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ORIGINAL ARTICLE

Pooled analysis of trastuzumab deruxtecan retreatment after recovery from grade 1 interstitial lung disease/pneumonitis

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Background: Trastuzumab deruxtecan (T-DXd), an antibody-drug conjugate treatment for multiple solid tumors, carries risk of interstitial lung disease/pneumonitis (ILD). Management guidelines generally mandate interrupting T-DXd treatment for grade 1 ILD, with possible retreatment following resolution of imaging findings. This pooled analysis examined T-DXd retreatment duration and ILD recurrence following recovery from grade 1 ILD.

Patients and methods: Data were pooled from nine clinical trials of patients with various human epidermal growth factor receptor 2 (HER2)-positive, HER2-low, or *HER2 (ERBB2)*-mutant solid tumors treated with T-DXd (5.4-8.0 mg/kg). ILD events were reported and graded by investigators and confirmed as drug related by an independent ILD adjudication committee. Patients who recovered from a first investigator-assessed grade 1 and adjudication committee-confirmed drug-related ILD event (ILD1) could receive T-DXd retreatment. Patients were evaluated until disease progression or data cut-off.

Results: Among 2145 pooled patients, 9% (193/2145) had grade 1 ILD1, of which 23.3% (45/193) were retreated with T-DXd. Median retreatment duration was 85 days (range 1-848 days); 17.8% (8/45) of patients received T-DXd retreatment for $\geq$1 year. ILD recurrence (ILD2) occurred in 33.3% (15/45) of retreated patients; median time to ILD2 from T-DXd retreatment was 64 days (range, 22-391 days) and were low-grade events (grade 1, $n = 6$; grade 2, $n = 9$; no grade $\geq$3 or fatal events). Reasons for T-DXd retreatment discontinuation were disease progression [33.3% (15/45)]; ILD recurrence [20% (9/45)]; non-ILD adverse events [17.8% (8/45)]; and physician's decision [4.4% (2/45)]. At the analysis cut-off, 24.4% (11/45) of retreated patients were still receiving treatment, and most patients with ILD2 [60% (9/15)] had recovered with/without sequelae.

Conclusions: This first large-scale pooled analysis demonstrates the safety of T-DXd retreatment after recovery from grade 1 ILD. ILD recurred in one-third of patients; all recurrence events were grade 1/2 and manageable using existing treatment guidelines. T-DXd retreatment following resolution of grade 1 drug-related ILD has potential to maximize therapeutic benefit.

Key words: interstitial lung disease, ILD, pneumonitis, trastuzumab deruxtecan, T-DXd, retreatment

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INTRODUCTION

Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate composed of an anti-human epidermal growth factor receptor 2 (HER2) antibody, a tetrapeptide-based cleavable linker, and a topoisomerase I inhibitor payload.[1-3] T-DXd is approved in various countries for

treating HER2-positive metastatic breast cancer (BC),[4] HER2-low metastatic BC,[5] HER2-positive advanced gastric or gastroesophageal junction adenocarcinoma,[6,7] metastatic non–small cell lung cancer (NSCLC) with activating *HER2* (*ERBB2*) mutations[8,9] and the treatment of unresectable or metastatic HER2-positive (immunohistochemistry 3+) solid tumors in patients who have received prior systemic treatment and have no alternative treatment options.[9-11]

T-DXd has demonstrated significant efficacy, with improved progression-free and overall survival across different tumor types, with a generally manageable safety profile.[4-10,12] The most common adverse events (AEs) are gastrointestinal and low-grade hematological AEs.[13] However, interstitial lung disease/pneumonitis (ILD) represents an important and identified risk. In a previously published pooled analysis of early T-DXd clinical trials across several tumor types, ILD occurred in 15.4% (177/1150) of patients, with an overall incidence of fatal grade 5 ILD of 2.2% (25/1150); in the previous analysis, 77.4% of the reported ILD cases were grade 1 [27.1% (48/177)] or grade 2 [50.3% (89/177)], 7.9% [14/177] were grade 3, 0.06% [1/177] were grade 4, and 14.1% (25/177) were grade 5.[14]

ILD is a heterogeneous group of lung disorders that manifests as inflammation and/or fibrosis of the lungs and is associated with several cancer therapies, including T-DXd.[13-17] ILD is characterized by chest radiographic abnormalities, decreased diffusing lung capacity for carbon monoxide and forced expiratory volume in 1 s on pulmonary function tests (reflecting impaired gas transfer and decreased lung volume), microscopic patterns of inflammation and fibrosis, and respiratory symptoms such as dyspnea and cough.[15,18] The National Cancer Institute Common Terminology Criteria for Adverse Events defines ILD grades as follows: grade 1 is asymptomatic with non-specific radiographic findings, grade 2 is symptomatic with medical intervention indicated, grade 3 involves severe symptoms that limit daily self-care activities and includes hypoxia requiring oxygen therapy, grade 4 is characterized by life-threatening respiratory compromise that necessitates urgent intervention such as intubation, and grade 5 ILD is fatal.[19] An independent multidisciplinary adjudication committee comprising specialist oncologists, pulmonologists, and radiologists from the United States, Europe, and Japan was established in 2017 to assess potential ILD events reported by investigators in patients treated with T-DXd.[14,15]

Although the identification of clinical factors associated with T-DXd–related ILD is still under investigation, a pooled analysis of extensively pretreated patients (3-10 lines of prior therapy) from nine T-DXd monotherapy trials identified that renal dysfunction, baseline hypoxia, age, and treatment in Japan were potentially associated with a higher incidence of any-grade ILD.[14] The mechanism of T-DXd–related ILD is unclear; further studies are necessary to clarify the mechanism of toxicity.

