San Antonio Breast Cancer Symposium® - December 9-12, 2025

PD13-11

Interim Analysis Results for the Effectiveness and Safety of Trastuzumab Deruxtecan in Patients with HER2-Low Breast Cancer and Brain Metastases: The HALLOW Study

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Objective

- The HALLOW study (UMIN000051259) aimed to bridge the gap between the DESTINY-Breast04 (DB-04) trial data and real-world data by investigating the effectiveness and safety of trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-low metastatic breast cancer (mBC) having a history of chemotherapy.
- Here, we report the interim analysis (IA) results for pts with brain metastases (BMs) in the HALLOW study.

Conclusions

- The current data provide preliminary support for the effectiveness and safety of T-DXd in pts with BMs, including active BMs, who were pts population not included in the DB-04 trial; however, longer follow-up and additional data are needed to confirm these findings. Additionally, any grade interstitial lung disease (ILD) was observed in 2 pts (4.8%) including one fatal case.

Plain language summary

Why did we perform this research?
There is a gap between clinical trial results (DESTINY-Breast04 trial) and everyday medical practice, for patients with HER2-low metastatic breast cancer (mBC), including those with triple-negative breast cancer (TNBC) and/or brain metastases (BMs). More data are needed on active or symptomatic brain metastases. To better understand how trastuzumab deruxtecan (T-DXd) works in patients with varied medical backgrounds in real-world settings, we conducted the HALLOW study to examine its effectiveness and safety in diverse patients with HER2-low mBC across Japan.

How did we perform this research?
We did an analysis part way through the HALLOW study (interim analysis), using data collected up to August 31, 2024, and focusing on patients with BMs. We measured effectiveness by looking at the length of time patients lived without their cancer growing, spreading, or worsening. Safety was assessed by looking at the data on side effects.

What were the findings of this research?
Forty-two patients, diagnosed with BMs by their doctors, were followed up for 4.1 months, on median. The median time before their cancer got worse (real-world progression-free survival, rwPFS) was 6.7 months in the patients whose BMs were also diagnosed by a third-party radiologist other than their primary physician. In 18% (6/33) of patients, the cancer shrank or disappeared in response to treatment (overall response rate, ORR). Most patients (77%) were still alive at 6 months (overall survival, OS). The median time before their cancer got worse or spread in the brain (IC-PFS) was 8.0 months. In 9% (2/22) of patients, the cancer in the brain shrank or disappeared after treatment. Serious side effects were experienced by 14 patients (33%) and were related to T-DXd in 7 (17%). One patient developed a lung condition called interstitial lung disease (ILD) and died.

What are the implications of this research?
These preliminary results provide useful information on the effectiveness and safety of T-DXd in patients with breast cancer having BMs, who were not included in clinical trials.

Where can I access more information?
Information about this study, including details about the treatments used and the patients who took part, can be found at https://center6.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000058453.

Poster

Supplementary material

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This study was 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).

Poster presented at SABCS2025 by Naoki Niikura.
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Introduction

- The DB-04 trial established T-DXd as the standard of care for pts with the mBC newly classified as HER2-low status (HER2 IHC 1+, or IHC 2+/ISH−).[1]
- However, in the DB-04 trial, the number of pts with hormone receptor–negative (HR−)/HER2-low mBC was limited, and pts with active BMs were excluded.
- Therefore, there is an urgent need to accumulate further evidence regarding the effectiveness and safety of T-DXd for such pts in real-world settings.

Methods

Figure 1. Study design

HALLOW study (UMIN000051259): **a multicenter, prospective observational study in real-world settings**

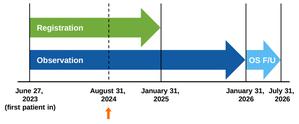
Patient population
- HER2-low (IHC 1+, IHC 2+/ISH−) diagnosed at local sites before T-DXd treatment
- mBC (HR− or HR+)
- With or without BMs
- Previously treated with chemotherapy
- T-DXd treatment is scheduled
- Informed consent
- ≥18 years old

T-DXd

Enrollment plan
- **Overall, 600 pts**
- ✓ Cohort 1 (HR−/HER2-low), 200 pts
- ✓ Cohort 2 (HR+/HER2-low), 400 pts

Exclusion criteria
- Pts who had hypersensitivity to any of the components of T-DXd, had active multiple malignancies (except in situ disease or intramucosal cancer that will be curable), or were judged by physicians to be ineligible for this study.

