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Impact of early tumor shrinkage on survival outcomes in patients with HER2-positive advanced gastric cancer treated with trastuzumab deruxtecan in third- or later-line settings

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Abstract

Background: Trastuzumab deruxtecan (T-DXd) has been approved for a third- or later-line treatment of HER2-positive advanced gastric cancer (AGC) in Japan. However, clinical data on the use of T-DXd in real-world practice remain insufficient. Although early tumor shrinkage (ETS) serves as an early on-treatment indicator of high treatment sensitivity, the use of ETS in predicting T-DXd efficacy remains unclear.

Objectives: This study aimed to evaluate the clinical efficacy and safety of T-DXd and investigate the clinical utility of ETS as a predictor of long-term efficacy and survival.

Design: Single-center retrospective cohort study

Methods: This study consecutively enrolled patients with HER2-positive AGC who received T-DXd as a third- or later-line treatment between March 2018 and December 2023. Data on patient characteristics, adverse events (AEs), and clinical outcomes were obtained from electronic medical records. Clinical efficacy was assessed using progression-free survival (PFS) and overall survival (OS). In patients with measurable lesions, the overall response rate (ORR), ETS, and depth of response (DpR) were evaluated. Prognostic outcomes were assessed using the log-rank test and the Cox proportional hazards model.

Results: A total of 65 patients received T-DXd, with a median age of 66 years (range, 31–82 years); 77% had HER2 immunohistochemistry score of 3+, 71% received T-DXd as a third-line treatment, and 32% required initial dose reduction. At a median follow-up of 33.6 months, the median PFS and OS were 4.5 months and 7.7 months, respectively. Among the 47 patients with measurable lesions, the ORR was 36%. A median DpR of 15.8% was observed, with higher DpR correlating with longer OS. ETS was achieved in 38% of the patients and was an independent predictor of favorable PFS (hazard ratio (HR), 0.21; 95% confidence interval (CI), 0.09–0.49; $p < 0.01$) and OS (HR, 0.23; 95% CI, 0.10–0.52; $p < 0.01$). Longer second-line treatment duration was independently associated with improved OS. Overall, grade ⩾3 AEs occurred in 37% of the patients. Initial dose reduction reduced AE-induced discontinuation of treatment without compromising efficacy.

Conclusion: T-DXd demonstrated notable efficacy and a manageable safety profile in patients with HER2-positive AGC. Rapid and deep tumor shrinkage may have a significant impact on survival.

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Plain language summary

Early tumor shrinkage as a predictor of survival in HER2-positive advanced gastric cancer patients treated with trastuzumab deruxtecan

This study investigated the impact of early tumor shrinkage on survival outcomes in patients with HER2- positive advanced gastric cancer (AGC) treated with trastuzumab deruxtecan (T-DXd). T-DXd, a targeted therapy, has shown promising results in treating HER2-positive AGC. In this retrospective study, 65 patients with HER2-positive AGC received T-DXd as a third- or later-line treatment in the real-world setting. The study found that early tumor shrinkage (ETS), defined as a significant reduction in tumor size early in treatment, was linked to better survival outcomes. Patients who experienced ETS had a significantly longer progression-free survival (PFS) and overall survival (OS) compared to those who did not. The study also showed that patients who achieved a deeper tumor response (DpR), indicating a greater reduction in tumor size, had better survival outcomes. Additionally, longer duration of secondline treatment was associated with improved survival. The safety of T-DXd was manageable, with common side effects being nausea, neutropenia, and fatigue. Importantly, starting T-DXd at a lower dose reduced the risk of treatment-related discontinuations without compromising effectiveness. These findings suggest that T-DXd demonstrated notable efficacy and a manageable safety profile in patients with HER2-positive AGC. ETS can serve as an important predictor of treatment success, helping to guide clinical decisions and improve patient outcomes in clinical practice

Keywords: depth of response, early tumor shrinkage, gastric cancer, HER2, trastuzumab deruxtecan

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Introduction

Gastric cancer is the fifth most common cancer and the third leading cause of cancer-related death worldwide.[1] Advanced gastric cancer (AGC), which is unsuitable for curative resection, is frequently diagnosed. Systemic chemotherapy prolongs survival among patients with AGC and improves their symptoms and quality of life (QoL).[2,3]

Human epidermal growth factor receptor 2 (HER2, also known as ERBB2) is a transmembrane tyrosine kinase encoded by the *ERBB2* proto-oncogene. Approximately 15%–20% of patients with AGC exhibit HER2 overexpression, which is often linked to gene amplification.[4,5] HER2-targeted therapies have been established as personalized treatments for these patients. Based on the phase III ToGA trial results,[6] trastuzumab (T-mab), a humanized monoclonal anti-HER2 antibody, in combination with chemotherapy, is the currently preferred first-line treatment.[2,3,7] Recently, the phase III KEYNOTE-811 trial demonstrated that adding pembrolizumab to T-mab and chemotherapy significantly improved progression-free survival (PFS), overall response rate (ORR), and overall survival (OS) compared to placebo with T-mab and chemotherapy in patients with HER2-positive AGC, thus establishing this regimen as the new standard of first-line care.[8]

Trastuzumab deruxtecan (T-DXd) is a HER2-targeted antibody–drug conjugate consisting of humanized immunoglobulin G1 anti-HER2 monoclonal antibody with the same amino acid sequence as T-mab, a tetrapeptide-based cleavable linker, and a potent topoisomerase I inhibitor payload.[9] The mechanism of action of T-DXd not only involves blocking HER2 signaling through an anti-HER2 antibody but also delivering cytotoxic drugs directly to HER2-positive tumor cells with high efficiency, while minimizing systemic exposure and off-target toxicity. T-DXd is expected to be effective against tumors with heterogeneous HER2 expression because of its

potent bystander effect on neighboring HER2-negative tumor cells via the high membrane permeability of its cytotoxic payload.[9] In the phase II DESTINY-Gastric01 trial, T-DXd demonstrated significant improvements over the physician's chosen chemotherapy in ORR (51% vs 14%), PFS (median, 5.6 months vs 3.5 months; hazard ratio (HR), 0.47; 95% confidence interval (CI), 0.31–0.71), and OS (median, 12.5 months vs 8.4 months; HR, 0.59; 95% CI, 0.39–0.88) in patients with HER2-positive AGC who had received at least two prior palliative systemic treatments, including T-mab, in Japan and South Korea.[10] In addition, a durable response to T-DXd was observed, with a median duration of response (mDOR) of 11.3 months. Being the only agent demonstrating improved outcomes compared to third-line chemotherapeutic treatment, T-DXd is prioritized for third-line treatment of HER2-positive AGC according to the Japanese guidelines for gastric cancer treatment.[7] However, data on the use of T-DXd in third- or later-line settings in real-world practice remain insufficient.[11–13]

