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Trastuzumab deruxtecan (T-DXd) vs ramucirumab (RAM) plus paclitaxel (PTX) in second-line (2L) treatment of patients (pts) with HER2+ unresectable/metastatic gastric cancer (GC)/gastroesophageal junction adenocarcinoma (GEJA): Additional data from DESTINY-Gastric04

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Objective

- We report additional safety and efficacy data from the primary data cutoff (October 24, 2024) of DESTINY-Gastric04, the first phase 3 study to evaluate trastuzumab deruxtecan (T-DXd) versus ramucirumab (RAM) plus paclitaxel (PTX) in patients with human epidermal growth factor receptor 2–positive (HER2+) unresectable/metastatic gastric cancer or gastroesophageal junction adenocarcinoma (GC/GEJA) in the second-line (2L) setting

Conclusions

- These additional data from DESTINY-Gastric04 provide further evidence of the clinically meaningful improvement in efficacy with T-DXd over RAM + PTX in the 2L setting in HER2+ unresectable/metastatic GC/GEJA, reinforcing its use as the global 2L standard of care
  - Overall survival (OS) data based on central HER2 testing further support the robustness of the primary endpoint findings
- Exposure-adjusted incidence rates (EAIRs) per 100 patient-years were lower in the T-DXd arm than in the RAM + PTX arm for grade ≥3, serious, and fatal treatment-emergent adverse events (TEAEs), and TEAEs associated with drug discontinuation, dose reduction, and drug interruption
- Patient-reported health-related quality of life was maintained with T-DXd

Plain Language Summary

Why did we perform this research?
Approximately 5%-17% of gastric cancer (GC) cases express human epidermal growth factor receptor 2 (HER2), a protein on the surface of some cancer cells.[1-4] Trastuzumab deruxtecan (T-DXd) is an anticancer therapy that targets HER2 and is approved to treat patients with metastatic GC or gastroesophageal junction adenocarcinoma (GEJA) that is HER2 positive (HER2+).[5-7] DESTINY-Gastric04 was performed to compare the treatment benefits and safety of T-DXd with ramucirumab plus paclitaxel, an alternative second-line treatment option, in patients with HER2+ metastatic GC or GEJA.[8] The primary analysis showed that patients who were given T-DXd had clinically meaningful longer overall survival than patients given ramucirumab plus paclitaxel.[8] We report additional data of T-DXd compared with ramucirumab plus paclitaxel from DESTINY-Gastric04.

How did we perform this research?
Patients who had gastric cancer that was confirmed as expressing HER2 from a recent sample of their cancer were eligible for enrollment into this phase 3 clinical trial. Patients were randomly assigned in a 1:1 ratio to 1 of 2 treatment groups. One group received T-DXd while the other group received ramucirumab plus paclitaxel. Patients were followed up throughout the trial to monitor their progress.

What were the findings of this research?
Results of this DESTINY-Gastric04 additional analysis were consistent with those reported previously in the primary analysis.[8] Exposure-adjusted incidence rates of treatment-emergent adverse events (TEAEs) were lower with T-DXd than RAM + PTX treatment for grade ≥3, serious, and fatal TEAEs, and TEAEs associated with study drug discontinuation, drug interruption, and dose reduction. Health-related quality of life reported by the patient was maintained during T-DXd treatment.

What are the implications of this research?
Additional efficacy data further supported an improvement in efficacy in patients given T-DXd over ramucirumab plus paclitaxel. Additional safety data further characterized and supported a generally manageable safety profile, with no new safety signals identified. These results reinforce T-DXd as a promising therapy choice to treat metastatic HER2+ gastric cancer that has progressed on first-line therapy.

Where can I access more information?
To learn more about the phase 3 DESTINY-Gastric04 trial please visit:
https://clinicaltrials.gov/study/NCT04704934

References

1. Bartley AN et al. *J Clin Oncol.* 2017;35:446-464.
2. Subasinghe D et al. *J Int Med Res.* 2023;51:1-16.
3. Uzunparmak B et al. *Ann Oncol.* 2023;34:1035-1046.
4. Van Cutsem E et al. *Gastric Cancer.* 2015;18:476-484.
5. Enhertu (fam-trastuzumab deruxtecan-nxki). Prescribing information. Daiichi Sankyo, Inc; 2024.
6. Nakada T et al. *Chem Pharm Bull.* 2019;67:173-185.
7. Ogitani Y et al. *Clin Cancer Res.* 2016;22:5097-5108.
8. Shitara K et al. *N Engl J Med.* 2025;393:336-348.

