MO6-3

Prognostic Factors for T-DXd Treatment in HER2+ Unresectable Advanced/Recurrent Gastric Cancer: EN-DEAVOR Sub-Analysis

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Background

- HER2 is overexpressed in approximately 20% of patients with G/GEJ cancer, and this has been associated with poor patient prognosis[1,2]
- T-DXd is a HER2-targeting ADC that has demonstrated efficacy in patients with HER2-positive advanced G/GEJ cancer (ECOG PS 0/1) in 3L+ (DESTINY-Gastric01 trial) and 2L (DESTINY-Gastric02 and 06 trials) settings with acceptable safety profiles[3,4]
- However, real-world data on treatment with T-DXd remain limited[5]
  - Moreover, evidence in patients not eligible for clinical trial participation (e.g., elderly patients and those with ECOG PS ≥2) is lacking

2L, second-line; 3L+, third- or later-line; ADC, antibody-drug conjugate; ECOG PS, Eastern Cooperative Oncology Group performance status; G/GEJ, gastric or gastroesophageal junction; HER2, human epidermal growth factor receptor 2; T-DXd, trastuzumab deruxtecan.

1. Ariga S. J Clin Med. 2023;12:3391. 2. Ma C, et al. Front Oncol. 2023;13:1080990. 3. Shitara K, et al. N Engl J Med. 2020;382:2419-2430. 4. Van Cutsem E, et al. Lancet Oncol. 2023;24:744-756.
5. Matsumoto T, et al. J Clin Med. 2022;11:2247.

Objectives

- The retrospective cohort study, EN-DEAVOR (UMIN000049032), assessed the real-world effectiveness and safety of T-DXd in patients with HER2-positive, unresectable, advanced/recurrent G/GEJ cancer in Japan

- The primary analysis of the study demonstrated the real-world effectiveness and safety of T-DXd in patients with HER2-positive, unresectable, advanced/recurrent G/GEJ cancer in Japan
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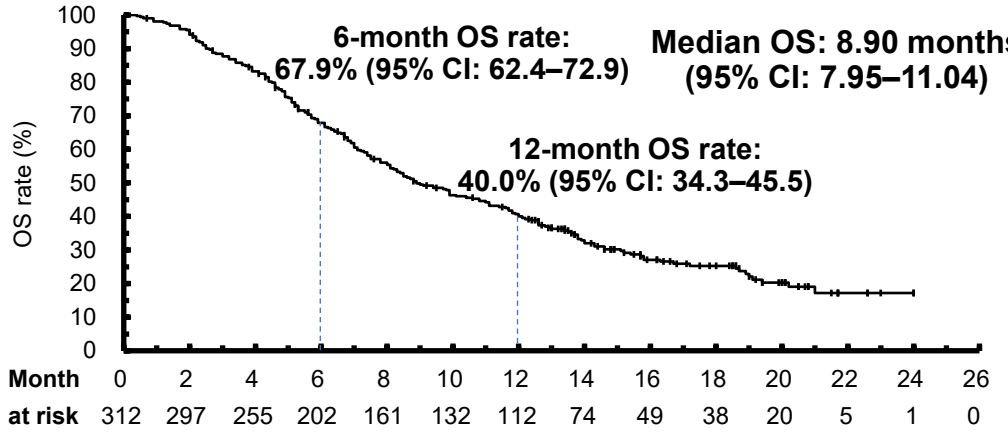
- This is a secondary analysis of the EN-DEAVOR study to investigate the prognostic factors for T-DXd used as third- or later-line treatment in gastric cancer. Univariate and multivariate analyses were performed to identify prognostic factors for rwPFS and ORR in this sub-analysis

