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DESTINY Gastric04

Trastuzumab deruxtecan vs ramucirumab plus paclitaxel in second-line treatment of patients with human epidermal growth factor receptor 2–positive (HER2+) unresectable and/or metastatic gastric cancer or gastroesophageal junction adenocarcinoma: Primary analysis of the randomized, phase 3 DESTINY-Gastric04 study

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On behalf of the DESTINY-Gastric04 investigators

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Key Takeaways

- **DESTINY-Gastric04** is a global, randomized, multicenter, open-label, phase 3 clinical trial designed to investigate the efficacy and safety of T-DXd versus RAM + PTX as **2L treatment** for **HER2+ metastatic GC/GEJA**

- In this primary analysis, **T-DXd demonstrated a statistically significant and clinically meaningful improvement in OS** compared with RAM + PTX **in patients with HER2+ metastatic GC/GEJA**
- **T-DXd also exhibited statistically significant improvement** over RAM + PTX **in PFS and confirmed ORR**
- T-DXd 6.4 mg/kg toxicities were generally manageable and consistent with its known safety profile in GC/GEJA

2L, second-line; GC, gastric cancer; GEJA, gastroesophageal junction adenocarcinoma; HER2, human epidermal growth factor receptor 2; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PTX, paclitaxel; RAM, ramucirumab; T-DXd, trastuzumab deruxtecan.

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Current Treatment Landscape in HER2+ Metastatic GC/GEJA

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- An estimated 5%-17% of GCs are HER2+ (IHC 3+ or IHC 2+/ISH+)[1-4]
- 1L therapy for patients with HER2+ metastatic GC/GEJA is chemotherapy plus trastuzumab, with pembrolizumab if PD-L1 is expressed (CPS ≥1)[5]
- Results from the phase 2 DESTINY-Gastric01/02/06 trials led to the approval of T-DXd in the 2L+ setting in patients with HER2+ metastatic GC/GEJA[6-8]
- The combination of RAM + PTX is the SOC in 2L GC/GEJA based on results from the phase 3 RAINBOW trial[9]

DESTINY-Gastric04 was conducted to evaluate T-DXd in a head-to-head phase 3 trial versus RAM + PTX in patients with HER2+ metastatic GC/GEJA

1L, first-line; 2L, second-line; CPS, combined positive score; GC, gastric cancer; GEJA, gastroesophageal junction adenocarcinoma; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; PD-L1, programmed death ligand 1; PTX, paclitaxel; RAM, ramucirumab; SOC, standard of care; T-DXd, trastuzumab deruxtecan.

1. Uzunparmak B et al. *Ann Oncol.* 2023;34:1035-46. 2. Van Cutsem E et al. *Gastric Cancer.* 2015;18:476-84. 3. Subasinghe D et al. *J Int Med Res.* 2023;51:03000605231154403. 4. Bartley AN et al. *J Oncol Pract.* 2017;13:53-7. 5. ESMO Gastric Cancer Living Guideline v1.4 September 2024. European Society for Medical Oncology, 2024. (Accessed April 2, 2025, at https://www.esmo.org/living-guidelines/esmo-gastric-cancer-living-guideline). 6. Shitara K et al. *N Engl J Med.* 2020;382:2419-30. 7. Van Cutsem E et al. *Lancet Oncol.* 2023;24:744-56. 8. Shen L et al. *Ann Oncol.* 2023;34:S1542-3. 9. Wilke H et al. *Lancet Oncol.* 2014;15:1224-35.

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Study Design

DESTINY-Gastric04: A Global, Multicenter, Randomized, Phase 3 Trial (NCT04704934)

Patient Population

- HER2+ (IHC 3+ or IHC 2+/ISH+)[a] GC/GEJA
- HER2 status confirmed locally or centrally[b] on a recent biopsy obtained after progression on trastuzumab
- ECOG PS 0 or 1
- No clinically active CNS metastases[c]

R 1:1

- T-DXd 6.4 mg/kg Q3W
- RAM + PTX[d]

Primary Endpoint
- OS

Secondary Endpoints
- PFS (INV)[e]
- Confirmed ORR (INV)[e]
- DCR (INV)[e]
- DOR (INV)[e]
- Safety

Exploratory Endpoints
- PROs[f]

Stratification factors
- HER2 status (IHC 3+ vs IHC 2+/ISH+)
- Geography (Asia [excluding mainland China] vs Western Europe vs mainland China/rest of world)
- Time to progression on 1L therapy (<6 months vs ≥6 months)

1L, first-line; ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; CNS, central nervous system; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D-5L, EuroQol 5-Dimension, 5-Level; FACT-Ga, Functional Assessment of Cancer Therapy-gastric; GC, gastric cancer; GEJA, gastroesophageal junction adenocarcinoma; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; INV, investigator; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; PTX, paclitaxel; Q3W, every 3 weeks; R, randomization; RAM, ramucirumab; RECIST v1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; T-DXd, trastuzumab deruxtecan; VAS, visual analog scale.

