ASCO Gastrointestinal Cancers Symposium, January 23–25, 2025

Poster 448

Updated results from the trastuzumab deruxtecan 5.4 mg/kg triplet combination of DESTINY-Gastric03: first-line T-DXd with fluoropyrimidine and pembrolizumab in advanced or metastatic HER2-positive gastric cancer, gastroesophageal junction adenocarcinoma, or esophageal adenocarcinoma

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Objective

- The objective of Part 2 (dose expansion) of the DESTINY-Gastric03 (DG-03) study was to evaluate first-line (1L) trastuzumab deruxtecan (T-DXd) alone or in combination with a fluoropyrimidine and/or pembrolizumab in human epidermal growth factor receptor 2–positive (HER2+) (immunohistochemistry [IHC] 3+ or IHC 2+ / in situ hybridization–positive [ISH+]) gastric cancer (GC), gastroesophageal junction adenocarcinoma (GEJA), or esophageal adenocarcinoma
  - Here, we report updated efficacy and safety results (data cutoff [DCO] August 19, 2024) for the T-DXd 5.4 mg/kg combination with fluoropyrimidine and pembrolizumab (arm F) with a time-matched analysis (DCO February 15, 2023) with T-DXd 6.4 mg/kg with fluoropyrimidine and pembrolizumab (arm D)

Conclusions

- T-DXd 6.4 mg/kg with fluoropyrimidine and pembrolizumab demonstrated antitumor activity (confirmed objective response rate [ORR]: 53.5%) in HER2+ GC, GEJA, or esophageal adenocarcinoma; however, it was associated with higher-than-expected toxicity
- At similar median durations of follow up, T-DXd 5.4 mg/kg and reduced-dose fluoropyrimidine with pembrolizumab showed promising early antitumor activity (confirmed ORR: 75.0%) in HER2+ GC, GEJA, or esophageal adenocarcinoma, with a manageable safety profile
- The time-matched analysis showed that lowering the dose of T-DXd to 5.4 mg/kg from 6.4 mg/kg and lowering the starting dose of capecitabine from 1000 mg/m^2 to 750 mg/m^2, improved tolerability of the triplet combination of T-DXd with fluoropyrimidine and pembrolizumab without decreasing the ORR
- These preliminary data provide encouragement for future development of T-DXd with fluoropyrimidine and pembrolizumab as a 1L treatment in HER2+ GC, GEJA, or esophageal adenocarcinoma

Plain language summary

Why did we perform this research?

Human epidermal growth factor receptor 2 (HER2) is a protein found at higher-than-normal levels in some cancers, including those in the stomach (gastric cancer [GC]), where the stomach meets the food pipe (gastroesophageal junction adenocarcinoma [GEJA]), and in the food pipe (esophageal adenocarcinoma).[1–3] These cancers are referred to as HER2-positive (HER2+) and the elevated levels of HER2 can promote tumor growth in some cancers.[1,3] Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate, which is a chemotherapy with a linker (together called deruxtecan [DXd]) joined to an antibody (trastuzumab). Trastuzumab binds to HER2 and internalizes into the cancer cell, where it releases the chemotherapy to kill tumor cells.[4,5] T-DXd is approved for patients with previously treated HER2+ GC or GEJA that has spread from its original site (advanced cancer).[6,7] Initial results of Part 2 of the DESTINY-Gastric03 (DG-03) study showed that T-DXd at a dose of 6.4 mg/kg or 5.4 mg/kg with chemotherapy and pembrolizumab (a cancer drug that targets a protein called programmed cell death protein 1) helped decrease the size of tumors in people with HER2+ GC, GEJA, or esophageal adenocarcinoma.[8]

How did we perform this research?

Part 2 of the DG-03 study evaluated the benefit and safety of T-DXd alone or in combination with chemotherapy and/or pembrolizumab in people with advanced HER2+ GC, GEJA, or esophageal adenocarcinoma who have not received any prior treatment. Here, we present updated results from T-DXd at a dose of 5.4 mg/kg with reduced-dose chemotherapy and standard dose pembrolizumab (arm F). Given the limited follow up of this treatment arm (length of time a person's health is monitored after treatment), a time-matched analysis with T-DXd at a dose of 6.4 mg/kg with full-dose chemotherapy and pembrolizumab (arm D) was performed.