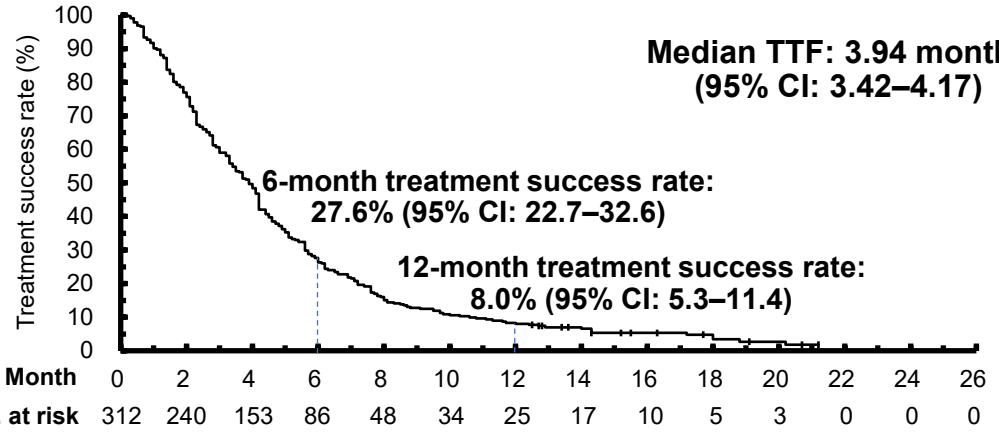
G/GEJ, gastric or gastroesophageal junction; HER2, human epidermal growth factor receptor 2; ORR, objective response rate; rwPFS, real-world progression-free survival; T-DXd, trastuzumab deruxtecan.

Results of the Primary Analysis: OS, rwPFS, and TTF (All Eligible Patients)

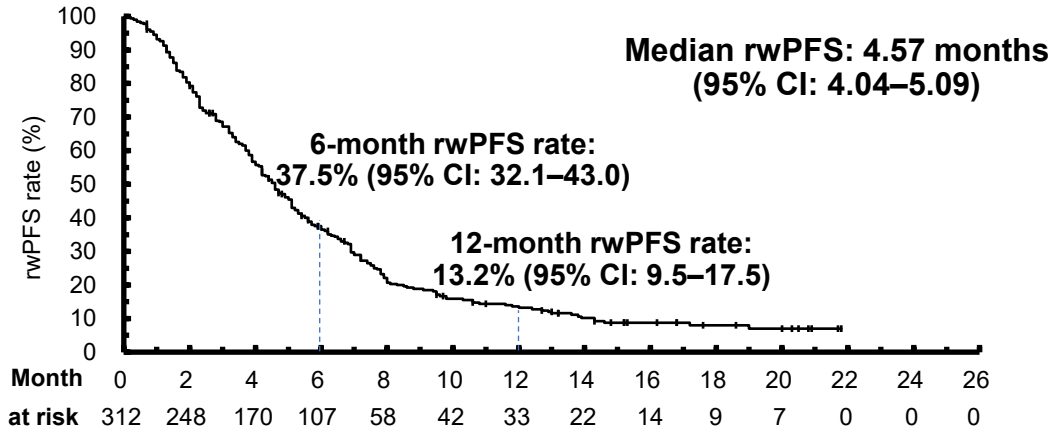
OS



TTF



rwPFS



Median follow-up period (T-DXd treatment duration): 8.31 months (n=312)