Poster

This study is sponsored by Daiichi Sankyo. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201).

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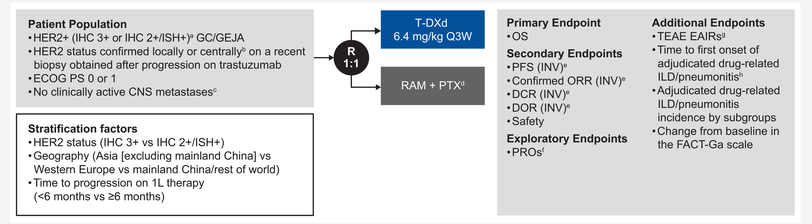
Introduction

- Among all cancer types, GC ranks fifth in terms of incidence and mortality[1]
- Approximately 5%-17% of GC cases are HER2+ (immunohistochemistry [IHC] 3+ or IHC 2+/in situ hybridization [ISH]–positive)[2-5]
- Results from the phase 2 DESTINY-Gastric01, DESTINY-Gastric02, and DESTINY-Gastric06 trials led to the approval of T-DXd in the 2L or later setting in patients with unresectable or metastatic HER2+ GC/GEJA[6-8]
- In patients with advanced or metastatic GC, an alternative 2L treatment option was RAM + PTX, regardless of HER2 status[9-11]
- In DESTINY-Gastric04, T-DXd demonstrated a statistically significant improvement in OS, progression-free survival (PFS), and confirmed objective response rate (cORR) over RAM + PTX in patients with HER2+ unresectable/metastatic GC/GEJA in the second-line setting[12]

Methods

- DESTINY-Gastric04 is a global, randomized, open-label, phase 3 study to assess the efficacy and safety of T-DXd 6.4 mg/kg versus RAM + PTX as a 2L therapy for patients with unresectable/metastatic GC/GEJA who were still HER2+(IHC 3+, IHC 2+/ISH+) by local or central testing after a trastuzumab-based regimen (**Figure 1**)
- Additional efficacy analyses included percentage change from baseline in the sum of target lesion diameters and time to response
- Concordance of central HER2 IHC analysis for patients screened based on local testing was conducted

Figure 1. DESTINY-Gastric04 study design



[a]As classified by 2018 ASCO-CAP guidelines.
[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 per RECIST v1.1.
[f]Based on EQ-5D-5L VAS and FACT-Ga subscales.
[g]EAIRs were measured to account for differences in treatment duration between T-DXd and RAM + PTX.
[h]Time to first onset of adjudicated ILD (days) was defined as the onset date of first ILD event adjudicated as drug-related - first dose date + 1.

Results

Patients

- At data cutoff (October 24, 2024), 246 patients were assigned to T-DXd and 248 to RAM + PTX
- Of 133 patients enrolled based on local HER2 test results, 122 patients also had central HER2 results
  - The positive percentage agreement for HER2+ status (IHC 3+ or IHC 2+/ISH+) between local and central testing was 79.5% (95% CI, 71.3-86.3)

Efficacy

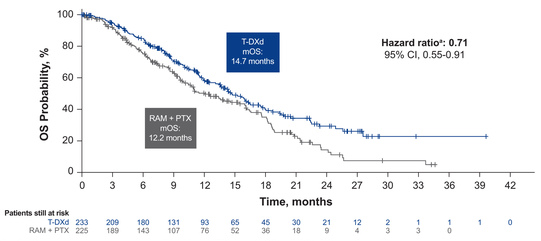
- Primary results from DESTINY-Gastric04 showed statistically significant improvements in OS, PFS, and cORR with T-DXd versus RAM + PTX (**Table 1**)[12]
  - T-DXd was associated with a 30% reduction in risk of death
  - OS results in patients with centrally confirmed HER2 status reinforced primary OS analysis results (**Figure 2**)