Study period



Data cutoff date for the IA in pts with BMs

Endpoints
- **Effectiveness**: OS, PFS, ORR, TTF, TTNT, TTD, PFS2, TTF2, TTNT2, DCR, CBR, DOR
  - ✓ **Pts with BMs**: IC-PFS, IC-ORR, IC-CBR, MDASI-BT (QOL)
- **Safety**: AEs of grade ≥3, ILD of grade ≥1, serious AEs, AEs leading to discontinuation of T-DXd, dose reduction of T-DXd, delay of T-DXd, and death.
- **QOL assessment**: EORTC QLQ-C30, QLQ-BR45

Endpoints of the present IA of data from pts with BMs are highlighted in red.

Definition of analysis set

This IA included pts diagnosed with BMs (current or past) by physician
- **Effectiveness analysis set**
  - ✓ Only pts with BMs confirmed by Brain-independent central review (Brain-ICR), based on brain MRI and/or CT images were included.
- **Effectiveness analysis set (Reliably evaluable per RECIST v1.1 only)**
  - ✓ This analysis population excluded the patients for whom only baseline images were available and not reliably assessed by Brain-ICR per RECIST v1.1.
- **Safety analysis set**
  - ✓ Pts who have received T-DXd at least once.

Results

Figure 2. Patient flow (at data cutoff, August 31, 2024)

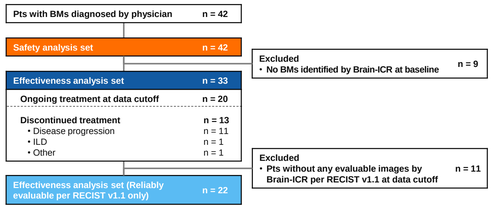


Table 1. Baseline characteristics

Effectiveness analysis set		All n = 33	Cohort 1 (HR−) n = 8	Cohort 2 (HR+) n = 25
Age (years)	Median (Q1, Q3)	55 (47, 65)	63 (49, 70)	54 (47, 58)
Sex	Female	33 (100)	8 (100)	25 (100)
HER2 status[a]	IHC 2+/ISH−	7 (21.2)	3 (37.5)	4 (16.0)
	IHC 1+	26 (78.8)	5 (62.5)	21 (84.0)
ECOG-PS	0	18 (54.5)	4 (50.0)	14 (56.0)
	1	12 (36.4)	4 (50.0)	8 (32.0)
	2	2 (6.1)	0 (0)	2 (8.0)
	Unknown	1 (3.0)	0 (0)	1 (4.0)
Metastasis (Site of metastasis)	Yes	33 (100)	8 (100)	25 (100)
	Liver	21 (63.6)	3 (37.5)	18 (72.0)
	Lung	20 (60.6)	4 (50.0)	16 (64.0)
	Bone	21 (63.6)	2 (25.0)	19 (76.0)
Prior surgery for breast cancer	Yes	25 (75.8)	6 (75.0)	19 (76.0)
	No	8 (24.2)	2 (25.0)	6 (24.0)
Lines of systemic therapy (metastatic setting)	Median (Q1, Q3)	5 (3, 7)	3 (1, 5)	5 (3, 7)
Lines of chemotherapy (metastatic setting)	Median (Q1, Q3)	2 (1, 3)	3 (1, 4)	2 (1, 2)
Baseline IC evaluation (by physician)				
Time from confirmation of BMs to start of T-DXd Tx (mo)	Median (Q1, Q3)	2.3 (1.1, 10.4)	3.0 (0.8, 10.4)	2.1 (1.1, 10.5)
Concomitant BM symptoms (epilepsy, convulsions, carcinomatous meningitis, etc)[b]	Yes	6/19 (31.6)	0/3 (0)	6/16 (37.5)
Steroid Tx for concomitant BM symptoms	Yes	10/32 (31.3)	2/8 (25.0)	8/24 (33.3)
Leptomeningeal dissemination (LMD)[c]	Yes	5/32 (15.6)	3/8 (37.5)	2/24 (8.3)
History of local therapy for BMs	Yes	27/32 (84.4)	5/8 (62.5)	22/24 (91.7)
	Whole-brain radiation	13/32 (40.6)	3/8 (37.5)	10/24 (41.7)
	Stereotactic radiation	15/32 (46.9)	2/8 (25.0)	13/24 (54.2)
	Tumor excision surgery	1/32 (3.1)	0/8 (0)	1/24 (4.2)
Baseline IC evaluation (by Brain-ICR)				
Sum of diameter of baseline (mm) (RECIST v1.1)	Median (Q1, Q3)	31.5 (18.4, 49.7) n = 17	25.0 (14.9, 40.6) n = 4	33.6 (21.2, 53.3) n = 13
No. of BMs[d]	1–9	15 (45.5)	5 (62.5)	10 (40.0)
	≥10	18 (54.5)	3 (37.5)	15 (60.0)
Meningeal carcinomatosis[e]	Yes	5 (15.2)	4 (50.0)	1 (4.0)
Active BMs[f]	Yes	33 (100)	8 (100)	25 (100)