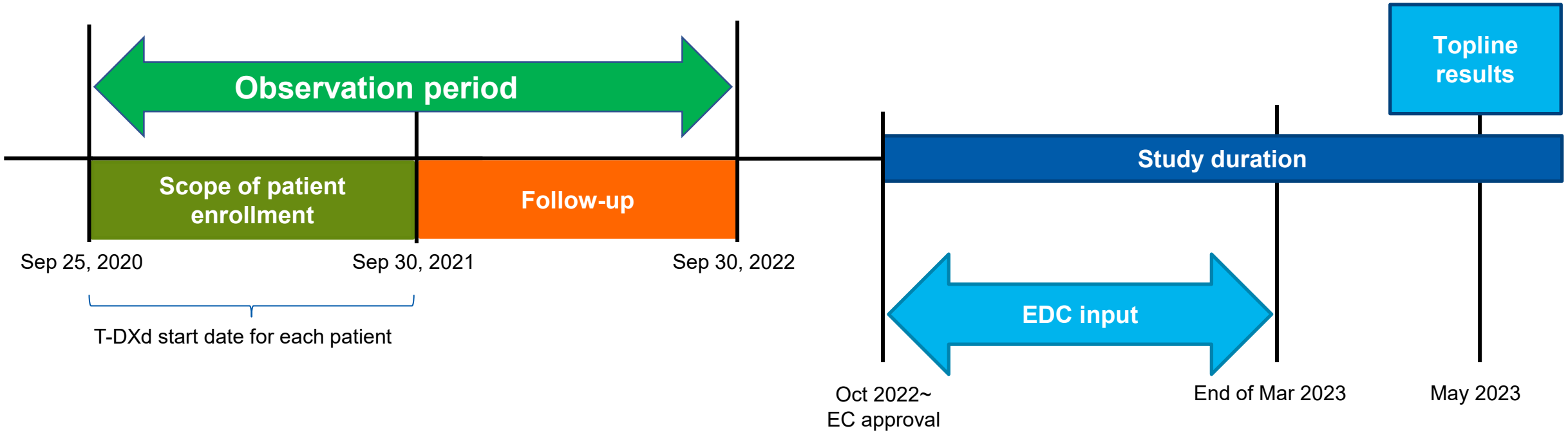
- The median OS, median rwPFS, and median TTF were 8.90, 4.57, and 3.94 months, respectively

Gastric Cancer. *2025;28:51-61. doi:10.1007/s10120-024-01555-w*

The median OS, rwPFS, and TTF were estimated using the Brookmeyer and Crowley method.
CI, confidence interval; OS, overall survival; rwPFS, real-world progression-free survival; T-DXd, trastuzumab deruxtecan; TTF, time to treatment failure.

Study Outline

- A non-interventional, observational, retrospective cohort study conducted at 63 sites in Japan
  - Enrollment period: September 25, 2020, to September 30, 2021, for the first dose of T-DXd
  - Observation period: September 25, 2020, to September 30, 2022



EC, ethics committee; EDC, electronic data capture; T-DXd, trastuzumab deruxtecan.

