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The effectiveness of post–trastuzumab deruxtecan (T-DXd) treatment regimens and the incidence of recurrent interstitial lung disease (ILD) in patients with HER2+ metastatic breast cancer who discontinued T-DXd due to ILD

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On behalf of the EN-SEMBLE study investigators

Objective

- The EN-SEMBLE study (jRCT1030220506) was carried out to investigate the effectiveness of subsequent treatments (Tx) following the discontinuation of trastuzumab deruxtecan (T-DXd), irrespective of the reason, in patients (pts) with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (mBC).[1]
- The present post hoc analysis of the EN-SEMBLE study was conducted to provide detailed data to inform subsequent Tx of pts who have discontinued T-DXd due to interstitial lung disease (ILD).

Conclusions

- The findings underline the importance of early ILD detection and management to enable pts to receive, and potentially benefit from, subsequent anti-HER2 targeted therapies.
- Notably, the recurrence/exacerbation rate of ILD in subsequent lines of therapy was low.

Plain language summary

Why did we perform this research?

Trastuzumab deruxtecan (T-DXd) is a medicine used to treat patients with HER2-positive metastatic breast cancer. While T-DXd can be effective, some patients develop a serious lung condition called interstitial lung disease (ILD) as a side effect. When ILD occurs, patients need to stop T-DXd treatment. Unfortunately, there is little information available about what treatments are best for such patients. This research aims to better understand this issue and help doctors make more informed decisions to support patient care.

How did we perform this research?

We used data from the EN-SEMBLE study and focused especially on patients who stopped taking T-DXd because of ILD. This research looked at two key questions:

1. How effective subsequent treatments are? / 2. How often does ILD occur after subsequent treatment?

What were the findings of this research?

- Of 664 patients, 146 had stopped taking T-DXd because of ILD. Doctors rated the severity of ILD as mild (grade 1) in 78 patients, moderate (grade 2) in 46, and severe (grade 3) in 18. For 4 patients, the grade was unknown.
- The patients had, on median, 7.2 months of real-world progression-free survival (PFS). This means the length of time that half of the patients in a study live with their disease without it getting worse or dying after starting a treatment.
- By ILD grade, real-world median PFS was 9.4 months for those with mild (grade 1) ILD, 6.9 months for those with moderate (grade 2) ILD, and 6.5 months for those with severe (grade 3) ILD.
- ILD recurrence occurred in 5 out of 146 patients (3.4%) during 1st treatment period after stopping T-DXd; in 2 out of 93 patients (2.1%) during 2nd treatment period.

What are the implications of this research?

- These findings highlight the importance of detecting and managing ILD early. Taking early approach can help patients receive the next anti-HER2 therapies and benefit from them.
- Patients who have stopped T-DXd due to ILD can be told that they are unlikely to have it again during subsequent treatment.

Where can I access more information?

- https://jrct.mhlw.go.jp/en-latest-detail/jRCT1030220506
- The original article, titled "Effectiveness of post-trastuzumab deruxtecan treatments and incidence of interstitial lung disease in HER2-positive metastatic breast cancer: a real-world, observational cohort study", was published in ESMO Open, August 2025 (available for free at https://doi.org/10.1016/j.esmoop.2025.105511).

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 ESMO2025 by Junji Tsurutani.
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Introduction

- ILD is recognized as a significant adverse event (AE) that requires permanent discontinuation of T-DXd at grade (Gr) ≥2. At the time of T-DXd approval in Japan, the label required discontinuation for ILD at any grade, and re-administration was not permitted.[2–4]
- Selecting an appropriate Tx sequence for pts who have discontinued T-DXd due to ILD remains an important clinical question; however, data on this issue are currently limited.

Methods

Figure 1. Study design

The EN-SEMBLE study: a nationwide cohort study in real-world settings in Japan

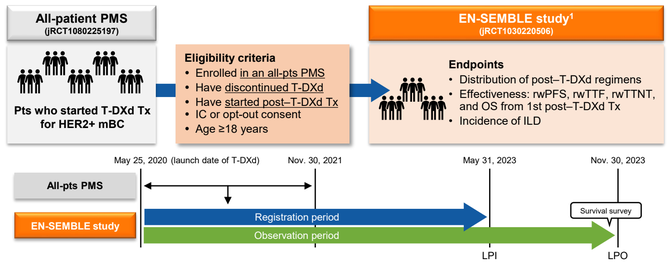
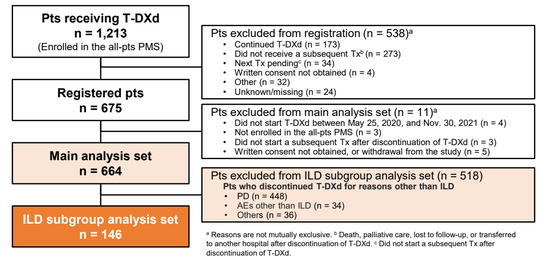