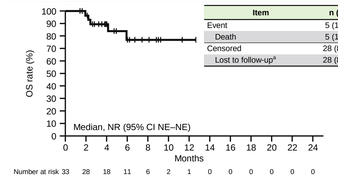
Data are n (%) unless otherwise indicated.
[a] HER2 and HR status were based on historical results at each local site. [b] This subgroup was limited to patients with confirmed concomitant symptoms. [c] LMD is based on historical diagnosis, not only based on imaging at each local site. [d] Based on the results of a Japanese prospective observational study, we categorized pts into two groups.[2,3] [e] Meningeal carcinomatosis was evaluated on imaging by Brain-ICR.
[f] Active BMs were defined as those meeting at least one of the following criteria:
- No local treatment (surgery, radiation therapy) was performed on the brain lesion.
- Regrowth of the brain lesion, or worsening of symptoms due to the brain lesion, after local treatment (surgery, radiation therapy) for the brain lesion.

Figure 3. Outcomes

- The median (Q1, Q3) follow-up period was 4.1 months (2.6, 6.7)[a].
- The median (Q1, Q3) T-DXd treatment period was 4.1 months (2.1, 6.2)[a].

OS

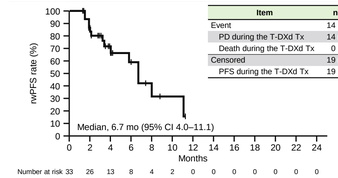
Effectiveness analysis set	All n = 33	Cohort 1 (HR−) n = 8	Cohort 2 (HR+) n = 25
Rate at 6 mo (95% CI)	77.1 (51.5–90.3)	80.0 (20.4–96.9)	77.3 (48.1–91.4)



Item	n (%)
Event	5 (15.2)
Death	5 (15.2)
Censored	28 (84.8)
Lost to follow-up[a]	28 (84.8)

rwPFS: for systemic PD as determined by physician

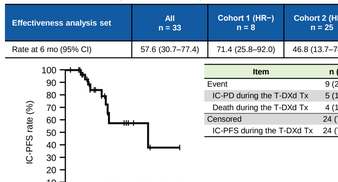
Effectiveness analysis set	All n = 33	Cohort 1 (HR−) n = 8	Cohort 2 (HR+) n = 25
Rate at 6 mo (95% CI)	59.0 (34.9–76.7)	85.7 (33.4–97.9)	46.6 (18.8–70.6)



Item	n (%)
Event	14 (42.4)
PD during the T-DXd Tx	14 (42.4)
Death during the T-DXd Tx	0 (0.0)
Censored	19 (57.6)
PFS during the T-DXd Tx	19 (57.6)

IC-PFS: evaluation by Brain-ICR per RECIST 1.1

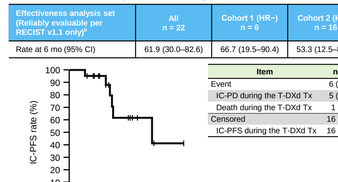
Effectiveness analysis set	All n = 33	Cohort 1 (HR−) n = 8	Cohort 2 (HR+) n = 25
Rate at 6 mo (95% CI)	57.6 (30.7–77.4)	71.4 (25.8–92.0)	46.8 (13.7–74.8)



Item	n (%)
Event	9 (27.3)
IC-PD during the T-DXd Tx	5 (15.2)
Death during the T-DXd Tx	4 (12.1)
Censored	24 (72.7)
IC-PFS during the T-DXd Tx	24 (72.7)

