FPN 185P

Safety, tolerability, and antitumor activity of T-DXd in patients with HER2-positive mBC and active brain metastases in DESTINY-Breast07

Carey Anders,[1] Sherene Loi,[2] Erika Hamilton,[3] Komal Jhaveri,[4] Peter Schmid,[5] Erhan Gökmen,[6] Seock-Ah Im,[7] Cengiz Karaçin,[8] Carlos Barrios,[9] Yeon Hee Park,[10] Sernaz Topaloğlu,[11] Sarice Boston,[12] Adam Konpa,[13] Shoubhik Mondal,[12] Fabrice André[14]

[1]Duke Cancer Institute, Durham, NC, US; [2]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [3]Sarah Cannon Research Institute, Nashville, TN, US; [4]Memorial Sloan Kettering Cancer Center, New York, NY, US; [5]Barts Cancer Institute, Queen Mary University of London, UK; [6]Ege University Faculty of Medicine, İzmir, Türkiye; [7]Seoul National University Cancer Research Institute, Seoul National University College of Medicine, Republic of Korea; [8]Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Türkiye; [9]Oncology Research Center, Hospital São Lucas da PUCRS, Porto Alegre, Brazil; [10]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [11]Trakya University Faculty of Medicine, Edirne, Türkiye; [12]AstraZeneca, Gaithersburg, MD, US; [13]AstraZeneca, Warsaw, Mazowieckie, Poland; [14]Gustave Roussy, Paris-Saclay University, Villejuif, France

Objectives

- The primary objective of Module 7 in the Phase 1b/2 DESTINY-Breast07 (DB-07) study is to assess the safety and tolerability of trastuzumab deruxtecan (T-DXd) monotherapy in patients with human epidermal growth factor receptor 2–positive (HER2+) metastatic breast cancer (mBC) and active brain metastases (BMs) in the first- or second-line setting
- Additional key objectives are to assess the antitumor activity of T-DXd per Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1) and Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria in the first- or second-line setting

Conclusions

- T-DXd demonstrates robust overall activity assessed by RECIST 1.1 per investigator; confirmed objective response rate (ORR) was 80.0%, median duration of response (DOR) was 18.1 months, and median progression-free survival (PFS) was 19.5 months
- T-DXd exhibits strong intracranial (IC) efficacy assessed by RANO-BM per blinded independent central review (BICR); the confirmed IC ORR was 60.0%, median IC DOR was 14.2 months, and median IC PFS was 15.4 months
- Safety and tolerability are consistent with the known profile of T-DXd; no new safety signals have been observed, and one Grade 5 adjudicated interstitial lung disease event has been reported

Plain language summary

Why are we performing this research?

Up to 50% of patients who have breast cancer with a higher than normal level of human epidermal growth factor receptor 2 (HER2-positive [HER2+] breast cancer) will develop tumors that spread from their original site to the brain (brain metastases [BMs]).[1,2] The development of BMs is associated with a poor quality of life, high rates of recurring cancer and death, and has limited treatment options.[1–4] We want to find out if systemic therapy (a therapy that affects the whole body) with trastuzumab deruxtecan (T-DXd) can be used to treat patients who have active BMs defined as untreated BMs or BMs that have grown, spread, or got worse (progressed) despite prior local radiation to shrink the brain tumors.

How are we performing this research?

In this part of the DESTINY-Breast07 study, we are assessing how safe and effective T-DXd is when used to treat participants with HER2+ breast cancer who have received no or one other anticancer drug for their metastatic cancer (cancer that has spread from its original site) and developed BMs.

What are the findings of this research?

Data from 35 participants are reported. No new side effects were identified; nausea (74%) and vomiting (46%) were the most common side effects associated with T-DXd; most participants had mild/moderate symptoms that required no/limited medical treatment or that did not limit/only limited some daily activities. In 80% of participants, T-DXd helped decrease the size or number of tumors throughout the body; 60% of participants had a decrease in the size or number of BMs. At the time of this analysis, the average length of time during which the antitumor activity of T-DXd was maintained (known as median duration of response) was 18 months for tumors throughout the body and 14 months for BMs only. The timepoint after starting treatment at which half of the participants were alive and progression free (known as median progression-free survival) was 20 months for tumors throughout the body and 15 months for BMs only.

What are the implications of this research?

These results suggest that T-DXd works well, and the side effects are consistent with previous studies when used for the treatment of patients with active BMs from HER2+ breast cancer.

Where can I access more information?