[a]As classified by the 2017 ASCO-CAP guidelines for HER2 testing in gastroesophageal adenocarcinoma. [b]Study protocol originally mandated HER2 status be determined centrally but was later amended to allow local determination. [c]Clinically active CNS metastases were defined as being untreated and symptomatic or requiring therapy with corticosteroids or anticonvulsants. Patients with clinically inactive CNS metastases could be enrolled. [d]RAM administered as 8 mg/kg on days 1 and 15 of each 28-day cycle and PTX administered as 80 mg/m^2 on days 1, 8, and 15 of each 28-day cycle. [e]Determined by investigator-based assessment on RECIST v1.1. [f]Based on EORTC EQ-5D-5L VAS and FACT-Ga subscales.

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Statistical Analysis

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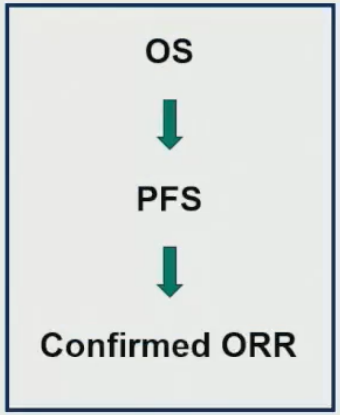
Planned sample size: 490

- 339 OS events were needed to ensure 90% power to detect an OS hazard ratio of 0.70 (overall 2-sided α error of 5%[a])

Interim OS analysis (planned after enrollment completion and 237 OS events [~70%[b]])

- OS, PFS, and confirmed ORR were tested hierarchically using a gatekeeping procedure to control for multiplicity[c]
- At DCO (October 24, 2024), there were 266 OS events and 322 investigator-assessed PFS events
- The superiority stopping boundary for OS was achieved at this interim analysis making this the primary analysis (2-sided $P < 0.0228$[d])

Hierarchical testing



DCO, data cutoff; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.
[a]1-sided error of 2.5%. [b]Information fraction. [c]Testing for these endpoints proceeded if the previous endpoint in the hierarchy was statistically significant. [d]Calculated based on the number of deaths by Lan-DeMets alpha-spending function, with an O'Brien-Fleming boundary.

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Patient Disposition

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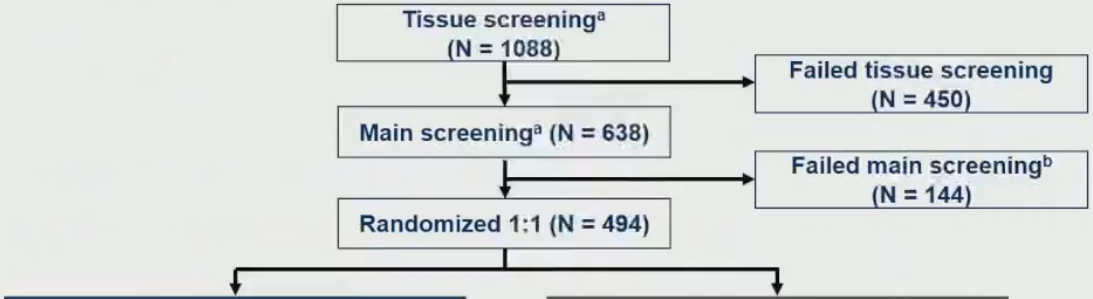

DCO, data cutoff; HER2, human epidermal growth factor receptor 2; PTX, paclitaxel; RAM, ramucirumab; T-DXd, trastuzumab deruxtecan.
DCO: October 24, 2024; Recruitment period: May 21, 2021-October 7, 2024
[a]Tissue screening started on the day a signed tissue screening informed consent form for HER2 testing was obtained; main screening started on the day the signed main informed consent form was obtained.
[b]Reasons for screen failure were not satisfying inclusion/exclusion criteria (n = 129), withdrawal by patient (n = 9), adverse event (n = 2), physician decision (n = 1), other (n = 3)

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Demographics and Baseline Characteristics

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	T-DXd n = 246	RAM + PTX n = 248
Age, median (range), years	63.2 (21.1-84.1)	64.3 (31.9-87.0)
Male, n (%)	187 (76.0)	205 (82.7)
Geography,[a] n (%)		
Asia (excluding mainland China)	57 (23.2)	60 (24.2)
Western Europe	140 (56.9)	139 (56.0)
Mainland China/ROW	49 (19.9)	49 (19.8)
Race, n (%)		
White	116 (47.2)	130 (52.4)
Black/African American	0	2 (0.8)
Asian	101 (41.1)	97 (39.1)
Other	28 (11.4)	19 (7.7)
ECOG PS, n (%)		
0 | 1	97 (39.4) | 148 (60.2)	88 (35.5) | 158 (63.7)
2 | missing	1 (0.4) | 0	1 (0.4) | 1 (0.4)
Primary tumor location, n (%)		
Gastric	153 (62.2)	149 (60.1)
GEJ	93 (37.8)	99 (39.9)

	T-DXd n = 246	RAM + PTX n = 248
HER2 status,[a,b] n (%)		
IHC 2+/ISH+	39 (15.9)	40 (16.1)
IHC 3+	207 (84.1)	208 (83.9)
Time to progression on 1L therapy,[a] n (%)		
<6 months	61 (24.8)	61 (24.6)
≥6 months	185 (75.2)	187 (75.4)
Prior treatment with ICI, n (%)		
Yes	39 (15.9)	38 (15.3)
No	207 (84.1)	210 (84.7)
Metastatic sites, n (%)		
<2	73 (29.7)	75 (30.2)
≥2	173 (70.3)	173 (69.8)
Presence of liver metastases, n (%)	147 (59.8)	158 (63.7)
Presence of brain metastases, n (%)	16 (6.5)	18 (7.3)

1L, first-line; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; ISH, in situ hybridization; PTX, paclitaxel; RAM, ramucirumab; ROW, rest of world; T-DXd, trastuzumab deruxtecan.
[a]Stratification factor by interactive response technology. [b]Local or central HER2 status.

