Trastuzumab deruxtecan for the treatment of patients with HER2-positive gastric cancer

Ther Adv Med Oncol
2021, Vol. 13: 1–9
DOI: 10.1177/1758835920986518

Daisuke Kotani and Kohei Shitara

***Abstract*:** Trastuzumab deruxtecan (T-DXd) is a novel anti-human epidermal growth factor receptor 2 (HER2) antibody–drug conjugate composed of a monoclonal anti-HER2 antibody and a topoisomerase I inhibitor, DX-8951 derivative (an exatecan derivative). T-DXd showed potential anti-tumor activities in HER2-positive gastric cancer cell lines and xenograft models. In the randomized, phase II trial DESTINY-Gastric01, T-DXd demonstrated a significantly higher objective response rate as a primary endpoint and a longer overall survival as a secondary endpoint in patients with pretreated HER2-positive advanced gastric cancer (AGC). Although adverse events caused by T-DXd were generally manageable, approximately 10% of patients experienced treatment-related interstitial lung disease. Based on the results of the DESTINY-Gastric01 trial, T-DXd was approved for HER2-positive pretreated AGC in Japan. This study reviews the preclinical and clinical data of T-DXd for treating HER2-positive gastric cancer.

Keywords: gastric cancer, HER2, T-DXd, trastuzumab deruxtecan

Received: 5 October 2020; revised manuscript accepted: 17 December 2020.

Introduction

Gastric cancer is the fifth most common type of cancer, with approximately 1,030,000 new cases diagnosed each year; moreover, it is the third leading cause of cancer-related death worldwide.[1]

Systemic chemotherapy is the standard treatment for patients with unresectable advanced gastric cancer (AGC). Combination therapy, including the combination of a fluoropyrimidine agent and a platinum agent [plus trastuzumab for human epidermal growth factor receptor 2 (HER2)-positive cases], is commonly used as a first-line treatment for AGC.[2–4] Furthermore, according to the RAINBOW study, paclitaxel plus ramucirumab (an anti-vascular endothelial growth factor receptor 2 monoclonal antibody) is recommended as a second-line treatment because this combination showed an improvement in overall survival (OS) compared with paclitaxel monotherapy.[5] In the third-line or later settings, nivolumab, a programmed death-1 monoclonal antibody, or trifluridine/tipiracil prolonged OS over placebo plus best supportive care.[6,7] More recently, in a first-line setting, pembrolizumab, a programmed death-1 monoclonal antibody, was not superior in combination with chemotherapy compared with chemotherapy alone for OS in both PD-L1 combined positive score (CPS) $\geqslant$1 and CPS$\geqslant$10 in the KEYNOTE-062 study.[8] In contrast, nivolumab plus chemotherapy significantly improved OS and progression-free survival (PFS) compared with chemotherapy alone in HER2-negative or HER2-unknown patients with CPS$\geqslant$5 in the CheckMate 649 study.[9] Moreover, OS was also prolonged in patients with CPS$\geqslant$1 for all enrolled patients. Based on these results, nivolumab plus chemotherapy will be considered as a new first-line standard treatment in patients with HER2-negative AGC. Meanwhile, in an Asian phase III trial of the ATTRACTION-4 study, nivolumab plus chemotherapy demonstrated a statistically significant improvement in PFS but not in OS, with a higher proportion of patients receiving subsequent therapy compared with the CheckMate 649 study (66% *versus* 39%).[10]

Correspondence to:
Kohei Shitara
Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba, 277-8577, Japan
kshitara@east.ncc.go.jp

Daisuke Kotani
Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan

The HER2 protein is overexpressed in 10–20% of patients with AGC.[11–15] Trastuzumab, an anti-HER2 monoclonal antibody, improved OS [median 13.8 *versus* 11.1 months; hazard ratio (HR) 0.74] and PFS (median 6.7 *versus* 5.5 months) when used in combination with first-line chemotherapy (capecitabine or 5-fluorouracil and cisplatin) *versus* chemotherapy alone in the phase III ToGA trial for patients with HER2-positive AGC defined as immunohistochemistry (IHC) 3+ or fluorescence *in situ* hybridization (FISH)-positive (ERBB2/CEP17 ⩾2.0). The survival benefit of trastuzumab was pronounced in IHC 3+ or HC 2+ FISH-positive patients (median OS, 16.0 *versus* 11.8 months; HR 0.65), which is the current consensus for the definition of HER2-positive patients.[4]

However, although several HER2-targeted therapies such as trastuzumab emtansine (T-DM1), lapatinib and pertuzumab have been approved for HER2-positive breast cancer in the adjuvant and metastatic settings, these agents have failed to demonstrate significant survival benefits in patients with HER2-positive AGC.[16–19]

More recently, a novel anti-HER2 antibody–drug conjugate (ADC), trastuzumab deruxtecan (T-DXd), demonstrated significant improvement in the objective response rate (ORR) and OS compared with standard chemotherapy in patients with previously treated HER2-positive AGC.[20]

The purpose of this review was to recapitulate the preclinical and clinical data on T-DXd for the treatment of gastric cancer.