Toxicity management guidelines from the United States Food and Drug Administration and European Medicines Agency labels for T-DXd state that T-DXd must be interrupted upon suspected ILD.[20,21] Corticosteroid therapy should be considered as soon as ILD is suspected, and treatment can be restarted for patients with grade 1 ILD if it resolves to grade 0, i.e. the disappearance of radiological findings associated with active ILD (residual scarring or fibrosis following recovery of ILD is not considered to be active disease), with a one-level dose reduction if resolution occurs >28 days from onset. T-DXd must be permanently discontinued for grade ≥2 ILD.[20,21] However, data regarding the risk of ILD recurrence with T-DXd retreatment are limited. Understanding the risks and benefits of T-DXd retreatment is critical to optimize efficacy and safety. We report an analysis of pooled data across nine phase I-III T-DXd clinical trials to characterize T-DXd retreatment and ILD recurrence following resolution of grade 1 ILD.

PATIENTS AND METHODS

Study populations

Data from 2145 patients with HER2-positive or HER2-low BC, HER2-positive gastric cancer, HER2-positive NSCLC, NSCLC with activating *HER2 (ERBB2)* mutations, or other solid tumors who had received at least one dose of T-DXd (5.4-8.0 mg/kg) monotherapy were pooled from nine clinical trials until the specified data cut-off (DCO) of each study (Figure 1; Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2025.07.015).

All AEs that were potential ILD events, defined by periodically updated preferred terms per the Medical Dictionary for Regulatory Activities, were graded and reported by investigators. Per the T-DXd toxicity management guidelines, asymptomatic ILD that was treated with corticosteroids was considered to be grade 1 ILD (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2025.07.015). These AEs were then retrospectively reviewed by an ILD adjudication committee using standardized data from the study site to confirm ILD status. If confirmed as drug-related ILD, the committee also determined the date of onset.[14] The adjudication committee could consider asymptomatic ILD that was treated with corticosteroids as grade 2. Confirmatory evaluations included computed tomography (CT) scans, laboratory evaluations, and pulmonologist/infectious diseases consultation records as clinically indicated.

In this analysis, the first potential ILD event reported by the investigator as grade 1 and confirmed as being drug related by the adjudication committee was defined as ILD1. Pooled data were analyzed to identify patients with ILD1 who received T-DXd retreatment following investigator-assessed ILD1 recovery. These patients were assessed for the duration of T-DXd retreatment and ILD recurrence. Subsequent ILD events of any grade, reported by the investigator and confirmed as being drug-related ILD by the adjudication committee, were defined sequentially as ILD2, ILD3, and so on.

Patients were followed up with chest CT scans for ILD resolution with clinically indicated imaging frequency based

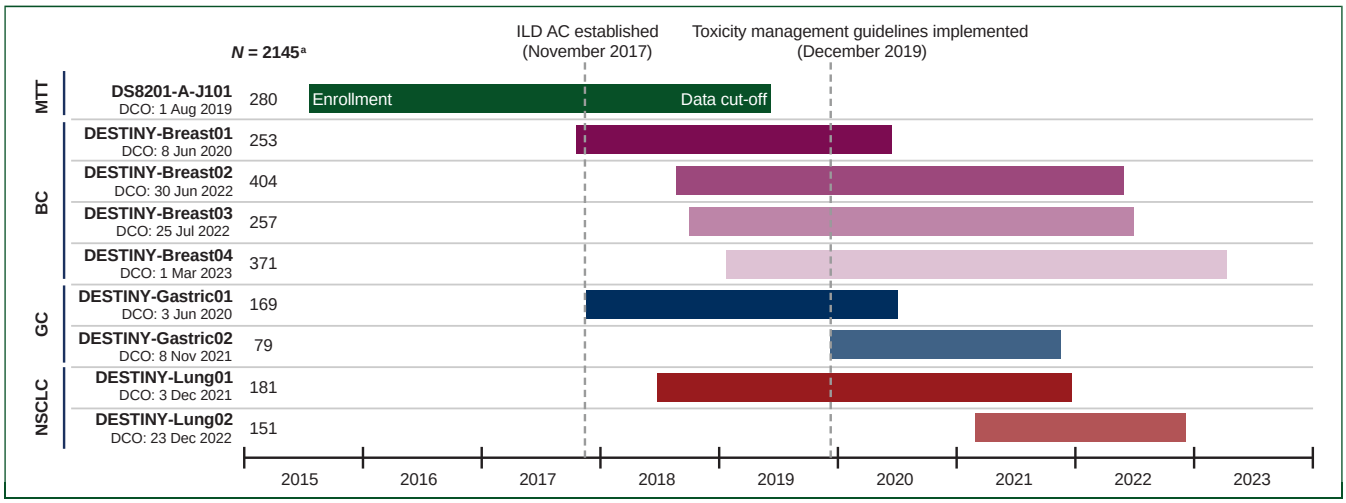

Figure 1. Clinical trials from which patients were pooled for this analysis.
AC, adjudication committee; BC, breast cancer; DCO, data cut-off; GC, gastric cancer; ILD, interstitial lung disease/pneumonitis; MTT, multiple tumor types; NSCLC, non—small cell lung cancer; T-DXd, trastuzumab deruxtecan.
[a]Only patients who received at least one 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.

on local guidelines at the investigator's discretion. Patients with ILD who showed improvement on CT scans but had residual fibrosis were noted as recovered with sequelae; patients with no signs of ILD or fibrosis were noted as recovered. Patients whose symptoms and/or scans were improving but had not yet resolved were noted as recovering.

