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Case Report **Medical Oncology**

Early-Onset Trastuzumab Deruxtecan–Associated Interstitial Lung Disease During First-Line Treatment of HER2-Positive Metastatic Breast Cancer with Hepatic Visceral Crisis: A Case Report and Systematic Review with Meta-Analysis

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Abstract

Background: Trastuzumab deruxtecan (T-DXd) is a HER2-directed antibody–drug conjugate (ADC) with substantial activity across HER2-expressing breast cancer. Interstitial lung disease (ILD)/pneumonitis is its most important adverse event of special interest and can be fatal. We report an early-onset, oxygen-requiring case and systematically review the incidence, timing, presentation, and management of T-DXd–associated ILD in breast cancer. ***Case presentation:*** A 47-year-old woman with de novo ER-negative, PR-negative, HER2-positive metastatic breast cancer (hepatic, pulmonary, and osseous metastases) and hepatic visceral crisis (total bilirubin 375 µmol/L) started T-DXd on 28 June 2026. After two cycles, bilirubin fell to 113 µmol/L and then normalised, with multisite radiological response. Approximately 5 weeks after the first dose she developed dyspnoea, non-productive cough, low-grade fever, tachycardia, and hypoxaemia (SpO_2 ≈88% on room air). CT pulmonary angiography excluded embolism and showed new bilateral ground-glass and consolidative opacities with interlobular septal thickening, while pulmonary metastases were regressing. Bronchoalveolar lavage (BAL) was negative for malignancy, fungi, and *Pneumocystis jirovecii*. Grade 3 T-DXd–associated ILD was diagnosed; T-DXd was permanently discontinued and prednisolone (≈1 mg/kg/day) plus empirical piperacillin–tazobactam and supplemental oxygen were started, with clinical stabilisation. ***Methods:*** Following PRISMA 2020, we searched PubMed/MEDLINE, Embase, Cochrane CENTRAL, Scopus, and major oncology congress proceedings to 31 October 2026 for prospective trials of T-DXd in breast cancer reporting ILD incidence and for case reports/series of T-DXd–associated ILD. Incidence was pooled with a DerSimonian–Laird random-effects model on the logit scale. ***Results:*** Eight prospective trials (3,341 T-DXd-treated patients) were pooled. Any-grade drug-related ILD occurred in 12.1% (95% CI 10.7–13.6; I^2 = 39%) and grade 5 ILD in 0.8% (95% CI 0.5–1.5). In metastatic disease the pooled incidence was 12.7% (11.4–14.0; I^2 = 0%); in HER2-positive metastatic disease, 13.1% (11.4–15.0). Case reports (7 patients) and national post-marketing data showed an organising-pneumonia–predominant imaging pattern, onset ranging from 2 to 9 cycles, frequent prolonged corticosteroid dependence, and use of cyclophosphamide, infliximab, mycophenolate, or tacrolimus in steroid-refractory cases. ***Conclusions:*** Roughly one in eight breast cancer patients receiving T-DXd develops ILD, and about 1% die of it. Onset can be early, and ILD can emerge during an excellent tumour response—discordant radiology (regressing nodules with new diffuse opacities) is a useful diagnostic clue. Structured respiratory surveillance, low threshold for CT, prompt exclusion of infection, permanent discontinuation for grade ≥2 events, and grade-appropriate corticosteroids remain central.

Keywords: Trastuzumab deruxtecan; interstitial lung disease; pneumonitis; HER2-positive breast cancer; antibody–drug conjugate; visceral crisis; systematic review; meta-analysis.

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1. INTRODUCTION

Trastuzumab deruxtecan (T-DXd) is an ADC composed of a humanised anti-HER2 IgG1 antibody, a cleavable tetrapeptide linker, and a topoisomerase I inhibitor payload (DXd) with a high drug-to-antibody ratio. Across the DESTINY-Breast programme it has improved outcomes in HER2-positive, HER2-low, and HER2-ultralow breast cancer, and its use has moved from later lines into first-line metastatic, neoadjuvant, and post-neoadjuvant settings [4–12]. As exposure broadens, more patients—including those outside trial eligibility—are at risk of its signature toxicity, ILD/pneumonitis.