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Subsequent Anticancer Therapy

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	T-DXd n = 246	RAM + PTX n = 248
Patients receiving any subsequent systemic anticancer treatment,[a] n (%)	126 (51.2)	118 (47.6)
Paclitaxel	63 (25.6)	8 (3.2)
Ramucirumab	43 (17.5)	8 (3.2)
Irinotecan	16 (6.5)	16 (6.5)
Nivolumab	14 (5.7)	14 (5.6)
Paclitaxel nanoparticle albumin-bound	13 (5.3)	0
Paclitaxel; ramucirumab	13 (5.3)	3 (1.2)
Trastuzumab	12 (4.9)	8 (3.2)
Calcium folinate; fluorouracil; irinotecan hydrochloride	11 (4.5)	12 (4.8)
Tipiracil hydrochloride; trifluridine	11 (4.5)	11 (4.4)
Fluorouracil	10 (4.1)	11 (4.4)
Oxaliplatin	10 (4.1)	1 (0.4)
Disitamab vedotin	5 (2.0)	12 (4.8)
Trastuzumab deruxtecan	3 (1.2)	52 (21.0)

- Of patients who discontinued study treatment from the RAM + PTX arm, 52 (21.0%) received T-DXd and 12 (4.8%) received disitamab vedotin as subsequent systemic anticancer therapy

PTX, paclitaxel; RAM, ramucirumab; T-DXd, trastuzumab deruxtecan
Received by ≥4% of patients in either arm, listed in descending order in the T-DXd arm.
[a]Patients may have received more than 1 type of subsequent anticancer therapy.

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OS: Primary Endpoint

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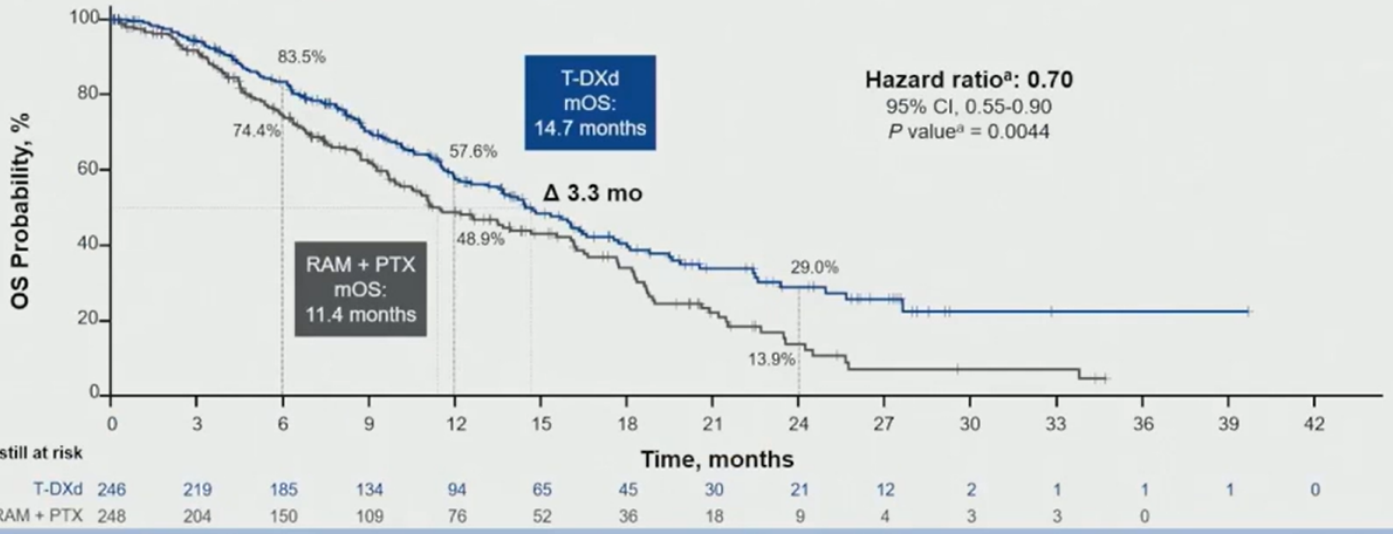

Patients still at risk

T-DXd	246	219	185	134	94	65	45	30	21	12	2	1	1	1	0
RAM + PTX	248	204	150	109	76	52	36	18	9	4	3	3	0		

T-DXd demonstrated a statistically significant and clinically meaningful improvement in OS compared with RAM + PTX in HER2+ GC/GEJA, showing a 30% reduction in risk of death

DCO, data cutoff; GC, gastric cancer; GEJA, gastroesophageal junction adenocarcinoma; HER2, human epidermal growth factor receptor 2; mOS, median overall survival; OS, overall survival; PTX, paclitaxel; RAM, ramucirumab; T-DXd, trastuzumab deruxtecan.

At DCO (October 24, 2024), the median duration of OS follow-up was 16.8 months for T-DXd and 14.4 months for RAM + PTX. Boundary for superiority: 2-sided $P < 0.0228$.

