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POOLED ANALYSIS OF TRASTUZUMAB DERUXTECAN (T-DXD) RETREATMENT AFTER RECOVERY FROM GRADE 1 INTERSTITIAL LUNG DISEASE/PNEUMONITIS (ILD)

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Declaration of Interests

Dr. Hope S. Rugo reports:

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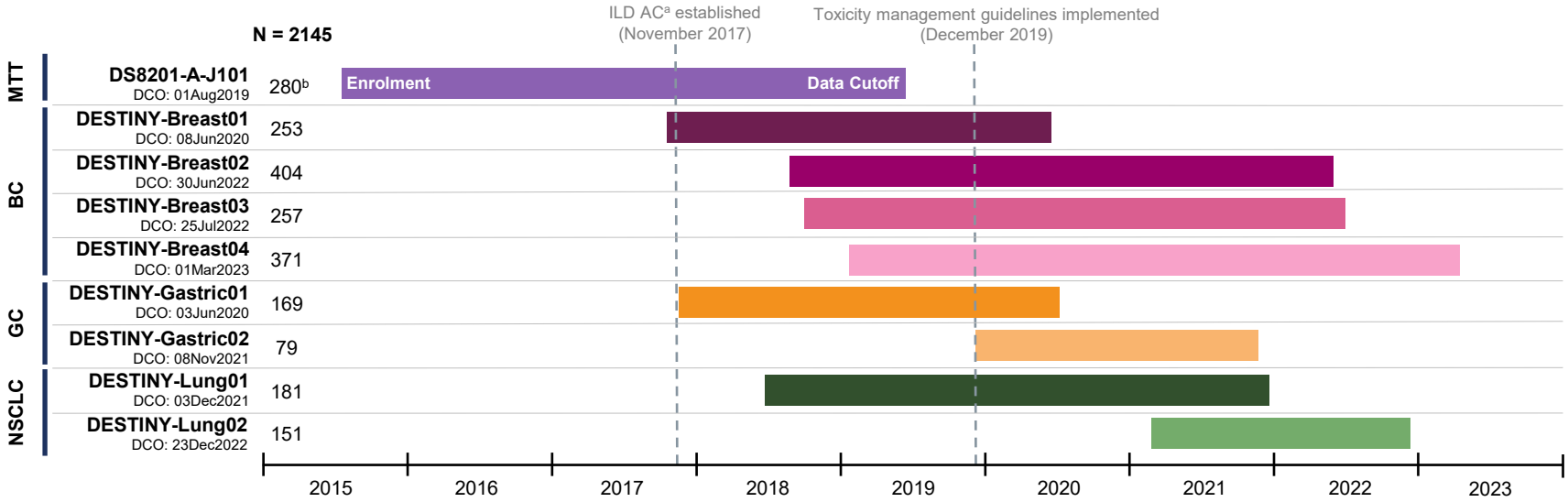
Background

- T-DXd is approved for the treatment of HER2+ and HER2-low[a] mBC, HER2+ mGC/GEJA, *HER2 (ERBB2)*-mutant NSCLC, and HER2+ (IHC 3+) solid tumors[b,1]
- ILD has been identified as an AE of special interest with T-DXd treatment[2-4]
- Incidence of ILD with T-DXd treatment is reported at ~15% across all indications; most of these ILD events are low-grade, being reported as either Gr 1 (27%) or Gr 2 (50%)[4], but ILD can be fatal if not appropriately managed
    - Current toxicity management guidelines require T-DXd to be withheld upon development of suspected Gr 1 ILD and treatment with T-DXd can be resumed following full recovery from ILD[c]; systemic steroid therapy for Gr 1 ILD can be initiated per investigator judgement[d,4]
    - Upon development of Gr ≥2 ILD T-DXd must be discontinued and systemic steroid therapy is indicated[4]

We characterize T-DXd retreatment and ILD recurrence in patients who recovered from an adjudicated investigator-assessed Gr 1 ILD event using data pooled across 9 clinical trials

AE, adverse event; Gr, Grade; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ILD, interstitial lung disease/pneumonitis; ISH, in situ hybridization; mBC, metastatic breast cancer; mGC/GEJA, metastatic gastric cancer/gastroesophageal junction adenocarcinoma; NSCLC, non–small cell lung cancer; T-DXd, trastuzumab deruxtecan.
[a]Defined as IHC 1+/2+ with ISH not-amplified. [b]For patients who have received systemic treatment and have no satisfactory alternative treatment options. [c]If ILD has not resolved within 18 weeks (126 days) of the last T-DXd dose then T-DXd should be discontinued; if ILD resolves in ≤28 days from onset T-DXd dose can be maintained. [d]Asymptomatic ILD should still be considered Gr 1 even if steroid therapy is administered.
1. Enhertu (fam-trastuzumab deruxtecan-nxki). Prescribing information. Daiichi Sankyo, Inc; 2024. 2. Swain SM et al. *Cancer Treat Rev.* 2022;106:102378. 3. Powell CA et al. *ESMO Open.* 2022;7:100554. 4. Rugo HS et al. *ESMO Open.* 2022;7:10553.