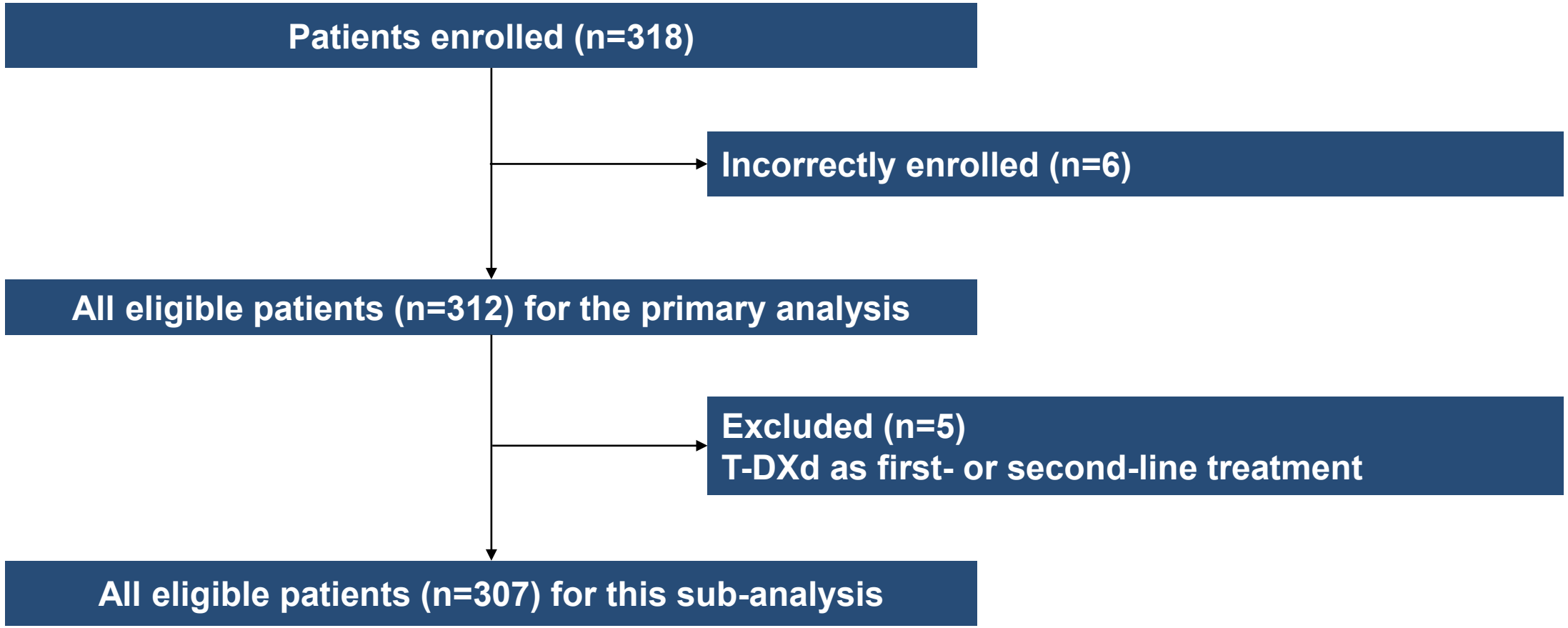
Eligibility Criteria

- Inclusion criteria:
  - Age ≥20 years
  - Histopathologically confirmed HER2-positive (IHC3+ or IHC2+ with ISH+) G/GEJ cancer
  - Unresectable, advanced/recurrent G/GEJ cancer that has progressed after cancer chemotherapy
  - T-DXd initiation date: September 25, 2020, to September 30, 2021

- Key exclusion criteria:
  - Patients with active, multiple primary malignancies that may affect the evaluation of T-DXd treatment
  - Patients who had received T-DXd in other interventional studies or at other sites
  - For this sub-analysis, patients who received T-DXd as first- or second-line therapies

G/GEJ, gastric or gastroesophageal junction; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, *in situ* hybridization; T-DXd, trastuzumab deruxtecan.

Patient Disposition



- Among the 318 patients enrolled, 307 were eligible for the analysis

T-DXd, trastuzumab deruxtecan.

Baseline Characteristics (All Eligible Patients)

		All eligible patients n=307
Male sex, n (%)		232 (75.6)
Age (years),, n (%)	<65	95 (30.9)
	≥65	212 (69.1)
ECOG PS, n (%)	0	131 (42.7)
	1	137 (44.6)
	2	32 (10.4)
	3	5 (1.6)
HER2 status at initial diagnosis, n (%)	IHC3+	213 (69.4)
	IHC2+ ISH+	84 (27.4)
Site of primary lesions: Stomach, n (%)		261 (85.0)
Any surgeries for primary lesions, n (%)		103 (33.6)
Histological type of primary lesions, n (%)	Diffuse	78 (25.4)
	Intestinal	169 (55.0)
	Others/ unknown	21 (6.8)/ 39 (12.7)

		All eligible patients n=307
≥2 metastatic organs, n (%)		189 (61.6)
Ascites: Yes, n (%)		132 (43.0)
Modified Glasgow Prognostic Score, n (%)	0	91 (30.4)
	1	134 (44.8)
	2	74 (24.7)
Median neutrophil-to-lymphocyte ratio		2.90
Number of previous lines of treatment for advanced or metastatic disease, n (%)	2	156 (50.8)
	≥3	151 (49.2)
Nivolumab treatment history, n (%)	Yes	127 (41.4)
	No	180 (58.6)
Duration of trastuzumab treatment before T-DXd treatment (months)	Median (range)	6.5 (0–81.5)
	25th percentile	3.5
	75th percentile	10.8

- Median patient age was 70.0 years
- A total of 37 (12.1%) patients had ECOG PS ≥2 and 132 (43.0%) had ascites
- Median duration of trastuzumab treatment before T-DXd treatment was 6.5 months

ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry, ISH, *in situ* hybridization; T-DXd, trastuzumab deruxtecan.