Early tumor shrinkage (ETS) serves as an early on-treatment indicator of high treatment sensitivity, whereas the depth of response (DpR) reflects the degree of tumor reduction. Both ETS and DpR have been associated with improved survival outcomes across various cancer types.[14–20] However, the use of ETS in predicting T-DXd efficacy in patients with HER2-positive AGC remains unclear. Therefore, we conducted a retrospective observational study to evaluate the clinical efficacy and safety of T-DXd and investigate the clinical utility of ETS as a predictor of long-term efficacy and survival.

Materials and methods

Study population

This retrospective single-institution study was conducted at the Cancer Institute Hospital of the Japanese Foundation for Cancer Research. Patients with HER2-positive AGC who were treated with T-DXd as a third- or later-line treatment between March 2018 and May 2024 were consecutively enrolled. Key inclusion criteria were patients (i) with non-resectable, recurrent/metastatic gastric adenocarcinoma, including adenocarcinoma of the esophagogastric junction, (ii) with histologically confirmed adenocarcinoma, (iii) with confirmed HER2-positive status, defined by gastric-specific criteria as HER2 immunohistochemistry (IHC) 3+ or HER2 IHC 2+ with in situ hybridization (ISH) positivity,[5] and (iv) who had previously received two or more lines of chemotherapy, including T-mab, for advanced disease. HER2 testing was required before the initiation of first-line therapy, and re-evaluation of the HER2 status before T-DXd administration was not mandatory.

T-DXd was administered intravenously once every 3 weeks at a dose of 6.4 mg/kg of body weight. Treatment was continued until disease progression, unacceptable toxicity, or discontinuation at the patient's request. The decision to initiate T-DXd at a reduced dose was made cautiously by the treating physicians, considering the patients' compromised health status and limited tolerance to previous therapies. In cases of clinically significant or unacceptable toxicity, dose interruption, dose reduction, and supportive therapy were implemented. Prophylactic antiemetic treatment was implemented according to established guidelines.[21]

This study was approved by the Ethics Review Board of our institution (IRB number: 2023-GB-015) and conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was publicly available on the hospital website, providing participants with the opportunity to opt out of the study. No additional informed consent was required. The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement,[22] which is available in the Supplemental Materials.

Assessments

Data on patient characteristics, adverse events (AEs), and clinical outcomes were obtained from the electronic medical records. Performance status (PS) was assessed according to the Eastern Cooperative Oncology Group (ECOG) PS. The clinicopathological data included age, sex, metastatic sites, number of metastatic organs, primary resection, HER2 status, and history of systemic chemotherapy. Hematological and nonhematological toxicities were assessed during T-DXd treatment according to the National

Cancer Institute Common Terminology Criteria Common Terminology Criteria for Adverse Events version 5.0.

The treatment response was assessed by the investigators according to the Response Evaluation Criteria in Solid Tumor (RECIST) 1.1 among patients with at least one measurable lesion. ORR was defined as the percentage of patients who achieved the best overall response of either complete response (CR) or partial response (PR). The disease control rate (DCR) was defined as the percentage of patients with the best overall response to CR, PR, or stable disease (SD). ETS was defined as a $\geqslant 20\%$ reduction in the sum of the longest diameters of RECIST target lesions from baseline, assessed at 8 ± 2 weeks after initiating T-DXd treatment.[14] DpR was defined as the percentage change from baseline in the sum of the longest diameters of RECIST target lesions at the nadir without new lesions or progression of non-target lesions.[14]

Statistical analysis

To evaluate patient characteristics, summary statistics were constructed by employing frequencies and proportions for categorical variables, and medians and ranges for continuous variables. Comparisons between groups were evaluated using the Mann–Whitney *U* test for continuous variables and using Fisher's exact test for categorical data. PFS was defined as the time from the first dose of T-DXd to the onset of either documented progressive disease (PD) or death from any cause. Duration of response (DOR) was defined as the time from the first documented objective response (CR or PR) to disease progression or death from any cause. OS was defined as the time from the first dose of T-DXd to death from any cause. For patients with no events reported before the October 2024 data cut-off for prognostic analysis, PFS, DOR, and OS were censored at the date of the last known contact when the patient was confirmed to be alive. Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. Prognostic variables that were significantly associated with PFS or OS in the univariable analyses were further evaluated using multivariable Cox proportional hazards model analyses with adjusted HRs and 95% CIs. Statistical significance was set at $p < 0.05$.

All statistical analyses were performed using EZR statistical software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). EZR is a modified version of the R Commander, designed to add specific statistical functions frequently used in biostatistics.[23]

Results

Cohort characteristics

Sixty-five patients received T-DXd treatment at our institute during the study period (Supplemental Figure S1). Overall, 71% were male and 23% had diffuse-type histology; the median age was 66 years (range, 31–82 years; Table 1). The ECOG PS was 0, 1, and 2 in 40%, 55%, and 5% of the patients, respectively. Forty-seven patients (71%) had measurable lesions, and 44 (68%) had two or more metastatic sites, including lymph node metastasis in 43 (66%) patients and peritoneal metastases in 38 (58%) patients. Prior to T-DXd treatment, 26 (40%) patients underwent primary resection. All patients were HER2-positive, with HER2 IHC 3+ in 77% and HER2 IHC 2+/ISH+ in 23% of the patients. T-DXd was administered as a third-line therapy in 46 (71%) patients. All patients had previously received T-mab, and 29 (45%) had been treated with nivolumab before T-DXd. Of the 58 patients who discontinued T-DXd treatment, nine discontinued due to AEs, 48 due to disease progression, and one underwent surgery. Among these, 31 (53%) received subsequent therapy involving immune checkpoint inhibitors (17 (55%) patients) (55%) and trifluridine/tipiracil (14 (44%) patients).