Methods

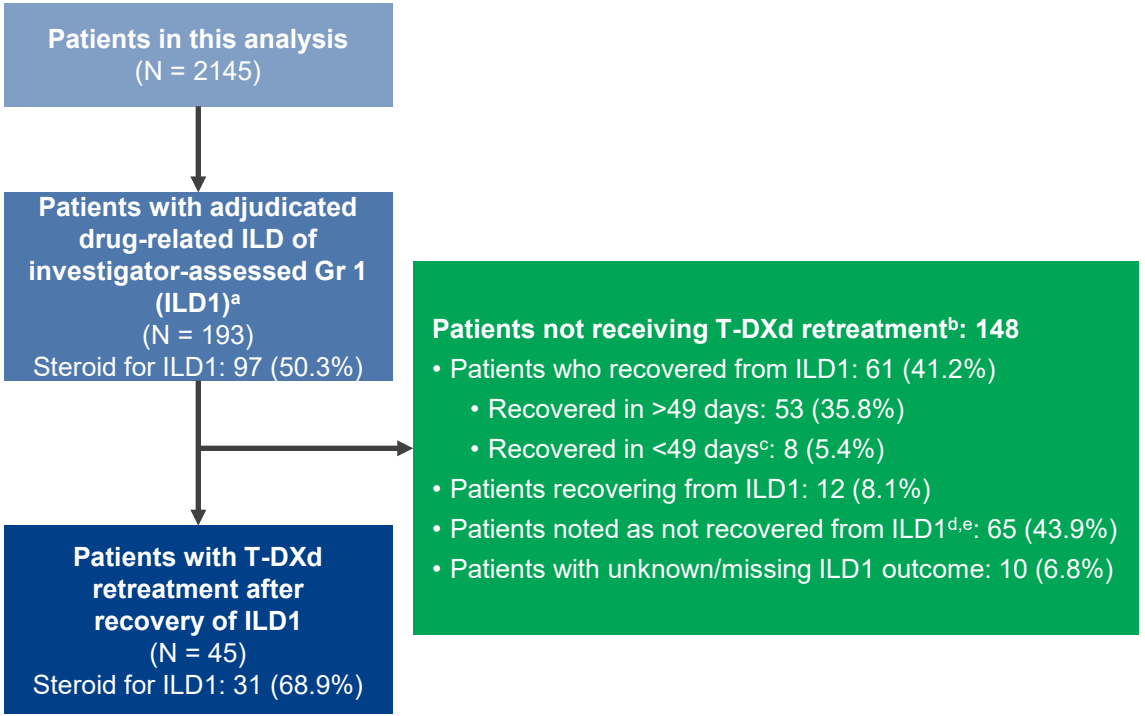


- Data were pooled from 9 clinical trials to identify patients with Gr 1 ILD as assessed by the investigators and confirmed by the adjudication committee (AC) who were retreated with T-DXd
  - All patients received at least 1 dose of T-DXd (5.4-8.0 mg/kg) monotherapy
- *T-DXd toxicity management guidelines recommend a dose reduction for retreatment if ILD takes longer than 28 days to resolve. At the time of study inclusions, guidelines recommended discontinuation of T-DXd if ILD had not resolved within 49 days from the last T-DXd dose[c]*

AC, adjudication committee; BC, breast cancer; DCO, data cutoff ; GC, gastric cancer; ILD, interstitial lung disease/pneumonitis; MTT, multiple tumor types; NSCLC, non–small cell lung cancer.
[a]Each AC session included an oncologist, a radiologist, and a pulmonologist. [b]Only patients who received at least 1 dose of T-DXd 5.4-8.0 mg/kg are included. The color bar for each study indicates the time from patient enrollment to data cut-off. [c]Guidelines have subsequently been updated to recommend discontinuation of T-DXd if ILD has not resolved within 126 days from the date of last drug dose.