Patients were monitored for disease progression per the relevant mandated trial follow-up criteria. The DCO for this analysis was set at 6 months after the last eligible pooled patient began T-DXd retreatment or at disease progression, whichever occurred first.

T-DXd toxicity management guidelines and retreatment

Toxicity management guidelines for T-DXd clinical trials were implemented in 2019 to improve the treatment of T-DXd—related ILD.[14] Before the guidelines recommended consideration of steroid therapy for grade 1 ILD, steroid use was at the investigator's discretion. Clinical trial guidelines were later updated to extend the retreatment eligibility window from grade 1 ILD onset to resolution to grade 0 from within 49 days to within 18 weeks (126 days), provided there was no disease progression (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2025.07.015). For the current analysis, ILD management and T-DXd retreatment was per the clinical trial guidelines in effect during the time of the individual studies.

RESULTS

Patient disposition and baseline characteristics

In the pool of 2145 patients in this analysis, 9.0% (193/2145) experienced grade 1 ILD1, 23.3% (45/193) of whom were retreated with T-DXd (Figure 2). Of the 193 patients who experienced grade 1 ILD1, 76.7% (148/193) were not retreated with T-DXd based on investigator decision or study protocol discontinuation requirements. In patients who were not retreated, 35.8% (53/148) recovered from ILD1 after >49 days since their last dose of T-DXd, 8.1% (12/148) were recovering from ILD1 at the DCOs of their respective studies, and 5.4% (8/148) recovered within 49 days of their last dose but did not receive T-DXd retreatment based on investigator decision. Additionally, 43.9% (65/148) of patients who were not retreated had not recovered from ILD by day 49 following ILD onset (including patients who died of other causes). Finally, 10 patients [6.8% (10/148)] had unknown or missing ILD1 outcomes (Figure 2). Investigators began retreating two patients at a date that was before the adjudication committee confirmed that ILD1 was recovered; these patients were excluded from the analysis and at the time of DCO, ILD1 for these patients progressed to grade 2 within 22 days of retreatment and to grade 3 within 47 days of retreatment, respectively.

Patient demographics and baseline characteristics for all pooled patients, patients with ILD1, and the 45 patients retreated with T-DXd are shown in Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2025.07.015. Median age of retreated patients was 59.1 years, 40.0% (18/45) of patients were aged ≥65 years, and 37.8% (17/45) were treated in Japan. Most retreated patients had an initial T-DXd dose of 5.4 mg/kg [64.4% (29/45)], had no lung comorbidities [93.3% (42/45)], and had ≥95% baseline blood oxygen saturation [SpO_2; 95.6% (43/45)]. Baseline renal function of retreated patients was normal in 40.0% (18/45), mildly impaired in 40.0% (18/45), moderately impaired in 15.6% (7/45), and severely impaired in 2.2% (1/45) of patients; 2.2% (1/45) of patients had missing data.

T-DXd retreatment

Median time from initial T-DXd treatment start date to onset of ILD1 was 210.0 days (range, 37-750 days) for the