In a pooled analysis of nine monotherapy studies (n = 1,150), adjudicated drug-related ILD occurred in 15.4% of patients, with grade 5 events in 2.2%; 77.4% of events were grade 1–2, 87.0% occurred within the first 12 months, and the median time to onset was 5.4 months [1]. Baseline factors associated with higher risk included age < 65 years, enrolment in Japan, dose > 6.4 mg/kg, SpO_2 < 95%, moderate/severe renal impairment, lung comorbidities, and > 4 years since diagnosis [1]. The current prescribing information reports ILD in 12% of patients treated at 5.4 mg/kg, with a median onset of 5.5 months (range 0.9–31.5) and fatal outcomes in 0.9% [2].

We describe an early, oxygen-requiring T-DXd–associated ILD in a patient treated first line for HER2-positive metastatic breast cancer complicated by hepatic visceral crisis, who was simultaneously responding dramatically to therapy. Because individual reports have limited generalisability, we combined the case with a systematic review and meta-analysis of prospective breast cancer trials and a structured synthesis of published case reports. The case report follows the CARE guidelines [24] and the review follows PRISMA 2020 [23].

2. CASE PRESENTATION

2.1 Patient information

A 47-year-old woman was diagnosed in June 2026 with de novo metastatic, estrogen receptor-negative, progesterone receptor-negative, HER2-positive breast cancer (HER2: 3+; histological grade III). Staging showed a right breast primary with skin thickening and right axillary lymphadenopathy, extensive hepatic and pulmonary metastases, and lytic lesions in the spine and pelvis. She had marked hepatic dysfunction with hyperbilirubinaemia (total bilirubin 375 µmol/L, ≈21.9 mg/dL) consistent with hepatic visceral crisis. No preior comorbidities, nor smoking history or prior lung disease ECOG PS 1. Because of the severity of her illness, a do-not-attempt-resuscitation order was established on 2 July 2026.

2.2 Anticancer treatment

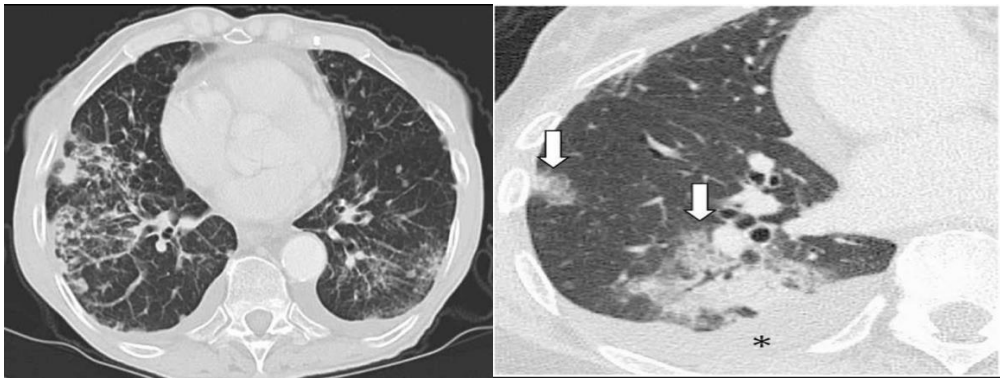
T-DXd was started on 28 June 2026 dose 5.4 mg/kg and the second cycle was given on 22 July 2026. After two cycles, bilirubin fell from 375 to 113 µmol/L and bilirubin, AST, and ALT subsequently returned to normal or near-normal levels. No thoracic radiotherapy, immune checkpoint inhibitor, or other pneumotoxic agent had been given.