Disposition of Patients Experiencing Grade 1 ILD

- 50.3% (97/193) of patients with a first event of Gr 1 ILD (ILD1) received steroid treatment
- 23.3% (45/193) of patients with ILD1 were retreated with T-DXd
  - 2 patients were retreated before ILD1 was confirmed resolved by the AC and their ILD1 event progressed to Gr 2 and Gr 3, respectively
- 76.7% (148/193) of patients with ILD1 were not retreated based on investigator assessment or treatment dose discontinuation requirements (per protocol)



AC, adjudication committee; Gr, Grade; ILD, interstitial lung disease/pneumonitis; ILD1; first Gr 1 ILD event; T-DXd, trastuzumab deruxtecan.
[a]If sequential adjudicated drug-related ILD events occurred with grade changes (following one after the other) the sequential events were regarded as 1 event with the worst grade and the last outcome in the series of events. [b]Based on investigator assessment or treatment dose discontinuation requirements (per protocol/label). [c]Did not receive T-DXd retreatment based on investigator decision. [d]Patients had evidence of ILD at day 49 post-ILD onset. [e]Patients who had an unresolved ILD1 event and died due to other causes were noted as not recovered from ILD at the time of DCO of each respective study.

Demographics and Baseline Characteristics

Baseline characteristics	All Tumor Types Pool (N = 2145)	ILD1 (N = 193)	T-DXd retreatment (N = 45)
Age, median (range), years	58.0 (20-96)	60.0 (30-88)	59.1 (30-79)
<65 years, n (%)	1524 (71.0)	130 (67.4)	27 (60.0)
≥65 years, n (%)	621 (29.0)	63 (32.6)	18 (40.0)
Sex, n (%)			
Female	1756 (81.9)	157 (81.3)	36 (80.0)
Country, n (%)			
Japan	586 (27.3)	89 (46.1)	17 (37.8)
Non-Japan	1559 (72.7)	104 (53.9)	28 (62.2)
ECOG PS, n (%)			
0	1100 (51.3)	115 (59.6)	22 (48.9)
1	1043 (48.6)	78 (40.4)	23 (51.1)
Tumor type, n (%)			
Breast cancer	1462 (68.2)	131 (67.9)	27 (60.0)
Gastric cancer	294 (13.7)	20 (10.4)	3 (6.7)
Lung cancer	350 (16.3)	39 (20.2)	15 (33.3)
Colorectal cancer	20 (0.9)	1 (0.5)	0
Other	19 (0.9)	2 (1.0)	0
Lung comorbidities,[a] n (%)			
No	2023 (94.3)	183 (94.8)	42 (93.3)

ECOG PS, eastern cooperative oncology group performance score; ILD, interstitial lung disease/pneumonitis; ILD1; first Gr 1 ILD event; T-DXd, trastuzumab deruxtecan.
[a]Includes asthma, chronic obstructive pulmonary disease, prior interstitial lung disease/pneumonitis, pulmonary fibrosis, pulmonary emphysema, and radiation pneumonitis.

Demographics and Baseline Characteristics (continued)

