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Review Article

Breakthroughs in the Systemic Treatment of HER2-Positive Advanced/Metastatic Gastric Cancer: From Singlet Chemotherapy to Triple Combination

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ABSTRACT

Gastric cancer is heterogeneous in morphology, biology, genomics, and treatment response. Alterations in human epidermal growth factor receptor 2 (HER2) overexpression, microsatellite instability (MSI) status, programmed death-ligand 1 (PD-L1) levels, and fibroblast growth factor receptor 2 (FGFR2) can be used as biomarkers. Since the combination of fluoropyrimidine/platinum plus trastuzumab that was investigated in the ToGA trial was approved as a standard of care in HER2-positive patients in 2010, no other agents showed efficacy in the first- (HELOISE, LOGiC, JACOB trials) and second- (TyTAN, GATSBY, T-ACT trials) line treatments. Despite the success in treating breast cancer, various anti-HER2 agents, including a monoclonal antibody (pertuzumab), an antibody-drug conjugate (ADC; trastuzumab emtansine [T-DM1]), and a small molecule (lapatinib) failed to translate into clinical benefits until the KEYNOTE-811 (first-line) and DESTINY-Gastri01 (≥second-line) trials were conducted. The incorporation of HER2-directed treatment with immune checkpoint inhibitors in the form of a monoclonal antibody or ADC is now approved as a standard treatment. Despite the promising results of new agents (engineered monoclonal antibodies, bi-specific antibodies, fusion proteins, and small molecules) in the early phase of development, the management of HER2-positive gastric cancer requires further optimization to achieve precision medicine with a chemotherapeutic backbone. Treatment resistance is a complex process that can be overcome using a combination of chemotherapy, targeted agents, and immune checkpoint inhibitors, including novel agents. HER2 status must be reassessed in patients undergoing anti-HER2 treatment with disease progression after the first-line treatment. As a general guideline, patients who need systemic treatment should receive chemotherapy plus targeted agents, anti-angiogenic agents, immune checkpoint inhibitors, or their combinations.

Keywords: HER2; Gastric cancer; Targeted; Immune checkpoint inhibitor

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Author Contributions

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INTRODUCTION

A plethora of genomic alterations, including human epidermal growth factor receptor 2 (HER2), epidermal growth factor receptor (EGFR), fibroblast growth factor receptor 2 (FGFR2), mesenchyme-epidermal-transforming factor receptor (MET), phosphatidylinositol 3-kinase (PI3K), mammalian target of rapamycin (mTOR) pathways, and microsatellite instability (MSI), are responsible for the heterogeneity of gastric cancer. The patterns of genomic alterations are diverse in each gene and in various tumors. HER2 aberrations include mutation (74%), kinase domain insertion (22%), insertion/deletion (1.5%), and fusion (0.7%), whereas extracellular domain mutations are the major aberrations in HER3 [1]. HER2 is a type I transmembrane tyrosine kinase growth factor receptor consisting of 1,255 amino acids encoded by the erythroblastic oncogene B-2 gene (*ERBB2)* located on chromosome 17q21 [2,3]. HER2 is an orphan receptor with a constitutively activated conformation that does not possess specific ligand or ligand-binding activity. HER2 dimerizes with HER1, HER3, and HER4 but favors HER3, which produces the most active signaling heterodimerization [4]. Since the first observation of HER2 overexpression in gastric cancer [5], HER2 overexpression has mainly been found in Epstein-Barr virus-positive tumors, the genome-stable and chromosomal instability (CIN) subtypes according to The Cancer Genome Atlas classification [6], and the MSS/TP53 inactive subtype according to the Asian Cancer Research Group classification [7]. Owing to CIN, HER2-positive tumors usually have a low tumor mutational burden. More than half of CIN tumors contain a low number of CD8+ cells but have a high number of CD68+ macrophages, suggesting that targeting immunosuppressive macrophages or controlling the immunosuppressive microenvironment might enhance immune checkpoint inhibitor activity [8]. HER2-positivity was defined as an immunohistochemistry (IHC) of 3+ or HER2 gene amplification (average copy number of more than six in the absence of an internal control probe or a signal ratio of HER2/chromosome 17 [HER2/CEP17] >2.2) by in situ hybridization. The prevalence of +3 positivity for HER2 was lower among Japanese patients (31%–63%) than in all patients (45%–67%) [9]. HER2 overexpression is usually caused by gene amplification, and subsequent heterodimerization with EGFR family members induces cell proliferation via the RAS/mitogen-activated protein kinase (MAPK) and PI3K/Akt pathways. Transphosphorylation results in pathway signaling (RAS/RAF/MEK/MAPK/MYC/c-jun) through HER2/HER1 and HER2/HER3 dimerization, Akt/mTOR activation through HER3 and PI3K signaling, up-regulation of the cyclin D/cyclin-dependent kinase complex, dysregulation of cell cycle homeostasis, proliferation, apoptosis evasion, and chemoresistance [10,11]. Negative HER2 was defined as IHC 0/+1, HER2/CEP17 <1.8 or less than four copies of the HER2 gene without an internal control probe. Although HER2 expression is strongly correlated with the Borrman type, Lauren's classification, tumor differentiation, lymph node status, venous invasion, and lymphovascular invasion, the prognostic value of HER2 remains uncertain. HER2 was the first routinely tested biomarker in gastric cancer, followed by MSI and programmed death-ligand 1 (PD-L1).

Following the success of the ToGA trial [12], treatment with monoclonal antibodies (pertuzumab and magetuximab), small molecules (afatinib, neratinib, pyrotinib, and tucatinib), ADCs (T-DM1, DS8201a, and RC48-ADC), immune checkpoint inhibitors (pembrolizumab, nivolumab, and ipilimumab), anti-angiogenesis agents (ramucirumab, bevacizumab, and apatinib), and novel agents (bi-specific antibody [ZW25], fusion protein [ALX148], chimeric antigen receptor T [CAR-T], and B cell and monocyte-based vaccine [BVAC-B]) has been attempted with or without chemotherapy. This review summarizes the evolution of anti-HER2 treatments and new emerging strategies that are expected to

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minimize toxicity and overcome resistance in advanced or metastatic gastric cancer. Early and localized cancers that require adjuvant or perioperative treatment will not be discussed.

DRUGS FOR PARADIGM SHIFT TREATMENT

Anti-HER2 monoclonal antibody

The crystalline fragment (Fc) binds to immune cells expressing Fc receptors, and serum complements to mediate antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis, and complement-dependent cytotoxicity. Trastuzumab is a human IgG1 monoclonal antibody that selectively binds to the extracellular domain IV of HER2 and prevents heterodimer formation, blocks signaling, modulates immunity by HER2 internalization, promotes cross-presentation to dendritic cells, and stimulates HER2-specific T cells [13]. A recent report showed that trastuzumab upregulates programmed cell death protein 1 (PD-1) and PD-L1 expression, induces cancer-specific CD4 and CD8 T-cell expansion, and modulates major histocompatibility complex (MHC) class II expression [14]. Neither high-dose trastuzumab administered during maintenance in the first-line treatment [15] nor trastuzumab administered as second-line treatment after first-line failure [16], afforded any additional survival benefit. Pertuzumab binds to extracellular domain II of HER2 and heterodimerizes with HER1, HER3 and HER4 [17]. Margetuximab (Margena) is a HER2 targeting chimeric Fc-optimized monoclonal antibody that enhances binding to activated FcR (CD16A; FcγRIIIa) and reduces its affinity for inhibitory FcR (CD32B; FcγIIb). CD16A is expressed in natural killer cells, natural killer T cells, γδ T cells, dendritic cells, macrophages, and monocytes [18]. Margetuximab also maintains a higher ADCC than trastuzumab, augments T-cell activity, and upregulates tumor cell PD-L1 expression, which amplifies both innate and adaptive immune responses, even against HER2-low cancer [19]. Margetuximab was granted as an orphan drug by the Food and Drug Administration (FDA) for gastric and gastroesophageal junction cancers in June 2020 (**Fig. 1**).

Immune checkpoint inhibitor

In cases of advanced or metastatic gastric cancer, and gastroesophageal junction adenocarcinoma with PD-L1 combined positive score (CPS) ≥1, after 2 or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy, HER2-targeted therapy and pembrolizumab was approved under the FDA's accelerated approval regulations based on tumor response rate and durability of response in accordance with KEYNOTE-059 (September 2017). The sponsor company withdrew U.S. accelerated approval following an Oncologic Drugs Advisory Committee evaluation because it failed to meet its post-marketing requirement of demonstrating an overall survival benefit (July 2021). Nivolumab was approved in Japan (September 2017) and later in Korea and Taiwan as a third-line regardless of HER2 expression. Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is an inhibitory checkpoint protein that is activated in T cells and downregulates immune response. The synergistic effect of nivolumab and a CTLA-4 inhibitor (ipilimumab) demonstrated clinical benefits in melanoma, with manageable toxicities. However, this combination as a first-line treatment in HER2-negative gastric cancer patients, was terminated because of high frequencies of toxicities, and the final results remain undisclosed [20]. Retifanlimab (MGA012; INCMGA00012) is a humanized IgG4k anti-PD-1 monoclonal antibody. When combined with margetuximab, it induces T-cell sensitization and tumor destruction by adaptive T-cell-mediated antitumor immunity [21]. Camrelizumab is a humanized IgG4k anti-PD-1, that shows antitumor activity in advanced gastric cancer [22].