What were the findings of this research?

Results from T-DXd at a dose of 5.4 mg/kg with reduced-dose chemotherapy and standard dose pembrolizumab (arm F) demonstrated that 75% of people had a response to the treatment. In addition, the time-matched analysis showed that reducing the dose of T-DXd to 5.4 mg/kg from 6.4 mg/kg, along with reducing the chemotherapy dosage, improved people's ability to tolerate the side effects of the triplet treatment without reducing its benefit.

What are the implications of this research?

These early results support the future development of the combination of T-DXd with chemotherapy and pembrolizumab as a treatment for people with advanced HER2+ GC, GEJA, or esophageal adenocarcinoma who have not received any prior treatment. Side effects appear more manageable at the reduced doses of T-DXd and chemotherapy. Further studies are needed to validate these findings.

Where can I access more information?

For more information about DG-03, please visit https://clinicaltrials.gov/study/NCT04379596, or please reach out to Professor Yelena Janjigian at janjigiy@mskcc.org

1. Gravalos C, Jimeno A. *Ann Oncol*. 2008;19:1523–1529; 2. Plum PS, et al. *BMC Cancer*. 2019;19:38; 3. Jørgensen JT, Hersom M. *J Cancer*. 2012;3:137–144; 4. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173–185; 5. Ogitani Y, et al. *Clin Cancer Res*. 2016;22:5097–5108; 6. Enhertu (fam-trastuzumab deruxtecan-nxki): highlights of prescribing information. 2024. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761139s028lbl.pdf (Accessed November 15, 2024); 7. Enhertu (trastuzumab deruxtecan): summary of product characteristics. 2023. Available from: https://www.ema.europa.eu/en/documents/product-information/enhertu-epar-product-information_en.pdf (Accessed November 15, 2024); 8. Janjigian YY, et al. Oral presentation at ESMO 2024 (Abstract 1401O)

Poster

This study was sponsored by AstraZeneca. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201).
Poster presented at ASCO GI 2025, January 23–25, San Francisco, CA, US by Professor Yelena Y Janjigian. Corresponding author email address: janjigiy@mskcc.org.

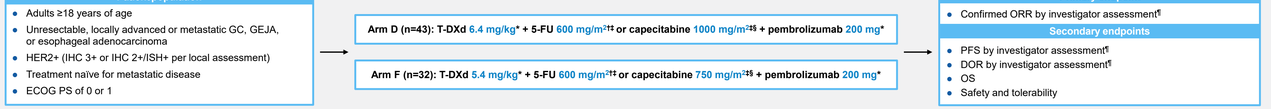
Introduction

- T-DXd is a HER2-directed antibody-drug conjugate,[1,2] T-DXd 6.4 mg/kg is approved for patients with locally advanced or metastatic HER2+ GC/GEJA who have received a prior trastuzumab-based regimen[3]
- Dual programmed cell death protein 1 and HER2 blockade in combination with standard chemotherapy (fluoropyrimidine / platinum-based regimens) have improved outcomes versus trastuzumab and standard chemotherapy in the 1L setting, specifically in tumors with a programmed cell death ligand 1 (PD-L1) combined positive score ≥1[4]
- Preliminary results (DCO May 6, 2024) from Part 2 of the DG-03 study showed promising antitumor activity with 1L T-DXd 6.4 mg/kg or 5.4 mg/kg with fluoropyrimidine and pembrolizumab in patients with advanced HER2+ GC, GEJA, or esophageal adenocarcinoma[5]
  - T-DXd 6.4 mg/kg with fluoropyrimidine and pembrolizumab was associated with higher-than-expected toxicity; however, early safety data from the T-DXd 5.4 mg/kg triplet combination demonstrated a more manageable safety profile[5]