IC-PFS: evaluation by Brain-ICR per RECIST v1.1

Effectiveness analysis set (Reliably evaluable per RECIST v1.1 only)[b]	All n = 22	Cohort 1 (HR−) n = 6	Cohort 2 (HR+) n = 16
Rate at 6 mo (95% CI)	61.9 (30.0–82.6)	66.7 (19.5–90.4)	53.3 (12.5–82.7)



Item	n (%)
Event	6 (27.3)
IC-PD during the T-DXd Tx	5 (22.7)
Death during the T-DXd Tx	1 (4.5)
Censored	16 (72.7)
IC-PFS during the T-DXd Tx	16 (72.7)

[a]At data cutoff (August 31, 2024), most pts are either currently receiving T-DXd or remain under ongoing observation. [b]Excluding patients determined to be NE by Brain-ICR.

Table 2. ORR and IC-ORR

	ORR (by physician)			IC-ORR (by Brain-ICR per RECIST v1.1)					
	Effectiveness analysis set			Effectiveness analysis set			Effectiveness analysis set (Reliably evaluable per RECIST v1.1 only)		
	All (n = 33)	Cohort 1 (HR−) (n = 8)	Cohort 2 (HR+) (n = 25)	All[a] (n = 32)	Cohort 1 (HR−) (n = 8)	Cohort 2[a] (HR+) (n = 24)	All (n = 22)	Cohort 1 (HR−) (n = 6)	Cohort 2 (HR+) (n = 16)
ORR, % (95% CI)	**18.2 (7.0–35.5)**	0.0 (0.0–36.9)	24.0 (9.4–45.1)	**6.3 (0.8–20.8)**	12.5 (0.3–52.7)	4.2 (0.1–21.1)	9.1 (1.1–29.2)	16.7 (0.4–64.1)	6.3 (0.2–30.2)
CR, n (%)	1 (3.0)	0 (0.0)	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PR, n (%)	5 (15.2)	0 (0.0)	5 (20.0)	2 (6.3)	1 (12.5)	1 (4.2)	2 (9.1)	1 (16.7)	1 (6.3)

[a] One case was excluded from the analysis of IC-ORR, because BMs were confirmed by Brain-ICR, but IC-ORR could not be calculated.

Figure 4. Swimmer plot

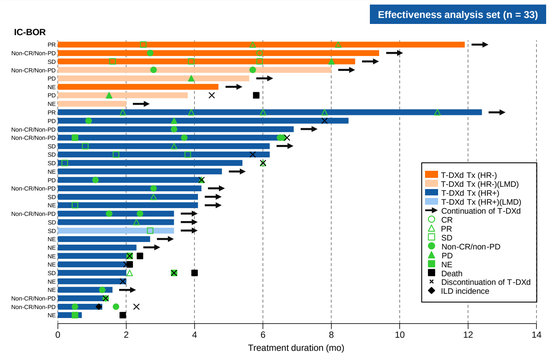


Table 3. Safety

Safety analysis set	All n = 42 (%)	Cohort 1 (HR−) n = 11 (%)	Cohort 2 (HR+) n = 31 (%)
AE of grade ≥3 Related to T-DXd treatment	18 (42.9) 11 (26.2)	5 (45.5) 3 (27.3)	13 (41.9) 8 (25.8)
Serious AE Related to T-DXd treatment	14 (33.3) 7 (16.7)	3 (27.3) 1 (9.1)	11 (35.5) 6 (19.4)
Interstitial lung disease (ILD) of grade ≥1 Related to T-DXd treatment T-DXd treatment-related ILD led to death	2 (4.8) 2 (4.8) 1 (2.4)	1 (9.1) 1 (9.1) 1 (9.1)	1 (3.2) 1 (3.2) 0 (0.0)
AE led to discontinuation of T-DXd	3 (7.1)	1 (9.1)	2 (6.5)
AE led to dose reduction of T-DXd (AE of grade ≥3 / ILD of grade ≥1)	1 (2.4)	1 (9.1)	0 (0.0)
AE led to delay of T-DXd (AE of grade ≥3 / ILD of grade ≥1)	7 (16.7)	2 (18.2)	5 (16.1)
AE led to death	1 (2.4)	1 (9.1)	0 (0.0)

Data are n (%).