2.3 Presentation

Before the planned third cycle, she reported approximately 10 days of progressive dyspnoea and non-productive cough with low-grade fever—an onset of roughly 5 weeks (≈ day 35) after the first dose. She denied chest pain, palpitations, orthopnoea, abdominal symptoms, or urinary/bowel symptoms. She was referred from the pre-chemotherapy assessment clinic to the emergency department. On examination: temperature 36.6 °C, heart rate 111/min, respiratory rate 20/min, SpO_2 97% on 2 L/min nasal oxygen (≈88% on room air), weight 51.5 kg. There were crackles over the left lower zone without increased work of breathing; cardiac and abdominal examinations were unremarkable and there was no peripheral oedema.

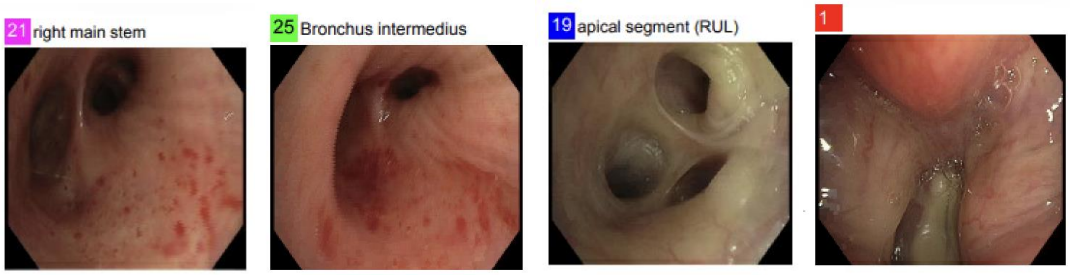
2.4 Investigations

Routine laboratory tests were unremarkable apart from markedly improved liver function tests (CBC with differential, CRP/procalcitonin witihin normal limit, blood cultures & respiratory viral PCR nprmal also). CT pulmonary angiography excluded pulmonary embolism and showed newly developed, widespread bilateral mixed ground-glass and consolidative opacities with interlobular septal thickening and trace bilateral pleural effusions. In contrast, pulmonary metastatic nodules had decreased in size; the breast primary, skin thickening, and axillary nodes had improved, and osseous metastases showed increasing sclerosis consistent with response (Figure 1: CT images — baseline vs. presentation).



Base line CT chest. **CT chest Post Cycle 1 of TDX-D**

BAL cytology showed alveolar macrophages, bronchial epithelial cells, and scant lymphocytes, with no malignant cells; special stains for *Pneumocystis jirovecii* and fungi were negative. BAL differential cell count, bacterial/mycobacterial cultures, galactomannan, respiratory PCR panel, CMV were negative.



Procedure Technique:

- After the numbing process of the oropharynx, the fiberoptic bronchoscope was inserted through the mouth down the oropharynx to the level of the vocal cords.. The bronchoscope was inserted through the vocal cords into the trachea. A systematic examination of all major, lobar, and segmental bronchi was begun.

Samples obtained:
· Bronchoalveolar lavage from RML and RLL utilizing 80mL of saline with lavage return of 20 ml.

- When this was completed, the area was then inspected and no evidence of active bleeding noted. The bronchoscope was withdrawn. The patient tolerated the procedure well. There were no immediate complications

Findings:

- The vocal cords appear normal. The subglottic space is normal.
- The trachea is of normal caliber. The carina is sharp. The tracheobronchial tree was examined to at least the first subsegmental level. Bronchial mucosa and anatomy are normal. There are no endobronchial lesions, and no mucosal abnormaliteis.
- there was tracheobronchmalacia
- Greenish secretion observed Right intermedius

Diagnosis:

Abnormal CXR, new bilateral infiltrates

2.5 Diagnostic assessment

The differential diagnosis comprised infection (bacterial, viral, *Pneumocystis*, fungal), cardiogenic pulmonary oedema, lymphangitic carcinomatosis or tumour progression, pulmonary embolism, and drug-induced ILD. The temporal relationship with T-DXd, new diffuse bilateral inflammatory changes, hypoxaemia, exclusion of embolism, negative BAL cytology and opportunistic-infection stains, and the concurrent regression of pulmonary metastases favoured T-DXd–associated ILD/pneumonitis. Because supplemental oxygen was required, the event met the CTCAE v5.0 definition of **grade 3** pneumonitis (severe symptoms; oxygen indicated) [25]. Causality was probable by the Naranjo algorithm.