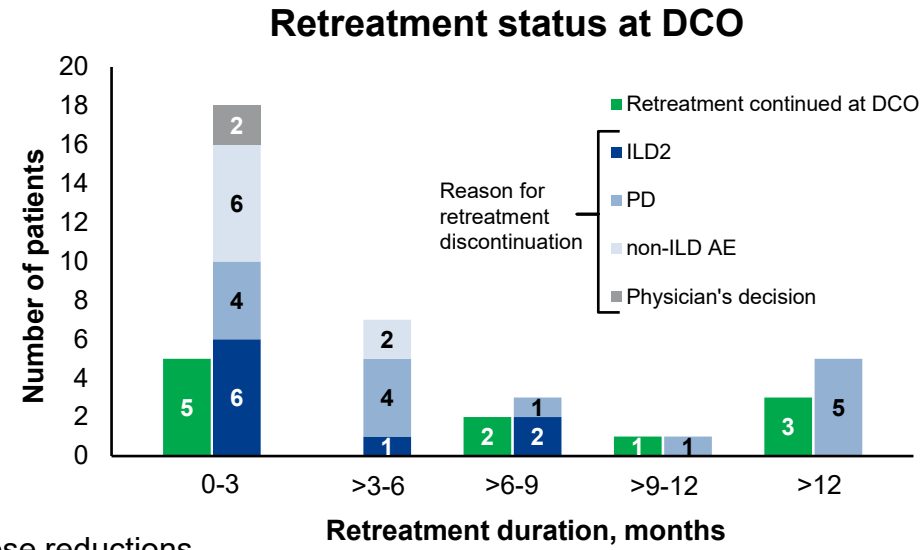
Baseline characteristics	All Tumor Types Pool (N = 2145)	ILD1 (N = 193)	T-DXd retreatment (N = 45)
T-DXd dose,[a] n (%)			
5.4 mg/kg	1449 (67.6)	117 (60.6)	29 (64.4)
6.4 mg/kg	669 (31.2)	72 (37.3)	16 (35.6)
>6.4 mg/kg	27 (1.3)	4 (2.1)	0
Baseline SpO_2, n (%)			
≥95%	2026 (94.5)	188 (97.4)	43 (95.6)
<95%	104 (4.8)	5 (2.6)	2 (4.4)
Missing	15 (0.7)	0	0
Renal function,[b] n (%)			
Normal (CrCl ≥90 mL/min)	1019 (47.5)	80 (41.5)	18 (40.0)
Mild impairment (CrCl 60 to <90 mL/min)	796 (37.1)	66 (34.2)	18 (40.0)
Moderate impairment (CrCl <60 mL/min)	306 (14.3)	41 (21.2)	7 (15.6)
Severe impairment (CrCl <30 mL/min)	4 (0.2)	2 (1.0)	1 (2.2)
Missing	20 (0.9)	4 (2.1)	1 (2.2)
Time since disease diagnosis, median (range), years	3.33 (0.0-29.7)	3.90 (0.0-22.7)	3.49 (0.1-22.7)
0 to ≤4 years	1065 (49.7)	87 (45.1)	21 (46.7)
>4 years	810 (37.8)	85 (44.0)	17 (37.8)
Missing	270 (12.6)	21 (10.9)	7 (15.6)

CrCl, creatinine clearance; ECOG PS, eastern cooperative oncology group performance score; ILD, interstitial lung disease/pneumonitis; ILD1; first Gr 1 ILD event; SpO_2, saturation of peripheral oxygen; T-DXd, trastuzumab deruxtecan.

[a]T-DXd dose at treatment initiation for each patient was recorded as the baseline dose in this analysis. [b]Renal function calculated based on creatinine clearance using the Cockcroft-Gault formula.

T-DXd Retreatment Characteristics

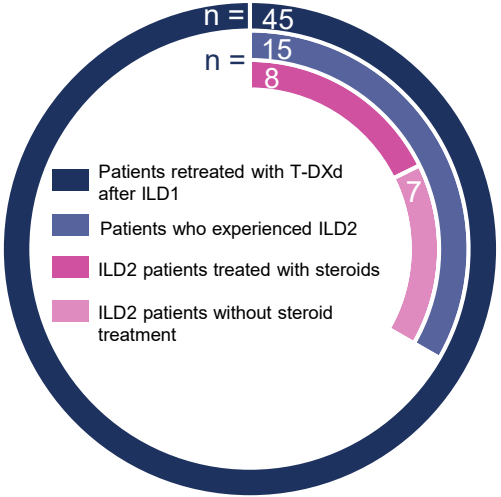
	T-DXd retreatment (N = 45)
Dose level of T-DXd retreatment	
Same dose, n (%)	31 (68.9)
Reduced dose, n (%)	14 (31.1)
Median time to retreatment after ILD1 onset (range), days	28 (8-48)
Median retreatment cycles (range)	5.0 (1-37)
Patients with ILD2 (n = 15)	5.0 (2-23)
Patients without ILD2 (n = 30)	4.5 (1-37)
Median retreatment duration (range), days	85.0 (1-848)
Patients with ILD2 (n = 15)	85.0 (22-648)
Patients without ILD2 (n = 30)	82.5 (1-848)



- 68.9% (31/45) of patients were retreated without any dose reductions
- 24.4% (11/45) of patients were still receiving T-DXd retreatment at the DCOs of each respective study
- Progressive disease was the main reason for T-DXd retreatment discontinuation (33.3% [15/45] of patients)
  - 20.0% (9/45) of patients discontinued retreatment due to recurrent ILD (ILD2)
- 33.3% (15/45) of patients were retreated for >6 months and 17.8% (8/45) of patients were retreated for >12 months

AE, adverse event; DCO, data cutoff; ILD, interstitial lung disease/pneumonitis; ILD1; first Gr 1 ILD event; ILD2, any-grade recurrent ILD event; PD, progressive disease; T-DXd, trastuzumab deruxtecan.