Methods

- DG-03 is a Phase 1b/2 multicenter, open-label, dose-escalation (Part 1) and -expansion (Parts 2, 3, and 4) study (NCT04379596; https://clinicaltrials.gov/study/NCT04379596).[6] In Part 2 of the DG-03 study, patients with HER2+ (IHC 3+ or IHC 2+/ISH+ by local testing) GC, GEJA, or esophageal adenocarcinoma, irrespective of PD-L1 status, and no prior treatment for metastatic disease were enrolled (**Figure 1**)
- A time-matched analysis was performed to evaluate the efficacy and safety of the T-DXd 6.4 mg/kg (arm D) and T-DXd 5.4 mg/kg (arm F) triplet combination regimens at similar durations of follow up

Figure 1. Study design (DESTINY-Gastric03 Part 2, arms D and F only)



Part 2 of the DG-03 study consists of six arms (A–F). Only arms D and F are presented in this poster
*IV Q3W; †continuous IV infusion Q3W on Days 1–5; ‡treatment with 5-FU or capecitabine will be decided by the investigator; §orally BID Q3W on Days 1–14; ¶per RECIST 1.1
5-FU, 5-fluorouracil; BID, twice daily; DG-03, DESTINY-Gastric03; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; GC, gastric cancer; GEJA, gastroesophageal junction adenocarcinoma; HER2+, human epidermal growth factor receptor 2–positive; IHC, immunohistochemistry; ISH+, in situ hybridization–positive; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, once every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan

Results

Patient characteristics

- At the DCO of February 15, 2023 (median duration of follow up: 6.9 months), **43 patients** had received T-DXd 6.4 mg/kg with 5-fluorouracil (5-FU) / capecitabine 1000 mg/m^2 and pembrolizumab (arm D)
  - The median age was 65.0 years and ten patients (23.3%) were female; 34 patients (79.1%) had HER2 IHC 3+ status confirmed by local testing (**Table 1**)
- At the DCO of August 19, 2024 (median duration of follow up: 7.8 months), **32 patients** had received T-DXd 5.4 mg/kg with 5-FU/capecitabine 750 mg/m^2 and pembrolizumab (arm F)
  - The median age was 61.0 years and three patients (9.4%) were female; 26 patients (81.3%) had locally confirmed HER2 IHC 3+ status (**Table 1**)

Table 1. Patient demographics and clinical characteristics

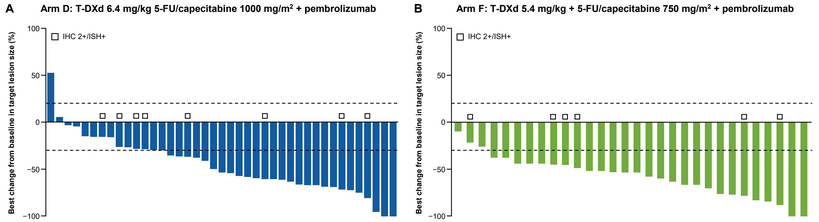
	DCO: February 15, 2023	DCO: August 19, 2024
	Arm D: T-DXd 6.4 mg/kg + 5-FU/capecitabine 1000 mg/m² + pembrolizumab n=43	Arm F: T-DXd 5.4 mg/kg + 5-FU/capecitabine 750 mg/m² + pembrolizumab n=32
Median age, years (range)	65.0 (41–80)	61.0 (20–78)
Female, n (%)	10 (23.3)	3 (9.4)
Race, n (%)		
Asian	19 (44.2)	15 (46.9)
Non-Asian	24 (55.8)	17 (53.1)
ECOG PS, n (%)		
0	23 (53.5)	17 (53.1)
1	20 (46.5)	15 (46.9)
Primary tumor site, n (%)		
Gastric	27 (62.8)	21 (65.6)
GEJ	8 (18.6)	7 (21.9)
Esophageal	8 (18.6)	4 (12.5)
Local HER2 status, n (%)		
IHC 3+	34 (79.1)	26 (81.3)
IHC 2+/ISH+	8 (18.6)	6 (18.8)
Missing	1 (2.3)	0
Central HER2 status,* n (%)		
IHC 3+	30 (69.8)	16 (50.0)
Missing	4 (9.3)	6 (18.8)

*In arm F, n=1 patient had HER2 IHC 0 status, n=3 patients had IHC 2+/ISH+ status, and n=6 patients had HER2 IHC 2+/ISH− status
5-FU, 5-fluorouracil; DCO, data cutoff; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; T-DXd, trastuzumab deruxtecan