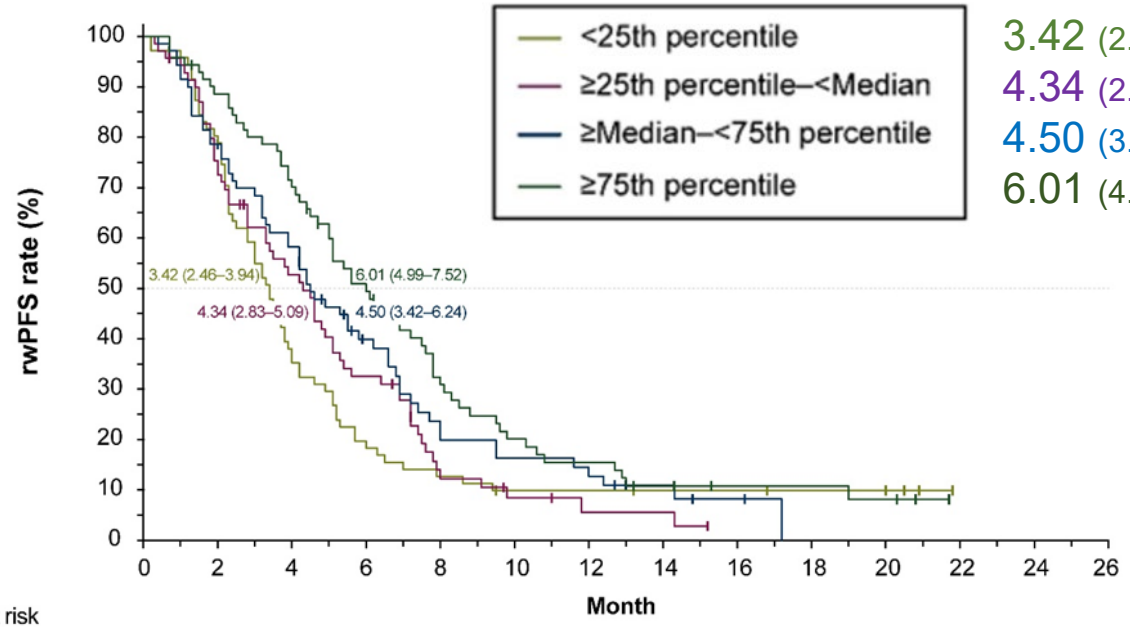
Univariate and Multivariate Analysis of rwPFS[a]

Factor	Category	Univariate analysis				Multivariate analysis[b]	
		Number of events (number of patients)	Median (95% CI)[c]	HR (95% CI)[d]	P value[d]	HR (95% CI)[d]	P value[d]
ECOG PS[e]	0	108 (131)	5.32 (4.50–6.34)	0.72 (0.56–0.92)	0.0077	0.78 (0.60–1.03)	0.0765
	≥1	155 (174)	3.88 (3.29–4.57)	Reference		Reference	
HER2 status (IHC and ISH): Before T-DXd treatment	IHC3+	180 (213)	4.86 (4.24–5.49)	0.68 (0.52–0.89)	0.0048	0.65 (0.49–0.86)	0.003
	IHC2+ and ISH+	77 (84)	3.48 (2.40–4.17)	Reference		Reference	
Any surgeries for primary lesions	Yes	87 (103)	5.78 (4.63–6.93)	0.70 (0.54–0.90)	0.0064	0.86 (0.65–1.15)	0.3203
	None	178 (204)	4.17 (3.45–4.57)	Reference		Reference	
Histological type of primary lesions	Intestinal	143 (169)	5.22 (4.53–6.24)	0.62 (0.46–0.82)	0.001	0.59 (0.43–0.79)	0.0006
	Diffuse	70 (78)	3.29 (2.27–4.17)	Reference		Reference	
Metastasis site: Peritoneum	None	166 (195)	5.06 (4.37–5.75)	0.76 (0.60–0.98)	0.0352	0.92 (0.68–1.23)	0.5673
	Yes	99 (112)	3.71 (2.96–4.57)	Reference		Reference	
Ascites[g]	None	142 (171)	5.32 (4.57–6.24)	0.65 (0.51–0.83)	0.0005	0.83 (0.61–1.13)	0.2337
	Yes	120 (132)	3.42 (2.69–4.21)	Reference		Reference	
mGPS[h]	0 and 1	192 (225)	5.06 (4.44–5.49)	0.64 (0.48–0.84)	0.0017	0.71 (0.53–0.95)	0.0215
	2	66 (74)	3.02 (2.20–3.94)	Reference		Reference	
Duration of trastuzumab treatment before T-DXd treatment (months)[e]	≥Median (≥6.5)	120 (142)	5.36 (4.44–6.47)	0.70 (0.55–0.91)	0.0062	0.75 (0.58–0.97)	0.0302
	<Median (<6.5)	125 (141)	3.71 (3.02–4.21)	Reference		Reference	