Clinical development of HER2-targeted therapy for AGC before T-DXd

Several HER2-targeted therapies have been investigated after the success of trastuzumab was demonstrated in the ToGA trial.

Lapatinib, a tyrosine kinase inhibitor that binds to the intracellular tyrosine kinase domains of epidermal growth factor receptor and HER2, has been shown to block autophosphorylation and downstream signaling. Furthermore, lapatinib has been investigated in first- or second-line settings in AGC patients with *HER2* amplification by FISH. In the TRIO-013/LOGiC trial, 545 patients with HER2-positive AGC were randomized to receive either standard chemotherapy, capecitabine and oxaliplatin, or standard chemotherapy plus lapatinib in the first-line setting. However, the primary endpoint of OS was not statistically improved with the addition of lapatinib (median 12.2 *versus* 10.5 months, HR 0.91, $p = 0.349$).[18] In a second-line setting, the TyTAN trial assessed the survival benefit of lapatinib plus paclitaxel in *HER2*-amplificated AGC regardless of the HER2 IHC score. The median OS was 11.0 months for lapatinib plus paclitaxel *versus* 8.9 months for paclitaxel alone with no significant difference ($p = 0.104$).[17]

Pertuzumab is a humanized monoclonal antibody that binds to the dimerization domain of HER2 and inhibits HER2 heterodimerization. A phase III JACOB trial that assessed the effect of adding pertuzumab to trastuzumab plus first-line chemotherapy for HER2-positive AGC patients failed to achieve the primary endpoint of OS.[19]

Trastuzumab emtansine (T-DM1) is an ADC composed of trastuzumab and a tubulin polymerization inhibitor, DM1. Although T-DM1 illustrated remarkable efficacy in HER2-positive metastatic breast cancer, no statistically significant survival benefit of T-DM1 was demonstrated compared with standard taxane chemotherapy in patients with pretreated HER2-positive AGC in the GATSBY trial (OS, median 7.9 *versus* 8.6 months; PFS, median 2.7 *versus* 2.9 months).[17]

Several potential mechanisms of resistance to HER2-targeted therapy were indicated in the previous studies. An exploratory analysis of the GATSBY trial suggested that patients with higher HER2 expression or gene amplification experienced a better treatment effect from T-DM1 than those with a lower HER2 status.[21] The heterogeneity of HER2-positive AGC with a downregulation in HER2 status post-progression on trastuzumab could explain the discrepant efficacy between patients with HER2-positive metastatic breast cancer and AGC. The focality of HER2 overexpression might attenuate T-DM1 activity, which was unable to induce a bystander effect for surrounding HER2-negative cells due to a non-cleavable linker.[22–24] Furthermore, genomic alterations including deletion of *ERBB2* exon 16 and mutations in the receptor tyrosine kinase, RAS, and PI3K pathways were reported as intrinsic and/or acquired resistance to trastuzumab.[25] In the phase II study of combining lapatinib with capecitabine and oxaliplatin as neoadjuvant therapy for HER2-positive AGC, baseline *CCNE1* amplification, which was present in 40% of HER2-positive tumors, was also associated with a

trend of lower response rate to study treatment.[26] Therefore, new agents that overcome these resistance mechanisms are necessary to improve the outcomes of HER2-positive gastric cancer.

Preclinical characteristics and early development of T-DXd

T-DXd is a novel HER2-targeting ADC composed of a humanized anti-HER2 antibody, an enzymatically cleavable peptide-linker, and a topoisomerase I inhibitor. After binding to HER2 on tumor cells, T-DXd is internalized and the linker is cleaved within the tumor cell by lysosomal enzymes. Once released, the DX-8951 derivative (DXd), which has more potent efficacy than irinotecan as a topoisomerase I inhibitor against various tumor xenograft models, binds to and inhibits topoisomerase I-DNA complexes, leading to the inhibition of DNA replication, cell cycle arrest, and tumor cell apoptosis. T-DXd has a higher drug-to-antibody ratio with homogenous conjugation compared with T-DM1. The high stability of the linker-payload of T-DXd in the plasma was demonstrated *in vitro* and *in vivo*, and the short half-life of DXd in the systemic circulation was also shown *in vivo*.[27] Notably, it has a bystander killing effect *in vitro* and in mouse xenograft models. In the presence of neighboring HER2-positive cells, adjacent HER2-negative tumor cells were also killed by T-DXd. Furthermore, T-DXd had no effect on non-adjacent HER2-negative tumor cells. T-DXd induced dose-dependent cell growth inhibition and reduced the tumor volume in an HER2-positive gastric cancer NCI-N87 xenograft model. Furthermore, T-DXd showed efficacy in HER2-positive T-DM1-resistant gastric cancer xenograft models.[28]