Efficacy

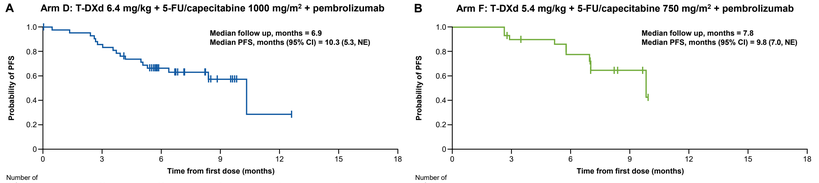
- The median duration of follow up was 6.9 months and 7.8 months for the T-DXd 6.4 mg/kg and 5.4 mg/kg triplet combination arms, respectively
- At similar periods of follow up, the confirmed ORR by investigator assessment was 53.5% in the T-DXd 6.4 mg/kg triplet combination arm (**Figure 2A**) and 75.0% in the 5.4 mg/kg triplet combination arm (**Figure 2B**)
  - In the T-DXd 6.4 mg/kg triplet combination arm, the ORR (n/N) was 55.9% (19/34) in patients with IHC 3+ and 44.4% (4/9) in patients with IHC 2+/ISH+
  - In the T-DXd 5.4 mg/kg triplet combination arm, the ORR (n/N) was 73.1% (19/26) in patients with IHC 3+ and 83.3% (5/6) in patients with IHC 2+/ISH+
- The median progression-free survival (PFS) by investigator assessment was 10.3 months in the T-DXd 6.4 mg/kg triplet combination arm (**Figure 3A**). Although data are immature, the median PFS was 9.8 months for the T-DXd 5.4 mg/kg triplet combination arm (**Figure 3B**)
- At the DCOs, the median duration of response and overall survival in both treatment arms were not estimable

Figure 2. Best percentage change in target lesion size from baseline



Assessments were by investigator using RECIST 1.1. Best percentage change is the maximum reduction or minimum increase from baseline in the target lesion size; the dashed lines at −30% and 20% change in target lesion size indicate the thresholds for partial response and progressive disease, respectively. HER2 status based on local test results
5-FU, 5-fluorouracil; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan

Figure 3. Kaplan-Meier estimates of PFS



Vertical lines indicate a censored observation. For PFS analyses (assessed by investigator per RECIST 1.1), patients who had not progressed or died, or who had progression or died after two or more missed visits, were censored at the latest evaluable RECIST assessment, or at Day 1 (randomization / treatment assignment / first dose) if there were no evaluable visits or no baseline assessment (unless the patient died within 13 weeks of baseline assessment)
5-FU, 5-fluorouracil; CI, confidence interval; NE, not estimable; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan

Safety and tolerability

- The median T-DXd treatment duration was 6.1 months in the T-DXd 6.4 mg/kg triplet combination arm and 6.9 months in the 5.4 mg/kg triplet combination arm
- All-causality adverse events (AEs) occurred in 100% of patients and 96.9% of patients in the T-DXd 6.4 mg/kg and 5.4 mg/kg triplet combination arms, respectively
- Grade ≥3 AEs were 88.4% in the T-DXd 6.4 mg/kg triplet combination arm and 46.9% in the T-DXd 5.4 mg/kg triplet combination arm. Serious AEs were 58.1% and 37.5% in the T-DXd 6.4 mg/kg and 5.4 mg/kg triplet combination arms, respectively
- Any AE leading to discontinuation of T-DXd was 23.3% in the T-DXd 6.4 mg/kg triplet combination arm and 6.3% in the 5.4 mg/kg triplet combination arm (**Table 2**)