[a]Two-sided P value from stratified log-rank test and stratified Cox proportional hazards model adjusted for stratification factor: HER2 status (IHC 3+ or IHC 2+/ISH+).

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Predefined OS Sensitivity Analyses

	T-DXd n = 246	RAM + PTX n = 248
OS censored for subsequent anticancer therapy, median (95% CI),[a] months	NE (18.8-NE)	15.5 (10.8-NE)
HR (95% CI)[b]	0.64 (0.44-0.93)	
RPSFT-adjusted OS, median (95% CI),[a] months	14.7 (12.1-16.6)	11.0 (9.4-14.2)
HR (95% CI)[c]	0.67 (0.49-0.89)	

- A RPSFT model was used to adjust the OS of patients in the RAM + PTX arm who received poststudy T-DXd or disitamab vedotin
- Sensitivity analysis results were consistent with the primary analysis favoring T-DXd

HR, hazard ratio; IHC, immunohistochemistry; NE, not estimable; OS, overall survival; PTX, paclitaxel; RAM, ramucirumab; RPSFT, rank-preserving structural failure time; T-DXd, trastuzumab deruxtecan.
[a]Median OS and OS rates at specified time points were calculated from Kaplan-Meier analysis. CI for median was computed using the Brookmeyer-Crowley method. [b]Unstratified Cox proportional hazards models are used when there are fewer than 5 events in any of the treatment groups per stratum. [c]95% CI was estimated using bootstrapping percentile method with seed 123.

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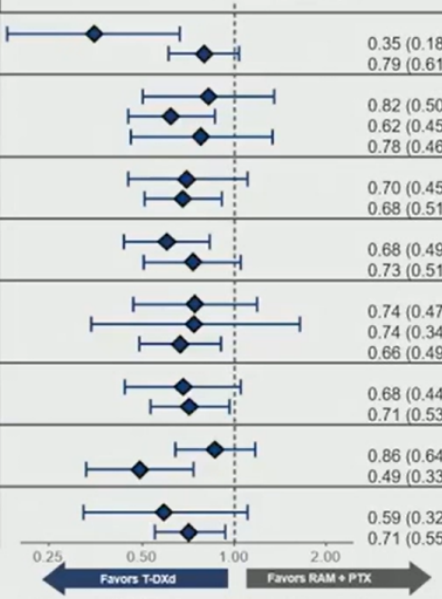
OS by Subgroups

	No. of Events/No. of Patients		OS, median (95% CI), months		Hazard Ratio (95% CI)
	T-DXd	RAM + PTX	T-DXd	RAM + PTX	
HER2 IHC status					
IHC 2+/ISH+	17/39	25/40	17.7 (9.1-NE)	7.4 (4.5-10.7)	0.35 (0.18-0.66)
IHC 3+	107/207	117/208	14.4 (11.9-16.4)	13.4 (10.8-16.5)	0.79 (0.61-1.03)
Geography					
Asia (excluding China)	31/57	34/60	14.4 (10.5-19.4)	16.1 (10.8-18.9)	0.82 (0.50-1.34)
Western Europe	67/140	79/139	15.7 (11.9-18.8)	11.1 (8.7-15.5)	0.62 (0.45-0.86)
Mainland China/ROW	26/49	29/49	14.8 (8.7-NE)	9.7 (7.4-16.0)	0.78 (0.46-1.33)
Time to progression on 1L					
<6 months	38/61	38/61	10.2 (8.1-14.4)	7.3 (5.0-10.1)	0.70 (0.45-1.10)
≥6 months	86/185	104/187	16.3 (13.7-19.4)	13.5 (11.0-17.6)	0.68 (0.51-0.91)
Age					
<65 years	69/140	75/130	15.7 (12.1-18.1)	11.1 (9.6-16.1)	0.68 (0.49-0.94)
≥65 years	55/106	67/118	13.7 (10.5-17.5)	11.5 (8.9-16.6)	0.73 (0.51-1.05)
Histologic subtype					
Intestinal	35/69	38/66	16.6 (11.5-20.5)	12.6 (9.9-18.3)	0.74 (0.47-1.18)
Diffuse	15/25	11/19	9.4 (7.9-16.0)	8.7 (4.6-16.1)	0.74 (0.34-1.64)
Others	74/152	93/163	14.7 (11.9-19.4)	11.1 (9.2-16.1)	0.66 (0.49-0.90)
ECOG PS					
0	38/97	45/88	18.1 (13.1-27.6)	17.6 (12.6-20.6)	0.68 (0.44-1.05)
1 or 2	86/149	96/159	13.9 (10.2-16.0)	9.9 (7.7-11.4)	0.71 (0.53-0.96)
Primary tumor location					
Gastric	83/153	83/149	11.9 (10.1-14.8)	11.4 (9.6-16.1)	0.86 (0.64-1.17)
GEJA	41/93	59/99	18.0 (14.7-22.5)	11.5 (9.2-16.2)	0.49 (0.33-0.74)
Prior treatment with ICI					
Yes	18/39	24/38	16.3 (10.2-NE)	10.1 (7.4-18.6)	0.59 (0.32-1.10)
No	106/207	118/210	14.4 (11.9-17.5)	12.6 (9.9-16.1)	0.71 (0.55-0.93)



1L, first-line; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJA, gastroesophageal junction adenocarcinoma; HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; ISH, in situ hybridization; OS, overall survival; PTX, paclitaxel; RAM, ramucirumab; ROW, rest of world; T-DXd, trastuzumab deruxtecan.