Characteristics and Outcome of recurrent ILD

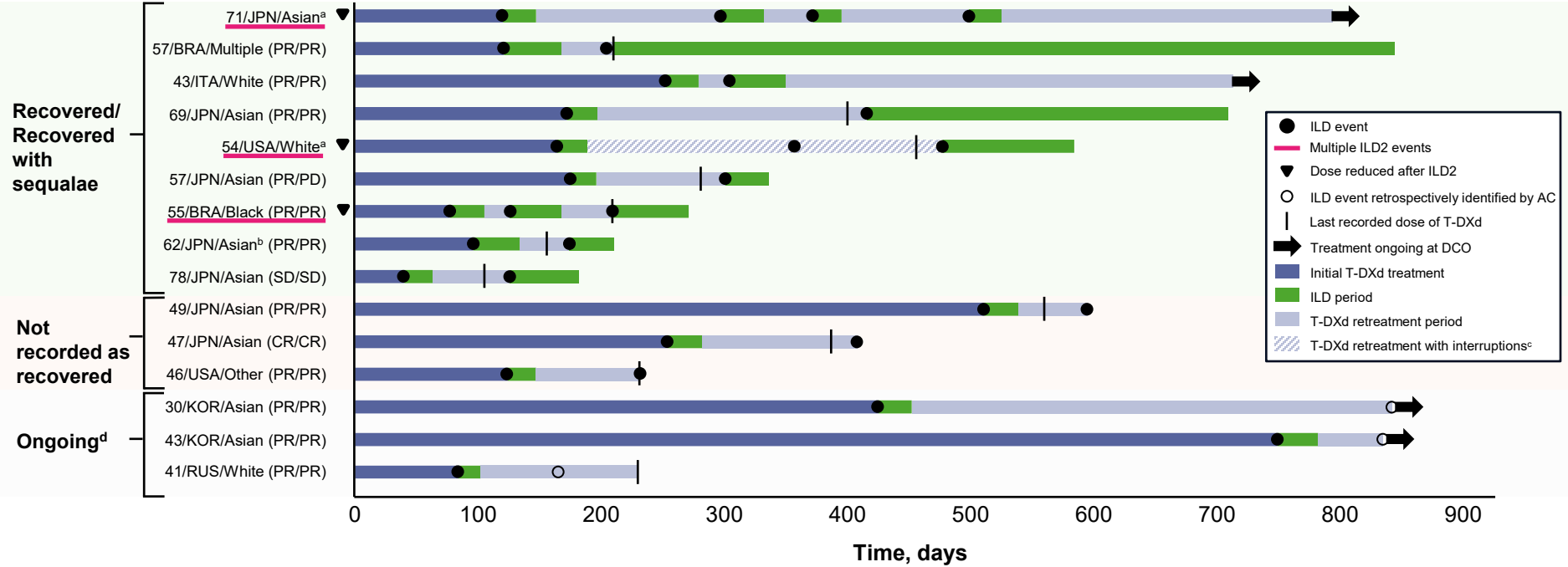


n (%)	With Steroid Treatment for ILD2[a] (n = 8)	Without Steroid Treatment for ILD2 (n = 7)	Total (n = 15)
Adjudicated Worst-Grade of ILD2			
1	2 (25.0)	4 (57.1)	6 (40.0)
2	6 (75.0)	3 (42.9)	9 (60.0)
≥3	0	0	0
Outcome of ILD2[b]			
Recovered/Recovered with sequalae	6 (75.0)	3 (42.9)	9 (60.0)
Not marked as recovered[c]	2 (25.0)	1 (14.3)	3 (20.0)
Ongoing[d]	0	3 (42.9)	3 (20.0)
Fatal	0	0	0

- 33.3% (15/45) of patients who were retreated with T-DXd[e] experienced ILD2
- Median time to ILD2[f] onset from T-DXd retreatment was 64 days (range, 22-391 days)
  - There were no fatal events or any adjudicated Gr ≥3 events
- 75% (6/8) of patients who were treated with steroids[g] for ILD2 recovered/recovered with sequalae

Gr, grade; ILD, interstitial lung disease/pneumonitis; ILD1; first Gr 1 ILD event; ILD2, any-grade recurrent ILD event; T-DXd, trastuzumab deruxtecan.
[a]Median duration of steroid treatment for the first recurrent ILD event, 40 days (range, 1-485). [b]Outcome of the first recurrent ILD event. [c]Patients were lost to follow-up. [d]Cases ongoing at time of analysis.
[e]All patients experiencing ILD2 were retreated with the same T-DXd dose level as dose at ILD1 onset, 3/15 patients had a dose reduction after ILD2. [f]Time to onset of the first recurrent ILD event.
[g]Management of ILD2 was carried out per the ILD guidelines at the time of the study[1] and steroid use for patients with Gr 1 events was determined by the investigator and thus varied amongst patients.
1. Powell CA et al. *ESMO Open.* 2022;7:100554.