A low concentration of DXd was released in the plasma; with increasing doses, the clearance rate decreased and the half-life was prolonged in cynomolgus monkeys. These results indicate that T-DXd has a dose-dependent pharmacokinetic profile. The biodistribution of T-DXd was restricted to the systemic circulation, and T-DXd was mainly excreted into the feces.[29] T-DXd was not vulnerable to *UGT1A1* metabolism, in contrast to other topoisomerase I inhibitors including irinotecan, according to an analysis of the DXd concentration in the bile.[29–32]

The main adverse events in cynomolgus monkeys included bone marrow suppression, gastrointestinal toxicities, and lung toxicities. Anemia and leukopenia only occurred at a dose of 78.8 mg/kg, and lung toxicities were induced at doses over 30 mg/kg. The highest non-severely toxic dose for cynomolgus monkeys was 30 mg/kg, and the preclinical safety profile was accepted for entry into human trials.[27]

Phase I study

A dose-escalation part of a phase I trial of T-DXd was performed in patients with breast, gastric, or gastro-esophageal carcinomas refractory to standard therapy regardless of HER2 status to evaluate safety and identify the maximum tolerated dose (MTD) or recommended phase II dose (RP2D). Twenty-four patients were enrolled and received T-DXd. T-DXd was administered intravenously once every 3 weeks with a dose ranging from 0.8 to 8.0 mg/kg. The MTD was not reached, and there were no dose-limiting toxic effects. Based on the safety and activity profiles, the most likely recommended phase II dosing scheme was 5.4 or 6.4 mg/kg. Gastrointestinal and hematological adverse events were the two most common types of adverse events. Among the 23 evaluable patients, including six with low HER2-expressing tumors, objective responses and disease control were achieved in 10 [43%, 95% confidence interval (CI): 23.2–65.5)] and 21 (91%, 95% CI: 72.0–98.9) patients, respectively. A pharmacokinetic analysis demonstrated a dose-dependent half-life and a median half-life of 5.7 days. Dose-dependent increases of the drug exposure area under the receiver operating characteristic curve (AUC) and maximum serum concentration (C_{max}) were also shown in doses ranging from 3.2 to 8 mg/kg. Although DXd is primarily metabolized by CYP3A4, no clinically significant drug interactions were observed during the co-administration with CYP3A4 inhibitors.[33]

Based on the results of the dose-escalation part of the phase I trial, a dose-expansion phase I trial was conducted. Among 44 patients with HER2-positive gastric or gastro-esophageal junction cancer treated at a dose of 5.4 or 6.4 mg/kg, 19 (43.2%; 95% CI 28.3–59.0) had a confirmed objective response. The median PFS was 5.6 months and the median OS was 12.8 months. The most frequent grade 3 or worse treatment-emergent adverse events were anemia (30%), neutropenia (20%), platelet decrease (18%), and leucopenia (16%).[34] These result suggest clinical anti-tumor activity and safety in patients with HER2-positive AGC.

Pivotal phase II study in patients with HER2-positive AGC

The DESTINY-Gastric01 trial was an open-label, randomized, phase II trial that assessed the efficacy and safety of T-DXd (6.4 mg/kg, every 3 weeks) *versus* a physician's choice of chemotherapy (irinotecan or paclitaxel) in patients with HER2-positive gastric or gastro-esophageal junction cancer who progressed after two or more previous therapies including trastuzumab. HER2 status was centrally assessed in the most recently available tumor samples and was diagnosed as high (score of 3+ or score of 2+ with positive results on *in situ* hybridization) or low (score of 2+ with negative results on *in situ* hybridization or score of 1+). The primary endpoint was the objective response by independent central review according to the Response Evaluation Criteria in Solid Tumors version 1.1 in patients with high-level HER2-positive disease. The key secondary endpoint was OS, which was statistically evaluated hierarchically if the primary endpoint was significant. A total of 188 patients underwent randomization in the primary cohort of high-level HER2-positive disease. Additionally, 80% of the patients were enrolled from Japan and 20% were from Korea. As defined in the protocol, all patients had received fluoropyrimidine, platinum, and trastuzumab before enrollment. Furthermore, more than 86% of patients had previously received taxane agents, 72% had received ramucirumab, and 33% had been treated with PD-1 or PD-L1 inhibitor. The ORR as the primary endpoint was significantly higher in the T-DXd group compared with the physician's choice group (51% *versus* 14%, $p < 0.001$). The confirmed ORR was also higher in the T-DXd *versus* physician's choice group (43% *versus* 12%). Notably, nine patients achieved a confirmed complete response with T-DXd, which is unexpected in this salvage treatment line setting. The median duration of response was 11.3 months with T-DXd and 3.9 months with chemotherapy. The disease control rate was also higher with T-DXd (85.7%). This trial demonstrated a statistically significant improvement in OS as a key secondary endpoint with T-DXd (median OS 12.5 *versus* 8.4 months, HR 0.59, $p = 0.01$). The PFS was also longer with T-DXd than with chemotherapy (median PFS 5.6 *versus* 3.5 months; HR 0.47). In a prespecified subgroup analysis, patients with HER2 score of 3+ disease achieved a higher objective response compared with those with score of 2+ with positive results on *in situ* hybridization (58% *versus* 29%). OS also tended to be more improved in patients with HER2 score of 3+ disease than those with score of 2+ with positive results on *in situ* hybridization.[20]

