. The promising nature of these results suggests that inhibiting *PD-1* may improve clinical outcomes by both augmenting the efficacy and slowing resistance to trastuzumab.[46] The ATTRACTION-2 trial established the safety of nivolumab as third-line therapy in gastric cancer and additionally provided evidence for clinically meaningful OS benefit.[47] Subsequently, the phase II INTEGA trial showed superior efficacy of nivolumab plus trastuzumab plus FOLFOX compared with a chemotherapy-free regimen of checkpoint inhibition and trastuzumab.[48] Ongoing trials include the MAHOGANY trial, assessing margetuximab plus anti-*PD-1* regimens with or without chemotherapy, the DESTINY-Gastric03 trial assessing trastuzumab deruxtecan plus durvalumab, and a trial examining the combinations of pyrotinib plus camrelizumab plus chemotherapy.

TYROSINE KINASE INHIBITORS

Using nontrastuzumab HER2-targeting agents was first attempted with tyrosine kinase inhibitors (TKIs), which inhibit phosphorylation and downstream signaling pathways. The TyTAN trial studied the use of lapatinib as second-line treatment for patients with gastric cancer with positive *HER2* status via FISH but variable expression levels via IHC. Lapatinib is a dual *EGFR* (*ErbB1*) and *HER2* (*ErbB2*) intracellular reversible TKI that has been used as second-line treatment of metastatic breast cancer that overexpresses *HER2*.[49] When compared with paclitaxel alone, there were no statistically significant differences in OS or PFS, although the ORR for the lapatinib treatment arm was 27% versus 8% for paclitaxel alone ($p < 0.001$).[50] However, as with the previously described studies, *HER2* status was a data point that significantly affected response to treatment. When analyzing only the subgroup of patients with the highest (IHC3+) *HER2* expression, there was a significant increase in both OS and PFS. The addition of lapatinib to capecitabine and

oxaliplatin in the setting of treatment-naïve *HER2*+ advanced cancer was also somewhat unsuccessful with no increase in OS, as demonstrated by the TRIO-013/LOGiC trial.[7] However, other TKIs are being investigated and have shown some promising results. A phase II trial of dacomitinib—which irreversibly inhibits *EGFR*, *HER2*, and *HER4*—had a favorable safety profile as monotherapy and was associated with higher activity in patients with higher *HER2* extracellular domain serum levels.[51] Other irreversible pan-*HER* inhibitors, such as afatinib, neratinib, and pyrotinib, have had promising results and yielded some insight into tyrosine kinase resistance patterns.[24,27,52] Several trials for tucatinib, another *HER2* TKI, in combination with other targeted therapies (trastuzumab, ramucirumab, ADCs), are in the recruiting phase.

TARGETED IMMUNE-ONCOLOGY APPROACHES (CAR T, CANCER VACCINES)

Another newer precision immunotherapy investigational approach to trastuzumab resistance in *HER2*+ gastric or GEJ cancer is chimeric antigen receptor T cells (CAR-T), which are T cells genetically modified to exhibit high affinity for their prospective antigen(s) and contribute to the antitumor microenvironment. CAR-T cells have shown promising results in the setting of hematologic malignancies, with continually growing research within the field of solid malignancies. There are several studies investigating the potential for *HER2*-targeted CAR-T and CAR-NK cells in solid cancers. Preclinical xenograft models have exhibited high affinity, enhanced tumor inhibition, and long-term survival for *HER2*-targeted CAR-T cells in advanced gastric cancer,[53] and there is currently a phase Ib/II clinical trial investigating dual-switch CAR-T cell BPX603 (NCT04650451). Therapeutic cancer vaccines may also be a promising platform for immunotherapy in *HER2*-expressing cancers. The TAEK-VAC-HerBy vaccine induces a cytotoxic T-lymphocyte–mediated immune response against *HER2*-positive tumor cells. There is currently a gastric cancer cohort within a phase I trial investigating the safety of this vaccine (NCT04246671). As ongoing research overcomes the barriers to CAR-T and therapeutic vaccines in solid malignancies, these novel immunotherapies may become more standard of care either in combination or as monotherapy in the future.

FUTURE DIRECTIONS AND CONSIDERATIONS

The landmark ToGA trial proved that there is a clinical benefit to using trastuzumab, which has become the standard of care in the treatment of advanced *HER2*+ gastric or GEJ cancer, much like breast cancer treatment. However, unlike breast cancer, *HER2* expression in gastric cancer is more heterogenous in nature, which correlates to worse treatment outcomes. Loss of *HER2* expression after anti-*HER2* treatment is another phenomenon that has led to the investigation of other pathways as potential targets. Although the KEYNOTE-811 and DESTINY-Gastric01 trials have shown the most success with FDA approvals in the first- and second-line settings[39,46], work is still being done to overcome the challenges of resistance by way of the agents described in this review. Although novel monoclonal antibodies against *HER2* have been largely unsuccessful, recent trials for margetuximab and bispecific zanidatamab have shown promising results. New developments within the arenas of ADCs and TKIs are other options to continue exploring. Expanding *HER2*-positivity detection methods to include liquid biopsies and next-generation sequencing could potentially provide reliable noninvasive alternatives beyond the traditional IHC and FISH testing approaches.[54,55] With the explosion of immunotherapy research within the last decade, one of the most exciting strategies in the future to combat *HER2*+ gastric or GEJ cancer is the combinatorial approach of various *HER2*-targeting agents with checkpoint inhibitors, CAR-T cells, and vaccines. Through simultaneous blockade of different pathways and taking advantage of the immune system, there continues to be progress and hope in the field of advanced *HER2*-positive gastric or GEJ adenocarcinoma.

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