Table 1. Primary efficacy results[12]

End Point	T-DXd n = 246	RAM + PTX n = 248	Treatment Effect (95% CI)[a]	*P* value[b]
OS, median (95% CI)	14.7 (12.1-16.6)	11.4 (9.9-15.5)	0.70 (0.55-0.90)	0.004
PFS, median (95% CI)	6.7 (5.6-7.1)	5.6 (4.9-5.8)	0.74 (0.59-0.92)	0.007
cORR, % (95% CI)[c]	44.3 (37.8-50.9)	29.1 (23.4-35.3)	15.1 (6.1-24.2)	<0.001

[a]The treatment effect for OS is a hazard ratio for death, for PFS is a hazard ratio for disease progression or death, and for cORR is an absolute difference (in percentage points).
[b]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+). The *P* value for cORR was calculated with the use of the Cochran–Mantel–Haenszel test with adjustment for the HER2 status stratification factor.
[c]Based on ORR eligible patients.

Figure 2. Primary analysis results of OS in patients with centrally confirmed HER2 status[12]



[a]Stratified Cox proportional hazards model was adjusted for the HER2 status (IHC 3+ or IHC 2+/ISH+) stratification factor.
This figure was adapted from *The New England Journal of Medicine*, Shitara K et al. Trastuzumab deruxtecan versus ramucirumab plus paclitaxel in gastric cancer 2025. doi: 10.1056/NEJMoa2503119. Copyright © 2025 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

- Patients with measurable lesions at baseline who received T-DXd had a higher percentage change from baseline in the sum of target lesion diameters compared with patients who received RAM + PTX
  - Mean (±SD): T-DXd: −38.7% (27.8%); RAM + PTX: −27.1% (28.8%)
  - Median (range): T-DXd: −40.0% (−100.0% to 21.9%); RAM + PTX: −26.7% (−100.0% to 50.0%)
- Median time to response was similar in both treatment groups (1.5 months)

Safety

- 244 patients in the T-DXd group and 233 patients in the RAM + PTX group were included in the safety analysis population
- EAIRs per 100 patient-years for grade ≥3, serious, and fatal TEAEs, and TEAEs associated with study drug discontinuation, dose reduction, and drug interruption were lower in the T-DXd arm than the RAM + PTX arm (**Table 2**)

Table 2. EAIRs of TEAEs

EAIRs[a] per 100 patient-years[b]	T-DXd n = 244	RAM + PTX n = 233
Treatment duration, median (range), months	5.4 (0.7-30.3)	4.6 (0.9-34.9)
Total patient-years of exposure[c]	133.4	103.4
All TEAEs, n (%)	244 (100.0)	228 (97.9)
EAIR	3957.4	3482.9
Grade ≥3 TEAEs, n (%)	166 (68.0)	172 (73.8)
EAIR	230.9	338.0
Serious TEAEs, n (%)	100 (41.0)	101 (43.3)
EAIR	89.3	113.0
Fatal TEAEs, n (%)	22 (9.0)	35 (15.0)
EAIR	15.1	31.0
TEAEs associated with drug discontinuation, n (%)	35 (14.3)	40 (17.2)
EAIR	24.3	39.7
TEAEs associated with dose reduction, n (%)	77 (31.6)	87 (37.3)
EAIR	72.2	117.0
TEAEs associated with study drug interruption, n (%)	137 (56.1)	141 (60.5)
EAIR	158.2	270.3

[a]EAIR was defined as the number of patients with at least 1 event incidence (n) divided by (the sum of the adjusted patient-years of exposure over patients in safety analysis set [adjusted patient-years of exposure]/100).
[b]Patient-years of exposure were time from first dose date to the first incident date of the AE if the patient had the AE, or time from first dose date to the end of AE collection if the patient did not have the AE.
[c]Patient-year exposure was total of treatment duration of all patients within each treatment group.