Individual Outcomes and Characteristics of Patients Retreated with T-DXd who Experienced ILD Recurrence (n = 15)



- 60% (9/15) of patients with ILD2 recovered/recovered with sequalae; 4 patients had treatment ongoing at DCO[e]

AC, adjudication committee; BRA, Brazil; CR, complete response; DCO, data cutoff; Gr, grade; ILD, interstitial lung disease/pneumonitis; ILD2, any-grade recurrent ILD event; ITA, Italy; JPN, Japan; KOR, Republic of Korea; PD, progressive disease; PR, partial response; RUS, Russia; T-DXd, trastuzumab deruxtecan; USA, United States of America.
[a]Best response before and after treatment was non-CR/non-PD. [b]Recovered with sequalae. [c]T-DXd treatment was not held at ILD2 onset but did not follow standard treatment cycle intervals. [d]ILD recurrence was retrospectively identified by the AC and events were noted as ongoing with missing outcome at the time of analysis. [e]Of each respective study

Conclusions

- 23% (45/193) of patients with a first Gr 1 ILD were retreated with T-DXd
    - 68.9% (31/45) of these patients were retreated without any dose reductions
- 17.8% (8/45) of patients received retreatment for >1 year
- 66.7% (30/45) of patients in this pooled analysis were retreated without any ILD recurrence
    - All recurrent ILD were low-grade events and generally manageable using existing treatment guidelines
    - Timely monitoring and management of ILD is critical for patient recovery
- Since the time of this study, guidelines were updated to extend the ILD recovery period for T-DXd retreatment eligibility from 49 days to 126 days (if no progression of disease) from the date of the last T-DXd dose
- Real-world studies with larger datasets will improve understanding of the risks and benefits of T-DXd retreatment following Gr 1 ILD
- T-DXd retreatment is safe and may result in clinically meaningful extension of treatment duration following recovery from a first episode of Gr 1 ILD

This analysis demonstrates promising potential for the re-initiation of T-DXd treatment following management and full recovery from Gr 1 ILD. This approach will optimize clinical outcomes and maximize therapeutic benefit for patients

Gr, grade; ILD, interstitial lung disease/pneumonitis; T-DXd, trastuzumab deruxtecan.

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Plain Language Summary

Why did we perform this research?

- Trastuzumab deruxtecan (T-DXd) is a human epidermal growth factor receptor 2-targeting antibody-drug conjugate that is approved for use in several solid cancers.[1] Interstitial lung disease and/or pneumonitis (ILD) is a group of lung disorders that is characterized by inflammation and/or fibrosis of the lungs and is an important adverse event that can occur with T-DXd treatment; fatal events have been reported.[2,3] T-DXd treatment must be withheld when ILD is suspected but treatment can be resumed when an asymptomatic ILD event (grade 1) fully resolves within a specified time.[2,4] However, there is little information about ILD reoccurring in the longer term once patients resume T-DXd treatment after recovering from their initial asymptomatic ILD event. This study characterized T-DXd retreatment and recurrent ILD in patients who recovered from grade 1 ILD

How did we perform this research?

- Data from patients treated with T-DXd across 9 clinical trials were pooled and analyzed for T-DXd retreatment and ILD recurrence. All ILD events that were reported by investigators were retrospectively reviewed and confirmed by an independent adjudication committee comprising expert oncologists, radiologists, and pulmonologists

What were the findings of this research and what are the implications?

- Results showed that T-DXd retreatment had favorable outcomes; approximately 18% of patients received retreatment for more than a year and 67% of retreated patients did not experience a recurrent ILD event. All recurrent ILD events were low grade (≤2) and were generally manageable using existing treatment guidelines. These results show that T-DXd retreatment after recovery from a first grade ILD event is safe and may lead to clinically meaningful extension of treatment duration. The findings reaffirm that timely monitoring and management of ILD is critical for patient recovery. The approach of T-DXd retreatment after grade 1 ILD recovery can optimize clinical outcomes and maximize therapeutic benefit for patients.

Where can I access more information?