Figure 2. Patients

- **mBC pts enrolled in the EN-SEMBLE study who had discontinued T-DXd due to ILD**



[a] Reasons are not mutually exclusive. [b] Death, palliative care, lost to follow-up, or transferred to another hospital after discontinuation of T-DXd. [c] Did not start a subsequent Tx after discontinuation of T-DXd.

Results

Summary of results

- Among 664 pts, 146 discontinued T-DXd due to ILD (**Figure 2, Table 1**), and the effectiveness and safety of subsequent Tx were investigated.
- Of these pts, 81.5% received a subsequent anti-HER2 therapy after discontinuation of T-DXd due to ILD (**Figure 3**).
- The rwPFS, rwTTF, rwTTNT and OS were numerically longer in pts with Gr 1 ILD compared with those with Gr 3 ILD during prior T-DXd Tx (**Figure 4**, **Table 2**).
- 5 of 146 pts (3.4%) experienced ILD recurrence/exacerbation during their 1st post–T-DXd Tx (**Table 4**).

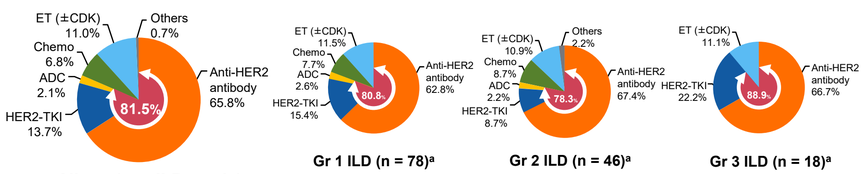
Table 1. Baseline characteristics

- A total of 146 pts discontinued T-DXd due to ILD. CTCAE grading (by the attending physician): Gr 1, 78 pts; Gr 2, 46 pts; Gr 3, 18 pts; unknown, 4 pts.

Characteristic[a]		All pts N = 146	ILD grade for discontinuation of T-DXd[b,c] Gr 1 n = 78 (53.4%)	Gr 2 n = 46 (31.5%)	Gr 3 n = 18 (12.3%)
Age, years[d]		63 (55, 70)	62.5 (55, 70)	64.5 (56, 69)	61.5 (51, 71)
Sex	Female	144 (98.6)	77 (98.7)	46 (100.0)	17 (94.4)
HER2 status	IHC 3+	103 (70.5)	59 (75.6)	30 (65.2)	11 (61.1)
	IHC 2+/ISH+	35 (24.0)	16 (20.5)	15 (32.6)	4 (22.2)
Hormone receptor status	Positive	95 (65.1)	45 (57.7)	34 (73.9)	13 (72.2)
ECOG-PS	0–1	123 (84.2)	67 (85.9)	40 (87.0)	15 (83.3)
Visceral metastasis	Yes	115 (78.8)	57 (73.1)	40 (87.0)	15 (83.3)
Brain metastasis	Yes	38 (26.0)	20 (25.6)	13 (28.3)	4 (22.2)
mBC status	*De novo* stage IV	50 (34.2)	31 (39.7)	12 (26.1)	5 (27.8)
	Recurrent	91 (62.3)	44 (56.4)	33 (71.7)	12 (66.7)
Lines of therapy prior to T-DXd initiation[d]		3.5 (2, 5)	4 (3, 5)	3 (2, 5)	3 (2, 5)
Objective overall response to T-DXd		98 (67.1)	58 (74.4)	28 (60.9)	9 (50.0)
Time to discontinuation of T-DXd due to ILD (duration of T-DXd Tx), mo[d]		6.2 (3.7, 9.7)	6.4 (3.7, 9.9)	6.2 (4.2, 9.9)	4.2 (2.8, 8.4)
Administration of steroids for ILD	Yes	72 (49.3)	14 (17.9)	38 (82.6)	17 (94.4)
Time from T-DXd discontinuation due to ILD to start of 1st post–T-DXd Tx, days[d]		50.5 (23, 90)	43 (21, 67)	66 (35, 114)	60 (50, 153)
ILD status: recovery status on day 1 of the 1st post–T-DXd Tx	Resolved	101 (69.2)	56 (71.8)	30 (65.2)	12 (66.7)
	Not resolved	42 (28.8)	22 (28.2)	14 (30.4)	5 (27.8)
	Unknown	3 (2.1)	0	2 (4.3)	1 (5.6)

[a] Data are n (%) unless otherwise indicated. [b] Grade determined by the attending physician according to CTCAE. [c] There were no pts with known Gr 4 ILD; the ILD grade of 4 pts was unknown. [d] Median (Q1, Q3).