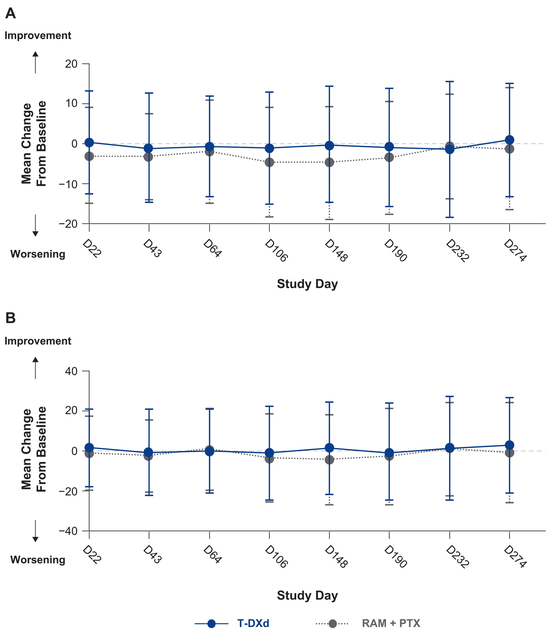
- The median time to first adjudicated drug-related ILD/pneumonitis onset was 104 days (range, 34-542 days) with T-DXd (34 patients) and 41 days (range, 13-58 days) with RAM + PTX (3 patients)
- Patients treated with T-DXd were more likely to experience adjudicated drug-related ILD/pneumonitis if they were ≥65 years of age or male, or had moderate renal impairment (**Table 3**)

Table 3. Adjudicated drug-related ILD/pneumonitis by subgroup

Subgroup	T-DXd % (n/N)	RAM + PTX % (n/N)
All patients	13.9 (34/244)	1.3 (3/233)
Age <65 years	10.8 (15/139)	0.8 (1/123)
Age ≥65 years	18.1 (19/105)	1.8 (2/110)
Female	6.9 (4/58)	0
Male	16.1 (30/186)	1.5 (3/194)
Normal renal function	12.1 (14/116)	1.8 (2/114)
Mild renal impairment	12.6 (11/87)	0
Moderate renal impairment	22.0 (9/41)	2.6 (1/38)

- Throughout the course of treatment, change from baseline in Functional Assessment of Cancer Therapy-Gastric (FACT-Ga) general and FACT-Ga gastric scales were maintained and did not deteriorate with either T-DXd or RAM + PTX, with no clinically meaningful changes from baseline observed (defined as a ≥10-point change from baseline) (**Figure 3**)

Figure 3. Change from baseline in FACT-Ga scales: (A) FACT-Ga general and (B) FACT-Ga gastric



Error bars represent standard deviation.
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 day 274.

Abbreviations

1L, first-line; 2L, second-line; ASCO-CAP, American Society of Clinical Oncology–College of American Pathologists; AE, adverse event; CNS, central nervous system; cORR, confirmed objective response rate; DCR, disease control rate; DOR, duration of response; EAIR, exposure-adjusted incidence rate; ECOG PS, Eastern Cooperative Oncology Group performance status; 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; mOS, median overall survival; mPFS, median progression-free survival; 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.

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Disclosures

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References

1. Bray F et al. *CA Cancer J Clin.* 2024;74:229-263.
2. Bartley AN et al. *J Clin Oncol.* 2017;35:446-464.
3. Subasinghe D et al. *J Int Med Res.* 2023;51:1-16.
4. Uzunparmak B et al. *Ann Oncol.* 2023;34:1035-1046.
5. Van Cutsem E et al. *Gastric Cancer.* 2015;18:476-484.
6. Shitara K et al. *N Engl J Med.* 2020;383:2419-2430.
7. Van Cutsem E et al. *Lancet Oncol.* 2023;24:744-756.
8. Shen L et al. *Ann Oncol.* 2023;34:S1542.
9. Lordick F et al. *Ann Oncol.* 2022;33:1005-1020.
10. Wilke H et al. *Lancet Oncol.* 2014;15:1224-1235.
11. De Vita F et al. *Future Oncol.* 2019;15:2723-2731.
12. Shitara K et al. *N Engl J Med.* 2025;393:336-348.

DESTINY Gastric04