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PFS by Investigator: Key Secondary Endpoint

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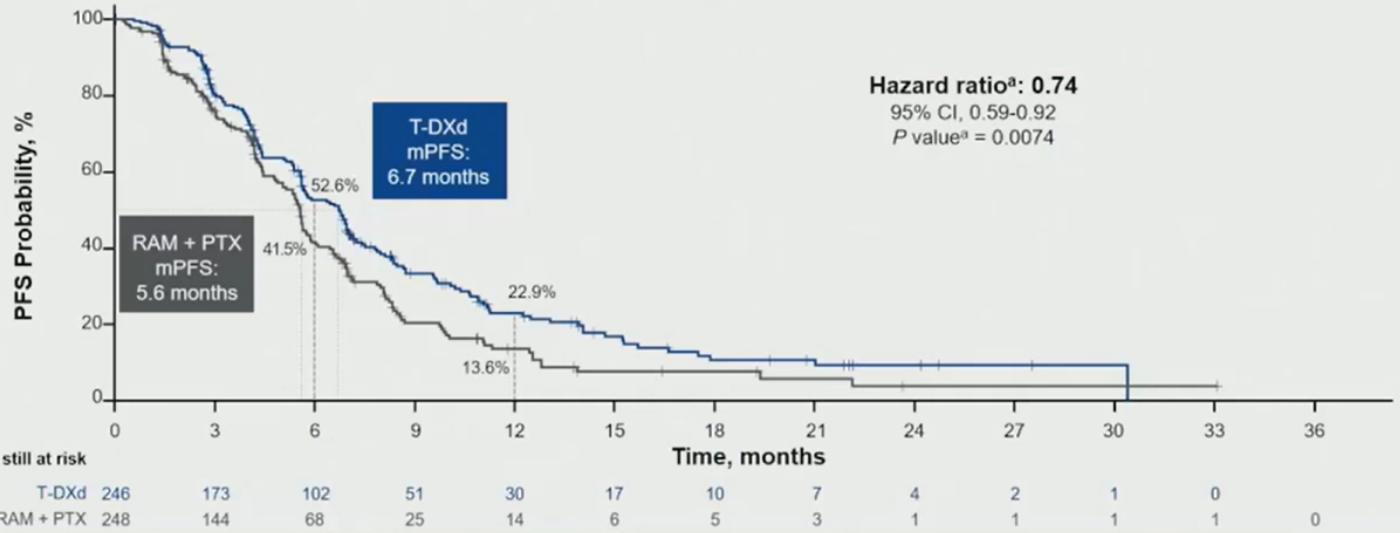

Hazard ratio[a]: 0.74
95% CI, 0.59-0.92
P value[a] = 0.0074

Patients still at risk

T-DXd	246	173	102	51	30	17	10	7	4	2	1	0
RAM + PTX	248	144	68	25	14	6	5	3	1	1	1	1	0

T-DXd demonstrated a statistically significant improvement in PFS compared with RAM + PTX in HER2+ GC/GEJA, showing a 26% reduction in risk of progression or death

GC, gastric cancer; GEJA, gastroesophageal junction adenocarcinoma; HER2, human epidermal growth factor receptor 2; mPFS, median progression-free survival; PFS, progression-free survival; PTX, paclitaxel; RAM, ramucirumab; T-DXd, trastuzumab deruxtecan.
Boundary for superiority: 2-sided $P < 0.0185$.
[a]Two-sided *P* value from stratified log-rank test and stratified Cox proportional hazards model adjusted for stratification factor: HER2 status (IHC 3+ or IHC 2+/ISH+).