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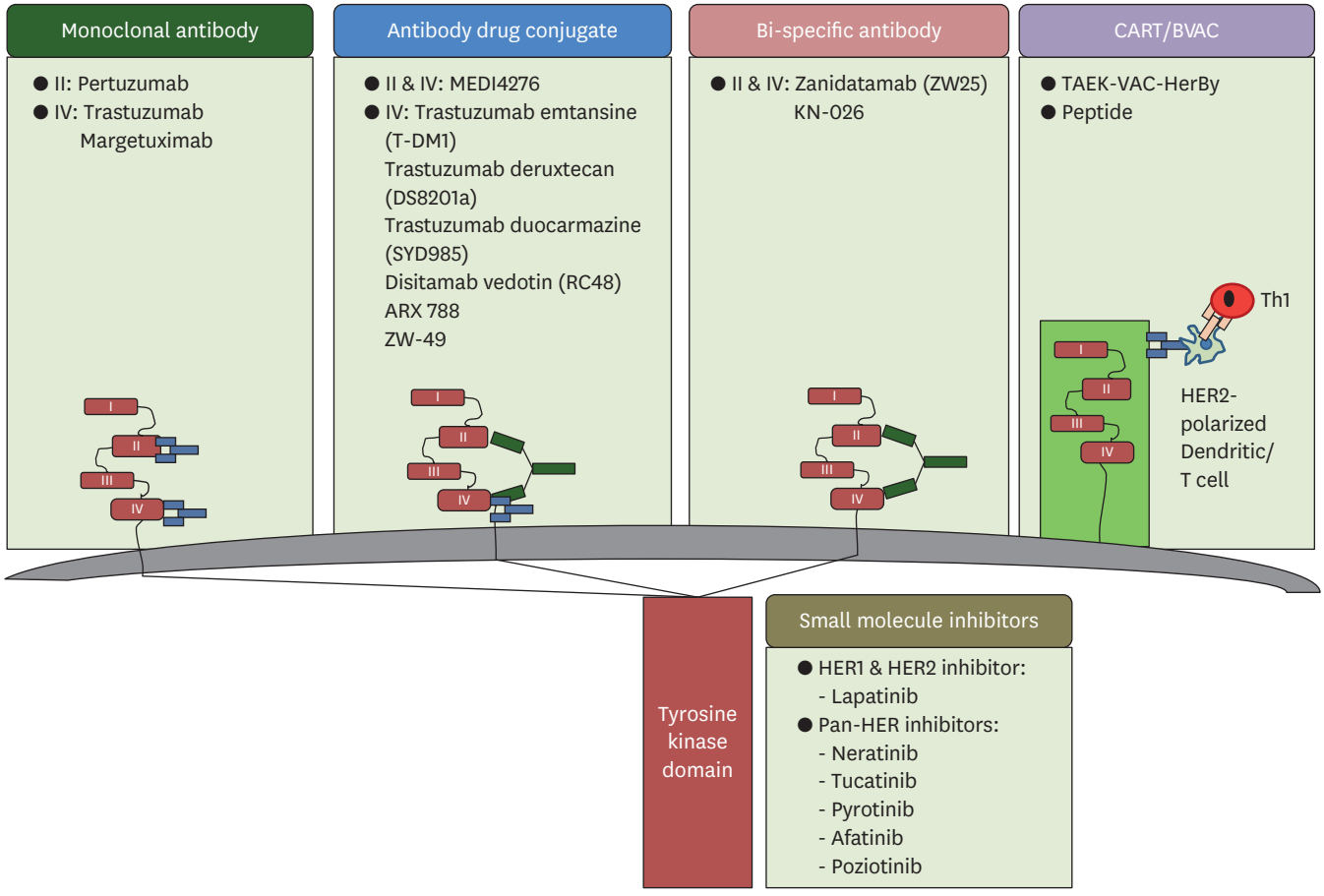

Fig. 1. Novel agents for HER2-directed treatment.
HER2 = human epidermal growth factor receptor 2.

ADCs

ADCs are combinations of a bioactive cytotoxic drug and a monoclonal antibody linked by a chemical bond, which have cytotoxicity, target specificity, stability, and favorable pharmacokinetics. T-DM1 is a combination of trastuzumab and microtubule inhibitor maytansine linked in a non-cleavable manner by maleimidomethyl cyclohexane carboxylate. Trastuzumab Deruxtecan (T-DXd. DS-8201a, Enhertu) is a combination of trastuzumab and topoisomerase I inhibitor payload linked by a cleavable tetrapeptide-based linker. It has a drug-to-antibody ratio of 8:1, which is higher local payload concentration than that of T-DM1 (3.5:1) [23]. The topoisomerase payload of T-DXd is 10 times more potent than that of SN-38, and it is membrane permeable, which allows for a bystander-killing effect on neighboring cells. These characteristics are effective in overcoming heterogeneous HER2 expression and limiting off-target toxicity in HER2-low subtype tumors [24]. Lower HER2 levels correlate with lower response rates due to the internalization of T-DXd by HER2-positive cells. T-DXd is effective against tumors overexpressing HER2 without gene amplification. This is an important factor in patients with a discordance between HER overexpression and amplification [25]. The independence of T-DXd activity from the presence of other genetic alterations suggests the possibility of using T-DXd to overcome resistance. T-DXd was the first drug to demonstrate efficacy in both Asian and Western patients with trastuzumab treatment failure. Interstitial lung disease occurred in 10% of the patients, which was managed with dose reductions and interruptions but may be a limiting factor in neoadjuvant and

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perioperative settings. In January 2021, the FDA approved T-DXd (Enhertu) for the treatment of advanced or metastatic HER2-positive gastric or gastroesophageal adenocarcinoma patients who had received a prior trastuzumab-based regimen.

Disitamab vedotin (RC48) consists of a hertuzumab, monomethyl auristatin E payload and a cleavable valine-citrulline linker. A pre-clinical study demonstrated a stronger antitumor response than that of T-DM1 [26], a bystander effect, and an ADCC-triggering effect. [vic-] trastuzumab duocarmazine (SYD985) is trastuzumab bound to a linker containing DNA-alkylating duocarmycin, with a drug-to-antibody ratio of 2.8:1 [27]. ZW49 contains bi-paratopic ZW25 and an auristatin payload [28]. A phase I trial is currently underway (NCT03821233). ARX788 is a HER2-targeted monoclonal antibody linked to tubulin inhibitor payload (AS269). A phase I study is currently underway (NCT03255070). MEDI4276 is a bi-paratopic tetravalent antibody targeting domains 2 and 4 of HER2 bound to a tubulysin payload with a drug-to-antibody ratio of 4.0 and exhibits a potent bystander effect [29]. MEDI4276 blocks HER2-HER3 heterodimerization in the presence of heregulin β-1. Trastuzumab deruxtecan and RC-48 entered phase 3 trials, although some differences in the overall response rate (ORR) were observed (trastuzumab deruxtecan, 51%; RC-48, 18%). Interstitial lung disease, pneumonitis, and ocular side effects are prominent with ADC treatment. Thus, optimal management and monitoring of these side effects during ADC treatment are important. ADC toxicity is largely driven by the linker/payload composition rather than by the anatomical distribution and expression of the target antigen. Therefore, ADCs sharing the same linker/payload composition tend to have the same maximum tolerable dose even when the target antigen is expressed in different tissues or organ compartments (**Fig. 1**, **Table 1**) [30].

Tyrosine kinase inhibitor (TKI)

Lapatinib is an HER1- and HER2-binding oral agent that blocks HER2 phosphorylation and activation. In contrast to the effect seen in breast cancer patients, it failed to show any clinical benefit in gastric cancer patients in both first- and second-line treatments. Diarrhea was the most common side effect in the first- (58%) and second- (77%) line treatments. Blood lapatinib concentrations were lower in patients who had undergone gastrectomy than in those who had not [31]. Afatinib, neratinib, poziotinib, pyrotinib, and tucatinib are pan-HER inhibitors that irreversibly bind to HER1, HER2, and HER4, and inhibit transphosphorylation. *EGFR*/*HER2* co-amplification is associated with afatinib sensitivity, whereas *MET* amplification is associated with resistance [32]. Patients treated with poziotinib combined with paclitaxel and trastuzumab showed 13 weeks of progression-free survival (PFS) (95% confidence interval [CI], 9.8–21.9) and 29.5 weeks of overall survival (OS)

Table 1. Selected trials with ADC monotherapy

Line	Trial (year)	Agent	Chemotherapy	Phase	Design	Indication	Results					
							ORR (%)	P	PFS (months)	P	OS (months)	P
Chemotherapy + Anti-HER2 monoclonal antibody												
2nd	GATSBY (2017)	T-DM1	Taxane	II/III	T-DM1 vs. C	GC	21 vs. 20	0.84	2.7 vs. 2.9	0.31	7.9 vs. 8.8	0.86
3rd	DESTINY-Gastric01 (2020)	T-DXd	Physician's choice of chemotherapy	II	T-DXd vs. C	GEJ/GC	51 vs. 14	0.001	5.6 vs. 3.5	-	12.5 vs. 8.4	0.01
≥2nd	DESTINY-Gastric02 (2021)	T-DXd	None	II	T-DXd	GEJ/GC	38	-	5.5	-	-	-
≥2nd	NCT03556345 (2021)	RC48	None	II	RC48	GEJ/GC	25	-	4.1	-	7.9	-
≥2nd	ACE-Gastric-01 (2021)	ARX788	None	I	ARX788	GEJ/GC	46	-	-	-	-	-
≥2nd	NCT02576548 (2021)	MEDI4276	None	I	MEDI4276	GC	0	-	1.8	-	6.5	-

ADC = antibody-drug conjugate; C = chemotherapy; GC = gastric cancer; GEJ = gastroesophageal junction.