2.6 Treatment, outcome, and follow-up

T-DXd was permanently discontinued. She received prednisolone 50 mg daily (≈ 0.97 mg/kg) for 14 days, empirical piperacillin–tazobactam, supplemental oxygen by nasal cannula, and incentive spirometry. She remained clinically stable on low-flow oxygen and was discharged with outpatient oncology follow-up to plan subsequent anti-HER2 therapy. Follow-up: repeat CT findings disease progression in the lungs. The clinical timeline is summarised in Table 1.

Table 1: Timeline of key clinical events

Date (2026)	Event
June	Diagnosis of de novo ER−/PR−/HER2+ metastatic breast cancer (liver, lung, bone); total bilirubin 375 µmol/L (hepatic visceral crisis)
28 June	T-DXd cycle 1
2 July	Do-not-attempt-resuscitation order documented
22 July	Hospital Admission.
≈ early August	Onset of dyspnoea, dry cough, low-grade fever (≈ day 35)
5 August	Pre-chemotherapy clinic → emergency department: SpO_2 ≈ 88% on room air, HR 111/min
11 August	CTPA: no PE; new bilateral GGO/consolidation with septal thickening; progressing metastases
13 August	Bronchoscopy/BAL: no malignancy; Pneumocystis and fungal stains negative
17 September	T-DXd permanently discontinued; prednisolone 50 mg/day, piperacillin–tazobactam, O_2
8 October	Discharge / follow-up: starting to give TDM-1 post TDX-D

3. Systematic Review: Methods

3.1 Protocol and reporting

The review was conducted according to PRISMA 2020 [23] and registered in PROSPERO. Two review questions were addressed: (i) the incidence and severity of drug-related ILD/pneumonitis in prospective trials of T-DXd in breast cancer; and (ii) the clinical presentation, management, and outcome of individual patients with T-DXd–associated ILD reported as case reports or series.

3.2 Information sources and search

PubMed/MEDLINE, Embase, Cochrane CENTRAL, and Scopus were searched from January 2015 to 31 October 2026, supplemented by ASCO, ESMO, and San Antonio Breast Cancer Symposium proceedings and reference lists of included articles and prior reviews [13,14]. The PubMed strategy was: ("trastuzumab deruxtecan"[tiab] OR "T-DXd"[tiab] OR "DS-8201"[tiab] OR "DS8201a"[tiab] OR "Enhertu"[tiab] OR "fam-trastuzumab deruxtecan"[Supplementary Concept]) AND ("Lung Diseases, Interstitial"[Mesh] OR "Pneumonia"[Mesh] OR pneumonitis[tiab] OR "interstitial lung disease"[tiab] OR ILD[tiab] OR "drug-induced lung"[tiab] OR "organizing pneumonia"[tiab]) AND ("Breast Neoplasms"[Mesh] OR breast[tiab]), adapted for other databases (Supplementary Table S1).

3.3 Eligibility criteria

Quantitative synthesis:

prospective phase 2–4 trials enrolling patients with breast cancer treated with T-DXd 5.4 mg/kg every 3 weeks (alone or with pertuzumab), reporting the number of patients with drug-related ILD/pneumonitis and the safety-population denominator. When several data cuts were published, the most mature report was used. Phase 1 dose-finding studies and analyses pooling multiple tumour types were excluded from pooling to avoid double counting, but were used for context [1].