ClinicalTrials.gov. A Phase 1b/2 Study of T-DXd Combinations in HER2-positive Metastatic Breast Cancer (DB-07). https://clinicaltrials.gov/study/NCT04538742.

1. Freedman RA, et al. *J Clin Oncol*. 2019;37:1081–1089; 2. Hackshaw MD, et al. *BMC Cancer*. 2021;21:967;
3. DeBusk K, et al. *J Manag Care Spec Pharm*. 2022;28:657–666; 4. Mounsey LA, et al. *Clin Breast Cancer*. 2018;18:29–37

Poster

Plain language summary

Supplementary material

Radiographic images

Please scan this quick response (QR) code with your smartphone camera or app to obtain a copy of these materials. Alternatively, please access at: https://bit.ly/3xNsVAM

Copies of this poster obtained through this QR code are for personal use only and may not be reproduced without permission from ESMO BC and the authors of this 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 ESMO BC 2024, May 15–17, Berlin, Germany, by Komal Jhaveri.

Corresponding author email address: carey.anders@duke.edu

Introduction

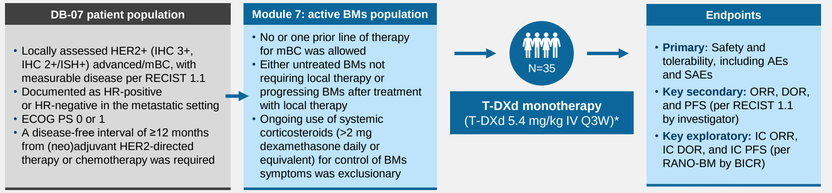
- The incidence of BMs in patients with HER2+ mBC is reported to be as high as 50%;[1,2] the recommended treatment includes local therapy such as surgical resection or radiotherapy[3,4]
- Despite available therapies, HER2+ mBC with BMs is associated with an impaired quality of life, and higher rates of recurrence and mortality compared with patients who do not have BMs[1,2,5,6]
- The DEBBRAH, ROSET-BM, and TUXEDO-1 studies – and a pooled DESTINY-Breast01, -02, and -03 analysis – have indicated the robust efficacy of T-DXd in patients with stable and active BMs;[7–10] however, these study results are based on limited data from later-line treatment settings
- This interim analysis of DB-07 Module 7 explored the safety, tolerability, and antitumor activity of T-DXd monotherapy (a systemic therapy) in patients with active BMs in the first- or second-line setting

Methods

- DB-07 is a Phase 1b/2 multicenter, open-label, modular study (NCT04538742)
- Data are reported for Module 7 (T-DXd 5.4 mg/kg every 3 weeks), and efficacy endpoints are reported per RECIST 1.1 by investigator and RANO-BM* by BICR **(Figure 1)**
- Eligible patients have HER2+ mBC and active BMs; active BMs are defined as patients with either untreated BMs not requiring local therapy or progressing BMs after treatment with local therapy
- Ongoing use of systemic corticosteroids (>2 mg dexamethasone daily or equivalent) for control of BMs symptoms was exclusionary
- Patients have received no or one prior line of therapy for mBC
- These data are from an interim analysis with a data cutoff (DCO) of December 22, 2023†

*RANO-BM standard response and progression criteria for the uniform assessment of BMs in clinical trials;[11] †the abstract reported data from the August 1, 2023 data cutoff

Figure 1. Study design (dose-expansion phase)



*Patients in Module 7 received the approved T-DXd dose for HER2+ breast cancer. AE, adverse event; BICR, blinded independent central review; BMs, brain metastases; DB-07, DESTINY-Breast07; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2+, human epidermal growth factor receptor 2–positive; HR, hormone receptor; IC, intracranial; IHC, immunohistochemistry; ISH, in situ hybridization; IV, intravenous; mBC, metastatic breast cancer; ORR, objective response rate; PFS, progression-free survival; Q3W, every 3 weeks; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SAE, serious adverse event; T-DXd, trastuzumab deruxtecan

Results and interpretation

Patient disposition and baseline characteristics

- In total, 35 patients were enrolled to this module; all patients received T-DXd monotherapy **(Tables 1 and 2)**
- The median actual treatment duration was 13.6 months (range: 2.6–29.0)*
- The median duration of follow up was 16.2 months

*Total treatment duration, excluding dose delays

Table 1. Patient disposition per RECIST 1.1

n (%)	T-DXd in patients with active BMs (N=35)
T-DXd ongoing	17 (48.6)
T-DXd discontinued	18 (51.4)
Objective disease progression	10 (28.6)
Withdrawal by patient	4 (11.4)
AE	2 (5.7)
Death	2 (5.7)