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(95% CI, 17.9–59.2). Dysregulation of the cyclin D1(CCND1)-cyclin-dependent kinase 4/6 (CDK4/6)-retinoblastoma (Rb) axis contributed to pyrotinib resistance, which was reversed by a CDK4/6 inhibitor [33]. HER2 mutation is found in 3.3%–9.1% of gastric cancers [34,35] and is mutually exclusive of HER2 amplification. In a phase 2 basket trial, neratinib did not show any activity against gastric cancer (NCT01953926) [1]. Poziotinib (NCT04172597) has also been investigated in cancers harboring HER2-activating mutations. Tucatinib is a selective TKI of HER2. It is 1,000-fold more selective than EGFR inhibitors and can minimize EGFR-related toxicities. After obtaining promising data when combined with trastuzumab to treat colon and breast cancers, even in the trastuzumab failure group, a second-line single-arm of paclitaxel, ramucirumab, trastuzumab, and tucatinib is being used in the treatment of gastric cancer, including an exploratory cohort study with serial tissue and cell-free DNA (cfDNA) follow-up (**Fig. 1**).

Novel biologic agent

Bi-specific antibody

Zanidatamab (ZW25) is a bi-specific antibody that binds to the extracellular domain II (pertuzumab-binding site) and IV (trastuzumab-binding site) of HER2 and can activate ADCC. KN026 is a bi-specific antibody that shows preliminary activity in HER2-positive (IHC3+/2+, ISH+) or HER2-low (IHC1+/2+, ISH- or IHC 0/1+, ISH+) tumors. Tebotelimab (MGD013) is a hinge-stabilized bi-specific dual affinity re-targeting (DART®) IgG4k molecule. It binds to two checkpoints, PD-1 and lymphocyte activation gene 3 (LAG3), which are expressed by CD4+ and CD8+ T cells and act as negative regulators of T-cell function. Tebotelimab inhibited their interaction with PD-L1, PD-L2, and MHC II (**Fig. 1**).

Fusion protein

ALX148 (Evorpacept) is a CD47 myeloid checkpoint inhibitor, a fusion protein engineered to contain an inactive Fc domain to minimize hematologic toxicity. CD47 is a self-recognition marker that elicits anti-phagocytic signals upon binding to signal regulatory protein α (SIRPα), a transmembrane protein, on the macrophage surface. Cancer cells with low CD47 expression levels are susceptible to macrophage-mediated destruction [36]. ALX 148 primed CD8 T cells with tumor specificity by increasing antigen presentation by dendritic cells and tumor-associated macrophages [37]. ALX148 is used in combination with trastuzumab or with chemotherapy plus trastuzumab and anti-angiogenesis agent [38]. MM-111 is a bi-specific antibody fusion protein that inhibits HER2-HER3 heterodimerization [39].

CAR-T cell

CAR-T cells are engineered T cells composed of an extracellular antigen-binding domain (single chain fragment variable domain; scFv) and the transmembrane co-stimulatory domain of a tumor-associated antigen in activated T cells. CAR-T cells prepared by transfecting T cells with CD137-anti-HER2 scFv were tested using in vitro and in vivo models with HER2-positive cells. Early clinical trials targeting HER2-poitive solid tumors to assess the safety are underway. Using CAR-T-cell therapy in solid cancers is challenging because of tumor antigen heterogeneity and difficulties in the penetration of CAR-T cells into tumors (**Fig. 1**) [40].

B cells and monocyte-based vaccines (BVACs)

BVACs transfected with the HER2 gene contain 3 components: autologous lymphocytes (B cells and monocytes) as antigen-presenting cells, tumor antigens, and alpha-galactosyl ceramide. BVACs induced natural killer (NK) cells, HER2-specific T cells, and HER2-specific antibodies, with fever as the most common treatment-related adverse event (TRAE) [41].

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CHEMOTHERAPY BACKBONE

In the early 2000s, chemotherapy was proven to prolong patient survival compared with best supportive care. Fluoropyrimidine and platinum became the standard first-line treatment regardless of histology, with an ORR of 35%–45% and an OS of 9–11 months. Based on the variability in practice patterns with regard to the preferred first-line chemotherapy, the fluoropyrimidine plus cisplatin regimen has been extrapolated to different backbones, such as fluoropyrimidine plus oxaliplatin (FOLFOX) and capecitabine plus oxaliplatin (XELOX). In a phase II single-arm trial, trastuzumab in combination with S1 and cisplatin showed 68% of ORR, a PFS of 7.8 months and an OS of 16 months [42]. In a meta-analysis, oxaliplatin plus capecitabine or fluorouracil showed better survival, and S1 plus cisplatin showed equivalent survival with a lower toxicity profile than the standard ToGA regimen (5-fluorouracil plus cisplatin; FP, capecitabine plus cisplatin; XP). The study results indicated that 5-fluorouracil and capecitabine could be replaced with S-1, whereas cisplatin could be replaced with oxaliplatin in association with trastuzumab [43]. Triplet chemotherapy (docetaxel, platinum, and fluoropyrimidine) did not show a survival benefit and resulted in more toxicity events than the ToGA regimen. In real-world settings (HerMES trial), oxaliplatin-based doublet (oxaliplatin and fluorouracil) and triplet (oxaliplatin, fluorouracil, leucovorin, and taxane) therapies showed longer PFS and OS than the ToGA regimen [44].

Options for second-line or later treatment are usually monotherapy, such as irinotecan, paclitaxel, docetaxel, capecitabine, S1, or TAS102, based on the previous lines regardless of HER2 status. The anti-vascular endothelial growth factor receptor (VEGFR) 2 antibody, ramucirumab, improved OS when combined with paclitaxel compared to that of paclitaxel monotherapy (RAINBOW) and was approved by the FDA in November 2014 [45].

MONOTHERAPY

Immune checkpoint inhibitor

In the last decade, breakthroughs have been made by immune checkpoint inhibitors in the treatment of gastric and gastroesophageal junction cancers, as described in the previous section. However, data related to HER2-positive gastric cancer are limited.

Third-line treatment

Nivolumab, an anti-PD-1 antibody, was approved in Japan following the results of the ATTRACTION-2 trial in September 2017 [46], and later in Korea and Taiwan. As the majority of patients in the ATTRACTION-2 trial had low or no HER2 expression, the effectiveness in HER2 positive patients has not yet been fully validated. In an exploratory subgroup analysis of patients previously treated with trastuzumab and assumed to be HER2-positive, the OS was longer in patients administered nivolumab than in those who received placebo (8.3 vs. 3.1 months). In contrast, the OS did not differ between HER2-negative patients (4.8 vs. 4.2 months). Pembrolizumab was approved by the FDA as a third-line treatment and beyond for PD-L1 positive (CPS ≥1) cases in September 2017 [47].

ADC

Second-line treatment

The phase 2/3 GATSBY trial compared T-DM1 with taxane in patients who failed to respond to fluorpyrimidine/platinum plus an anti-HER2 agent [48]. T-DM1 was not superior to

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taxane in OS (7.9 vs. 8.6 months: hazard ratio [HR], 1.15; 95% CI, 0.87–1.51) and PFS (2.7 vs. 2.9 months: HR,1.13; 95% CI, 0.89–1.43). Pre-specified exploratory biomarkers did not demonstrate the superiority of T-DM1 over taxane for survival in any subgroup [49]. However, patients with heterogeneous (30%–79% of the tumor area) or focal (<30% of the tumor area) HER2-positive staining patterns showed lower efficacy of T-DM1 than homogenously expressed cases (>80% of the tumor area). To determine whether the DESTINY-Gastric01 data could be repeated in Western patients, the single-arm phase II DESTINY-Gastric02 trial (NCT04014075) was conducted in Western patients requiring a HER2 central retest following previous trastuzumab treatment. The ORR was 38% (95% CI, 27.3–49.6) and the PFS was 5.5 months (95% CI, 4.2–7.3). The severity of drug-related interstitial lung disease (ILD) was less than or equal to grade 2 [50].