Efficacy

At a median follow-up period of 33.6 months, the median PFS (mPFS) was 4.5 months (95% CI, 3.8–5.6) and the median OS (mOS) was 7.7 months (95% CI, 5.7–9.7; Supplemental Figure S2). Among the 47 patients with measurable lesions, ORR and DCR were 36.2% and 87.2%, respectively (Supplemental Table S1). The ORR and DCR for T-DXd were comparable between the third- and fourth-line or later treatments. In the third-line setting, the ORR and DCR were 35.5% and 87.1%, respectively, whereas in the fourth- or later-line setting, the

Table 1. Patient characteristics.

Characteristics ($n = 65$)	n (%)
Age	
Median (range), years	66 (31–82)
Sex	
Male	46 (71%)
Female	19 (29%)
ECOG PS	
0	26 (40%)
1	36 (55%)
2	3 (5%)
Primary tumor site	
EGJ	12 (18%)
Stomach	53 (82%)
HER2 status	
IHC 3+	50 (77%)
IHC 2+/ISH+	15 (23%)
Histological type	
Diffuse	15 (23%)
Intestinal	50 (77%)
Prior gastrectomy	
Yes	26 (40%)
No	39 (60%)
Measurable lesions	
Yes	47 (71%)
No	19 (29%)
Number of metastatic organs	
1	21 (32%)
⩾2	44 (68%)
Metastatic sites	
Liver	27 (42%)
Peritoneum	38 (58%)
Lymph node	43 (66%)
Lung	16 (25%)
Bone	4 (6%)
Brain	2 (3%)
Number of prior treatment	
2	46 (71%)
⩾3	19 (29%)
Prior use of T-mab	
Yes	65 (100%)
No	0 (0%)
Prior use of nivolumab	
Yes	29 (45%)
No	36 (55%)
T-mab efficacy in first-line	
CR/PR	49 (75%)
SD	11 (17%)
PD	3 (5%)
Unknown	2 (3%)
Duration of T-mab in first-line	
Median (range), months	10.2 (2.1–117.8)
Treatment efficacy in second-line	
CR/PR	25 (38%)
SD	21 (32%)
PD	14 (22%)
Unknown	5 (8%)
Duration of second-line treatment	
Median (range), months	4.8 (0.7–29.8)

(Continued)

Table 1. (Continued)

CR, complete response; ECOG, Eastern Cooperative Oncology Group; EGJ, esophagogastric junction; IHC, immunohistochemistry; ISH, in situ hybridization; PD, progressive disease; PR, partial response; PS, performance status; SD, stable disease; T-mab, trastuzumab.

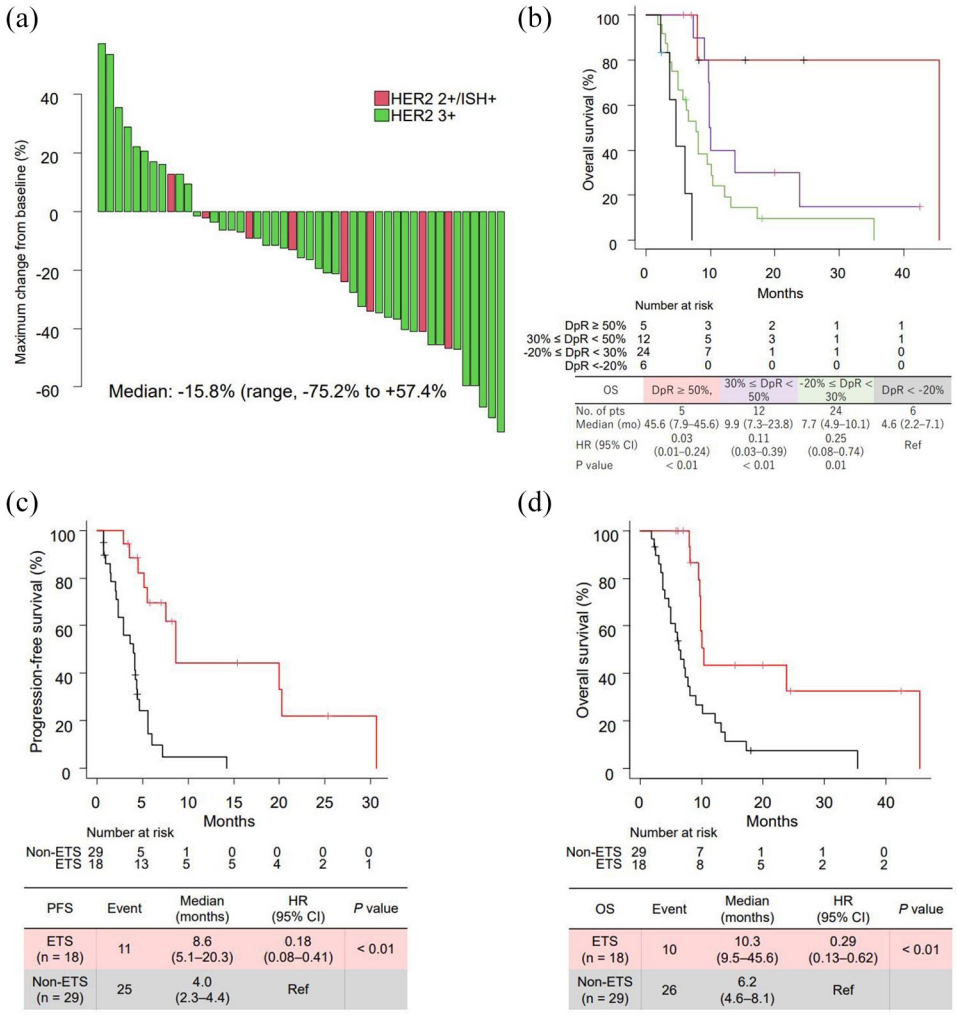


Figure 1. ETS and DpR analyses for 47 patients with measurable HER2-positive advanced gastric cancer. (a) Waterfall plot depicting the percentage reduction in tumor burden from baseline, with green bars indicating HER2 IHC 3+ status and red bars representing HER2 IHC 2+/ISH+ status. (b) Kaplan–Meier curves estimating overall survival for DpR categorized into four groups: DpR ⩾ 50%, 30% ⩽ DpR < 50%, -20% ⩽ DpR < 30%, and DpR < –20%. Kaplan–Meier estimates of (c) progression-free survival (PFS) and (D) overall survival (OS) according to ETS status.