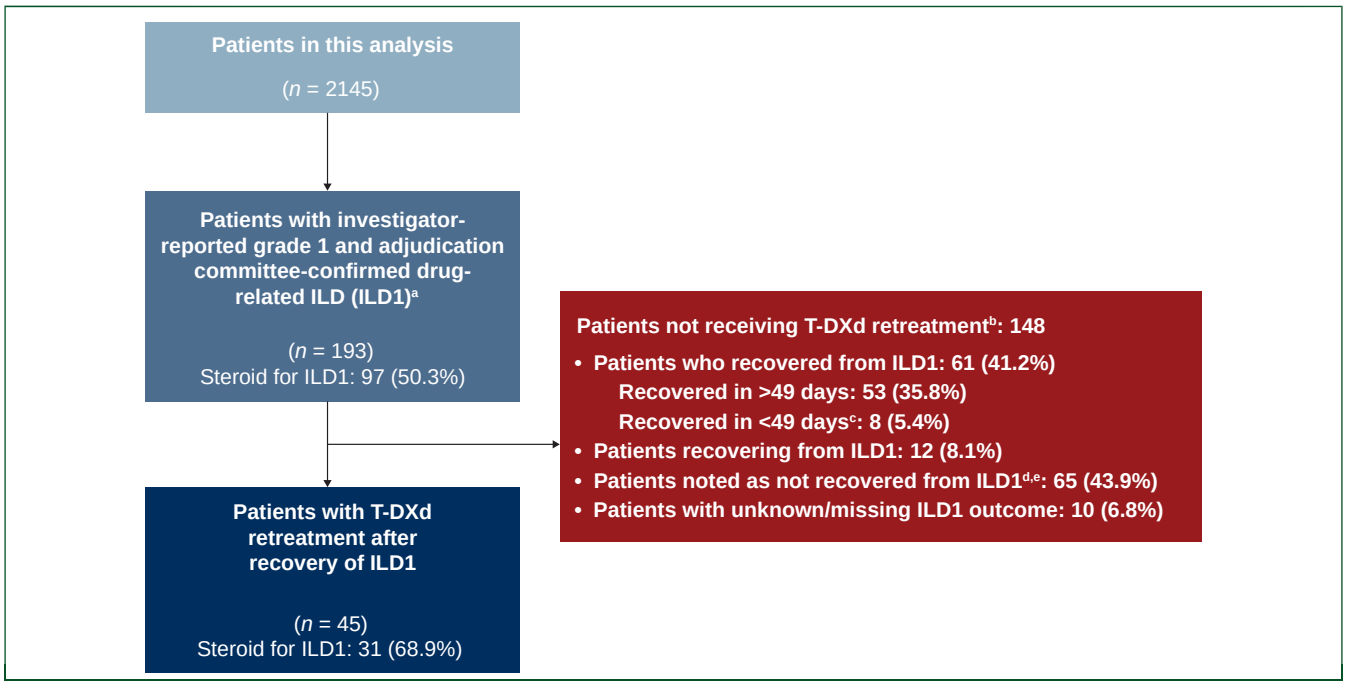

Figure 2. Patient disposition.
AC, adjudication committee; DCO, data cut-off; ILD, interstitial lung disease/pneumonitis; ILD1, first investigator-assessed grade 1 and AC-confirmed drug-related ILD event; T-DXd, trastuzumab deruxtecan.
[a]If sequential adjudicated drug-related ILD events occurred with grade changes (following one after the other), the sequential events were regarded as one 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 following 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.

45 retreated patients. Median time to start T-DXd retreatment after ILD1 onset was 28 days (range, 8-48 days), and median retreatment duration without disease progression was 85 days/5 treatment cycles (range, 1-848 days/1-37 cycles) (Table 1). The T-DXd retreatment dose was the same as the initial dose for 68.9% (31/45) of patients (Table 1) and was based on the time to recovery from ILD1 assessed by the investigators per the toxicity management guidelines in the T-DXd study protocols. At the DCO of this analysis, T-DXd retreatment was ongoing for 24.4% (11/45) of patients (Figure 3).

The objective response rate for those patients who were retreated was 82.2% (37/45) before retreatment. After T-DXd retreatment, 13.3% (6/45) of patients experienced progressive disease, 4.4% (2/45) had missing best response data, and 4.4% (2/45) had improved best response (one from stable disease to partial response; one from partial to complete response). The remaining patients maintained their previous best response.

Most T-DXd retreatment discontinuations occurred within 6 months of retreatment, primarily due to progressive disease [33.3% (15/45)]; 20.0% (9/45) of retreated patients discontinued retreatment due to ILD2. Retreatment continued without disease progression for >6 months for 33.3% (15/45) of patients and for >12 months for 17.8% (8/45) of patients (Figure 3).

ILD/pneumonitis recurrence (ILD2) after T-DXd retreatment of grade 1 ILD

At the DCO of this analysis, 66.7% (30/45) of patients were successfully retreated without experiencing ILD2; 33.3% (15/45) of retreated patients experienced ILD2. Median time to ILD2 onset from retreatment was 64 days (range, 22-391 days). Median retreatment duration was similar for patients with and without ILD2 (85.0 days/5.0 cycles versus 82.5 days/4.5 cycles, Table 1). All ILD2 events were low grade, with the adjudicated worst grade of ILD2 being grade 1 for 40% (6/15) and grade 2 for 60% (9/15) of patients; 88.9% (8/9) of patients with grade 2 ILD2 had been retreated with T-DXd without a dose reduction (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2025.07.015). There were no ILD2 events >grade 2 (Table 2). Most patients [60% (9/15)] recovered from ILD2 or recovered with sequelae (Figure 4; Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2025.07.015). T-DXd retreatment maintained the best tumor response for 93.3% (14/15) of patients who experienced ILD2; one patient developed progressive disease after an initial partial response.

Among the 15 patients who experienced recurrent ILD, 3 patients had multiple adjudicated recurrent ILD events after retreatment. Specifically, two patients had two recurrent ILD events each, and one patient had three

Table 1. T-DXd retreatment

	T-DXd retreatment ($N = 45$)
Median time to onset of ILD1[a] (range), days	210.0 (37-750)
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)

AC, adjudication committee; ILD, interstitial lung disease/pneumonitis; ILD1, first investigator-assessed grade 1 and AC-confirmed drug-related ILD event; ILD2, investigator-assessed AC-confirmed any-grade recurrent ILD event; T-DXd, trastuzumab deruxtecan.

[a]Time from initial T-DXd treatment start date to onset of first grade 1 ILD1.

recurrent ILD events. Retreatment with T-DXd after recovery from ILD2 continued with a dose reduction for these patients (Figure 4). At the DCO for this analysis, information on the outcome of ILD2 was missing for 20% (3/15) of patients, as no outcome for ILD2 was recorded in the clinical reporting forms. For a further 20% (3/15) of patients, ILD2 was retrospectively identified by the adjudication committee but was not reported by the investigator, resulting in missing outcomes (Figure 4).