Third-line treatment

The randomized phase II DESTINY-Gastric01 study conducted in Asian patients treated with T-DXd (DS8201a, trastuzumab deruxtecan, Enhertu), who progressed after at least two previous regimens, including trastuzumab, showed OS prolongation (12.5 vs. 8.4 months: HR, 0.59; 95% CI, 0.39–0.88) compared to chemotherapy (paclitaxel or irinotecan) [51]. Importantly, 10% of patients experienced drug-related ILD, but there were no fatal drug-induced ILD events. On January 15, 2021, the FDA approved T-DXd for patients who had received a prior trastuzumab-containing regimen, and it was the first drug to improve survival in patients who failed trastuzumab treatment. The recommended dose is 6.4 mg/kg every 3 weeks, which is higher than the dose for HER2-positive breast cancer. A subsequent exploratory analysis of the HER2-low cohort (IHC2+/ISH− or IHC+1) in the DESTINY-Gastric01 trial reported an ORR of 26.3% and 9.5% and an OS of 7.8 and 8.5 months, respectively, suggesting a clinical benefit of T-DXd in HER2-low patients [52]. A phase II study of RC48-C008 was performed including patients with HER2 overexpressing tumors (IHC2+ or 3+, regardless of the fluorescence in situ hybridization [FISH] result), who received at least 2 prior treatment lines and showed an ORR of 24.8% (95% CI, 17.5–33.3) and an OS of 7.9 months (95% CI, 6.7–9.9) [26]. Leukopenia was the most frequent TRAE. The first-in-human phase I trial of SYD985 showed an ORR of 6% (95% CI, 0.2–30.2) and PFS of 3.2 months (95% CI, 1.6–5.3) [53]. A phase I study of ARX788 in patients with pretreated HER2-positive gastric cancer showed an ORR of 42.9% with 1.3 mg/kg and 46.2% with 1.5 mg/kg treatment dosages [54]. In a phase I trial of MEDI4276 in previously treated HER2-positive patients, none of the gastric cancer patients showed a response [55]. Unfavorable pharmacokinetic profiles and high toxicity are challenging (**Table 1**).

TKI

Second-line or later treatment

Phase I or small phase II trials of small-molecule TKIs are ongoing. Afatinib monotherapy resulted in an ORR of 10%. A phase I trial of pyrotinib combined with SHR6390 showed an ORR of 60% and neratinib is currently in a basket trial (SUMMIT/NCT01953926) [1].

Angiogenesis inhibitor

Second-line or later treatment

In second-line treatments, ramucirumab monotherapy prolonged OS compared to placebo (REGARD), which was approved by the FDA in April 2014 [56]. In the third-line treatment, apatinib (rivoceranib), a VEGFR2-inhibiting TKI, improved OS over placebo in Chinese patients previously treated with at least two lines of treatment [57]; however, a global study (ANGEL) failed to confirm this benefit [58].

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Bi-specific antibody

Second-line or later treatment

In a phase II trial with KN026, the HER2-positive and HER2-low groups showed an ORR of 56% and 14%, respectively, and a duration of response of 9.7 and 6.3 months, respectively [59].

CHEMOTHERAPY-BASED DUAL COMBINATION

Anti-HER2 monoclonal antibody

First-line treatment

The ToGA trial confirmed, for the first time, that chemotherapy (fluorouracil/cisplatin) combined with trastuzumab prolonged PFS (6.7 vs. 5.5 months: HR, 0.71; 95% CI, 0.59–0.85) and OS (13.8 vs. 11.1 months: HR, 0.74, 95% CI, 0.60–0.91) compared to doublet chemotherapy [12]. In a post hoc analysis, the HER2 overexpression subgroup (IHC2+/FISH + or IHC3+) showed an improvement in OS (16.0 vs. 11.8 months: HR, 0.65; 95% CI, 0.51–0.83), suggesting that higher levels of HER2-overexpression are a prerequisite for trastuzumab efficacy. Based on this trial, trastuzumab was the first molecular-targeted antibody drug approved for advanced HER2-positive gastric or gastroesophageal cancer in combination with chemotherapy (cisplatin plus capecitabine or 5-fluorouracil) as a first-line treatment in January 2010 by the European Commission and in October 2010 by the FDA. Phase II trials of trastuzumab with XELOX [60,61], or S1 plus oxaliplatin (SOX) [62] showed promising ORR, PFS, and OS, followed by similar combined trials with HERBIS-1 [42], CGOG1001 [61], and meta-analyses [60,63]. In general, ORR ranged from 39% to 82%, PFS ranged from 5.7 to 11.6 months, and OS ranged from 11.2 to 27.6 months [9]. No increase in adverse cardiac events was found when trastuzumab was added to chemotherapy. The HEROX trial replaced fluorouracil and cisplatin with capecitabine and oxaliplatin with trastuzumab as the first-line treatment [64]. The HELOISE phase III trial, which compared a standard dose (8 mg/kg loading, 6 mg/kg thereafter) to an escalated-dose (8 mg/kg loading, 10 mg/kg thereafter) of trastuzumab with XP combination, did not show a difference in OS, although the serum trough concentrations were increased in the dose-escalated group; thus, a high dose of trastuzumab is not recommended [15]. In the ToGA trial, maintenance treatment was administered after 6 cycles of induction treatment in 54% of the trastuzumab cohort. Although several retrospective studies have demonstrated the efficacy and safety of trastuzumab maintenance, a small prospective study did not show any benefit of maintenance [65]. Thus, owing to the lack of good-quality data, the current guidelines do not recommend maintenance treatment for HER2-positive gastric cancer patients [66,67]. Following the completion of the ToGA trial, trastuzumab-based treatment has been administered clinically as a standard treatment. In the Netherlands, the HER2 testing rate has increased continuously since its introduction in 2010 to 77% in 2016, showing a higher OS in patients with HER2-positive (8.8 months) than that in HER2-negative (7.4 months, and non-tested patients (5.6 months) [68]. A similar trend in improved OS was observed in patients after trastuzumab-based therapy (18.0 months: 95% CI, 15.5–20.6) compared with those who received non-trastuzumab-based treatment (11.2 months: 95% CI, 10.8–11.6) in Korea [69]. As the phase II JOSHUA trial showed higher trough concentrations after treatment with 840 mg of pertuzumab every 3 weeks than a pertuzumab-loading dose of 840 mg followed by 420 mg [70], the phase III JACOB trial compared chemotherapy and trastuzumab plus pertuzumab with chemotherapy and trastuzumab [71]. Although the OS was prolonged (17.5 vs. 14.2 months: HR, 0.84; 95% CI, 0.71–1.00), the JACOB study failed to verify OS improvement by dual inhibition with trastuzumab and pertuzumab (**Table 2**).

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jgc Journal of Gastric Cancer

Table 2. Selected trials with chemotherapy-based dual combinations

Line	Trial (year)	Agent	Chemotherapy	Phase	Design	Indication	Results					
							ORR (%)	P	PFS (months)	P	OS (months)	P
Chemotherapy + Anti-HER2 monoclonal antibody												
1st	ToGA (2010)	Trastuzumab	FP/XP	III	CT vs. C	GEJ/GC	47 vs. 35	0.001	6.7 vs. 5.5	0.0002	13.8 vs 11.1	0.0046
1st	HERBIS-1 (2014)	Trastuzumab	SP	II	CT	GEJ/GC	68	-	7.8	-	16.0	-
1st	CGOG1001 (2016)	Trastuzumab	XELOX	II	CT	GEJ/GC	67	-	9.2	-	19.5	-
1st	HELOISE (2017)	Trastuzumab	XP	III	CT (8 mg) vs. CT (6 mg)	GEJ/GC	59 vs. 57	0.76	5.7 vs. 5.6	0.822	12.5 vs 10.6	0.2401
1st	WJOG7212G (2018)	Trastuzumab	SP	II	CT	GEJ/GC	61	-	5.9	-	16.5	-
1st	HEROX (2019)	Trastuzumab	XELOX	II	CT	GEJ/GC	47	-	7.1	-	13.8	-
1st	KSCC/HGCSG (2020)	Trastuzumab	SOX	II	CT	GC	82	-	7.0	-	27.6	-
1st	JOSHUA (2014)	Pertuzumab	XP	II	C+TP (840 mg) vs. C+TP (420 mg)	GC	88 vs. 55	-	-	-	-	-
1st	JACOB (2018)	Pertuzumab	XP/FP	III	CTP vs. CT	GEJ/GC	18 vs. 14	0.057	8.5 vs. 7.2	0.73	17.5 vs. 14.2	0.057
2nd	T-ACT (2020)	Trastuzumab	Pax	III	PaxT vs. Pax	GEJ/GC	32 vs. 33	1.0	3.7 vs. 3.2	0.33	10.0 vs. 10.5	0.20
Chemotherapy + Tyrosine kinase inhibitor												
1st	LOGiC (2016)	Lapatinib	XELOX	III	CL vs C	GEA	53 vs. 39	0.0031	6.0 vs. 5.4	0.038	12.2 vs. 10.5	0.3492
2nd	TyTAN (2014)	Lapatinib	Pax	III	CL vs C	GC	27 vs. 9	0.001	5.4 vs. 4.4	0.2441	11.0 vs. 8.9	0.1044
Chemotherapy + Bi-specific antibody												
1st	NCT03929666 (2021)	Zanidatamab	XELOX/FP/ mFOLFOX6	II	C+Z	GEA	68	-	-	-	16.4	-
2nd	NCT02892123 (2021)	Zanidatamab	Pax/ Capecitabine	I	C+Z	GEA	60	-	-	-	-	-

C = chemotherapy; FOLFOX = 5-fluorouracil, leucovorin plus oxaliplatin; FP = 5-fluorouracil and cisplatin; GC = gastric cancer; GEA = gastroesophageal adenocarcinoma; GEJ = gastroesophageal junction; L = lapatinib; P = pertuzumab; Pax = paclitaxel; SOX = S1 plus oxaliplatin; SP = S1 plus cisplatin; T = trastuzumab; XELOX = capecitabine plus oxaliplatin; XP = capecitabine plus cisplatin; Z = zanidatamab.