CI, confidence interval; DpR, depth of response; ETS, early tumor shrinkage; HR, hazard ratio; IHC, immunohistochemistry; ISH, in situ hybridization; mo, months; Ref, reference.

ORR and DCR were 35.7% and 85.7%, respectively. The mDOR was 8.6 months (95% CI, 5.5–21.7; Supplemental Figure S3(A)). Patients who achieved CR or PR showed a longer mOS of 13.8 months (95% CI, 9.0–45.6), compared with those with SD (mOS, 7.7 months; 95% CI, 4.9–10.1) or PD (mOS, 4.6 months; 95% CI, 2.2–7.1; Supplemental Figure S3(B)).

The median baseline sum of target lesion diameters was 43.4 mm (range, 10.2–187.7 mm), with a median maximum percentage change from baseline of −15.8% (range, −75.2% to +57.4%), indicating a median DpR of 15.8% (Figure 1(a)). To assess prognostic outcomes, tumor reduction was categorized into four groups: DpR ⩾ 50%, 30% ⩽ DpR < 50%, −20% ⩽ DpR < 30%, and DpR < −20%. Among the patients, 10.6%, 25.5%, 51.1%, and 12.8% achieved DpR ⩾ 50%, 30% ⩽ DpR < 50%, −20% ⩽ DpR < 30%, and DpR < −20%, respectively. A higher DpR was correlated with a longer mOS ($p < 0.01$; Figure 1(b)). Patients achieving DpR ⩾ 50% had the most favorable mOS at 45.6 months (95% CI,

7.9–45.6), followed by 9.9 months (95% CI, 7.3–23.8) for DpR of 30% to <50%, 7.7 months (95% CI, 4.9–10.1) for DpR of −20% to <30%, and 4.6 months (95% CI, 2.2–7.1) for DpR < −20%. To minimize potential immortal time bias when analyzing prognostic outcomes across varying intervals for maximum tumor reduction assessment, an 18-week landmark analysis was conducted (Supplemental Figure S4). Patients who achieved a higher DpR demonstrated more favorable PFS and OS.

To assess the impact of early tumor reduction on the prognosis of patients treated with T-DXd, the association between ETS and clinical outcomes was analyzed. ETS was achieved in 18 (38.3%) of the 47 patients with target lesions. There was no significant association between ETS and the clinicopathological features, including HER2 IHC status, metastatic sites, number of prior treatment lines, treatment response, first-line T-mab treatment duration, or second-line treatment response and duration (Supplemental Table S2). The maximum tumor reduction from baseline was significantly greater in patients with ETS (median, 40.7%; range, 20.8–75.2) compared to those without ETS (median, 6.3%; range, −57.4 to 45.6), with a strong correlation observed between ETS and the DpR (Supplemental Figure S5). Notably, all patients with DpR ⩾ 50% were included in the ETS group. The ORR and DCR were 77.8% and 100%, respectively, in the ETS group and 10.3% and 79.3%, respectively, in the non-ETS group (Supplemental Table S1). Patients who achieved ETS showed greater survival benefits than those who did not. The mPFS was significantly longer in the ETS group at 8.6 months (95% CI, 5.1–20.3) versus 4.0 months (95% CI, 2.3–4.4) in the non-ETS group (HR, 0.18; 95% CI, 0.08–0.41; $p < 0.01$; Figure 1(c)). The mOS was also prolonged in the ETS group at 10.3 months (95% CI, 9.5–45.6) compared to 6.2 months (95% CI, 4.6–8.1) in the non-ETS group (HR, 0.29; 95% CI, 0.13–0.62; $p < 0.01$; Figure 1(d)). This trend persisted even among patients without ETS stratified by the presence of PD as the best overall response (Supplemental Figure S6). In multivariable Cox proportional hazards analysis, ETS was significantly associated with prolonged PFS (HR, 0.21; 95% CI, 0.09–0.49; $p < 0.01$; Supplemental Table S3) and OS (HR, 0.23; 95% CI, 0.01–0.52; $p < 0.01$; Table 2).

Subgroup analysis

Treatment efficacy was analyzed according to the HER2 status. The PFS did not differ significantly between patients with HER2 IHC 3+ and those with HER2 IHC 2+/ISH+ (mPFS, 4.5 months (95% CI, 3.5–5.5) vs 4.1 months (95% CI, 0.9–8.6); $p = 0.65$; Supplemental Figure S7). Similar outcomes were noted for HER2 status (HER2 IHC 3+ vs HER2 IHC 2+/ISH+) in terms of ORR (35.9% vs 37.5%), DCR (84.6% vs 100%), and ETS (38.5% vs 37.5%; Supplemental Figure S8). In contrast, patients with HER2 IHC 3+ tended to have a longer OS than those with HER2 IHC 2+/ISH+ (mOS, 9.0 months (95% CI, 6.5–10.0) vs 5.6 months (95% CI, 1.8–7.3); $p = 0.06$; Supplemental Figure S7). DOR also tended to be longer in patients with HER2 IHC 3+ (mDOR, 20.0 months; 95% CI, 5.1–30.7) compared with those with HER2 IHC 2+/ISH+ (mDOR, 8.6 months; 95% CI, 4.1–8.6; Supplemental Figure S8). Median DpR was similar between patients with HER2 IHC 3+ (15.6%; 95% CI, −5.0 to 25.6) and HER2 IHC 2+/ISH+ (19.7%; 95% CI, −2.4 to 41.8). However, only patients with HER2 IHC 3+ achieved a DpR ⩾ 50%, with five (12.8%) of 39 patients with measurable HER2 IHC 3+ AGC (Supplemental Figure S8).