Qualitative synthesis:

case reports, case series, and post-marketing cohorts describing individual patients with breast cancer and T-DXd–associated ILD, in English. Reviews, editorials, and non-breast tumours were excluded.

3.4 Study selection, data extraction, and quality appraisal

Two reviewers independently screened titles/abstracts and full texts, resolving disagreements by consensus or a third reviewer. Extracted variables were trial phase, setting, HER2 status, regimen, safety population, any-grade and grade ≥3 and grade 5 ILD, and the method of ILD ascertainment (independent adjudication vs. investigator report). For case reports we extracted age, tumour subtype, cycles to onset, presentation, CT pattern, CTCAE grade, BAL findings, treatment, rechallenge, and outcome. Case reports were appraised with the JBI critical appraisal checklist for case reports [29]; trial-level risk of bias was judged with emphasis on ILD ascertainment (adjudicated vs. investigator-reported) and follow-up maturity.

3.5 Statistical analysis

Proportions were logit-transformed and pooled with a DerSimonian–Laird random-effects model [26]; a 0.5 continuity correction was applied to zero-event arms. Study-level 95% CIs were Clopper–Pearson. Heterogeneity was quantified with Cochran's Q and I^2. Prespecified subgroup/sensitivity analyses: metastatic vs. early disease; HER2-positive vs. HER2-low/ultralow; exclusion of trials without independent adjudication. Analyses were performed in Python 3 (NumPy/SciPy) and can be reproduced in R (meta::metaprop).

4. Systematic Review: Results

4.1 Study selection

The study selection process is shown in Figure 1. Thirteen studies were included: eight prospective trials in the meta-analysis [4–6,8–12], four case reports/series describing seven patients [16–19], and one national post-marketing surveillance cohort [15].

4.2 Characteristics of included trials

The eight trials enrolled 3,341 T-DXd-treated patients across later-line HER2-positive (DESTINY-Breast01, -02, -03, -12), first-line HER2-positive (DESTINY-Breast09, with pertuzumab), HER2-low/ultralow (DESTINY-Breast04, -06), and post-neoadjuvant early disease (DESTINY-Breast05) settings

(Table 2). Seven trials used independent adjudication; DESTINY-Breast12 reported investigator-assessed events [11].