Second-line treatment

The randomized phase II T-ACT study compared paclitaxel versus paclitaxel plus trastuzumab in patients who failed first-line treatment based on a trastuzumab beyond the progression strategy [16]. Most second-line trials performed before the Rainbow trial, which supports the standard of care with paclitaxel and ramucirumab combination, adopted paclitaxel monotherapy as a control arm. There were no differences in PFS and OS between the two treatment groups. For third-line and beyond treatments, trastuzumab plus single-agent chemotherapy has been attempted, but not in a data-driven approach (**Table 2**).

ADC

Second-line treatment

A phase II study comparing T-DM1 plus capecitabine versus T-DM1 in pretreated patients was terminated by the sponsor (NCT01702558).

TKI

First-line treatment

The LOGiC trial compared capecitabine and oxaliplatin plus either lapatinib or placebo. There was no difference in OS (12.2 vs. 10.5 months: HR, 0.91; 95% CI, 0.73–1.12) even though PFS (6.0 vs. 5.4 months) and ORR (53% vs. 39%) showed superiority over placebo. The pre-planned subgroups (Asian and <60 years of age) showed improved OS, whereas gastrectomy showed a negative impact due to the lower absorption of lapatinib [72].
A possible explanation for the failure of the LOGiC study was the patient selection by FISH study alone. Other explanations could be the fact that 23% of patients underwent gastrectomy, which ameliorated lapatinib absorption, and the lack of ADCC activity found by treatment with monoclonal antibodies. A single-arm trial of cisplatin and fluoropyrimidine

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jgc Journal of Gastric Cancer

plus afatinib did not show any benefit compared to ToGA, with an ORR of 42.9%, PFS of 5.0 months and OS of 8.7 months (**Table 2**) [73].

Second-line treatment

The phase III TyTAN study compared lapatinib and paclitaxel with paclitaxel alone in Asian patients. Among them, 6% had previously received trastuzumab treatment. No difference was found in OS (11.0 vs. 8.9 months: HR, 0.84; 95% CI, 0.64–1.11) or PFS (5.4 vs. 4.4 months: HR, 0.85; 95% CI, 0.63–1.13) between the 2 groups. The IHC3+ subgroup showed better OS (HR, 0.59; 95% CI, 0.37–0.93) and PFS (HR, 0.54; 95% CI, 0.33–0.90), whereas no differences were found in the IHC2+ and IHC 0/1+ subgroups, suggesting that optimal screening of HER2 is needed [31]. Temporal heterogeneity in HER2 expression may also have caused negative results (**Table 2**).

Bi-specific antibody

First-line treatment

Zanidatamab in combination with chemotherapy (CAPOX, or cisplatin plus fluorouracil, or modified 5-fluorouracil, leucovorin plus oxaliplatin (mFOLFOX6); NCT03929666), as a first-line treatment, showed a 68% ORR and an OS of 16.4 months (**Table 2**) [74].

Second-line treatment

Zanidatamab monotherapy in a phase I trial (ZW25-101) showed an ORR of 33% and a disease control rate of 61% (NCT02892123). When combined with chemotherapy, zanidatamab plus paclitaxel and zanidatamab plus capecitabine have ORRs of 50% and 57%, respectively (NCT02892123) (**Table 2**) [75]. Based on the promising results of an ongoing phase I study (NCT02892123), the FDA granted a breakthrough designation to zanidatamab with standard chemotherapy as a first-line treatment in November 2020. The FDA (June 2017) and the European Medicines Agency (November 2020) have also designated zanidatamab as an orphan drug for gastric cancer treatment (**Table 2**).

CHEMOTHERAPY-BASED TRIPLE COMBINATION

Combination of chemotherapy, anti-HER2 monoclonal antibody, and immune checkpoint inhibitor

First-line treatment

Treatment strategies for both HER2-positive and negative tumors are rapidly evolving. The scientific rationale for using this triple combination is to facilitate tumor responses via tumor targeting through cross-priming, chemotherapy-induced immunogenic cell death, or modification of the immunosuppressive microenvironment. Proof-of-concept data from two single-arm phase II trials of pembrolizumab in combination with chemotherapy plus trastuzumab have been reported [76,77]. Janjigian et al. [76] reported an ORR of 91% (95% CI, 78–97), 13 months of PFS (95%CI, 8.6–not reached [NR]), and 27.3 months of OS (95% CI, 18.8–NR). PD-L1 positivity and a high tumor mutation burden were not correlated with PFS. No associations were found between the tumor response depth, response duration, and number of clonal neoantigens. PFS was associated with HER2 plasma copy number but not with tissue HER2 copy number, suggesting that plasma copy number better reflected tumor heterogeneity. The PANTHERA trial (NCT02901301) [77] reported a 95% tumor shrinkage rate and an ORR of 77% (95% CI, 61.4–88.2) with a PFS of 8.6 (95% CI, 7.2–16.4) and an OS of 19.3 (95% CI, 16.5–NR) months. Patients with HER2 amplification had longer PFS than

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jgc Journal of Gastric Cancer

patients without amplification (22.0 vs. 7.6 months: HR, 0.28; P=0.01). Moreover, RTK/RAS pathway alterations and a high neoantigen load corrected with HLA-B were associated with better survival. The PFS of both phase II trials compared favorably to the PFS of 6.7 months in patients administered the ToGA regimen, regardless of PD-L1 expression. None of the patients discontinued pembrolizumab because of immune-related adverse events. Consequently, a phase III KEYNOTE-811 study (NCT03615326) was conducted to evaluate the efficacy and toxicity of triple combination therapy (chemo-immuno-targeted agent combination) compared to standard dual combination therapy (chemo-targeted agent combination) [78]. The protocol-specified interim analysis results showed a better ORR (74.4%; 95% CI, 66.2–81.6 vs. 51.9%; 95% CI, 43.0–60.7) compared to standard treatment. Based on this 22.7% improvement in the ORR (95% CI, 11.2–33.7; P=0.00006), the triple combination elicited deeper and more durable responses and long-term remission with tolerable TRAEs, which included pneumonitis and colitis. Among the responders, 50.5% and 44.1% were in the ongoing state of pembrolizumab and placebo treatment groups, respectively. In the interim analysis, 84.4% of enrolled patients had PD-L1 CPS ≥1, although the trial was performed regardless of PD-L1 status, and a numerically different ORR was found in PD-L1-positive patients compared to those with PD-L1-negative tumors. We await the results of whether the PD-L1-enriched group benefited more than PD-L1-negative patients among the HER2 positive group. The FDA granted accelerated approval for pembrolizumab, trastuzumab, and chemotherapy as first-line treatments based on the pre-specified interim analysis of the first 264 patients of the ongoing KEYNOTE-811 trial in May 2021. The National Comprehensive Cancer Network guidelines recommend this combination as a category 2A treatment, regardless of PD-L1 expression, but the European Medicines Agency has yet to decide. If the KEYNOTE-811 trial showed improved OS by adding pembrolizumab to the standard of care, it will become the new standard first-line treatment following the ToGA trial and a rationale for implementing it clinically as a strategy for the treatment of the earlier stages of gastric cancer.

The randomized phase II INTEGA trial (NCT03409848) compared ipilimumab or FOLFOX in combination with nivolumab and trastuzumab, and evaluated the feasibility of triple combination and chemotherapy-free regimens. The primary end-point of 12-month OS rate was 57% (95% CI, 41–71) and 70% (95% CI, 54–81) in the ipilimumab and FOLFOX regimens, respectively, while the OS following treatment with the ipilimumab and FOLFOX regimens was 16.4 (95% CI, 8.3–25.9) and 21.8 (95% CI, 12.7–30.8) months, respectively. HER3+ patients showed longer PFS and OS than those with IHC2+/ISH-positive disease, but the effect of these combinations was independent of PD-L1 expression [79]. An early cfDNA increase of >20% and an acquired truncating *ERBB2* sequence variation have been suggested as markers of a poor clinical course. The clinical outcomes of patients treated with the FOLFOX arm with trastuzumab and nivolumab were better than those of patients treated with the ipilimumab arm with trastuzumab and nivolumab, although the latter showed an OS that was within a numeric range comparable to that in the ToGA trial. These data reconfirmed the importance of a first-line chemotherapy backbone for an early response and durable disease control to optimize patient outcomes, especially in those with a high tumor burden status. The chemotherapy-free regimen results also provide insight to clinicians as they offer an alternative option for patients who are unsuitable for chemotherapy, have a borderline performance status, or possess underlying organ dysfunction or comorbidities. Another phase Ib/II study (NCT04276493) compared two dosages of zanidatamab combined with XELOX and tislelizumab as the first-line therapy. The ORR was 75.8% (95% CI, 57.7–88.9), PFS was 10.9 months (95% CI, 8.2–NR), and the most common TRAEs were diarrhea (24.2%) and increased lipase levels (9.1%). Overall, this treatment regimen showed tolerable safety and efficacy (**Table 3**) [80].