More recently, the results of an exploratory cohort from the DESTINY-Gastric01 study enrolling HER2-low expression were presented at the European Society of Medical Oncology 2020. Twenty and 24 patients were enrolled in the IHC2+/ISH– and IHC1+ cohorts, respectively. The confirmed ORR was 26.3% in the IHC2+/ISH– cohort and 9.5% in the IHC1+ cohort. The median PFS was 4.4 and 2.8 months, and the median OS was 7.8 and 8.5 months, respectively.[35] The adverse events observed were generally manageable and comparable to those observed in previous studies and in the DESTINY-Gastric01 primary cohort.[20] These results suggest that IHC status might be important for predicting the efficacy of T-DXd, but they also suggest that T-DXd has some clinical activity against T-DXd for HER2-low gastric cancer. Additional biomarker analyses using fresh biopsy samples or ctDNA are now ongoing.

Safety

Although the safety profile of T-DXd in patients with AGC is generally manageable, a higher proportion of patients discontinued therapy owing to adverse events in the T-DXd group compared with the physician's choice group (15% *versus* 6%) in the DESTINY-Gastric01 trial, indicating some points to note for physicians. The most common grade 3 or higher adverse events were neutropenia (51% in the T-DXd group *versus* 24% in the physician's choice group), anemia (38% *versus* 23%), leucopenia (21% *versus* 11%), and decreased appetite (17% *versus* 13%). There was no significant difference in the frequency of febrile neutropenia between the two groups (5% *versus* 3%). Notably, 12 patients (10%) had T-DXd-related interstitial lung disease (ILD) or pneumonitis as determined by an independent adjudication committee, with a median time to first onset of 84.5 days (range, 36–638).[20] Therefore, important points for managing the safety of T-DXd in clinical practice are summarized below.

ILD or pneumonitis

ILD or pneumonitis is a notable toxicity resulting from treatment with T-DXd. T-DXd-related lung toxicities including ILD or pneumonitis were observed in 10% of patients in the DESTINY-Gastric01 trial.[20] Additionally, ILD occurred in 14% of HER2-positive breast cancer patients in the DESTINY-Breast01 trial.[36] A pooled analysis of 655 patients who received T-DXd from seven

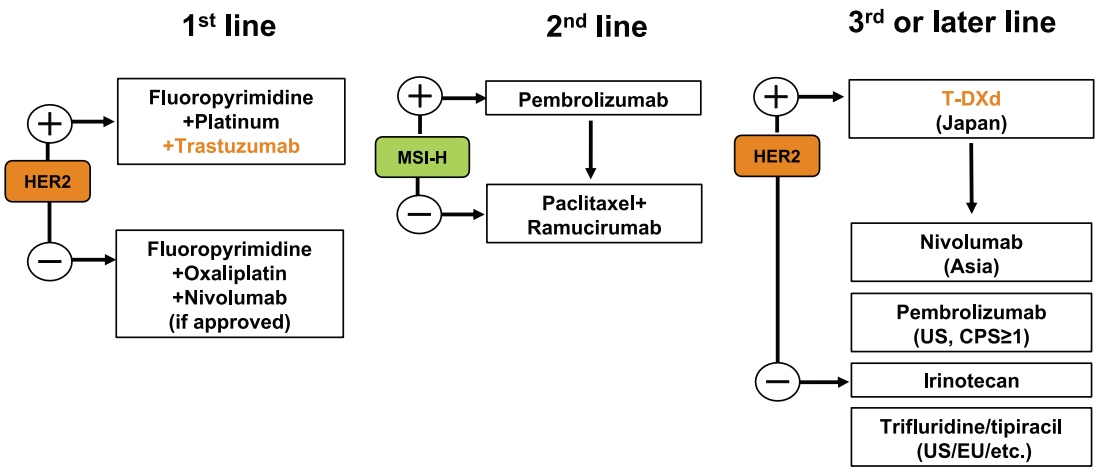

Figure 1. Treatment strategy for advanced gastric cancer.