Second-line treatment duration exceeding the median of 4.8 months was also independently associated with improved OS in patients receiving T-DXd (HR, 0.45; 95% CI, 0.21–0.97; $p = 0.04$; Table 2). In addition, multivariable Cox proportional hazards analysis indicated a trend toward favorable PFS in patients with a second-line treatment duration ⩾ 4.8 months (Supplemental Table S3). For patients with a second-line treatment duration ⩾ 4.8 months, mPFS was 4.6 months (95% CI, 3.6–20.0), compared to 4.1 months (95% CI, 2.9–5.6) in those with duration <4.8 months (HR, 0.51; 95% CI, 0.24–1.03; $p = 0.06$; Figure 2(a)). The mOS was significantly longer at 9.8 months (95% CI, 6.0–15.9) in those with duration ⩾ 4.8 months versus 6.2 months (95% CI, 4.9–7.9) in those with duration <4.8 months (HR, 0.43; 95% CI, 0.21–0.88; $p = 0.02$; Figure 2(b)).

Safety

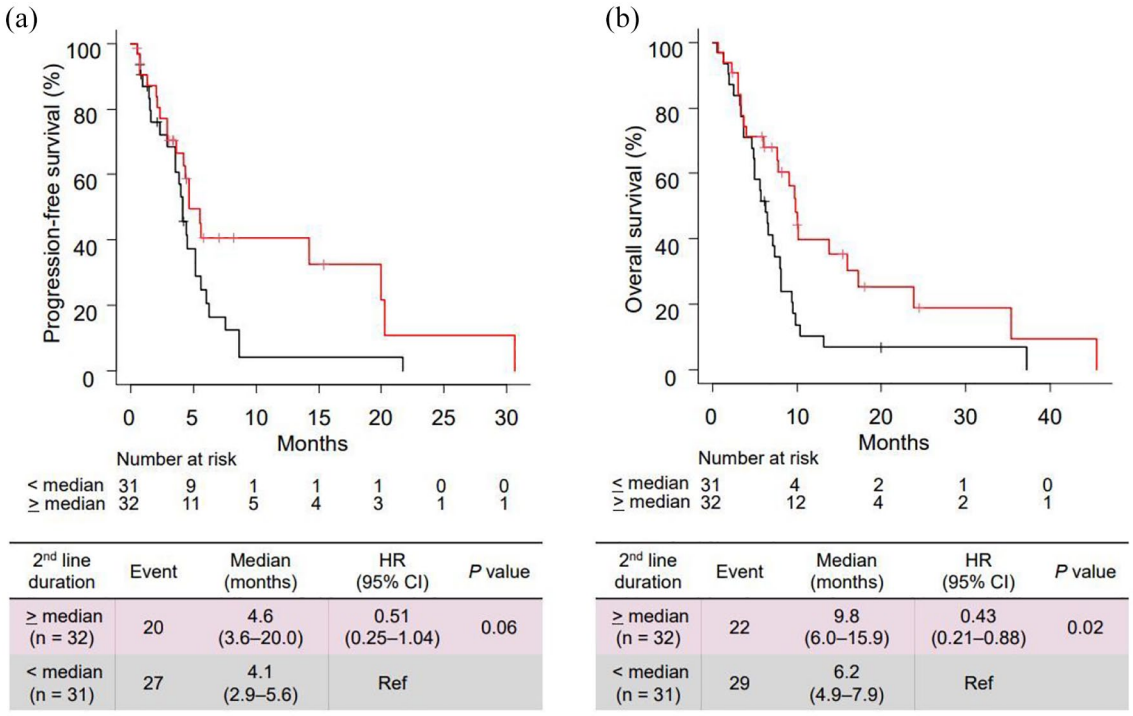
AEs among the study population are summarized in Table 3. Overall, AEs of any grade and grade ⩾ 3 were recorded in 64 (98.5%) and 24 (36.9%) patients, respectively. Neutropenia and

Table 2. Cox proportional hazard model analysis for OS in 47 patients with measurable lesions.

Variables	Univariate			Multivariate		
	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Sex (male vs female)	1.48	0.67–3.26	0.33			
Age (⩾65 vs <65)	1.26	0.62–2.54	0.53			
ECOG PS (⩾1 vs 0)	2.05	1.01–4.15	0.04	3.29	1.42–7.58	<0.01
Prior gastrectomy (yes vs no)	0.60	0.29–1.21	0.15			
HER2 status (IHC 3+ vs IHC 2+/ISH+)	0.54	0.28–1.04	0.06			
Liver meta (yes vs no)	0.99	0.51–1.92	0.97			
Lung meta (yes vs no)	1.5	0.72–3.09	0.28			
Peritoneal meta (yes vs no)	1.4	0.71–2.75	0.33			
Lymph node meta (yes vs no)	1.24	0.55–2.78	0.61			
No. of meta (⩾2 vs 1)	1.98	0.80–4.90	0.14			
Prior nivolumab (yes vs no)	1.22	0.63–2.38	0.56			
ETS (yes vs no)	0.29	0.13–0.62	<0.01	0.23	0.10–0.52	<0.01
Response in first-line T-mab (CR/PR vs SD/PD)	0.87	0.38–2.02	0.75			
Duration of first-line T-mab (⩾ median vs < median)*	1.11	0.56–2.20	0.76			
Response in second-line treatment (CR/PR vs SD/PD)	0.46	0.22–0.94	0.03	0.68	0.24–1.96	0.47
Duration of second-line treatment (⩾median vs <median)**	0.43	0.21–0.88	0.02	0.45	0.21–0.97	0.04
Initial dose reduction (yes vs no)	0.43	0.19–0.99	0.049	0.31	0.12–0.82	0.02
Adverse events ⩾ grade 3 (yes vs no)	0.64	0.32–1.30	0.22			