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jgc Journal of Gastric Cancer

Table 3. Selected trials with chemotherapy-based triple and quadruple combinations

Line	Trial (year)	Agent	Chemotherapy	Phase	Design	Indication	Results					
							ORR (%)	P	PFS (months)	P	OS (months)	P
TRIPLE: Chemotherapy + Anti-HER2 monoclonal antibody + Immune checkpoint inhibitor												
1st	NCT02954536 (2020)	Trastuzumab, Pembrolizumab	FP or XP	II	C+T+P	GEA	91	-	13.0	-	27.3	-
1st	PANTHERA (2022)	Trastuzumab, Pembrolizumab	XP	Ib/II	C+T+Pem	GEJ/GC	77	-	8.6	-	19.3	-
1st	KEYNOTE-811 (2021)	Trastumab, Pembrolizumab	FP or XELOX	III	C+T+Pem vs. C+T	GEJ/GC	74 vs. 52	0.00006	-	-	-	-
1st	INTEGA (2022)	Trastuzumab, Nivolumab, Ipilimumab	FOLFOX	II	C+T+N vs. T+N+I	GEA	56 vs. 32		10.7 vs. 3.2		21.8 vs. 16.4	
TRIPLE: Chemotherapy + Anti-HER2 monoclonal antibody + Angiogenesis inhibitor												
1st	NCT01191697 (2015)	Trastuzumab, Bevacizumab	XELOX	II	C+T+B	GEA	77	-	13.9	-	26.9	-
1st	B-DOCT (2016)	Trastuzumab, Bevacizumab	XELOX+Docetaxel	II	C+T+B	GEJ/GC	74	-	10.8	-	17.9	-
TRIPLE: Chemotherapy + Bi-specific antibody + Immune checkpoint inhibitor												
1st	NCT04276493 (2022)	Zanidatamab, Tielslizumab	XELOX	Ib/II	C+Z+Ties	GEJ/GC	76	-	10.9	-	-	-
TRIPLE: Chemotherapy + Anti-HER2 monoclonal antibody + Fusion protein												
2nd	NCT01774851 (2014)	Trastuzumab, MM-111	Pax	II	Pax+T+MM-111 vs. Pax+T	GEA	-	-	9.6 vs. 23.3 weeks	0.01	32.1 vs. 56.1 weeks	0.45
QUADRUPLE: Chemotherapy + Anti-HER2 monoclonal antibody + Angiogenesis inhibitor + Fusion protein												
2nd	ASPEN-01 (2021)	Trastuzumab, ALX148, Ramucirumab	Pax	I	Pax+T+R+ALX148	GEJ/GC	72	-	9.8	-	NR	-

C = chemotherapy; FOLFOX = 5-fluorouracil, leucovorin plus oxaliplatin; FP = 5-fluorouracil and cisplatin; GC = gastric cancer; GEA = gastroesophageal adenocarcinoma; GEJ = gastroesophageal junction; I = ipilimumab; N = nivolumab; P = pertuzumab; Pax = paclitaxel; Pem = pembrolizumab; R = ramucirumab; T = trastuzumab; Ties = tieslelizumab; XELOX = capecitabine plus oxaliplatin; XP = capecitabine plus cisplatin; Z = zanidatamab.

Combination of chemotherapy, anti-HER2 monoclonal antibody, and angiogenesis inhibitor

Two small phase II studies investigated the combination of oxaliplatin, capecitabine, docetaxel, trastuzumab, and bevacizumab [81] and oxaliplatin, capecitabine, trastuzumab, and bevacizumab [82], which showed a prolonged PFS duration of 10.8 and 13.9 months, respectively, and OS duration of 17.9 and 26.9 months, respectively (**Table 3**).

Combination of chemotherapy, anti-HER2 monoclonal antibody, and fusion protein

A second-line randomized trial comparing paclitaxel and trastuzumab plus MM-111 with paclitaxel and ramucirumab was terminated earlier than planned because of poor survival in the MM-111 cohort (NCT01774851) (**Table 3**).

CHEMOTHERAPY-BASED QUADRUPLE COMBINATION

Combination of chemotherapy, anti-HER2 monoclonal antibody, angiogenesis inhibitor and fusion protein

Second-line treatment

The ASPEN-01 phase I study enrolled patients and used four drugs for treatment (ALX148, trastuzumab, ramucirumab, and paclitaxel [ATRP]), which showed an ORR of 72% (**Table 3**) [38].

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CHEMOTHERAPY-FREE COMBINATION

Many ongoing trials aim to determine whether a combination of immune checkpoint inhibitors, angiogenesis inhibitors, and targeted agents could replace traditional chemotherapy in a biomarker-selected group. The involvement of PD-L1 in anti-HER2 treatment supports the rationale for combining anti-HER2 treatment with immune checkpoint inhibitors. Trastuzumab upregulates PD-L1 in cancer cells by interacting with NK cells and stimulating interferon γ secretion from immune effector cells. Trastuzumab also downregulates the release of immunosuppressive factors (CCL2, CCL21, VEGF, and CXCL1) from the microenvironment. Trastuzumab relieves inhibition of the cyclic GMP-AMP synthase (cGAS) stimulator of the interferon gene pathway by recruiting AKT1 and restores the innate immune system. In addition, trastuzumab enhances the HER2-specific T-cell response, activates T-cell and dendritic cell transportation, and induces peripheral memory T-cell expansion. The combination of an immune checkpoint inhibitor and VEGF-directed therapy remains to be explored. Besides HER2 heterogeneity, there is a lack of a clear understanding of biological heterogeneity among immune markers, which limits treatment efficiency (**Table 4**).

Anti-HER2 monoclonal antibody and immune checkpoint inhibitor

First-line treatment

Interim analysis of margetuximab and retifanlimab (an anti-PD-1 inhibitor) in non-MSI-H, PD-L1-positive (CPS ≥1) patients in the phase II/III MAHOGANY trial (NCT04082364) showed an ORR of 53% (95% CI, 36%–69%). Overall, the ORR was similar across the CPS expression subgroups (50.0% in CPS 1–9 vs. 56% in CPC ≥10). The median duration of response was 10.3 months (95% CI, 4.6–NR), and three patients discontinued treatment because of immune-related adverse events. The most common TRAEs are fatigue, infusion-related reactions, rash, and diarrhea [83]. The ORR of the MAHOGNY cohort A (53%) was similar to that of trastuzumab plus chemotherapy, such as in the ToGA (47%), HELOISE (59%), and JACOB (48%) trials, the control group in KEYNOTE-811 (52%), and other chemotherapy-free regimens, including KEYNOTE-062 (15%–25%) and KEYNOTE-061 (16%). Although the ORR exceeded the pre-specified futility boundary (53%), the sponsor discontinued the study because the study design would no longer meet the requirements for approval due to recent significant evolution of chemotherapy combinations, whereas chemotherapy-free trials were less effective than hoped.

Second-line and later treatments

A phase Ib/II trial (CP-MGAH22-05) of margetuximab plus pembrolizumab was conducted as proof-of-concept for synergism in patients who had received at least one previous line of therapy [19]. It showed an ORR of 18.5% (95% CI, 11.2–27.9), 2.7 months (95% CI, 1.61–4.3) of PFS, 12.5 months (95% CI, 9.1–14.1) of OS, suggesting clinically meaningful outcomes in

Table 4. Selected trials with chemotherapy-free regimen

Line	Trial (year)	Agent	Chemotherapy	Phase	Design	Indication	Results		
							ORR (%)	PFS (months)	OS (months)
Double: Anti-HER2 monoclonal antibody + Immune checkpoint inhibitor									
1st	MAHOGANY Cohort A (2022)	Margetuximab	None	II	Margetximab+Retifanlimab	GEA/PD-L1+	53	6.4	NR
≥2nd	CP-MGAH22-05 (2020)	Margetuximab	None	Ib/II	Margetuximab+Pembrolizumab	GEA	18	2.7	12.5
Double: Anti-HER2 bi-specific antibody + Anti-PD-L1/CTLA4 bi-specific antibody									
≥2nd	NCT04040699 (2021)	KN026, KN046	None	I	KN026+KN046	GEJ/GC	86	5.8	-

GC = gastric cancer; GEA = gastroesophageal adenocarcinoma; GEJ = gastroesophageal junction.

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trastuzumab-refractory patients [19]. A trend toward higher ORRs was observed in Asian patients than in American patients (35.7% vs. 8.3%). In an analysis of circulating tumor DNA (ctDNA) subgroups, the ORR was the highest in the IHC3+/PD-L1-positive and HER2 amplification subgroups (44%). These results suggest that HER2 amplification by ctDNA can be used to reassess HER2 status without post-progression tissue biopsy.