Figure 3. Distribution of 1st post–T-DXd Tx



There were no pts with known Gr 4 ILD; the ILD grade of 4 pts was unknown.
[a] The denominator for percentage calculations.

Figure 4. Kaplan–Meier curve for rwPFS and OS (Time from initiation of the 1st post–T-DXd Tx)

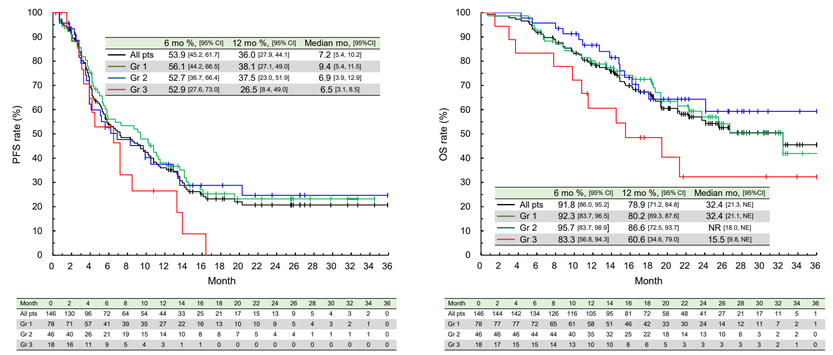


Table 2. Outcomes for 1st post–T-DXd Tx by ILD grade leading to discontinuation of T-DXd

	All pts (any grade) N = 146	ILD grade for discontinuation of T-DXd[a,b] Gr 1 n = 78	Gr 2 n = 46	Gr 3 n = 18
Follow-up period, mo[c]	17.5 (11.4, 24.8)	18.5 (11.8, 25.5)	16.7 (12.4, 24.2)	15.0 (9.8, 21.3)
rwPFS	7.2 [5.4, 10.2]	9.4 [5.4, 11.5]	6.9 [3.9, 12.9]	6.5 [3.1, 8.5]
rwTTF	6.5 [5.1, 9.1]	7.3 [5.3, 11.3]	6.1 [3.8, 10.9]	5.7 [3.1, 7.2]
rwTTNT	7.8 [5.9, 10.8]	10.7 [5.8, 14.3]	7.6 [4.9, 13.4]	7.1 [3.8, 11.3]
OS	32.4 [21.3, NE]	32.4 [21.1, NE]	NR [18.0, NE]	15.5 [9.8, NE]

Data are median [95% CI], months, unless otherwise indicated.
[a] Grade determined by the attending physician according to CTCAE. [b] There were no pts with known Gr 4 ILD; the ILD grade of 4 pts was unknown. [c] Median (Q1, Q3).

Table 3. Outcomes for 1st post–T-DXd Tx by subsequent regimen

	All pts N = 146 (100%)	1st post–T-DXd Tx regimen: Anti-HER2 antibody[a] n = 96 (65.8%)	HER2-TKI n = 20 (13.7%)	ADC n = 3 (2.1%)	Chemo n = 10 (6.8%)	ET ± CDK4/6i n = 16 (11.0%)	Others n = 1 (0.7%)
rwPFS	7.2 [5.4, 10.2]	8.5 [5.3, 12.2]	8.9 [4.3, 13.6]	2.1 [0.7, NE]	4.9 [0.7, 14.3]	6.5 [2.0, 9.4]	NR [NE, NE]
wTTF	6.5 [5.1, 9.1]	6.9 [5.0, 11.0]	8.9 [4.3, 13.6]	2.1 [0.7, NE]	4.6 [0.7, 14.1]	4.7 [1.2, 6.7]	NR [NE, NE]
rwTTNT	7.8 [5.9, 10.8]	8.3 [5.8, 12.9]	11.1 [5.2, 17.3]	2.8 [1.0, NE]	5.4 [0.7, 18.5]	6.1 [2.1, 10.7]	NR [NE, NE]
OS	32.4 [21.3, NE]	26.7 [19.3, NE]	NR [11.7, NE]	10.9 [5.1, NE]	18.5 [0.7, NE]	NR [19.3, NE]	NR [NE, NE]

Data are median [95% CI], mo.
[a] Combinations of anti-HER2 therapy alongside chemotherapy, ET, or a CDK4/6i were classified as anti-HER2 therapy.