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PFS by Subgroups

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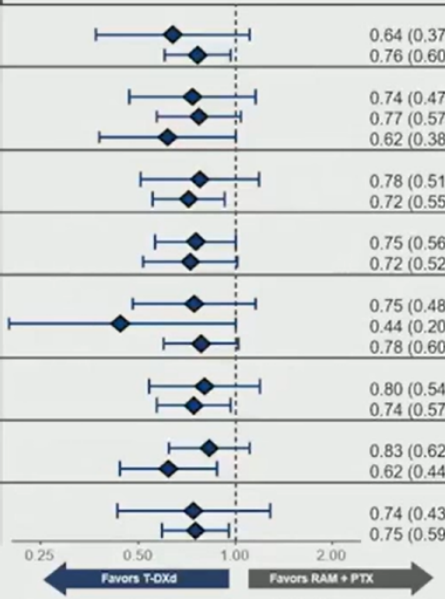
	No. of Events/No. of Patients		PFS, median (95% CI), months		Hazard Ratio (95% CI)
	T-DXd	RAM + PTX	T-DXd	RAM + PTX	
HER2 IHC status					
IHC 2+/ISH+	27/39	27/40	4.4 (3.0-9.7)	3.6 (2.4-5.4)	0.64 (0.37-1.11)
IHC 3+	139/207	129/208	6.7 (5.6-7.1)	5.6 (5.1-6.4)	0.76 (0.60-0.97)
Geography					
Asia (excluding China)	39/57	37/60	6.9 (4.4-10.9)	5.4 (4.0-8.1)	0.74 (0.47-1.16)
Western Europe	94/140	83/139	5.9 (5.6-6.9)	5.6 (4.8-5.9)	0.77 (0.57-1.04)
Mainland China/ROW	33/49	36/49	7.2 (4.2-9.6)	5.6 (4.4-7.0)	0.62 (0.38-1.00)
Time to progression on 1L					
<6 months	49/61	41/61	5.4 (4.0-5.7)	4.2 (2.8-5.0)	0.78 (0.51-1.18)
≥6 months	117/185	115/187	6.9 (5.9-8.1)	5.6 (5.4-6.6)	0.72 (0.55-0.93)
Age					
<65 years	96/140	86/130	6.8 (5.7-7.5)	5.6 (4.2-6.4)	0.75 (0.56-1.00)
≥65 years	70/106	70/118	5.7 (5.3-7.8)	5.6 (4.8-6.5)	0.72 (0.52-1.01)
Histologic subtype					
Intestinal	47/69	36/66	6.3 (5.1-8.7)	4.9 (4.2-5.6)	0.75 (0.48-1.67)
Diffuse	13/25	13/19	6.9 (5.6-14.0)	4.2 (2.6-8.0)	0.44 (0.20-1.00)
Others	106/152	107/163	6.7 (5.6-7.2)	5.6 (5.3-6.5)	0.78 (0.60-1.02)
ECOG PS					
0	63/97	43/88	6.9 (5.6-8.3)	6.0 (4.4-7.9)	0.80 (0.54-1.19)
1 or 2	103/149	113/159	6.3 (5.1-7.0)	5.5 (4.4-5.7)	0.74 (0.57-0.97)
Primary tumor location					
Gastric	102/153	86/149	5.9 (5.1-7.4)	5.6 (4.4-6.8)	0.83 (0.62-1.10)
GEJA	64/93	70/99	6.9 (5.7-8.0)	5.5 (4.4-5.8)	0.62 (0.44-0.88)
Prior treatment with ICI					
Yes	28/39	27/38	7.2 (4.4-9.6)	5.4 (4.2-8.1)	0.74 (0.43-1.27)
No	138/207	129/210	6.4 (5.6-7.0)	5.6 (4.8-5.8)	0.75 (0.59-0.95)



1L, first-line; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJA, gastroesophageal junction adenocarcinoma; HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; ISH, in situ hybridization; PFS, progression-free survival; PTX, paclitaxel; RAM, ramucirumab; ROW, rest of world; T-DXd, trastuzumab deruxtecan.

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Confirmed ORR and DOR[a,b]

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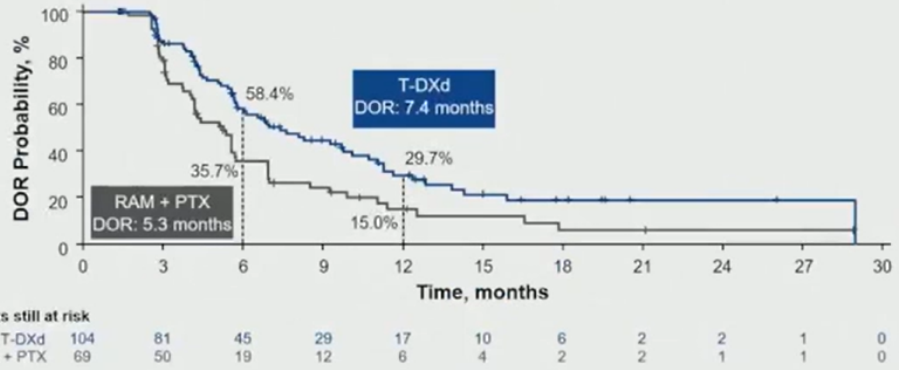
	T-DXd n = 246	RAM + PTX n = 248
Confirmed ORR (95% CI),[c] %	**44.3 (37.8-50.9)**	**29.1 (23.4-35.3)**
P value[d]	0.0006	
Difference (95% CI),[e] %	15.1 (6.1-24.2)	
DOR, median (95% CI), mo	**7.4 (5.7-10.1)**	**5.3 (4.1-5.7)**
DCR (95% CI), %	**91.9 (87.7-95.1)**	**75.9 (70.0-81.2)**
Confirmed BOR, n (%)		
CR[f]	7 (3.0)	3 (1.3)
PR	97 (41.3)	66 (27.8)
SD[g]	112 (47.7)	111 (46.8)
PD	13 (5.5)	22 (9.3)
NE	6 (2.6)	35 (14.8)



The confirmed ORR was 15.1% greater with T-DXd compared with RAM + PTX (*P* = 0.0006), with longer DOR

BOR, best overall response; CR, complete response; DCO, data cutoff; DCR, disease control rate; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; NE, not evaluable; PD, progressive disease; PR, partial response; ORR, objective response rate; PTX, paclitaxel; RAM, ramucirumab; SD, stable disease; T-DXd, trastuzumab deruxtecan

ORR-eligible patients are those who were randomly assigned at least 77 days (ie, 2 × 6 weeks − 1 week) before DCO date of interim analyses. Confirmed BOR, ORR, and DCR are calculated using the eligible patients as the denominator.