Table 2. Safety and tolerability

	DCO: February 15, 2023	DCO: August 19, 2024
n (%)	Arm D: T-DXd 6.4 mg/kg + 5-FU/capecitabine 1000 mg/m² + pembrolizumab n=43	Arm F: T-DXd 5.4 mg/kg + 5-FU/capecitabine 750 mg/m² + pembrolizumab n=32
All-causality AEs	43 (100)	31 (96.9)
Treatment-related AEs*	40 (93.0)	27 (84.4)
Grade ≥3 AEs	**38 (88.4)**	**15 (46.9)**
Treatment-related Grade ≥3 AEs*	33 (76.7)	11 (34.4)
SAEs	**25 (58.1)**	**12 (37.5)**
Treatment-related SAEs*	19 (44.2)	5 (15.6)
All-causality AEs leading to death	4 (9.3)	0
Treatment-related AEs leading to death*	4 (9.3)	0
Any AE leading to discontinuation of T-DXd	**10 (23.3)**	**2 (6.3)**
Any AE leading to dose reduction of T-DXd	13 (30.2)	5 (15.6)
Any AE leading to dose interruption of T-DXd†	23 (53.5)	9 (28.1)
Any AE leading to discontinuation of any IP	**16 (37.2)**	**7 (21.9)**

*Assessed by the investigator as possibly related to any of the investigational products; †interruptions include delays
5-FU, 5-fluorouracil; AE, adverse event; DCO, data cutoff; IP, investigational product; SAE, serious adverse event; T-DXd, trastuzumab deruxtecan

Acknowledgments

The authors acknowledge Gordon Cohen, Rushee Jolly, and Arthur Lambert for their strategic contribution to the development of the abstract. Under the guidance of the authors and in accordance with Good Publications Practice (GPP), medical writing and editorial support was provided by Carmen Grimaldos, PhD, of Helios Medical Communications, part of the Helios Global Group, and was funded by AstraZeneca.

Disclosures

Yelena Y Janjigian reports stock options with Inspirna; honoraria from AbbVie, AmerisourceBergen, Arcus Biosciences, AskGene Pharma, Inc., Astellas, AstraZeneca, Basilea Pharmaceutica, Bayer, Bristol Myers Squibb, Daiichi Sankyo, eChinaHealth, ED Medresources Inc., Eisai Co., Ltd., Eli Lilly, Geneos Therapeutics, GSK, Guardant Health, HC Wainwright & Co., HMP Education, Imedex, Imugene, Inspirna, Lynx Health, Merck, Merck Serono, Mersana Therapeutics, Paradigm Medical Communications, Pfizer, Physicians' Education Resource®, LLC, Research to Practice, Sanofi, Seagen, Silverback Therapeutics, Suzhou Liangyihui Network Technology Co., Ltd., TotalCME, WebMD, LLC, Zymeworks Inc.; consulting or participation on an advisory board with AbbVie, AmerisourceBergen, Arcus Biosciences, AskGene Pharma, Inc., Astellas, AstraZeneca, Basilea Pharmaceutica, Bayer, Bristol Myers Squibb, Clinical Care Options, Daiichi Sankyo, ED Medresources Inc., Eisai Co., Ltd., Eli Lilly, Geneos Therapeutics, GSK, Guardant Health, HC Wainwright & Co., HMP Education, Imedex, Imugene, Inspirna, Lynx Health, Merck, Merck Serono, Mersana Therapeutics, Michael J Hennessy Associates, Paradigm Medical Communications, PeerView Institute, Pfizer, Physicians' Education Resource®, LLC, Research to Practice, Sanofi, Seagen, Silverback Therapeutics, TotalCME, Zymeworks Inc.; research funding from Arcus Biosciences, Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Cycle for Survival, US Department of Defense, Eli Lilly, Fred's Team, Genentech/Roche, Inspirna, Merck, National Cancer Institute, Stand Up To Cancer, Transcenta; travel, accommodation, or expenses with Bristol Myers Squibb, Merck; other relationships with Axis Medical Education, Clinical Care Options, Research to Practice.

References

1. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173–185
2. Ogitani Y, et al. *Clin Cancer Res*. 2016;22:5097–5108
3. Enhertu (fam-trastuzumab deruxtecan-nxki): highlights of prescribing information. 2024. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761139s028lbl.pdf (Accessed November 15, 2024)
4. Janjigian YY, et al. *Lancet*. 2023;402:2197–2208
5. Janjigian YY, et al. Oral presentation at ESMO 2024 (Abstract 1401O)
6. NCT04379596. Updated. October 30, 2024. Available from: https://clinicaltrials.gov/study/NCT04379596 (Accessed November 6, 2024)

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