Anti-HER2 monoclonal antibody and bi-specific antibody

First-line treatment

KN026 (a bi-specific antibody targeting 2 distinct epitopes on the HER2 receptor) combined with KN046 (an anti-PD-L1 and anti-CTLA4 bi-specific antibody) showed an ORR of 86%. Grade ≥3 TRAEs were neutropenia, thrombocytopenia, immune-mediated endocrinopathy, encephalitis, and infusion-related reactions (3.1% each) (NCT03925974) [84]. Due to the highly immunogenic nature of HER2-positive tumors, a chemotherapy-free regimen with a combination of anti-HER2 treatment and an immune checkpoint inhibitor is a strategy with high effectiveness potential, especially in patients who cannot tolerate chemotherapy.

TKI and CDK4/6 inhibitor

Second-line and later treatments

A phase I trial of pyrotinib combined with a CDK4/6 inhibitor (SHR6390) reported an ORR of 60% in pretreated patients (NCT03480256) [33].

THE ONGOING STUDIES

Anti-HER2 monoclonal antibody-based combination

First-line treatment

The phase II/III MAHOGANY study explored margetuximab plus retifanlimab (an anti-PD-1 IgG4 monoclonal antibody) with and without chemotherapy and margetuximab plus tebotelimab (a bi-specific IgG4 monoclonal antibody of anti-PD-1 and anti-LAG3) with chemotherapy as a first-line therapy (**Table 5**) [21].

Antibody-drug conjugate-based combination

First-line treatment

As T-DXd upregulates MHC class I expression of cancer cells and dendritic cell activation markers, the ongoing DESTINY-Gastric03 trial has multiple comparators: T-DXd monotherapy, T-DXd with chemotherapy, T-DXd with durvalumab (a PD-L1 inhibitor), and T-DXd with chemotherapy and durvalumab. Part 1 will enroll previously treated patients, and a first-line treatment will be provided in part 2 (NCT04379596) (**Table 5**) [85].

Second-line treatment

DESTINY-Gastric04 is a phase III trial comparing second-line T-DXd with paclitaxel plus ramucirumab (NCT04704934). The RC48-007 trial is a phase III study comparing RC-48 with the physician's choice of chemotherapy or apatinib in patients who received at least two prior systemic chemotherapies (NCT04714190) (**Table 5**).

TKI-based combination

First-line treatment

A trial of tucatinib in combination with trastuzumab on the backbone of oxaliplatin-based chemotherapy or pembrolizumab is underway (SGNTUC-024, NCT04430738) (**Table 5**).

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Table 5. Selected ongoing trials

Line	Trial	Agent	Chemotherapy	Phase	Design	Indication	End point
Anti-HER2 monoclonal antibody-based combination							
1st	KETNOTE-811	Trastuzumab, Pembrolizumab	XLOX/FOLFOX	III	C+T+Pem vs. C+T	GEJ/GC	OS and PFS
1st	INTEGA	Trastuzumab, Nivolumab, Ipilimumab	FOLFOX	II	T+N+I vs. T+N+C	GEJ/GC/GEA	OS
1st	MAHOGANY	Margetuximab, Retifanlimab, Tebotalimab	XELOX/mFOLFOX6	II/III	M+RE vs. M+RE+C vs. M+TEB + C vs. M+C vs. M+C+T	GEJ/GC	II: ORR III: OS
ADC monotherapy/ADC-based combination							
1st	DESTINY-Gastric03	T-DXd, Trastuzumab, Durvalumab	5FU/Capecitabine/FP/XP/XELOX/FOLFOX	Ib/II	C+T vs. T-D vs. T-D+C vs. T-D+C+Du vs. T-D+Du	GEJ/GC	ORR
2nd	DESTINY-Gastric04	T-DXd	Paclitaxel, Ramucirumab	III	T-D vs. C+R	GEJ/G	OS
3rd	NCT04714190	RC48	Paclitaxel, Irinotecan, Apatinib	III	RC48 vs. C	GC	OS
Tyrosine kinase inhibitor-based combination							
1st	SGNTUC-024	Tucatinib, Trastuzumab, Pembrolizumab	FOLFOX, XELOX	Ib/II	C+T+TU, C+T+TU+Pem, T+TU+Pem	GI	DLT
2nd	MOUNTAINEER-02	Tucatinib, Trastuzumab	Paclitaxel, Ramucirumab	II/III	C+R+T+TU vs. C+R	GEJ/GC	OS/PFS
2nd	NCT02501603	Afatinib	Paclitaxel	II	C+AF	GEJ/GC	PFS
2nd	NCT01746771	Poziotinib	Paclitaxel	I/II	C+T+PO	GEJ/GC	ORR
Bi-specific antibody-based combination							
1st	HERIZON-GEA-01	Zanidatamab, Tieslelizumab	XELOX/FP/mFOLFO6	III	C+T vs C+Z vs. C+Z+Ties	GEJ/GC	OS
Fusion protein-based combination							
≥2nd	ASPEN-06	ALX148 Trastuzumab	Paclitaxel Ramucirumab	III	C+R+T+ALX vs. C+R	GEJ/GC	OS
HER2 mutation targeting monotherapy							
≥2nd	NCT04639219	TDXd	None	II	T-D	HER2 mutation solid cancer	ORR
≥2nd	NCT04172597	Poziotinib	None	II	PO	HER2 mutation solid cancer	ORR

AF = afatinib; C = chemotherapy; Du = durvalumab; FOLFOX = 5-fluorouracil, leucovorin plus oxaliplatin; FP = 5-fluorouracil and cisplatin; GC = gastric cancer; GEA = gastroesophageal adenocarcinoma; GEJ = gastroesophageal junction; GI = gastrointestinal; I = ipilimumab; L = lapatinib; N = nivolumab; P = pertuzumab; Pax = paclitaxel; Pem = pembrolizumab; PO = poziotinib; R = ramucirumab; RE = retifanlimab; SOX = S1 plus oxaliplatin; SP = S1 plus cisplatin; T = trastuzumab; T-D = trastuzumab deruxtacen; TEB = tebotalimab; TU = tucatinib; XELOX = capecitabine plus oxaliplatin; XP = capecitabine plus cisplatin; Z = zanidatamab.

Second-line treatment

Phase II/III MOUNTAINEER-02 tests paclitaxel, ramucirumab, and the combination of trastuzumab and tucatinib in phase II and compares the four drugs to standard paclitaxel plus ramucirumab treatment in phase III (NCT04499924) [86]. Two afatinib or poziotinib phase II trials, in combination with paclitaxel, are ongoing (NCT0152276 and NCT02501603) (**Table 5**).

Bi-specific antibody-based combination

First-line treatment

Trials of zanidatamab plus chemotherapy of the physician's choice (FP, mFOLFOX6, XELOX) (NCT03929666) and zanidatamab in combination with chemotherapy and tislelizumab (an anti-PD-1 monoclonal antibody) have been initiated (HERIZON-GEA-01, NCT04276493) (**Table 5**).

Fusion protein-based combination

Second-line treatment

The ASPEN-06 phase III trial compared ALX148 (evorpacept), trastuzumab, ramucirumab and paclitaxel (ATRP) with standard-of-care paclitaxel and ramucirumab (NCT05002127) (**Table 5**).

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jgc Journal of Gastric Cancer

Vaccine-based combination

Second-line or later treatments

A HER2-directed vaccine (TAEK-VAC-HerBy) trials in combination with a HER2-targeting antibody (trastuzumab or pertuzumab) (NCT04246671) or a peptide vaccine (NCT02276300) to induce humoral immunity against HER2-expressing cancer are ongoing.