clinical trials reported that 66 of 665 cases (9.9%) were diagnosed as ILD by investigators, with 13 cases (2.0%) being grade 3 or higher. The ILD adjudication committee determined that 30 of 66 cases were drug-related ILD. Life-threatening events were uncommon (0.4%) at a recommended dose of 5.4 mg/kg for breast cancer, and careful monitoring for respiratory symptoms including dyspnea, cough, chest tightness, or fever is still important. Furthermore, although the analyzed sample size was small, a higher dose of T-DXd and a Japanese origin were associated with an increased risk of ILD after adjusting for the patient's baseline characteristics.[37] If ILD is suspected in patients receiving T-DXd, early diagnosis with appropriate imaging, laboratory tests, and pulmonary consultation, in addition to the interruption or discontinuation of T-DXd, are necessary, and administration of corticosteroids are recommended.

Nausea and vomiting

There was no significant difference in the frequency of grade 3 or higher nausea between the T-DXd group and the physician's choice group in the DESTINY-Gastric01 trial. Additionally, no patients experienced grade 3 or higher vomiting in either group. However, any grade of nausea and vomiting tended to be higher in the T-DXd group compared with the physician's choice group (nausea, 63% *versus* 47%; vomiting, 26% *versus* 8%).[20] Therefore, T-DXd was classified as having a moderate emetic risk, with a 30–90% frequency of emesis in the absence of effective antiemetic prophylaxis, in the National Comprehensive Cancer Network (NCCN) Guidelines version 2, 2020.[38] Although there are no available data regarding the proactive prevention of chemotherapy-induced nausea and vomiting related to T-DXd treatment, the combination of dexamethasone, serotonin (5HT3) receptor antagonists, and/or neurokinin 1 (NK1) antagonists or olanzapine should be recommended based on the NCCN guidelines.[38]

Future perspectives

Based on the results of the DESTINY-Gastric01 trial, T-DXd was approved in Japan for the treatment of patients with HER2-positive unresectable advanced or recurrent gastric cancer that has progressed after chemotherapy. T-DXd is now recommended in the Japanese Gastric Cancer Association treatment guidelines as the third-line treatment for HER2-positive gastric cancer (Figure 1).[39]

Additional studies on T-DXd for the treatment of AGC are also ongoing (Table 1). The DESTINY-Gastric02 trial (NCT04014075) is an open-label, single-arm phase II trial to assess the efficacy and safety of T-DXd in HER2-positive AGC patients who have been treated with previous trastuzumab containing chemotherapy in non-Asian populations. The primary endpoint is the ORR by independent central review, similar to the DESTINY-Gastric01 trial. Seventy-two patients will be enrolled.

In terms of combination with immune checkpoint inhibitors, preclinical models suggest that T-DXd enhances tumor recognition by T cells. DXd was shown to upregulate CD86 expression on bone marrow-derived dendritic cells (DCs), resulting in an increase in tumor-infiltrating DCs. T-DXd

Table 1. Clinical trials of T-DXd in HER2-positive gastric cancer.

Study	Phase	Design	Efficacy endpoints	Status
NCT02564900	I	Dose-escalation study of T-DXd in subjects with advanced solid malignant tumors with dose-expansion in HER2-positive gastric cancer	ORR 43.2% (19/44) DCR 79.5% (35/44) Median OS 12.8 months Median PFS 5.6 months	Reported
NCT03329690 DESTINY-Gastric01	II	Multi-cohort study of T-DXd Primary cohort: Randomized part of T-DXd *versus* irinotecan or paclitaxel in HER2-positive gastric cancer refractory to trastuzumab containing therapy Exploratory cohort: single-arm study of T-DXd for patients with HER2-low gastric cancer (IHC2+/ISH– or IHC1+)	Primary cohort: ORR 51% *versus* 14% Confirmed ORR 43% *versus* 12% Median OS 12.5 *versus* 8.4 months Median PFS 5.6 *versus* 3.5 months Exploratory cohort: Confirmed ORR 26.3% in IHC2+/ISH–, 9.5% in IHC1+ Median PFS 4.4 months in IHC2+/ISH–, 2.8 months in IHC1+ Median OS 7.8 months in IHC2+/ISH–, 8.5 months in IHC1+	Reported
NCT04014075 DESTINY-Gastric02	II	Single-arm study of T-DXd in HER2-positive gastric cancer at second-line	Primary: ORR	Recruiting
NCT04379596 DESTINY-Gastric03	Ib/II	Dose-escalation and dose-expansion study of T-DXd combinations in HER2-positive gastric cancer Arm 1A: T-DXd and 5-FU Arm 1B: T-DXd and capecitabine Arm 1C: T-DXd and durvalumab Arm 1D: T-DXd and 5-FU or capecitabine and oxaliplatin Arm 1E: T-DXd, durvalumab and 5-FU or capecitabine Arm 2A: Trastuzumab, 5-FU/capecitabine, and cisplatin/oxaliplatin Arm 2B: T-DXd monotherapy Arm 2C: T-DXd, 5-FU or capecitabine, and oxaliplatin Arm 2D: T-DXd, 5-FU or capecitabine, and durvalumab	Part 1: adverse events Part 2: ORR	Recruiting