AE, adverse event; BMs, brain metastases; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; T-DXd, trastuzumab deruxtecan

Table 2. Patient demographics and disease characteristics

	T-DXd in patients with active BMs (N=35)
Median age, years (range)	49.0 (33.0–70.0)
Female, n (%)	35 (100)
Race, n (%)	
White	21 (60.0)
Asian	12 (34.3)
Black or African American	2 (5.7)
HER2 status, n (%)	
IHC 3+*	34 (97.1)
IHC 2+/ISH+	1 (2.9)
HR status, n (%)	
Positive	19 (54.3)
Negative	16 (45.7)
ECOG PS, n (%)	
0	18 (51.4)
1	17 (48.6)
Received prior HER2-targeted therapy for mBC, n (%)	18 (51.4)
No prior local treatment for BMs, n (%)	24 (68.6)

*Regardless of ISH status
BMs, brain metastases; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan

Safety

- The most common any-grade adverse events (AEs) were nausea and vomiting **(Table 3)**
- Grade 3 nausea and vomiting events were reported in three patients (8.6%) and one patient (2.9%), respectively (no Grade 4 or Grade 5 vomiting events were reported)
- The most common Grade ≥3 AEs were neutropenia (20.0%),* nausea (8.6%), fatigue (5.7%), and lymphopenia (5.7%)
- Adjudicated drug-related interstitial lung disease/pneumonitis was reported in three patients (8.6%)

*Grouped term including neutropenia, decreased neutrophil count, and febrile neutropenia events

Table 3. Safety overview

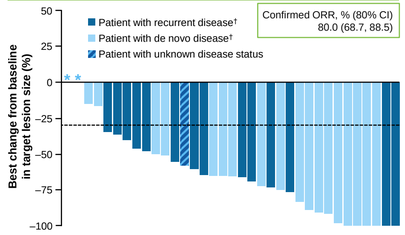
n (%)	T-DXd in patients with active BMs (N=35)
Any-grade AE	35 (100)
Any-grade AE by preferred term (>30% of patients)	
Nausea	26 (74.3)
Vomiting	16 (45.7)
Anemia	13 (37.1)
Constipation	13 (37.1)
Neutropenia	13 (37.1)
Decreased appetite	11 (31.4)
Fatigue	11 (31.4)
AE Grade ≥3	18 (51.4)
AE associated with T-DXd interruption	16 (45.7)
AE associated with T-DXd dose reduction	8 (22.9)
AE associated with T-DXd discontinuation	2 (5.7)*
Any SAE	5 (14.3)
AE leading to death	2 (5.7)†
AESI	
LV dysfunction	0
Pneumonitis (adjudicated as ILD related to T-DXd)	3 (8.6)
Grade 2	2 (5.7)
Grade 5	1 (2.9)‡

*Both AEs were reported as adjudicated ILD/pneumonitis; †cerebral hemorrhage reported by investigator as not related to T-DXd, n=1 and adjudicated ILD/pneumonitis related to T-DXd, n=1; ‡patient presented with symptoms of dyspnea, dry cough, and coryza on Day 66 of study treatment and was admitted to hospital 4 days later; HRCT was performed, and ground-glass and reticular opacities were found. Patient had no evidence of infection or cancer progression within the thorax. Radiotherapy was previously administered to the chest. Patient was administered 1 g of methyl prednisolone and antibiotics but experienced clinical worsening
AE, adverse event; AESI, adverse event of special interest; BMs, brain metastases; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; LV, left ventricular; SAE, serious adverse event; T-DXd, trastuzumab deruxtecan

Efficacy

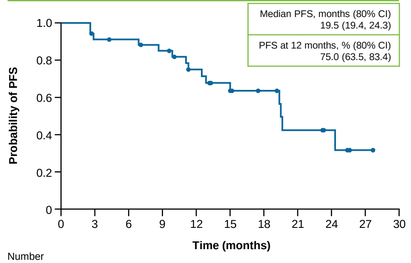
- Overall and best target lesion response per RECIST 1.1 by investigator **(Figure 2)**
  - Confirmed ORR (complete or partial response) was reported in a total of 28 patients (80.0%); complete response was reported in four patients (11.4%) and partial response in 24 patients (68.6%)
  - Stable disease was reported in seven patients (20.0%); no patients had disease progression
  - Median DOR was 18.1 months
- PFS per RECIST 1.1 by investigator
  - Median PFS was 19.5 months (80% CI 19.4, 24.3) **(Figure 3)**
  - By DCO, there were a total of 15 PFS events (42.9%)
- Overall and best IC target lesion response per RANO-BM by BICR **(Figure 4)**
  - Confirmed IC ORR (complete or partial response) was reported in a total of 21 patients (60.0%); complete response was reported in 12 patients (34.3%) and partial response was reported in nine patients (25.7%)
  - Stable disease was reported in 11 patients (31.4%), no patients had disease progression, the response of one patient (2.9%) was not evaluable, and there was no evidence of disease in two patients (5.7%)
  - Median IC DOR was 14.2 months
- IC PFS per RANO-BM
  - Median IC PFS was 15.4 months (80% CI 13.6, NC) **(Figure 5)**
  - By DCO, there were a total of 13 IC PFS events (37.1%)