- To learn more about the trials included in this study please visit: **J101** (https://clinicaltrials.gov/study/NCT02564900), **DESTINY Breast-01** (https://clinicaltrials.gov/study/NCT03248492), **DESTINY Breast-02** (https://clinicaltrials.gov/study/NCT03523585), **DESTINY Breast-03** (https://clinicaltrials.gov/study/NCT03529110), **DESTINY Breast-04** (https://clinicaltrials.gov/study/NCT03734029), **DESTINY Gastric-01** (https://clinicaltrials.gov/study/NCT03329690), **DESTINY Gastric-02** (https://clinicaltrials.gov/study/NCT04014075), **DESTINY Lung-01** (https://clinicaltrials.gov/study/NCT03505710), **DESTINY Lung-02** (https://clinicaltrials.gov/study/NCT04644237)

ILD, interstitial lung disease/pneumonitis; T-DXd, trastuzumab deruxtecan.

1. Enhertu (fam-trastuzumab deruxtecan-nxki). Prescribing information. Daiichi Sankyo, Inc; 2022. 2. Powell CA et al. *ESMO Open.* 2022;7:100554. 3. Rugo HS et al. *ESMO Open.* 2022;7:10553.
4. Cortes J et al. *NEJM.* 2022;386:1143-54

Current Toxicity Management Guidelines for ILD

Asymptomatic ILD (Grade 1)	• Consider corticosteroid treatment (e.g., ≥0.5 mg/kg prednisolone or equivalent)
	• Interrupt T-DXd until ILD is resolved to grade 0, then:
	  ○ If resolved in ≤28 days from onset, maintain dose
	  ○ If resolved in >28 days from onset, reduce dose by 1 level
	  ○ However, if the event grade 1 ILD has not resolved within **18 weeks (126 days)**[a] from the last infusion, the drug should be discontinued

Grade 2 ILD	• Promptly initiate systemic corticosteroids (e.g., ≥1 mg/kg prednisolone or equivalent) for ≥14 days followed by a gradual taper over ≥4 weeks • If clinical or diagnostic observations worsen or do not improve within 5 days, consider increasing steroid dose or escalating care as clinically indicated • Permanently discontinue T-DXd in patients who are diagnosed with any symptomatic ILD
Grade 3 or 4 ILD	• Hospitalization required • Permanently discontinue T-DXd in patients who are diagnosed with any symptomatic ILD • Promptly initiate high-dose methylprednisolone IV treatment (e.g. 500-1000 mg/day for 3 days), followed by ≥1 mg/kg prednisolone (or equivalent) for ≥14 days, followed by a gradual taper over ≥4 weeks • If clinical or diagnostic observations do not improve within 3-5 days, consider other immunosuppressants and/or treat per local practice

All events of ILD, regardless of severity or seriousness, should be followed until resolution, including after drug discontinuation

ILD, interstitial lung disease/pneumonitis; IV, intravenous; T-DXd, trastuzumab deruxtecan.

[a]ILD toxicity management guidelines at the time of each study that was included in this analysis recommended T-DXd discontinuation if the ILD event had not resolved within 49 days from the date of the last dose

Individual ILD2 Outcomes and T-DXd Retreatment Status

Patient Age/Country/Race	Initial Dose,[a] (mg/kg)	Retreatment Dose, (mg/kg)	Retreatment Duration,[b] (months)	Time to ILD2 After Retreatment, (days)	ILD2 Grade by AC	ILD2 Outcome at DCO	Retreatment Status at DCO
71/JPN/Asian[c]	5.4	4.4	21.29	151	1	Recovered/Recovered with sequalae	Ongoing
57/BRA/Multiple	5.4	5.4	1.41	36	2	Recovered/Recovered with sequalae	Discontinued
43/ITA/White	5.4	4.4	14.29	26	1	Recovered/Recovered with sequalae	Ongoing
69/JPN/Asian	5.4	5.4	6.70	220	2	Recovered/Recovered with sequalae	Discontinued
54/USA/White[c]	5.4	5.4	8.80	169	2	Recovered/Recovered with sequalae	Discontinued
57/JPN/Asian[c]	6.4	6.4	2.79	106	2	Recovered/Recovered with sequalae	Discontinued
55/BRA/Black	5.4	5.4	2.79	22	2	Recovered/Recovered with sequalae	Discontinued
62/JPN/Asian	6.4	5.4	0.76	41	1	Recovered/Recovered with sequalae	Discontinued
78/JPN/Asian	5.4	4.4	1.41	64	2	Recovered/Recovered with sequalae	Discontinued
49/JPN/Asian	6.4	6.4	0.72	57	2	Not recorded as recovered	Discontinued
47/JPN/Asian	6.4	5.4	3.48	127	1	Not recorded as recovered	Discontinued
46/USA/Other	6.4	5.4	2.79	85	1	Not recorded as recovered	Discontinued
30/KOR/Asian[d]	5.4	5.4	9.92	391	2	Ongoing[e]	Ongoing
43/KOR/Asian[d]	5.4	5.4	1.45	54	2	Ongoing[e]	Ongoing
41/RUS/White[d]	5.4	5.4	4.21	64	1	Ongoing[e]	Discontinued