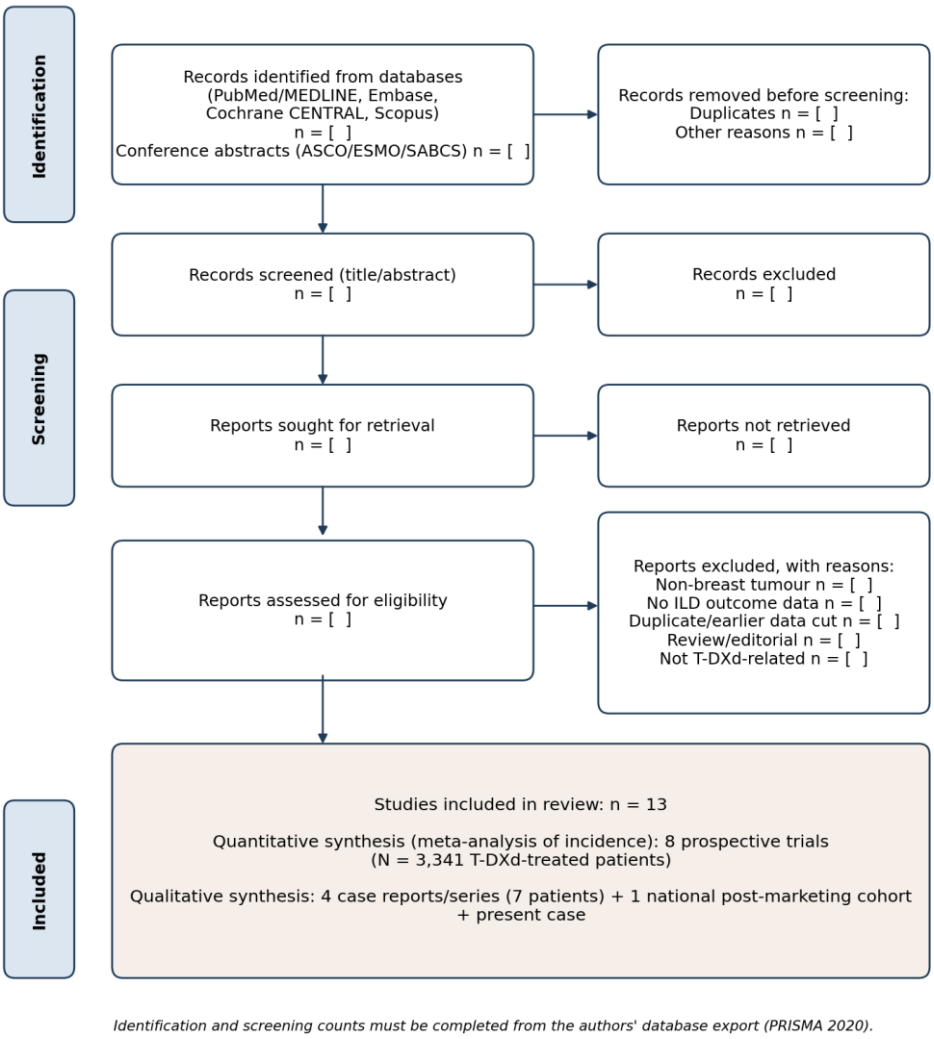


Figure 1: PRISMA 2020 flow diagram of study selection.

Table 2: Drug-related ILD/pneumonitis in prospective trials of T-DXd 5.4 mg/kg in breast cancer

Trial (ref)	Population / setting	Phase	ILD any grade, n/N (%)	Grade 5, n (%)	Ascertainment
DESTINY-Breast01 [4]	HER2+ mBC, post-T-DM1	2	25/184 (13.6)	4 (2.2)	Adjudicated
DESTINY-Breast02 [5]	HER2+ mBC, post-T-DM1	3	42/404 (10.4)	2 (0.5)	Adjudicated
DESTINY-Breast03 [6]	HER2+ mBC, second line	3	39/257 (15.2)	0	Adjudicated
DESTINY-Breast04 [8]	HER2-low mBC, post-chemo	3	45/371 (12.1)	3 (0.8)	Adjudicated
DESTINY-Breast06 [9]	HR+ HER2-low/ultralow mBC, post-ET	3	49/434 (11.3)	3 (0.7)	Adjudicated
DESTINY-Breast09 [10]	HER2+ mBC, first line (+ pertuzumab)	3	46/381† (12.1)	2 (0.5)	Adjudicated
DESTINY-Breast12 [11]	HER2+ mBC ± brain metastases	3b/4	73/504 (14.5)	9 (1.8)	Investigator
DESTINY-Breast05 [12]	HER2+ EBC, residual disease	3	77/806 (9.6)	2 (0.2)	Adjudicated
Pooled (random effects)			12.1% (10.7–13.6)	0.8% (0.5–1.5)	

mBC, metastatic breast cancer; EBC, early breast cancer; ET, endocrine therapy. †Denominator derived from the reported 46 events (12.1%); verify against the NEJM safety population. DESTINY-Breast03 values are from the updated (OS) analysis, in which incidence rose from 10.5% at the interim analysis to 15.2% with longer exposure.