Steroid treatment of ILD

From the total pool of patients with grade 1 ILD1, 50.3% (97/193) received steroids for management of ILD1 (Figure 2), with a median duration of steroid treatment of 30.0 days (range, 1-974 days). Of patients who were retreated with T-DXd, 68.9% (31/45) received steroids for ILD1. The median time for ILD1 recovery for retreated patients was 24 days (range, 3-40 days) for patients who received steroids (68.9%; 31/45) and 19.5 days (range, 6-30 days) for those who did not (31.1%; 14/45) (Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2025.07.015). ILD2 occurred in 32.3% (10/31) of patients who received steroids for ILD1 and in 35.7% (5/14) of patients who did not.

Of the 15 retreated patients who experienced ILD2, 53.3% (8/15) received steroids for ILD2 (Table 2) with a median duration of steroid treatment of 40 days (range, 1-485 days) (Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2025.07.015); 25% (2/8) of these patients had adjudicated grade 1 ILD2 while 75% (6/8) had adjudicated grade 2 ILD2 (Table 2). Of the eight patients who received steroids for ILD2, 75.0% (6/8) recovered or recovered with sequelae; of the seven patients who did not receive steroids for ILD2, 42.9% (3/7) recovered or recovered with sequelae and 42.9% (3/7) had ILD2 that was ongoing at the DCO of this analysis because it was identified by the adjudication committee and not the investigator. The adjudicated worst grade of recurrent ILD was grade 1 for 25.0% (2/8) and grade 2 for 75.0% (6/8) of patients who received steroids for ILD2 and 57.1% (4/7) and 42.9% (3/7), respectively, for those who did not receive steroids for ILD2 (Table 2).

DISCUSSION

This large-scale analysis of pooled patient data from nine early T-DXd clinical trials characterizes ILD recurrence and outcomes following T-DXd retreatment after resolution of grade 1 ILD. Of the patients retreated with T-DXd, most [66.7% (30/45)] did not experience ILD recurrence, with 17.8% (8/45) of patients receiving retreatment for >1 year; 31.1% (14/45) of patients received a dose reduction for retreatment. ILD recurrence was identified in 33.3% of retreated patients and was manageable using existing toxicity management guidelines (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2025.07.015),[14] with all recurrent events being either grade 1 or 2. Of nine patients who experienced ILD2 while being retreated with T-DXd without a dose reduction, eight (88.9%) had grade 2 ILD2 (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2025.07.015), although low patient numbers limit interpretation. Four patients who experienced recurrent ILD were receiving T-DXd retreatment at the DCO of this analysis. Importantly, there were no ILD events >grade 2.

A previous pooled analysis demonstrated that most patients (87%) develop ILD within 12 months of starting treatment, with a median time to onset of adjudicated drug-related ILD of 5.4 months (range, <0.1-46.8 months).[14] These data are supported by a recent real-world study conducted in France, which evaluated patients treated with T-DXd and reported an ILD incidence of 11.2% with a median onset of ∼2.7 months (82 days).[22] The rate of adjudicated T-DXd—related ILD in patients with BC from DESTINY-Breast01 was 15.5%; there was no evidence of cumulative T-DXd toxicity, with a conditional probability of developing T-DXd—related ILD after 12 months of treatment being 1.8%.[23,24] The rate of ILD in DESTINY-Breast04 was 12.1% despite the longer duration of follow-up than DESTINY-Breast01 (18.4 versus 11.1 months).[5,24] Incidences of ILD across early T-DXd clinical trials are described in detail in Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2025.07.015,[4-10,12,24-31] with higher incidence in patients with HER2-positive NSCLC and NSCLC with activating *HER2* mutations receiving T-DXd 6.4 mg/kg.

Results of the current analysis describe a short time to onset of recurrent ILD, with a median time from retreatment to ILD2 onset of 64 days and all retreatment discontinuations due to ILD2 occurring within 9 months of retreatment; closer monitoring of retreated patients for ILD in early retreatment cycles may be of benefit.

Two previous studies identified that an independent adjudication committee determined the time of onset of ILD as earlier than reported by investigators (in 53.2% and 24.6% of cases with a median difference of 43.0 and 29.5 days, respectively).[14,32] In our analysis, ILD2 was