5-fluorouracil, 5-FU; DCR, disease control rate; HER2, human epidermal growth factor type 2; IHC, immunohistochemistry; ISH, *in situ* hybridization; ORR; objective response rate; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan.

also increased tumor-infiltrating CD8+ T cells and enhanced PD-L1 and major histocompatibility complex class I expression on tumor cells. Furthermore, combination therapy with T-DXd and anti-PD-1 antibodies was more effective than either monotherapy.[40] These promising results in preclinical models have accelerated clinical trials evaluating combinations of T-DXd with checkpoint inhibitors in patients with not only AGC but also breast cancer, non-small-cell lung cancer, and urothelial cancer. The DESTINY-Gastric03 trial (NCT04379596) is a phase I/II trial assessing the safety and efficacy of T-DXd combinations in patients with HER2-positive AGC. This exploratory study is composed of two parts: the first part assesses the occurrence of adverse events and serious adverse events whereas the second part aims to evaluate the ORR. Part 1 is structured as follows: Arm 1A, T-DXd and 5-fluorouracil; Arm 1B, T-DXd and capecitabine; Arm 1C, T-DXd and durvalumab; Arm 1D, T-DXd and 5-fluorouracil or capecitabine and oxaliplatin; Arm 1E, T-DXd, durvalumab and 5-fluorouracil or capecitabine; the study population is composed of patients with progression after at least one prior trastuzumab containing regimen. Part 2 evaluates the clinical activities of T-DXd monotherapy; the combination of

T-DXd, 5-fluorouracil or capecitabine, and oxaliplatin; and the combination of T-DXd, 5-fluorouracil or capecitabine, and durvalumab, compared with trastuzumab, 5-fluorouracil or capecitabine, and cisplatin or oxaliplatin as an active comparator in patients with previously untreated disease.

Furthermore, there is still room for improvement in HER2-low AGC. In patients with HER2-low metastatic breast cancer, defined as IHC2+/ISH– or IHC1+, a consistent objective response regardless of IHC status was observed in a phase Ib study (35.7% and 38.5% in patients with IHC1+ and IHC2+, respectively).[41] A phase III DESTINY-Breast04 trial (NCT03734029) is ongoing to compare the efficacy and safety of T-DXd *versus* physician's choice chemotherapy in patients with HER2-low metastatic breast cancer. However, the response was attenuated to 9.5% in patients with IHC1+ AGC, indicating the importance of properly selecting patients who will benefit from T-DXd treatment. Considering possible heterogeneity of HER2 expression between primary and metastatic tumors and the loss of HER2 positivity after anti-HER2 therapy including trastuzumab in patients with HER2-positive AGC,[42,43] further biomarker analysis is important. Actually, fresh biopsy tissues just before T-DXd treatment and circulating tumor DNA are currently under investigation using samples from the DESTINY-Gastric 01 trial.

Conclusion

Although several HER2-targeted therapies have been investigated in HER2-positive AGC, until recently, trastuzumab has been the only approved anti-HER2 agent. The newer HER2 ADC, T-DXd, demonstrated a superior response rate and survival benefit over conventional chemotherapy and was therefore approved for HER2-positive AGC in September 2020 in Japan. Overall, its safety profile is manageable; however, a relatively high incidence of lung toxicities (approximately 10%) should be noted in clinical practice. Furthermore, clinical trials developing new combinations with other agents including cytotoxic chemotherapy and/or immunotherapy in earlier line treatments are ongoing.

Conflict of interest statement

DK reports receiving honoraria from Takeda, Chugai, Lilly, Merck Serono, Taiho, Ono, and Sysmex. KS reports grants and personal fees from Taiho Pharmaceutical during the conduct of this study; as well as grants and personal fees from Astellas Pharma, Ono Pharmaceutical, Eli Lilly and Company, and Merck Pharmaceutical; personal fees from Bristol-Myers Squibb, Takeda Pharmaceuticals, Pfizer Inc., Novartis, AbbVie Inc, GlaxoSmithKline, and Yakult; and grants from Dainippon Sumitomo Pharma, Daiichi Sankyo, Chugai Pharma, and Medi Science, outside the submitted work.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

References

1. Bray F, Ferlay J, Soerjomataram I, *et al.* Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; 68: 394–424.
2. Koizumi W, Narahara H, Hara T, *et al.* S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol* 2008; 9: 215–221.
3. Cunningham D, Starling N, Rao S, *et al.* Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 2008; 358: 36–46.
4. Bang YJ, Van Cutsem E, Feyereislova A, *et al.* Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010; 376: 687–697.
5. Fuchs CS, Tomasek J, Yong CJ, *et al.* Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* 2014; 383: 31–39.
6. Kang YK, Boku N, Satoh T, *et al.* Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017; 390: 2461–2471.
7. Shitara K, Doi T, Dvorkin M, *et al.* Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2018; 19: 1437–1448.