[a]Based on investigator assessment. [b]Based on ORR-eligible patients. [c]Based on Clopper-Pearson method for single proportion. [d]Stratified analysis using the Cochran-Mantel-Haenszel test adjusted for stratification factor: HER2 status (IHC 3+ or IHC 2+/ISH+). [e]2-sided 95% CI for the difference in ORR is based on Wald method using continuity correction. [f]CR patients without target lesions at baseline were included. [g]Non-CR/non-PD patients without target lesions at baseline were included.

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Overall Safety Summary

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	Safety analysis set N = 477	
	T-DXd n = 244	RAM + PTX n = 233
Any TEAE, n (%)	244 (100)	228 (97.9)
Drug-related	227 (93.0)	213 (91.4)
Grade ≥3 TEAEs, n (%)	166 (68.0)	172 (73.8)
Drug-related	122 (50.0)	126 (54.1)
Serious TEAEs, n (%)	100 (41.0)	101 (43.3)
Drug-related	45 (18.4)	41 (17.6)
TEAEs associated with dose discontinuation, n (%)	35 (14.3)	40 (17.2)
Drug-related	28 (11.5)	31 (13.3)
TEAEs associated with dose interruption, n (%)	137 (56.1)	141 (60.5)
Drug-related	94 (38.5)	119 (51.1)
TEAEs associated with dose reduction, n (%)	77 (31.6)	87 (37.3)
Drug-related	76 (31.1)	84 (36.1)
TEAEs associated with death, n (%)	22 (9.0)	35 (15.0)
Drug-related[a]	4 (1.6)	2 (0.9)

- Median treatment duration:
  - **T-DXd:** 5.4 mo (range, 0.7-30.3 mo)
  - **RAM + PTX**: 4.6 mo (range, 0.9-34.9 mo)
- Similar incidence of drug-related grade ≥3 TEAEs, serious TEAEs, treatment discontinuations, and deaths were observed in the 2 arms

ILD, interstitial lung disease; mo, months; PTX, paclitaxel; RAM, ramucirumab; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
[a]Drug-related adverse events that were associated with death occurred in 4 patients (1.6%) who received T-DXd (upper gastrointestinal hemorrhage, intestinal obstruction, sudden death, and death not otherwise specified in 1 patient each) and in 2 patients (0.9%) who received RAM + PTX (gastric perforation and ILD in 1 patient each).

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Confirmed ORR and DOR[a,b]

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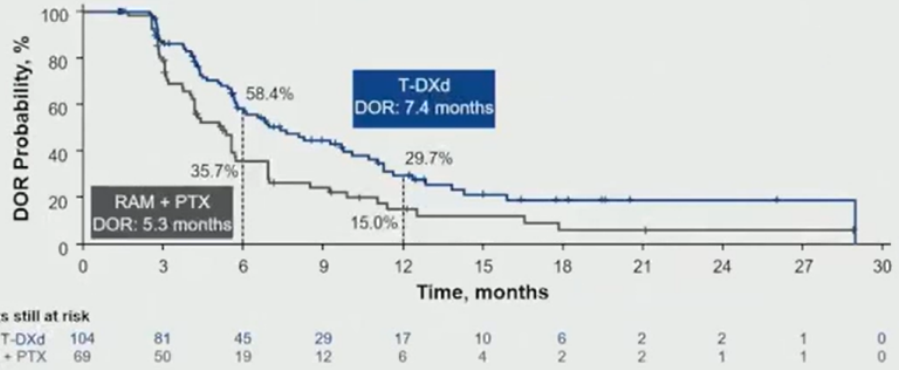
	T-DXd n = 246	RAM + PTX n = 248
Confirmed ORR (95% CI),[c] %	**44.3 (37.8-50.9)**	**29.1 (23.4-35.3)**
P value[d]	0.0006	
Difference (95% CI),[e] %	15.1 (6.1-24.2)	
DOR, median (95% CI), mo	**7.4 (5.7-10.1)**	**5.3 (4.1-5.7)**
DCR (95% CI), %	**91.9 (87.7-95.1)**	**75.9 (70.0-81.2)**
Confirmed BOR, n (%)		
CR[f]	7 (3.0)	3 (1.3)
PR	97 (41.3)	66 (27.8)
SD[g]	112 (47.7)	111 (46.8)
PD	13 (5.5)	22 (9.3)
NE	6 (2.6)	35 (14.8)



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ORR eligible patients are those who were randomly assigned at least 77 days (ie, 2 × 6 weeks − 1 week) before DCO date of interim analyses. Confirmed BOR, ORR, and DCR are calculated using the eligible patients as the denominator

[a]Based on investigator assessment. [b]Based on ORR eligible patients. [c]Based on Clopper-Pearson method for single proportion. [d]Stratified analysis using the Cochran-Mantel-Haenszel test adjusted for stratification factor: HER2 status (IHC 3+ or IHC 2+/ISH+). [e]2-sided 95% CI for the difference in ORR is based on Wald method using continuity correction. [f]CR patients without target lesions at baseline were included. [g]Non-CR/non-PD patients without target lesions at baseline were included.