Table 4. Details of pts with ILD recurrence/exacerbation during post–T-DXd Tx

- During the 1st post–T-DXd Tx period, 5/146 pts (3.4%) experienced ILD recurrence/exacerbation.
  - By ILD grade during T-DXd Tx[a] : Gr 1, 2/78 pts (2.6%); Gr 2, 1/46 pts (2.2%); and Gr 3, 2/18 pts (11.1%).
- During the 2nd post–T-DXd Tx period, 2/93 pts (2.2%) experienced ILD recurrence/exacerbation.
  - By ILD grade during T-DXd Tx[a] : Gr 1, 1/46 pts (2.2%); Gr 2, 1/31 pts (3.2%); and Gr 3, 0/12 pts (0%).
- There was no overlap between the cases of ILD recurrence during the 1st and the 2nd post–T-DXd Tx periods.

No.	Age	Sex	mBC status	T-DXd Tx period: T-DXd Tx Period, mo	T-DXd Tx BOR	ILD information: CTCAE grade	Steroid use	ILD status[b]	1st post–T-DXd Tx period: 1st post–T-DXd Tx Regimen	ILD incidence Yes/No	ILD incidence Onset day	Discontinuation reason	BOR	2nd post–T-DXd Tx period: 2nd post–T-DXd Tx Yes/No	2nd post–T-DXd Tx Regimen	ILD incidence Yes/No	ILD incidence Onset day	BOR
1	59	F	Recurrent	3.7	PR	3	Yes	Resolved	Tra+Per+Eri	Yes	23	ILD	SD	Yes	Lapa+Cape	No	–	PD
2	60	F	*De novo*	7.9	SD	1	None	Not resolved	Tra	Yes	255	Ongoing	SD	No	–	–	–	–
3	73	F	Recurrent	5.6	PR	1	Yes	Resolved	Eri	Yes	161	ILD	SD	No	–	–	–	–
4	68	F	Recurrent	5.6	PR	2	Yes	Not resolved	Tra+Eri	Yes	22	ILD	SD	Yes	Vinorelbine	No	–	SD
5	81	F	Recurrent	14.1	SD	3	Yes	Resolved	Tra+Per+Eri	Yes	39	ILD	NE	No	–	–	–	–
6	66	F	*De novo*	19.5	PR	2	None	Not resolved	Tra	No	–	Others	SD	Yes	Lapa+Cape	Yes	43	SD
7	52	F	*De novo*	1.7	PR	1	None	Not resolved	Tra+vinorelbine	No	–	PD	PD	Yes	Tra+Pacli	Yes	78	PD

[a] There were no pts with known Gr 4 ILD; the ILD grade of 4 pts was unknown. [b]Resolved status on day 1 of the 1st post–T-DXd Tx.

Limitations

- A key limitation is the potential for selection bias, as the study includes only cases of ILD caused by T-DXd in pts who were able to start subsequent Tx.
- There is a difference between Gr 1 and Gr 3 ILD patients in the interval from discontinuation of T-DXd to initiation of the 1st post–T-DXd Tx. The prolonged recovery period required for Gr 3 ILD may lead to treatment delays, potentially contributing to shorter rwPFS due to more pronounced disease relapse. These disparities may introduce bias into the prognostic analysis stratified by grade, warranting cautious interpretation of the findings.
- The sample size of the subgroups was small.

Abbreviations

ADC, antibody–drug conjugate; AE, adverse event; BOR, best overall response; Cape, capecitabine; CDK, cyclin-dependent kinase; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; Chemo, chemotherapy; CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; ECOG-PS, Eastern Cooperative Oncology Group performance status; Eri, eribulin; ET, endocrine therapy; F, female; Gr, grade; HER2, human epidermal growth factor receptor 2; IC, informed consent; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, *in situ* hybridization; jRCT, Japan Registry of Clinical Trials; Lapa, lapatinib; LPI, last patient in; LPO, last patient out; mBC, metastatic breast cancer; mo, months; NE, not evaluable; NR, not reached; OS, overall survival; Pacli, paclitaxel; PD, progressive disease; Per, pertuzumab; PFS, progression-free survival; PMS, post-marketing surveillance; PR, partial response; pts, patients; Q, quartile; rwPFS, real-world progression-free survival; rwTTF, real-world time to treatment failure; rwTTNT, real-world time to next treatment; SD, stable disease; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor; Tra, trastuzumab; Tx, treatment(s).

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Disclosures

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