*Duration of first-line trastuzumab treatment (⩾median 10.2 months vs <10.2 months).
**Duration of second-line treatment (⩾median 4.8 months vs <median 4.8 months).
CI, confidence interval; CR, complete response; ECOG, Eastern Cooperative Oncology Group; ETS, early tumor shrinkage; HR, hazard ratio; IHC, immunohistochemistry; ISH, in situ hybridization; meta, metastasis; PD, progressive disease; PR, partial response; PS, performance status; SD, stable disease; T-mab, trastuzumab.

anemia were the most common hematologic AEs, occurring in 21 (32.3%) and 6 (9.2%) patients, respectively. Grade ⩾3 neutropenia and febrile neutropenia were observed in 17 (26.2%) and 2 (3.1%) patients, respectively. The most common nonhematological AEs were nausea, anorexia, and fatigue, which occurred in 63 (96.9%), 27 (41.5%), and 23 (35.4%) patients, respectively. The most frequent grade ⩾3 nonhematological AE was nausea, observed in 21 patients (32.3%). Grade ⩾3 anorexia and fatigue were each observed in only 2 (3.1%) patients. In addition, interstitial lung disease occurred in eight (14%) patients, with five, two, and one patient classified as grade 1, 2, and 3, respectively. No previously unreported treatment-related AEs or deaths were observed. Nine patients discontinued T-DXd due to the following toxicities: hematological toxicities in two patients, gastrointestinal toxicities in three patients, and interstitial lung disease in one



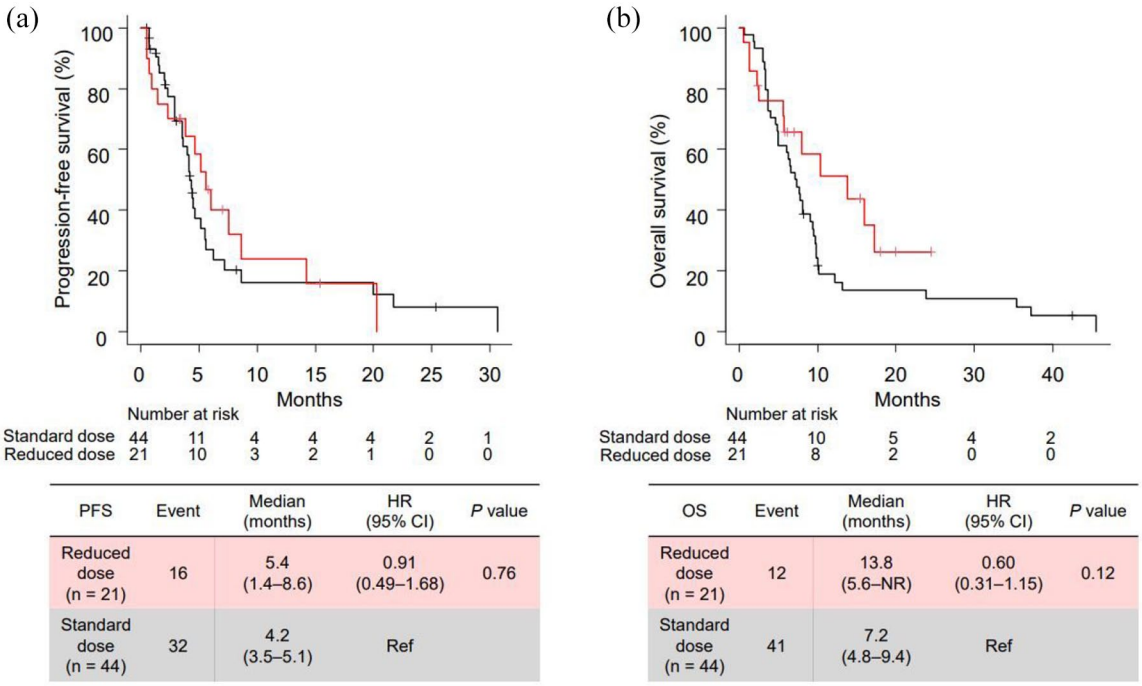
2nd line duration	Event	Median (months)	HR (95% CI)	*P* value
≥ median (n = 32)	20	4.6 (3.6–20.0)	0.51 (0.25–1.04)	0.06
< median (n = 31)	27	4.1 (2.9–5.6)	Ref	

2nd line duration	Event	Median (months)	HR (95% CI)	*P* value
≥ median (n = 32)	22	9.8 (6.0–15.9)	0.43 (0.21–0.88)	0.02
< median (n = 31)	29	6.2 (4.9–7.9)	Ref	

Figure 2. Kaplan–Meier estimates of (a) progression-free survival and (b) overall survival based on second-line treatment duration (⩾ median 4.8 months or < 4.8 months).
CI, confidence interval; HR, hazard ratio; Ref, reference.

Table 3. Adverse events.

Adverse events	All patients (*n* = 65)		Dose reduction	Standard dose	*p* Value
	Grade ⩾ 3, *n* (%)	Any grade, *n* (%)	(*n* = 21)	(*n* = 44)	
Nausea	21 (32.3%)	63 (96.9%)	19 (90.5%)	44 (100%)	0.19
Neutropenia	17 (26.2%)	21 (32.3%)	9 (42.9%)	12 (27.3%)	0.33
Febrile neutropenia	2 (3.1%)	2 (3.1%)	0 (0%)	2 (4.5%)	0.82
Anemia	4 (6.2%)	6 (9.2%)	4 (19.0%)	2 (4.5%)	0.15
Anorexia	2 (3.1%)	27 (41.5%)	7 (33.3%)	20 (45.5%)	0.51
Fatigue	2 (3.1%)	23 (35.4%)	8 (38.1%)	15 (34.1%)	0.97
Diarrhea	0 (0%)	7 (10.8%)	3 (14.3%)	4 (9.1%)	0.84
Neuropathy	0 (0%)	6 (9.2%)	2 (9.5%)	4 (9.1%)	1.00
Skin rash	0 (0%)	2 (3.1%)	0 (0%)	2 (4.5%)	0.82
Liver dysfunction	2 (3.1%)	3 (4.6%)	1 (4.8%)	2 (4.5%)	1.00
Interstitial lung disease	1 (1.5%)	7 (10.8%)	2 (9.5%)	5 (11.4%)	1.00
Ileus	1 (1.5%)	1 (1.5%)	0 (0%)	1 (2.3%)	1.00
Gastrointestinal bleeding	1 (1.5%)	1 (1.5%)	1 (4.8%)	0 (0%)	0.70