4.3 Pooled incidence

The pooled incidence of any-grade drug-related ILD was 12.1% (95% CI 10.7–13.6) with moderate heterogeneity (I^2 = 39%) (Figure 2). Grade 5 ILD occurred in 0.8% (0.5–1.5; I^2 = 47%). Heterogeneity was driven mainly by the lower incidence in the post-neoadjuvant DESTINY-Breast05 trial (fixed 14 cycles); restricted to metastatic disease, the incidence was 12.7% (11.4–14.0; I^2 = 0%) and grade 5 ILD 1.0% (0.6–1.7). Results were similar for HER2-positive metastatic disease (13.1%, 11.4–15.0; I^2 = 16%) and HER2-low/ultralow disease (11.7%, 9.6–14.1; I^2 = 0%). Excluding the investigator-reported DESTINY-Breast12 trial gave 11.6% (10.3–13.1; I^2 = 24%) (Table 3). These estimates are consistent with previous meta-analyses reporting 11.4% in 1,193 patients [14] and 11.7% in 1,970 patients, in which ILD was more frequent at 6.4 than 5.4 mg/kg (22.7% vs. 10.2%) and 80.2% of events were grade 1–2 [13].

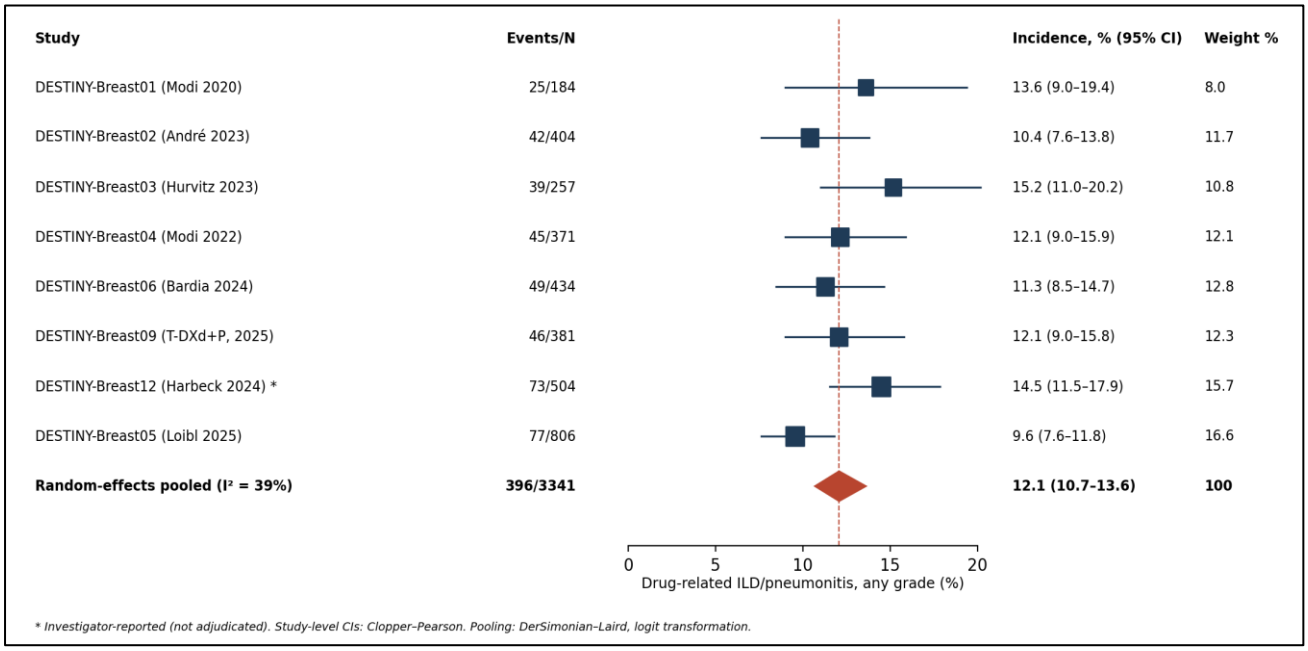


Figure 2: Forest plot of the incidence of drug-related ILD/pneumonitis (any grade) with T-DXd in prospective breast cancer trials

Table 3: Subgroup and sensitivity analyses (random effects)