8. Shitara K, Van Cutsem E, Bang YJ, *et al.* Efficacy and safety of pembrolizumab or pembrolizumab plus chemotherapy vs chemotherapy alone for patients with first-line, advanced gastric cancer: the KEYNOTE-062 phase 3 randomized clinical trial. *JAMA Oncol* 2020; 6: 1571–1580.
9. Moehler M, Shitara K, Garrido M, *et al.* Nivolumab (nivo) plus chemotherapy (chemo) versus chemo as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer (GC/GEJC)/esophageal adenocarcinoma (EAC): first results of the CheckMate 649 study. *Ann Oncol* 2020; 31, S1191.
10. Boku N, Ryu MH, Oh DY, *et al.* Nivolumab plus chemotherapy versus chemotherapy alone in patients with previously untreated advanced or recurrent gastric/gastroesophageal junction (G/GEJ) cancer: ATTRACTION-4 (ONO-4538-37) study. *Ann Oncol* 2020; 31(Suppl. 4): S1142–S1215.
11. Van Cutsem E, Bang YJ, Feng-Yi F, *et al.* HER2 screening data from ToGA: targeting HER2 in gastric and gastroesophageal junction cancer. *Gastric Cancer* 2015; 18: 476–484.
12. Gravalos C and Jimeno A. HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target. *Ann Oncol* 2008; 19: 1523–1529.
13. Yan SY, Hu Y, Fan JG, *et al.* Clinicopathologic significance of HER-2/NEU protein expression and gene amplification in gastric carcinoma. *World J Gastroenterol* 2011; 17: 1501–1506.
14. Halon A, Donizy P, Biecek P, *et al.* HER-2 expression in immunohistochemistry has no prognostic significance in gastric cancer patients. *ScientificWorldJournal* 2012; 2012: 941259.
15. Tsapralis D, Panayiotides I, Peros G, *et al.* Human epidermal growth factor receptor-2 gene amplification in gastric cancer using tissue microarray technology. *World J Gastroenterol* 2012; 18: 150–155.
16. Thuss-Patience PC, Shah MA, Ohtsu A, *et al.* Trastuzumab emtansine versus taxane use for previously treated HER2-positive locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma (GATSBY): an international randomised, open-label, adaptive, phase 2/3 study. *Lancet Oncol* 2017; 18: 640–653.
17. Satoh T, Xu R-H, Chung HC, *et al.* Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of HER2-amplified advanced gastric cancer in Asian populations: TyTAN–a randomized, phase III study. *J Clin Oncol* 2014; 32: 2039–2049.
18. Hecht JR, Bang YJ, Qin SK, *et al.* Lapatinib in combination with Capecitabine plus Oxaliplatin in human epidermal growth factor receptor 2-positive advanced or metastatic gastric, esophageal, or gastroesophageal adenocarcinoma: TRIO-013/LOGiC–a randomized phase III trial. *J Clin Oncol* 2016; 34: 443–451.
19. Tabernero J, Hoff PM, Shen L, *et al.* Pertuzumab plus trastuzumab and chemotherapy for HER2-positive metastatic gastric or gastro-oesophageal junction cancer (JACOB): final analysis of a double-blind, randomised, placebo-controlled phase 3 study. *Lancet Oncol* 2018; 19: 1372–1384.
20. Shitara K, Bang Y-J, Iwasa S, *et al.* Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. *N Engl J Med* 2020; 382: 2419–2430.
21. Shah MA, Kang Y-K, Thuss-Patience PC, *et al.* Biomarker analysis of the GATSBY study of trastuzumab emtansine versus a taxane in previously treated HER2-positive advanced gastric/gastroesophageal junction cancer. *Gastric Cancer* 2019; 22: 803–816.
22. Grabsch H, Sivakumar S, Gray S, *et al.* HER2 expression in gastric cancer: rare, heterogeneous and of no prognostic value - conclusions from 924 cases of two independent series. *Cell Oncol* 2010; 32: 57–65.
23. Grillo F, Fassan M, Sarocchi F, *et al.* HER2 heterogeneity in gastric/gastroesophageal cancers: from benchside to practice. *World J Gastroenterol* 2016; 22: 5879–5887.
24. Hofmann M, Stoss O, Shi D, *et al.* Assessment of a HER2 scoring system for gastric cancer: results from a validation study. *Histopathology* 2008; 52: 797–805.
25. Janjigian YY, Sanchez-Vega F, Jonsson P, *et al.* Genetic predictors of response to systemic therapy in esophagogastric cancer. *Cancer Discov* 2018; 8: 49–58.
26. Kim ST, Banks KC, Pectasides E, *et al.* Impact of genomic alterations on lapatinib treatment outcome and cell-free genomic landscape during HER2 therapy in HER2+ gastric cancer patients. *Ann Oncol* 2018; 29: 1037–1048.
27. Ogitani Y, Aida T, Hagihara K, *et al.* DS-8201a, a novel HER2-targeting ADC with a novel DNA topoisomerase I inhibitor, demonstrates a promising antitumor efficacy with differentiation from T-DM1. *Clin Cancer Res* 2016; 22: 5097–5108.
28. Ogitani Y, Hagihara K, Oitate M, *et al.* Bystander killing effect of DS-8201a, a novel anti-human epidermal growth factor receptor