PFS	Event	Median (months)	HR (95% CI)	*P* value
Reduced dose (n = 21)	16	5.4 (1.4–8.6)	0.91 (0.49–1.68)	0.76
Standard dose (n = 44)	32	4.2 (3.5–5.1)	Ref	

OS	Event	Median (months)	HR (95% CI)	*P* value
Reduced dose (n = 21)	12	13.8 (5.6–NR)	0.60 (0.31–1.15)	0.12
Standard dose (n = 44)	41	7.2 (4.8–9.4)	Ref	

Figure 3. Kaplan–Meier estimates for (a) progression-free survival (PFS) and (b) overall survival (OS), comparing initial dose reduction of T-DXd with the standard initial dose.
CI, confidence interval; HR, hazard ratio; Ref, reference.

patient. Grade > 3 AEs were not independent predictors of PFS (HR, 0.85; 95% CI, 0.43–1.70; $p = 0.65$; Supplemental Table S3) or OS (HR, 0.64; 95% CI, 0.32–1.30; $p = 0.22$; Table 2).

Overall, 35 patients (53.9%) required T-DXd dose reduction during treatment, with 21 (32.3%) patients starting at a reduced dose from the first cycle. No significant clinicopathological differences were noted between patients who received the standard dose in the first cycle and those who received a reduced dose initially (Supplemental Table S4). The decision to initiate T-DXd at a reduced dose was cautiously made by the treating physicians in consideration of the patient's compromised health status and limited tolerance to previous therapies. No significant differences in toxicity were observed between the patients who received the standard initial T-DXd dose and those who received a reduced dose. However, 18.6% of patients on the standard dose discontinued treatment owing to AEs, compared with only 4.8% of those on the initially reduced dose. In addition, 31.8% of the patients who started with the standard dose required dose reductions in later cycles. No significant difference in the ORR was observed between the two groups (Supplemental Table S1). PFS did not differ significantly between these groups (mPFS, 5.4 months (95% CI, 1.4–8.6) for reduced dose vs 4.2 months (95% CI, 3.5–5.1) for standard dose; HR, 0.91 (95% CI, 0.49–1.68); Figure 3). OS was also similar between the two groups (mOS, 13.8 months (95% CI, 5.6– not reached (NR)) for the reduced dose vs 7.2 months (95% CI, 4.8–9.4) for the standard dose; HR, 0.60 (95% CI, 0.31–1.15)). In multivariable Cox proportional hazards analyses, initial dose reduction was an independent predictor of OS (HR, 0.31; 95% CI, 0.12–0.82; $p = 0.02$; Table 2), but not PFS (HR, 0.72; 95% CI, 0.35–1.46; $p = 0.36$; Supplemental Table S3).

Discussion

ETS has been demonstrated as an alternative early on-treatment predictor of treatment efficacy with regard to PFS and OS across various cancer types.[15–18,24] Retrospective analyses suggest that ETS may be a predictor of PFS and OS in patients who receive first-line platinum doublet chemotherapy[25] and nivolumab plus chemotherapy[18] for

HER2-negative AGC and T-mab-containing chemotherapy[19,20] for HER2-positive AGC. However, the utility of ETS for predicting T-DXd efficacy in patients with HER2-positive AGC has not yet been elucidated. To the best of our knowledge, this is the first study to demonstrate efficacious ETS in patients with HER2-positive AGC treated with T-DXd. ETS effectively stratified prognostic outcomes as independent factors for improved PFS and OS in real-world patients, and most patients who exhibited ETS achieved greater tumor shrinkage. These findings indicate that ETS may serve as an important early predictor of patient sensitivity to T-DXd. Furthermore, ETS may be clinically significant in terms of QoL, as patients with AGC often experience tumor-related symptoms and declining QoL due to increased tumor burden when there is no response to second-line treatment.[26] In addition, previous data indicate that second-line treatment failure is typically followed by decreased ECOG PS within approximately 1.5 months.[27] Therefore, ETS may facilitate faster symptom relief and improve QoL in symptomatic patients by promptly reducing tumor burden, delaying the onset of new tumor-related symptoms, and preventing QoL deterioration in asymptomatic patients.[17,28–30] Although subsequent lines of treatment following disease progression provide survival benefits,[31,32] declining QoL and poor ECOG PS are also primary concerns when making decisions about later-line therapies. In this study, 31 (53%) patients received subsequent treatment after discontinuing T-DXd, a rate comparable to that (48%) in the DESTINY-Gastric01 trial. Considering the high ETS rate among patients treated with T-DXd, this therapy may improve QoL. Consequently, selecting a third-line therapy with a potentially greater response, such as T-DXd, may be crucial for maintaining the QoL and ECOG PS, thereby enabling the transition to subsequent therapies.

T-DXd is often clinically administered to patients ineligible for clinical trials due to comorbidities or frailty. Therefore, real-world data can provide valuable information to guide therapeutic decisions and optimize T-DXd treatment. This study presented the real-world clinical outcomes of T-DXd as a third- or later-line treatment in patients with HER2-positive AGC, with mPFS and mOS of 4.5 months and 7.7 months, respectively. The ORR was 36.2%, and the mDOR was 8.6 months. These results were slightly less favorable than those obtained in the DESTINY-Gastric01 trial.[10] Although the median age in this study was similar to that in the DESTINY-Gastric01 trial, patients in our cohort had a lower proportion of ECOG PS 0. The DESTINY-Gastric01 trial excluded patients with PS $\geqslant 2$, while 4.6% of patients in this study exhibited ECOG PS 2. At our institution, patients with good ECOG PS and without severe comorbidities usually participate in clinical trials and were thus excluded from this study. Another notable difference was the higher incidence of peritoneal metastases (58%) and nonmeasurable lesions (29%) in our cohort, which may have contributed to the poorer outcomes.[13] In contrast, the clinical outcomes of this study were consistent with previous real-world data, reinforcing the reproducible efficacy of T-DXd in real-world settings.[11,12] Importantly, the ORR and PFS in this real-world study were higher than those reported in trials of trifluridine/tipiracil,[33] nivolumab,[34] and irinotecan[10] as third- or later-line treatments. These findings indicate that T-DXd should be the preferred third-line treatment for HER2-positive AGC.