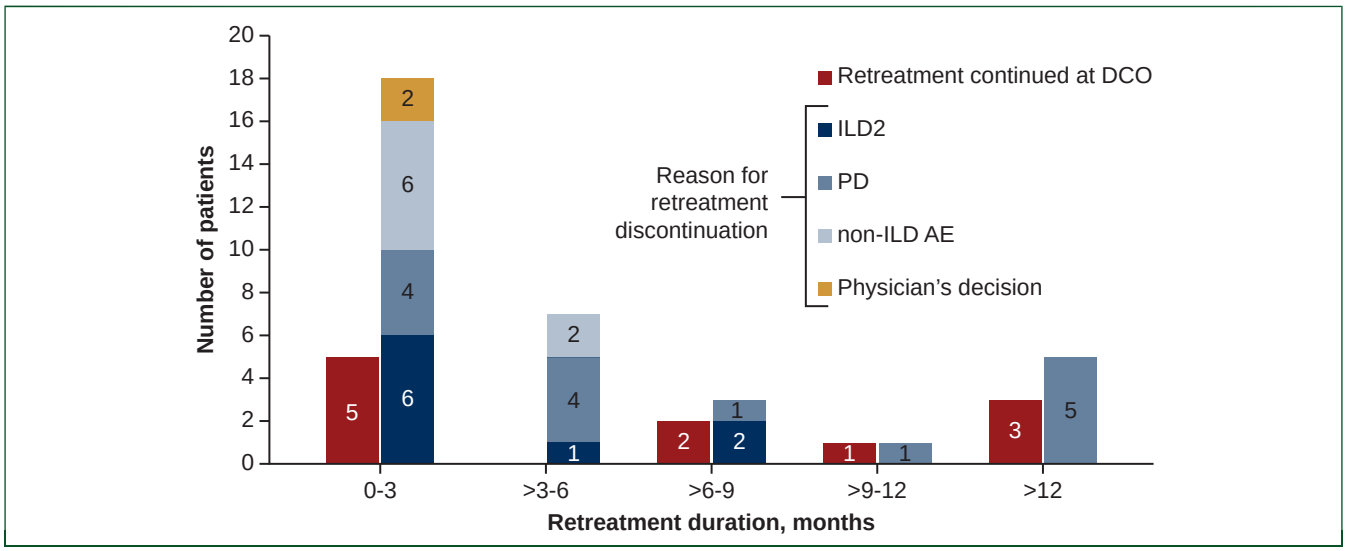

Figure 3. T-DXd retreatment status at the DCO of this analysis.
AE, adverse event; DCO, data cut-off; ILD, interstitial lung disease/pneumonitis; ILD2, investigator-assessed adjudication committee-confirmed any-grade recurrent ILD; PD, progressive disease; T-DXd, trastuzumab deruxtecan.

identified in two retreated patients by the adjudication committee and not the investigator. These results highlight the need for continuous and thorough monitoring to identify ILD as early as possible.

Diagnosis of drug-related ILD should be approached in a comprehensive and multidisciplinary manner to ensure that the ILD is detected promptly and managed appropriately.[15,33-35] High-resolution CT (HRCT) scans of the lungs are crucial in evaluating ILD occurrence because they can identify ground-glass opacities associated with ILD. HRCT scans, along with a comprehensive review of patient history, are recommended before initiating T-DXd treatment because pre-existing lung comorbidities (such as asthma and chronic obstructive pulmonary disease) are associated with a higher incidence of drug-related ILD.[13,14,33,34,36] Pre-existing interstitial lung disease was part of the exclusion criteria for the trials included in this analysis.[4-9,24-26] Additionally, imaging patterns of ground-glass opacities can correlate with ILD prognosis; patterns associated with a diffuse alveolar damage-type of ILD are linked to poor prognosis and resistance to steroid therapy.[15,16,32,33,37] Several studies have explored biomarkers and diagnostic tests to enhance the monitoring and identification of ILD, aiming to improve ILD management; however, these studies have not yet led to definitive recommendations.[38-41]

Table 2. Grade and outcome of ILD2

n (%)	With steroid treatment for ILD2 (*n* = 8)	Without steroid treatment for ILD2 (*n* = 7)	Total with ILD2 (*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
Adjudicated outcome of ILD2[a]			
Recovered/ recovered with sequelae	6 (75.0)	3 (42.9)	9 (60.0)
No outcome recorded in CRF[b]	2 (25.0)	1 (14.3)	3 (20.0)
Ongoing[c]	0	3 (42.9)	3 (20.0)
Fatal	0	0	0

AC, adjudication committee; CRF, clinical reporting form; DCO, data cut-off; ILD, interstitial lung disease/pneumonitis; ILD2, investigator-assessed AC-confirmed any-grade recurrent ILD event.
[a]Outcome of the first recurrent ILD event as assessed by investigators and confirmed by the AC.
[b]Patients were lost to follow-up.
[c]Cases ongoing at the DCO of this analysis.

Diagnosing drug-related ILD before symptoms develop is critical to ensuring optimal outcomes for patients. Patients should be proactively monitored for ILD; in real-world clinical practice, health care experts recommend HRCT imaging every 6-12 weeks in the first year of T-DXd treatment. More frequent scans are recommended for patients with pre-existing respiratory symptoms and poor renal function, and those treated in Japan.[13,34] A multidisciplinary approach is important, with a pulmonologist consultation to exclude other known causes of ILD (e.g. infectious etiology) and confirm drug-related ILD, and comprehensive education on ILD should be provided to the entire health care team.[13-15,34] Additionally, patients should be informed about the risk of ILD, how to recognize potential symptoms, and the importance of immediately reporting any new signs or symptoms.[13,15,36]

T-DXd toxicity management guidelines recommend consideration of steroids for management of grade 1 ILD and mandate steroid therapy for grade ≥2 ILD (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2025.07.015). Although the effect of steroids on ILD management may vary,[16] patients with grades 2-4 ILD have been shown to be responsive to steroid