- HER2 status, histological type of primary lesions, modified Glasgow Prognostic Score, and prior trastuzumab duration (≥median) were independent predictors of rwPFS

*Sex, age, site of primary lesions, number of metastases, liver metastases, LDH, ALP, number of lines at previous therapy, CrCl, Hb, NLR, and nivolumab treatment history were also analyzed in the univariate model.
**Factors with a significant P value (<0.05) in the univariate analysis were included in the multivariate model. a: N=307 unless otherwise specified, b: Factors with P<0.05 in the univariate analysis were included in the multivariate analysis, c: Brookmeyer and Crowley method. d: Using the Cox proportional hazards model, e: n=305, g: n=303, h: n=299
ALP, alkaline phosphatase; CI, confidence interval; CrCl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; Hb, hemoglobin; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IHC, immunohistochemistry, ISH, *in situ* hybridization; LDH, lactate dehydrogenase; mGPS, modified Glasgow Prognostic Score; NLR, neutrophil-to-lymphocyte ratio; rwPFS, real-world progression-free survival; T-DXd, trastuzumab deruxtecan.

Kaplan–Meier Analysis of rwPFS by Duration of Trastuzumab Treatment Before T-DXd Treatment



Number at risk

<25th percentile	71	57	26	14	9	6	6	5	5	4	4	0	0	0
≥25th percentile–<Median	70	52	34	21	7	4	2	2	0	0	0	0	0	0
≥Median–<75th percentile	71	55	40	22	11	9	7	4	2	0	0	0	0	0
≥75th percentile	71	62	49	34	21	13	10	6	4	4	3	0	0	0

- There was a trend toward longer mPFS among patients with longer prior trastuzumab treatment

mPFS, median progression-free survival; rwPFS, real-world progression-free survival; T-DXd, trastuzumab deruxtecan.

Univariate and Multivariate Analysis of ORR[a]

Factor	Category	Univariate analysis				Multivariate analysis[b]	
		Number of events (number of patients)	Percentage (95% CI)[c]	OR[d] (95% CI)	P value[d]	OR[d] (95% CI)	P value[d]
ECOG PS[e]	0	42 (97)	43.3 (33.3–53.7)	1.04 (0.61–1.77)	0.8932		
	≥1	53 (125)	42.4 (33.6–51.6)	Reference			
HER2 status: Before T-DXd treatment	IHC3+	70 (147)	47.6 (39.3–56.0)	1.86 (1.02–3.40)	0.0441	1.62 (0.86–3.07)	0.1354
	IHC2+ and ISH+	22 (67)	32.8 (21.8–45.4)	Reference		Reference	
Any surgeries for primary lesions	Yes	40 (82)	48.8 (37.6–60.1)	1.51 (0.87–2.61)	0.1435		
	None	55 (142)	38.7 (30.7–47.3)	Reference			
Histological type of primary lesions	Intestinal	65 (132)	49.2 (40.4–58.1)	1.58 (0.81–3.08)	0.176		
	Diffuse	19 (50)	38.0 (24.7–52.8)	Reference			
Metastasis site: Peritoneum	None	72 (161)	44.7 (36.9–52.7)	1.41 (0.77–2.56)	0.2645		
	Yes	23 (63)	36.5 (24.7–49.6)	Reference			
Ascites[f]	None	63 (137)	46.0 (37.4–54.7)	1.43 (0.82–2.49)	0.2102		
	Yes	31 (83)	37.3 (27.0–48.7)	Reference			
mGPS[g]	0 and 1	76 (159)	47.8 (39.8–55.9)	1.98 (1.05–3.76)	0.0357	1.91 (0.98–3.71)	0.0575
	2	18 (57)	31.6 (19.9–45.2)	Reference		Reference	
Duration of trastuzumab treatment before T-DXd treatment (months)[h]	≥Median (≥6.5)	50 (97)	51.5 (41.2–61.8)	2.25 (1.28–3.96)	0.005	2.02 (1.13–3.63)	0.0181
	<Median (<6.5)	35 (109)	32.1 (23.5–41.7)	Reference		Reference	