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AEs of Special Interest

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Adjudicated drug-related ILD/pneumonitis

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd (n = 244)	7 (2.9)	26 (10.7)	1 (0.4)	0	0	34 (13.9)
RAM + PTX (n = 233)	0	0	2 (0.9)	0	1 (0.4)	3 (1.3)

Left ventricular dysfunction[a]

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd (n = 244)	0	3 (1.2)	3 (1.2)	0	0	6 (2.5)
RAM + PTX (n = 233)	2 (0.9)	2 (0.9)	0	0	0	4 (1.7)

- ILD/pneumonitis events in the T-DXd arm were mainly low-grade, with no grade 4 or 5 events
  - Adjudicated drug-related ILD/pneumonitis occurred in 34 patients (13.9%) treated with T-DXd and 3 patients (1.3%) treated with RAM + PTX
- Incidence of left ventricular dysfunction was similar across both arms

AE, adverse event; ILD, interstitial lung disease; LVEF, left ventricular ejection fraction; PTX, paclitaxel; RAM, ramucirumab; T-DXd, trastuzumab deruxtecan.
[a]Includes preferred terms of ejection fraction decreased, cardiac failure, cardiac failure acute, cardiac failure congestive, and left ventricular dysfunction.

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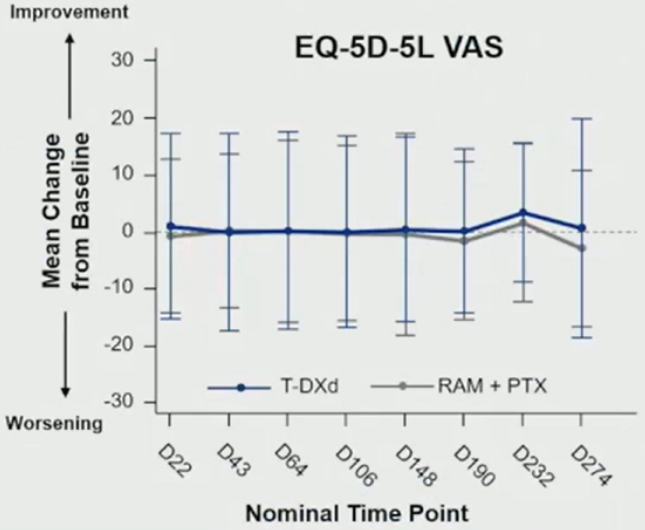
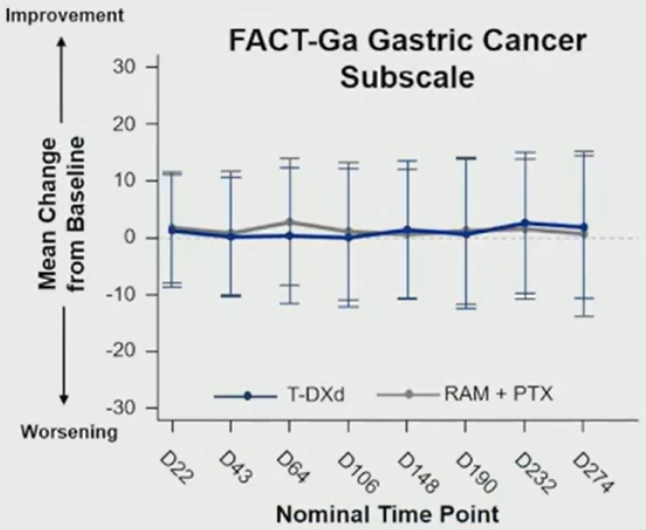
Patient-Reported Outcomes[a-c]





Patient HRQOL was maintained during treatment with T-DXd; baseline scores on the EQ-5D-5L VAS and FACT-Ga subscale remained stable, with no clinically meaningful changes[d]

D, day; EQ-5D-5L, EuroQol 5-Dimension, 5-Level; FACT-Ga, Functional Assessment of Cancer Therapy-gastric; HRQOL, health-related quality of life; PTX, paclitaxel; RAM, ramucirumab; T-DXd, trastuzumab deruxtecan; VAS, visual analog scale
[a]Median treatment duration was 5.4 months with T-DXd and 4.6 months with RAM + PTX. [b]Baseline completion rates for the EQ-5D-5L VAS and FACT-GA subscale were 98.2% and 99.1%, respectively, in the T-DXd arm, and 99.5% and 97.5% in the RAM + PTX arm. [c]Results for an arm were no longer considered informative once the number of patients who had the specified visit dropped below 10%, which occurred after D274. [d]Defined as a ≥10 point change from baseline.

Conclusions

DESTINY Gastric04

- **T-DXd demonstrated a statistically significant and clinically meaningful improvement in OS** compared with RAM + PTX in patients with HER2+ metastatic GC/GEJA in the 2L setting (median, 14.7 vs 11.4 months, respectively, with 30% reduction in risk of death: **HR, 0.70 [*P* = 0.0044]**)
- **Improvement in PFS, confirmed ORR, DCR,** and **DOR** was also observed **with T-DXd**
- The toxicity profile of T-DXd 6.4 mg/kg was generally manageable and was consistent with its known safety profile, with **no new safety signals identified**
  - Patient-reported QOL was maintained with T-DXd; scores were comparable in the T-DXd versus RAM + PTX arm
- Results support further evaluation of T-DXd in an earlier line setting

DESTINY-Gastric04 confirms T-DXd as the global 2L standard-of-care therapy for patients with HER2+ metastatic GC/GEJA

2L, second-line; DCR, disease control rate; DOR, duration of response; GC, gastric cancer; GEJA, gastroesophageal junction adenocarcinoma; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PTX, paclitaxel; QOL, quality of life; RAM, ramucirumab; T-DXd, trastuzumab deruxtecan.

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