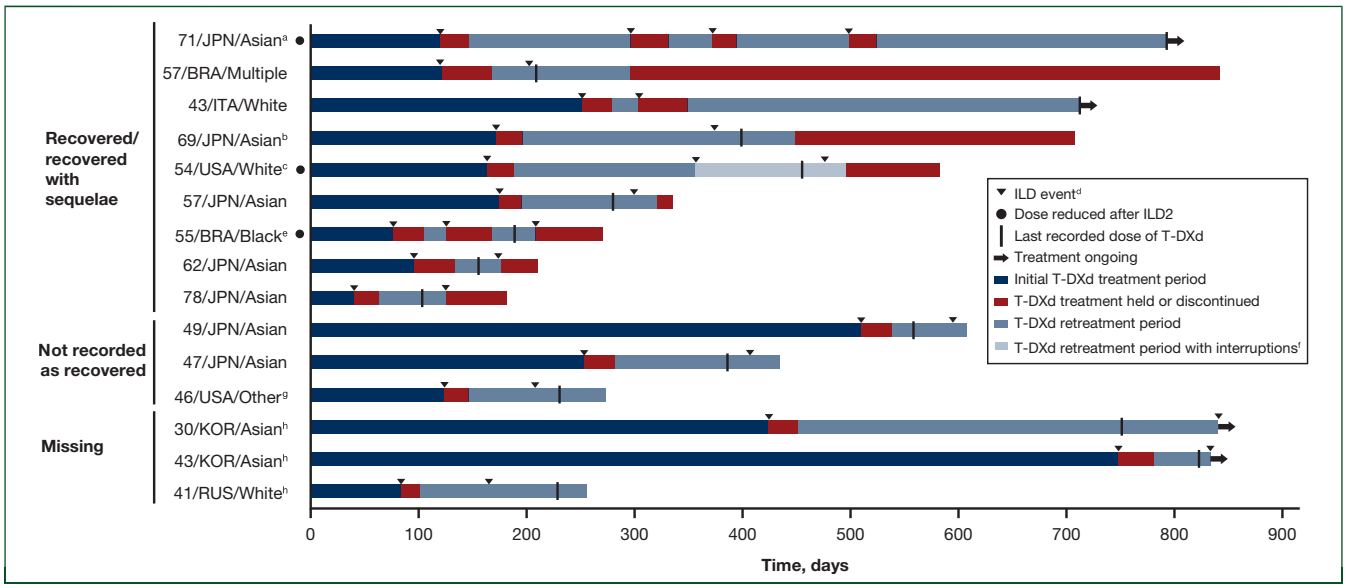

Figure 4. Individual retreatment profiles for patients who experienced ILD recurrence. The T-DXd treatment period is defined as the period from the first dose of study drug to 47 days after the last dose of study drug.

AC, adjudication committee; BRA, Brazil; DCO, data cut-off; ILD, interstitial lung disease/pneumonitis; ILD1, first investigator-assessed grade 1 and AC-confirmed drug-related ILD event; ILD2, investigator-assessed AC-confirmed any-grade recurrent ILD event; ILD3, investigator-assessed AC-confirmed any-grade second recurrent ILD event; ILD4, investigator-assessed AC-confirmed any-grade third recurrent ILD event; ITA, Italy; JPN, Japan; KOR, Republic of Korea; RUS, Russia; T-DXd, trastuzumab deruxtecan; USA, United States of America.

[a]The patient experienced three recurrent ILD events: ILD1 onset was within 120 days of treatment, ILD2 within 150 days of retreatment following ILD1 resolution, ILD3 within 40 days of retreatment following ILD2 resolution, and ILD4 within 104 days of retreatment following ILD3 resolution. The worst grade of recurrent ILD for this patient was grade 1, and T-DXd retreatment was ongoing at the DCO of this analysis, with a total retreatment duration of 21.3 months (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2025.07.015).

[b]The AC identified ILD2 as occurring 42 days earlier than the investigator-reported date.

[c]The patient experienced two recurrent ILD events: ILD1 onset was within 164 days of treatment, ILD2 within 168 days of retreatment following ILD1 resolution, and ILD3 120 days after ILD2. Upon ILD2 onset, T-DXd retreatment for this patient was not held until resolution of ILD2 but treatment cycles were delayed. The worst grade of recurrent ILD for this patient was grade 2 resulting in discontinuation of T-DXd; the patient was recovering with sequelae from all ILD events at DCO without disease progression (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2025.07.015).

[d]All ILD1 events are described with the investigator-reported dates of onset while all ILD2 events and onwards (ILD3 and ILD4) are described using the adjudication committee dates of onset.

[e]The patient experienced two recurrent ILD events: ILD1 onset was within 77 days of treatment, ILD2 within 21 days of retreatment following ILD1 resolution, and ILD3 within 41 days of retreatment following ILD2 resolution. The worst grade of recurrent ILD for this patient was grade 2, resulting in discontinuation of T-DXd; the patient was recovering with sequelae from all ILD events at DCO without disease progression (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2025.07.015).

[f]T-DXd treatment was not held at ILD2 onset but did not follow standard treatment cycle intervals.

[g]The AC identified ILD2 as occurring 23 days earlier than the investigator-reported date.