Figure 2. Best percent change in target lesion size with T-DXd monotherapy in patients with active BMs per RECIST 1.1



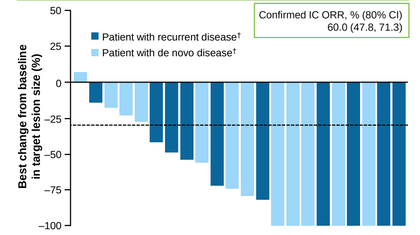
Dashed reference line at −30% indicates the threshold for partial response
*Patients had 0% change from baseline; †disease status at original diagnosis
BMs, brain metastases; CI, confidence interval; ORR, objective response rate; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; T-DXd, trastuzumab deruxtecan

Figure 3. PFS per RECIST 1.1



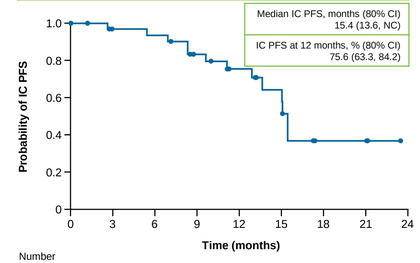
CI, confidence interval; PFS, progression-free survival; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1

Figure 4. Best percent change in IC target lesion size with T-DXd monotherapy in patients with active BMs per RANO-BM criteria*



Dashed reference line at −30% indicates the threshold for partial response
*Two patients had no evidence of intracranial disease, and 11 patients had non-target intracranial lesions only; †disease status at original diagnosis. BMs, brain metastases; CI, confidence interval; IC, intracranial; ORR, objective response rate; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; T-DXd, trastuzumab deruxtecan

Figure 5. IC PFS per RANO-BM criteria



CI, confidence interval; IC, intracranial; NC, not calculable; PFS, progression-free survival; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases

Acknowledgments

We thank the patients and their families for their participation and the study site staff for their contributions. Medical writing support, under the direction of the authors, was provided by Katie Ryding, PhD, of Helios Medical Communications, part of Helios Global Group, and was funded by AstraZeneca in accordance with Good Publication Practice guidelines (http://www.ismpp.org/gpp-2022).

Disclosures

Carey Anders reports consulting or advisory roles for AstraZeneca, Athenex, Eisai, Elucida Oncology, Genentech/Roche, Immunomedics, Ipsen, Roche, and Seagen; travel, accommodation, and expenses from Eisai; patents, royalties, and other intellectual property from Jones & Bartlett and UptoDate.com; and honoraria from AstraZeneca, Eisai, Elucida Oncology, Genentech/Roche, Immunomedics, Ipsen, Puma Biotechnology, and Seagen.

References

1. Freedman RA, et al. *J Clin Oncol*. 2019;37:1081–1089;
2. Hackshaw MD, et al. *BMC Cancer*. 2021;21:967;
3. Gennari A, et al. *Ann Oncol*. 2021;32:1475–1495;
4. Ramakrishna N, et al. *J Clin Oncol*. 2022;40:2636–2655;
5. DeBusk K, et al. *J Manag Care Spec Pharm*. 2022;28:657–666;
6. Mounsey LA, et al. *Clin Breast Cancer*. 2018;18:29–37;
7. Pérez-García JM, et al. *Neuro Oncol*. 2023;25:157–166;
8. Niikura N, et al. *NPJ Breast Cancer*. 2023;9:82;
9. Bartsch R, et al. *Nat Med*. 2022;28:1840–1847;
10. Hurvitz SA, et al. *Ann Oncol*. 2023;34(Suppl. 2);S335–S336;
11. Lin NU, et al. *Lancet Oncol*. 2015;16:e270–278

DESTINY BREAST07