Summary of results

- After a median follow-up of 4.1 mo, the estimated median rwPFS was 6.7 mo and estimated ORR was 18.2% in pts with active BMs confirmed by Brain-ICR at data cutoff (August 31, 2024).
- The estimated OS rate at 6 mo was 77.1%.
- Among 33 pts with active BMs, estimated median IC-PFS was 8.0 months, with an IC-ORR of 6.3%.
- Grade ≥3 AEs occurred in 18 pts (42.9%), of whom 11 (26.2%) experienced AEs related to T-DXd.
- Additionally, ILD of grade ≥1 was observed in 2 pts (4.8%), including one case of grade 5 ILD.

Abbreviations

AE, adverse event; BMs, brain metastases; BOR, best overall response; Brain-ICR, Brain-independent central review; CBR, clinical benefit rate; CI, confidence interval; DCR, disease control rate; DOR, duration of response; F/U, follow-up; IA, interim analysis; IC, intracranial; ICR, independent central review; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, in situ hybridization; LMD, leptomeningeal dissemination; mBC, metastatic breast cancer; MDASI-BT, MD Anderson Symptom Inventory for Brain Tumor; mo, months; NE, not evaluable; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Q, quartile; QLQ-BR45, Quality of Life Questionnaire – Breast Cancer; QLQ-C30, Quality of Life Questionnaire (30 items); rw, real-world; TTD, time to deterioration; TTF, time to treatment failure; TTNT, time to next treatment; Tx, treatment.

Acknowledgments

Under the guidance of the authors and in accordance with Good Publication Practice, medical writing and editorial support were provided by Kim Howell, and were funded by Daiichi Sankyo.

Declaration of interest

I (Naoki Niikura) received honoraria and supports of medical writing from Daiichi Sankyo Co., Ltd., and my institution received research funding from Daiichi Sankyo Co., Ltd., related to the presented work. Outside the presented work, he received honoraria from Chugai Pharmaceutical Co., Ltd., Eli Lilly Japan K.K., MSD K.K., Daiichi Sankyo Co., Ltd., AstraZeneca K.K., and Pfizer Japan Inc.; and his institution received research funding from Chugai Pharmaceutical Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Eisai Co., Ltd., Daiichi Sankyo Co., Ltd., and Novartis Pharma K.K.

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Supplementary Material

Supplementary Table 1. BOR and IC-BOR

	BOR by physician			IC-BOR by Brain-ICR per RECIST v1.1					
	Effectiveness analysis set			Effectiveness analysis set			Effectiveness analysis set (Reliably evaluable per RECIST v1.1 only)		
	All (n = 33)	Cohort 1 (HR−) (n = 8)	Cohort 2 (HR+) (n = 25)	All[a] (n = 32)	Cohort 1 (HR−) (n = 8)	Cohort 2[a] (HR+) (n = 24)	All (n = 22)	Cohort 1 (HR−) (n = 6)	Cohort 2 (HR+) (n = 16)
CR	1 (3.0)	0 (0)	1 (4.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
PR	5 (15.2)	0 (0)	5 (20.0)	2 (6.3)	1 (12.5)	1 (4.2)	2 (9.1)	1 (16.7)	1 (6.3)
SD	11 (33.3)	4 (50.0)	7 (28.0)	8 (25.0)	1 (12.5)	7 (29.2)	8 (36.4)	1 (16.7)	7 (43.8)
Non-CR/non-PD	2 (6.1)	1 (12.5)	1 (4.0)	8 (25.0)	2 (25.0)	6 (25.0)	8 (36.4)	2 (33.3)	6 (37.5)
PD	5 (15.2)	1 (12.5)	4 (16.0)	4 (12.5)	2 (25.0)	2 (8.3)	4 (18.2)	2 (33.3)	2 (12.5)
NE[b]	9 (27.3)	2 (25.0)	7 (28.0)	10 (31.3)	2 (25.0)	8 (33.3)	0 (0)	0 (0)	0 (0)

Data are n (%).

[a] One case was excluded from the analysis of IC-BOR, because BMs were confirmed by Brain-ICR, but IC-BOR could not be calculated.

[b] This analysis dataset includes pts who were ongoing at the data cutoff date, had a short observation period, or had died early. In these cases, CT/MRI images other than baseline were missing, and Brain-ICR could only classify them as NE.

Abbreviations: BOR, best overall response; Brain-ICR, Brain-independent central review; IC, intracranial, NE, not evaluable.

Poster presented at SABCS2025 by Naoki Niikura. Corresponding author’s email address: nniikura@tokai.ac.jp