2 antibody-drug conjugate, in tumors with human epidermal growth factor receptor 2 heterogeneity. *Cancer Sci* 2016; 107: 1039–1046.

29. Nagai Y, Oitate M, Shiozawa H, *et al.* Comprehensive preclinical pharmacokinetic evaluations of trastuzumab deruxtecan (DS-8201a), a HER2-targeting antibody–drug conjugate, in cynomolgus monkeys. *Xenobiotica* 2019; 49: 1086–1096.
30. Inoue K, Sonobe M, Kawamura Y, *et al.* Polymorphisms of the UDP–glucuronosyl transferase 1A genes are associated with adverse events in cancer patients receiving irinotecan-based chemotherapy. *Tohoku J Exp Med* 2013; 229: 107–114.
31. Charasson V, Haaz MC and Robert J. Determination of drug interactions occurring with the metabolic pathways of irinotecan. *Drug Metab Dispos* 2002; 30: 731–733.
32. Lampe JW, Bigler J, Horner NK, *et al.* UDP-glucuronosyltransferase (UGT1A1_28 and UGT1A6_2) polymorphisms in Caucasians and Asians: relationships to serum bilirubin concentrations. *Pharmacogenetics* 1999; 9: 341–349.
33. Doi T, Shitara K, Naito Y, *et al.* Safety, pharmacokinetics, and antitumour activity of trastuzumab deruxtecan (DS-8201), a HER2-targeting antibody–drug conjugate, in patients with advanced breast and gastric or gastro-oesophageal tumours: a phase 1 dose-escalation study. *Lancet Oncol* 2017; 18: 1512–1522.
34. Shitara K, Iwata H, Takahashi S, *et al.* Trastuzumab deruxtecan (DS-8201a) in patients with advanced HER2-positive gastric cancer: a dose-expansion, phase 1 study. *Lancet Oncol* 2019; 20: 827–836.
35. Yamaguchi K, Bang Y, Iwasa S, *et al.* Trastuzumab deruxtecan (T-DXd; DS-8201) in patients with HER2-low, advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma: results of the exploratory cohorts in the phase II, multicenter, open-label DESTINY-Gastric01 study. *Ann Oncol* 2020; 31(Suppl. 4): S841–S73.
36. Modi S, Saura C, Yamashita T, *et al.* Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. *N Engl J Med* 2020; 382: 610–621.
37. Powell CA, Ross D, Gemma A, *et al.* Characterization, monitoring and management of interstitial lung disease in patients with metastatic breast cancer: analysis of data available from multiple studies of DS-8201a, a HER2-targeted antibody drug conjugate with a topoisomerase I inhibitor payload. *Cancer Res* 2018; 18: P6-17-06.
38. National Comprehensive Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Antiemesis Version2. 2020. https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf
39. http://www.jgca.jp/pdf/news202009.pdf (in Japanese). (accessed 1 November 2020)
40. Iwata TN, Ishii C, Ishida S, *et al.* A HER2-targeting antibody-drug conjugate, trastuzumab deruxtecan (DS-8201a), enhances antitumor immunity in a mouse model. *Mol Cancer Ther* 2018; 17: 1494–1503.
41. Modi S, Park H, Murthy RK, *et al.* Activity and safety of trastuzumab deruxtecan in patients with HER2-low-expressing advanced breast cancer: results from a phase Ib study. *J Clin Oncol* 2020; 38: 1887–1896.
42. Peng Z, Zou J, Zhang X, *et al.* HER2 discordance between paired primary gastric cancer and metastasis: a meta-analysis. *Chin J Cancer Res* 2015; 27: 163–171.
43. Seo S, Ryu MH, Park YS, *et al.* Loss of HER2 positivity after anti-HER2 chemotherapy in HER2-positive gastric cancer patients: results of the GASTric cancer HER2 reassessment study 3 (GASTHER3). *Gastric Cancer* 2019; 22: 527–535.