AC, adjudication committee; BRA, Brazil; DCO, data cutoff; ILD, interstitial lung disease/pneumonitis; ILD2, second any-grade ILD event; ITA, Italy; JPN, Japan; KOR, Republic of Korea; RUS, Russia; T-DXd, trastuzumab deruxtecan; USA, United States of America.

[a]T-DXd dose at original treatment initiation. [b]Retreatment duration was from retreatment start date until the last recorded dose. [c]These patients had multiple ILD2 cases. [d]ILD2 was retrospectively identified by the AC. [e]Cases ongoing at time of analysis.

Potential Factors of Interest for ILD

Baseline characteristics	T-DXd Retreatment (N = 45)	ILD Recurrence[a] (N = 15)	No ILD Recurrence (N = 30)
Age, median (range), years	59.1 (30-79)	54.2 (30-79)	65.3 (39-78)
<65 years, n (%)	27 (60.0)	12 (80.0)	15 (50.0)
≥65 years, n (%)	18 (40.0)	3 (20.0)	15 (50.0)
Sex, n (%)			
Female	36 (80.0)	12 (80.0)	24 (80.0)
Country, n (%)			
Japan	17 (37.8)	7 (46.7)	10 (33.3)
Non-Japan	28 (62.2)	8 (53.3)	20 (66.7)
ECOG PS, n (%)			
0	22 (48.9)	10 (66.7)	12 (40.0)
1	23 (51.1)	5 (33.3)	18 (60.0)
Tumor type, n (%)			
Breast cancer	27 (60.0)	10 (66.7)	17 (56.7)
Gastric cancer	3 (6.7)	0	3 (10.0)
Lung cancer	15 (33.3)	5 (33.3)	10 (33.3)
Colorectal cancer	0	0	0
Other	0	0	0
Lung comorbidities,[b] n (%)			
No	42 (93.3)	13 (86.7)	29 (96.7)

Baseline characteristics	T-DXd Retreatment (N = 45)	ILD Recurrence[a] (N = 15)	No ILD Recurrence (N = 30)
T-DXd dose, n (%)			
5.4 mg/kg	29 (64.4)	10 (66.7)	19 (63.3)
6.4 mg/kg	16 (35.6)	5 (33.3)	11 (36.7)
>6.4 mg/kg	0	0	0
Baseline SpO_2, n (%)			
≥95%	43 (95.6)	14 (93.3)	29 (96.7)
<95%	2 (4.4)	1 (6.7)	1 (3.3)
Missing	0	0	0
Renal function,[c] n (%)			
Normal (CrCl ≥90 mL/min)	18 (40.0)	7 (46.7)	11 (36.7)
Mild impairment (CrCl 60 to <90 mL/min)	18 (40.0)	5 (33.3)	13 (43.3)
Moderate impairment (CrCl <60 mL/min)	7 (15.6)	3 (20.0)	4 (13.3)
Severe impairment (CrCl <30 mL/min)	1 (2.2)	0	1 (3.3)
Missing	1 (2.2)	0	1 (3.3)
Time since disease diagnosis, median (range), years	3.49 (0.1-22.7)	3.59 (0.1-8.2)	3.48 (0.5-22.7)
0 to ≤4 years	21 (46.7)	7 (46.7)	14 (46.7)
>4 years	17 (37.8)	6 (40.0)	11 (36.7)
Missing	7 (15.6)	2 (13.3)	5 (16.7)

- Variables considered as potential factors of interest for ILD occurrence did not show any clear correlation with ILD occurrence or reoccurrence in this analysis

CrCl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance score; ILD, interstitial lung disease/pneumonitis; SpO_2, saturation of peripheral oxygen; T-DXd, trastuzumab deruxtecan.
[a]Recurrence of any-grade ILD. [b]Includes asthma, chronic obstructive pulmonary disease, prior interstitial lung disease/pneumonitis, pulmonary fibrosis, pulmonary emphysema, and radiation pneumonitis.
[c]Renal function calculated based on creatinine clearance using the Cockcroft-Gault formula.