MECHANISM OF RESISTANCE TO ANTI-HER2 TREATMENT

The inevitable resistance to anti-HER2 treatment remains an important issue when treatments proven to be effective in breast cancer continue to fail in treating gastric cancer and highlights the distinct HER2 biology of gastric cancer. The frequency of intratumoral HER2 heterogeneity has been reported to be 14%–79% and 23%–54% by IHC and FISH analyses, respectively [87,88]. This heterogeneity is caused by biological inconsistencies in HER2 expression and interobserver variability between local and central results based on a modified scoring system developed specifically for gastric cancer [89,90]. The majority of the discrepancies were observed in HER2-positive cases by local evaluation, which were interpreted as negative when reviewed at a central laboratory. Variability in the ORR (32%–68%) among trastuzumab plus standard chemotherapy as first-line treatment implies that not all patients with HER2-positive tumors benefit from trastuzumab treatment [42,91]. As there are no guidelines for assessing the type and grade of heterogeneity, an optimized threshold of ≥40% HER2 positive cancer cells and a HER2/CEP17 ratio of >3.0 were suggested for determining trastuzumab benefit. In the case of HER2+ or less (HER1+, HER-0), a HER2/CEP 17 ratio of ≥3.69 and a HER2 copy number of >7.75 suggest better outcomes of trastuzumab treatment [92]. Patients with heterogeneous HER2 expression in the primary tumor have shorter PFS after trastuzumab-containing first-line treatment than those with homogenous HER2 expression [93]. Heterogeneity of 5.7%–10% was observed between the primary and metastatic lesions [94,95], which increased the HER2 false-positive rate. Loss of HER2 expression or mutation after anti-HER treatment is another cause of treatment failure. The T-ACT trial showed that 69% of patients lost HER2 amplification during disease progression after first-line treatment with trastuzumab-containing regimen failure [16]. The GASTHER3 trial showed that 41% of patients converted to HER2 negative after first-line treatment failure, and three patients who received T-DM1 as a second-line treatment showed no response [96], suggesting that biological changes during anti-HER2 treatment could be the basis of acquired resistance. Loss of HER2 positivity occurred more frequently in the IHC 2+ group, and mutations were found mainly in the kinase domain of HER2 (kinase domain 66%, extracellular domain 26%, and transmembrane domain 8%). The concordance of HER2 alterations between cfDNA and metastatic tumors (88%) suggests the potential of cfDNA as a patient selection criterion and a treatment monitoring marker [97]. As liquid biopsy guarantees deeper insight into heterogeneity, ctDNA can be a complementary tool in predicting real-time tumor response to anti-HER2 treatment and monitoring [98], especially when the specimen volume or tissue accessibility is an issue. Alterations in the HER2 receptor secondary to aminotruncation caused a loss of the binding region. The failure of the heterodimerization of HER2 with HER1, HER2, and HER4, and with IGFR1 and IGFR2, which are found mainly in breast cancer, may also lead to resistance in gastric cancer. Sustained activation of the intracellular signaling pathways of HER2, such as MAPK/ERK and PI3K/mTOR, or cross-talk pathways, such as hepatocyte growth factor (HGF)/MET, TGF-β/ZEB2, the FGFR family, and the abnormal overexpression of CCNE1, induce resistance to anti-HER2 treatment. Among them, aberrant activation of the Akt/

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jgc Journal of Gastric Cancer

mTOR pathway, amplification of MET or hyperactivation of HGF, and co-amplification of HER1 and HER2 are linked to primary resistance. Other alterations, such as acquired HER2 mutation, EGFR amplification, FGFR2 fusion, HER3 overexpression, activation of MAP/ERK downstream pathways, and epithelial-to-mesenchymal transition, contribute to the development of acquired resistance. miRNAs are non-coding RNAs that regulate target genes at the post-transcriptional level may underspin resistance [99]. Most anti-HER2 monoclonal antibodies bind to Fcγ receptors (FcγR) on natural killer cells, antigen-presenting cells, effector immune cells. Changes in the microenvironment, such as FcγR genetic variations, tumor antigen expression levels, the density and activity of immune cells, and local antibody concentrations, which block monoclonal antibody binding to immune cells, determine the activity of immunotherapy [100]. These biological and clinical factors cause challenges in the spatial and temporal heterogeneity of HER2 and emphasize the importance of reassessing HER2 status for rechallenge with anti-HER2 treatment after treatment failure.

CONCLUSION

Currently, trastuzumab plus chemotherapy is the first-line treatment for HER2-positive gastric cancer patients. Anti-HER2 therapy is generally more effective when combined with chemotherapy or immunotherapy. The chemotherapy backbone is very important from a synergism, feasibility, and safety point of view. The triple combination of chemotherapy, anti-HER2 treatment, and immune checkpoint inhibitors is likely to be licensed within a couple of years, replacing the ToGA regimen (**Fig. 2**). Numerous ADCs, cell therapies, and vaccines that activate the immune system are in early phase trials, except for trastuzumab deruxtecan, which was the first ADC licensed by the FDA for use in previously treated patients. Some early ADC trials were terminated owing to toxicity issues. Interstitial pneumonitis and

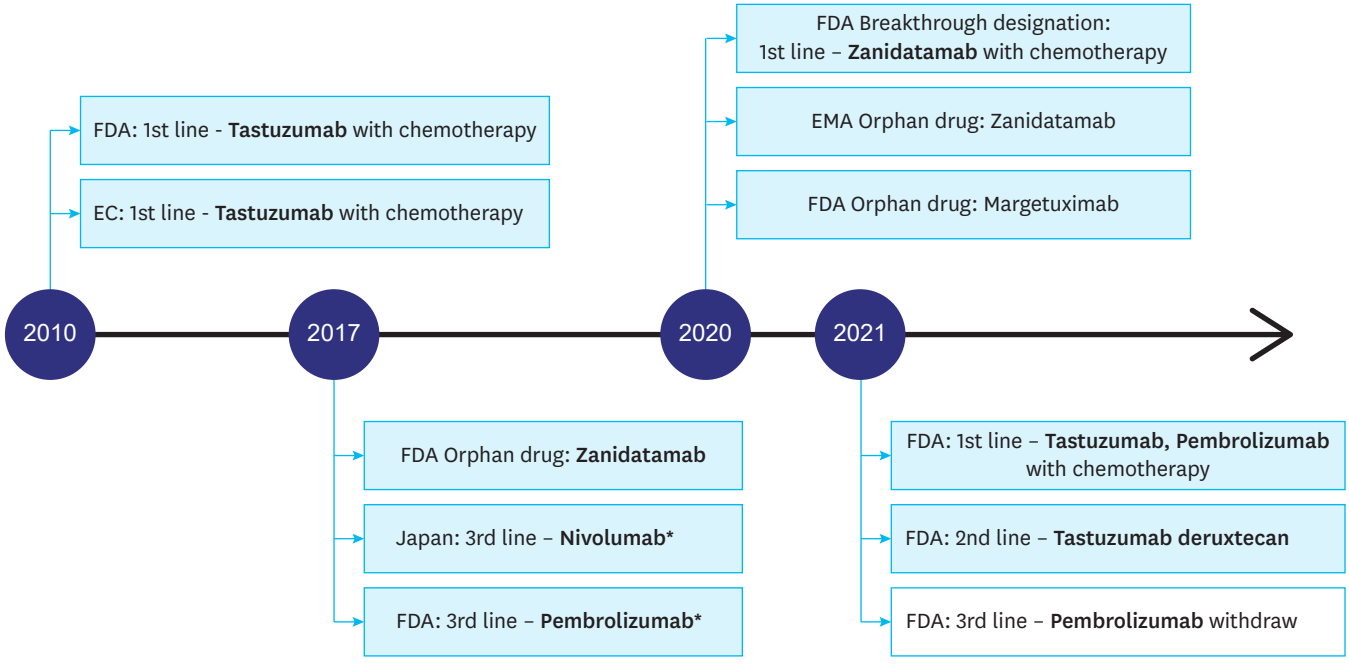

Fig. 2. History of drug approvals for the treatment of HER2-positive gastric cancer.
HER2 = human epidermal growth factor receptor 2; EC = European Commission; FDA = Food and Drug Administration; EMA = European Medicines Agency.
*Regardless of HER2 state for the third line.

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jgc Journal of Gastric Cancer

<table>
<tr><th>1st line</th><th>2nd line</th><th>3rd line</th></tr>
<tr><td>● Recommendation:
- Fluoropyrimidine (5-fluorouracil, capcitabine) + Platinum (cisplatin) + trastuzumab + pembrolizumab
- Fluoropyrimidine (5-FU, capecitabine, S1) + Platinum (cisplatin, oxaliplatin) + trastuzumab</td><td>● Recommendation:
- Trastuzumab deruxtecan
- Ramucirumab ± paclitaxel</td><td rowspan="2">● Options regardless of HER2 state:
- Nivolumab
- Irinotecan
- FOLFIRI
- Taxane
- TAS102
- Ramucirmab
- Zanidatamab
- Pembrolizumab or Nivorumab + ipilimumab in MSI-H</td></tr>
<tr><td>● Options:
- Pembrolizuab + margetuximab ± chemotherapy</td><td>● Options:
- Tucatinib + trastuzumab
- Margetuximab + pembrolizumab
- Zanidatamab
- Taxane
- Irinotecan
- FOLFIRI</td></tr>
</table>

Fig. 3. Recommendations for each line of treatment in HER2-positive gastric cancer.
HER2 = human epidermal growth factor receptor 2; FOLFIRI = 5-fluorouracil, folinic acid, and irinotecan; MSI = microsatellite instability.

ocular side effects are particularly important. Although chemotherapy-free regimens with targeted therapy and immunotherapy may not have shown a significant improvement in treatment, small advancements have created a strategy of precision medicine, whereas chemotherapy was the only standard treatment. Among TKIs, tucatinib is the leading agent used in combination with trastuzumab in second-line settings. Currently, there is no approved treatment for HER2 mutations. The optimal cutoff for HER2 overexpression needs to be thoroughly investigated. A reassessment of HER2 status is needed after disease progression in anti-HER2 treatment. As targeted treatment has disadvantages in molecularly heterogeneous cancers, a new treatment strategy is needed after understanding the mode of action, sensitivity, and resistance mechanisms. As a general guideline, patients who need systemic treatment should receive chemotherapy-based treatment with targeted agents, anti-angiogenic agents, immune checkpoint inhibitors, or their combinations with optimal dose modifications (**Fig. 3**).

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