In the DESTINY-Gastric01 trial, T-DXd showed better efficacy in patients with HER2 IHC 3+ AGC than those with HER2 IHC 2+/ISH+ AGC.[35] In the present study, the median PFS was comparable regardless of HER2 status. However, long-term PFS was observed in patients with AGC and HER2 IHC 3+ (Supplemental Figure S7(A)). In addition, improved OS was noted in patients with HER2 IHC 3+, with a mOS of 9.0 months, compared to 5.6 months in those with HER2 IHC 2+/ISH+ (Supplemental Figure S7(B)). These findings may suggest that durable responses are more likely to be achieved in patients with HER2 IHC 3+. Therefore, we assessed the DpR and DOR in 47 patients with measurable lesions (Supplemental Figure S8). Notably, patients with HER2 IHC 3+ AGC showed a higher rate of deep tumor shrinkage (DpR $\geqslant$ 50%, 12.8% vs 0%) and achieved a longer mDOR (20.0 months vs 8.6 months) than those with HER2 IHC 2+/ISH+ AGC. HER2 IHC 3+ status may be associated with enhanced response durability, potentially contributing to prolonged OS. Loss of HER2 expression was reported in 29%–69% of AGC patients following first-line T-mab treatment,[36–39] raising concerns that HER2 loss may negatively impact T-DXd efficacy. However, the DESTINY-Gastric01 trial

demonstrated a high ORR for T-DXd, although HER2 status was mostly determined based on archived samples collected before first-line T-mab treatment and was not reassessed immediately before T-DXd initiation.[35] Notably, in the present study, a longer second-line treatment duration was significantly associated with improved prognostic outcomes in patients treated with T-DXd, consistent with previous studies,[11,12] and suggests the potential recovery of HER2 expression and sensitivity during second-line chemotherapy without HER2-targeted agents. HER2 status was not re-evaluated through re-biopsies before T-DXd treatment herein, and there are no detailed reports on sequential HER2 status changes. An ongoing EN-MARK study (jRCTs031240055) has assessed biomarker dynamics, including HER2 status, across treatment lines using tissue and liquid biopsies after first-line T-mab treatment, which will provide insight into the optimal utilization of T-DXd clinically.

The safety profile of T-DXd observed in this study was generally consistent with its established profile, with the most common AEs being gastrointestinal or hematologic. Although no new safety concerns were observed, 15.3% of patients discontinued T-DXd due to AEs, which is comparable to that observed in the DESTINY-Gastric01 trial. Twenty-one (32.3%) patients received T-DXd treatment at a reduced dose from the first cycle, based on careful consideration by the treating physicians. The recommended dose of T-DXd for AGC (6.4 mg/kg) is higher than that recommended for other cancers, such as non-small cell lung cancer and breast cancer (5.4 mg/kg). Data from non-small cell lung cancer studies suggest that higher doses (6.4 mg/kg) are associated with greater AE risk.[40] The primary reason for dose reduction was poor tolerability during previous first- and second-line treatments, which included dose reductions, extended intervals between doses, and frequent dose interruptions, possibly due to AEs. In this study, initiating T-DXd at a reduced dose did not appear to compromise treatment efficacy, suggesting that starting at a lower dose may be a reasonable option for selected patients, particularly those who have shown limited tolerance to toxicity from prior chemotherapy. Importantly, despite the patient selection process, 18.6% of patients who received the standard dose of T-DXd discontinued treatment due to AEs, compared to only 4.8% of those who began with a reduced initial dose. There were no significant clinicopathological differences, including ECOG PS, age, and number of metastases, between patients who received the standard dose and those who received a reduced dose (Supplemental Table S4). Further clinical studies are needed to identify the optimal population for dose reduction.

This study had several limitations. First, it was conducted as a single-center retrospective analysis at a cancer-specialized hospital in Japan, potentially introducing selection bias and limiting the generalizability of our findings. The retrospective and exploratory nature of this study restricts the interpretability of our results. Due to this design, nonhematologic AEs may not have been fully captured in the medical records. Second, the relatively small sample size limited the statistical power of the study. Although these limitations highlight the need for further validation and large-scale studies, this study offers valuable insights into the potential benefits of T-DXd treatment.

Conclusion

This study demonstrated the real-world clinical efficacy and manageable safety profile of T-DXd as a third-line or later treatment for patients with HER2-positive AGC. Rapid and substantial tumor shrinkage may contribute to improved survival.

Declarations

Ethics approval and consent to participate

This study involves human participants and was approved by the Certified Review Board at the Cancer Institute Hospital of the Japanese Foundation for Cancer Research (IRB number: 2023-GB-15). The protocol was described on the hospital website, and subjects were provided the opportunity to opt out; therefore, no additional consent was required from patients.

Consent for publication

Consent for publication was obtained from the patients.

Author contributions

Koshiro Fukuda: Data curation; Formal analysis; Investigation; Writing – original draft.

Hiroki Osumi: Formal analysis; Investigation.

Keitaro Shimozaki: Formal analysis; Investigation.

Keisho Chin: Formal analysis; Investigation.

Mariko Ogura: Formal analysis; Investigation.

Shota Fukuoka: Formal analysis; Investigation.

Shohei Udagawa: Formal analysis; Investigation.

Koichiro Yoshino: Formal analysis; Investigation.

Mikako Tamba: Formal analysis; Investigation.

Takeru Wakatsuki: Formal analysis; Investigation.

Eiji Shinozaki: Formal analysis; Investigation.

Kensei Yamaguchi: Formal analysis; Investigation.

Akira Ooki: Conceptualization; Formal analysis; Project administration; Supervision; Validation; Writing – original draft; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The data used for this study, although not available in a public repository, will be made available to other researchers upon reasonable request.

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Supplemental material

Supplemental material for this article is available online.

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