- Duration of prior trastuzumab treatment (≥median) was a positive prognostic factor for ORR in the multivariate analysis (OR [95% CI]: 2.02 [1.13–3.63])

*Sex, age, site of primary lesions, number of metastases, liver metastases, LDH, ALP, number of lines at previous therapy, CrCl, Hb, NLR, and nivolumab treatment history were also analyzed in the univariate model.
**Factors with a significant P value (<0.05) in the univariate analysis were included in the multivariate model. a: N=224 unless otherwise specified, b: Factors with P<0.05 in the univariate analysis were included in the multivariate analysis, c: Clopper-Pearson method, d: Using the logistic regression model, e: n=222, f: n=220, g: n=216, h: n=223

ALP, alkaline phosphatase; CI, confidence interval; CrCl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; Hb, hemoglobin; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IHC, immunohistochemistry, ISH, *in situ* hybridization; LDH, lactate dehydrogenase; mGPS, modified Glasgow Prognostic Score; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; ORR, objective response rate; T-DXd, trastuzumab deruxtecan.

Safety: Most Common (>4%) Grade ≥3 TEAEs (All Eligible Patients)

	All n = 307	Duration of trastuzumab treatment before T-DXd	
		≥Median (≥6.5 months) n = 141	<Median (<6.5 months) n = 142
Adverse events, n (%)	149 (48.5)	68 (48.2)	67 (47.2)
Hematotoxicity	88 (28.7)	45 (31.9)	37 (26.1)
Non-hematotoxicity	86 (28.0)	36 (25.5)	42 (29.6)
Neutrophil count decreased	61 (19.9)	34 (24.1)	23 (16.2)
Anemia	29 (9.4)	15 (10.6)	14 (9.9)
Anorexia	27 (8.8)	9 (6.4)	15 (10.6)
Interstitial pneumonia	14 (4.6)	4 (2.8)	8 (5.6)
Nausea	13 (4.2)	4 (2.8)	9 (6.3)

- The overall incidence rate of grade ≥3 adverse events was similar in patients with duration of prior trastuzumab treatment ≥median and <median (48.2% vs. 47.2%)

TEAEs were coded using MedDRA version 26.0. Multiple selections were possible when reporting TEAEs.
MedDRA, Medical Dictionary for Regulatory Activities; T-DXd, trastuzumab Deruxtecan; TEAE, treatment-emergent adverse event.

Conclusions

- HER2 status IHC 3+, intestinal type primary lesions, mGPS 0 and 1, and longer duration of prior trastuzumab treatment (≥median [≥6.5 months]) were identified as positive prognostic factors for rwPFS in patients with advanced gastric or GEJ cancer treated with T-DXd in the third- or later-line settings
- The longer duration of prior trastuzumab treatment (≥median) was the only positive prognostic factor for ORR
- These findings provide insights into the treatment strategies for patients with advanced gastric cancer, and patients with the stated prognostic factors may be recommended for T-DXd

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; mPFS, median progression-free survival; rwPFS, real-world progression-free survival; T-DXd, trastuzumab deruxtecan.

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- Daiichi Sankyo and AstraZeneca entered into a global collaboration to jointly develop and commercialize T-DXd in March 2019, except in Japan where Daiichi Sankyo maintains exclusive rights for T-DXd. Daiichi Sankyo is responsible for the manufacturing and supply of T-DXd

Disclosures

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