[h]ILD2 was retrospectively identified by the AC but was not reported by the investigator, resulting in missing outcomes at the DCO of this analysis.

treatment.[32] Our analysis suggests that steroids may be beneficial for management of recurrent ILD; 53.3% (8/15) of patients with ILD2 received steroids, 75% (6/8) of whom recovered or recovered with sequelae, although low patient numbers preclude making definitive conclusions. Additionally, the frequency of follow-up HRCT chest scanning affects assessment of ILD recovery time by investigators; scans conducted with long intervals may not accurately assess recovery time, possibly impacting the ability to evaluate the effect of steroid therapy. Current clinical guidelines recommend follow-up HRCT imaging every 2-4 weeks, or as clinically indicated, and close clinical monitoring for patients with ILD.[13-15,34]

The severity of drug-related ILD in T-DXd monotherapy clinical trials has tended to decrease over time, with fewer grade 5 (fatal) events (Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2025.07.015). This suggests that growing familiarity with T-DXd and ILD management guidelines, including monitoring and early detection, coupled with other factors such as earlier treatment may be reducing the severity of high-grade T-DXd—related ILD.

A previous multivariate analysis identified lower SpO_2, presence of lung comorbidities, treatment in Japan, and impaired renal function as potentially associated with a higher incidence of drug-related ILD, but did not identify any significant difference between the 5.4 mg/kg and 6.4 mg/kg doses of T-DXd.[14] In this study, a greater proportion of patients treated in Japan and patients with lung comorbidities developed ILD2, although no other trends were observed.

A recent study on T-DXd retreatment in a real-world cohort of patients in the United States following grade 1 ILD identified that 28.6% (4/14) of retreated patients experienced recurrent ILD (three grade 1 and one grade 2) with a median onset of ILD recurrence of 148 days (range, 47-273 days).[42] These data are comparable to those reported here describing an incidence of recurrent ILD of

33.3%, though the median onset of ILD recurrence was shorter in this analysis (64 days; range, 22-391 days). Our study is also supported by another recent real-world analysis in the United States that demonstrated a long duration of clinical benefit and no grade 5 toxicity with T-DXd retreatment after recovery from grade 1 ILD.[43]

This study is the largest pooled analysis to date investigating T-DXd retreatment following resolution of drug-related ILD, including >2000 patients across nine clinical trials. It provides the first evidence base for the characterization of ILD recurrence after T-DXd retreatment. This analysis only included patients who were retreated with T-DXd following the T-DXd toxicity management guidelines, which only allow for patients who experienced grade 1 ILD to be considered for retreatment.

This analysis has some important limitations. The trials included were early T-DXd clinical trials, resulting in underrepresentation of patients with tumor types included in subsequent T-DXd clinical trials. Future analyses with additional patients across broader tumor types may be useful. Most of the trials included in this analysis (seven of nine) began enrollment before the formal introduction of T-DXd toxicity management guidelines for ILD. Consequently, some patients developed ILD before the guidelines mandated follow-up until death or ILD resolution, leading to a few cases with unknown or missing outcomes for ILD recurrence at the DCO for this analysis. Moreover, for initial ILD events that occurred before the guidelines were introduced, management and retreatment decisions were based on investigator judgment, potentially reducing the number of eligible patients. Per local prescribing information at the time of some studies, retreatment with T-DXd following ILD of any grade was not allowed in Japan, further limiting the number of patients who could be included. Furthermore, the time to ILD resolution would be affected by the frequency of follow-up HRCT scans, which were conducted at the investigator's discretion rather than at standardized intervals across all trials included.

Although all ILD cases in this analysis were confirmed through adjudication based on standardized data from the reporting site, the adjudication committee only reviewed events that were reported as potential ILD by investigators. Thus, this study does not assess accuracy of ILD diagnosis and reporting by investigators. Additionally, since the original data capture relied on investigator data entry via an electronic recording system for the trial databases, any incomplete data, such as inconsistent reporting on steroid use for patients with ILD, could not be included. The relatively low number of patients with ILD recurrence limited detailed analysis of factors of interest relating to ILD occurrence and recurrence as well as a robust, statistically significant result of the identified trend between T-DXd retreatment and efficacy outcomes. Finally, this analysis included patients from clinical trials with stringent inclusion and exclusion criteria, many of whom were heavily pretreated and may not fully represent clinical practice. Studies characterizing T-DXd retreatment in real-world patient populations could further the understanding of ILD recurrence.

In conclusion, this pooled analysis demonstrates that T-DXd can be readministered after recovery from grade 1 ILD, without high-grade reoccurrences of ILD. T-DXd retreatment following resolution of grade 1 ILD, in accordance with T-DXd toxicity management guidelines, may prolong treatment duration and maximize therapeutic benefits for patients with metastatic/locally advanced cancer. Early detection of ILD is crucial for prompt intervention, timely resolution, and effective retreatment with T-DXd following grade 1 ILD to optimize therapeutic outcomes.

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DATA SHARING

Anonymized individual participant data (IPD) on completed studies and applicable supporting clinical study documents may be available upon request at https://vivli.org/. In cases where clinical trial data and supporting documents are provided pursuant to our company policies and procedures, Daiichi Sankyo Companies will continue to protect the privacy of our clinical trial participants. Details on data sharing criteria and the procedure for requesting access can be found at this web address: https://vivli.org/ourmember/daiichi-sankyo/.

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