Analysis	Trials	Incidence, % (95% CI)	I^2
All trials — any grade	8	12.1 (10.7–13.6)	39%
Metastatic disease only	7	12.7 (11.4–14.0)	0%
HER2-positive metastatic	5	13.1 (11.4–15.0)	16%
HER2-low/ultralow metastatic	2	11.7 (9.6–14.1)	0%
Adjudicated trials only	7	11.6 (10.3–13.1)	24%
Grade 5 — all trials	8	0.8 (0.5–1.5)	47%
Grade 5 — metastatic only	7	1.0 (0.6–1.7)	32%

4.4 Real-world and imaging data

In the Japanese nationwide post-marketing surveillance, 130 of 138 physician-reported cases were adjudicated as T-DXd–related ILD; 76.9% were grade 1–2, the commonest CT patterns were organising pneumonia (63.1%), hypersensitivity pneumonitis (16.9%), and diffuse alveolar damage (DAD, 14.6%), and 83.1% of steroid-treated cases responded [15]. An expanded analysis of 2,801 patients (381 adjudicated cases) confirmed organising pneumonia as the predominant pattern (67.7%), found that ILD could occur throughout treatment including fatal cases beyond 12 months, and identified DAD as the pattern with the poorest prognosis despite high-dose steroids or immunosuppressants ref: Oncologist 2026; doi:10.1093/oncolo/oyag340 — add author list. Japanese patients have roughly double the risk of patients enrolled elsewhere (HR 2.08) [1,15].

4.5 Synthesis of case reports

Seven previously reported patients were identified (Table 4). Onset ranged from 2 to 9 cycles. Two reports described ILD emerging while pulmonary metastases were shrinking [16], mirroring our case. Courses were frequently protracted: both patients reported by Gocho *et al.,*required long-term corticosteroids, one complicated by pneumomediastinum and persistent respiratory failure, and neither could resume anticancer therapy [16]. Steroid-refractory disease was rescued with

cyclophosphamide in a grade 4 case with extensive liver metastases [17] and with mycophenolate, infliximab, and tacrolimus in another [18]. Rechallenge at reduced dose after grade 2 ILD resulted in recurrence [19].

Table 4: Published cases of T-DXd–associated ILD in breast cancer and the present case

Report	Patient / subtype	Onset	Presentation & CT	Management	Outcome
Gocho 2022, case 1 [16]	57 F, advanced BC (15-yr history), lung metastases	After 4 cycles	Dyspnoea, fever; diffuse consolidation and reticulation with shrinking metastatic nodules	Long-term corticosteroids	Poor improvement; pneumomediastinum; persistent respiratory failure; no further chemotherapy
Gocho 2022, case 2 [16]	F, advanced BC (9-yr history)	NR	Left-predominant GGO, bilateral effusions; BAL lymphocytes 50%	Long-term corticosteroids	Improved with mild residual fibrosis; no further chemotherapy
Alhuthali 2026, case I [19]	66 F, HER2+ mBC	9 cycles (143 days)	Cough, fever, dyspnoea; peripheral nodular consolidation (OP pattern); grade 2	T-DXd stopped; prednisolone 60 mg, tapered	Recurrence on reduced-dose rechallenge → permanent discontinuation; switched to tucatinib–trastuzumab–capecitabine
Alhuthali 2026, case III [19]	47 F, HER2+ mBC	2 cycles (46 days)	Chronic cough, anorexia, fatigue, declining PS	extract	extract
Alhuthali 2026, case II [19]	HER2+ mBC	Within 2–9 cycles	extract	extract	extract
Zhang 2025 [17]	49 F, HER2-low mBC, severe liver metastases	extract	Acute chest tightness, SpO_2 50–70% on air, large effusions; grade 4	Steroids → cyclophosphamide (steroid-refractory)	Rapid clinical/radiological improvement; discharged
Fakih 2025 [18]	F, HER2+ mBC; pre-existing interstitial lung abnormalities	During anti-HER2 therapy after prior T-DXd	GGO with interlobular septal thickening; rising O_2 need	Methylprednisolone 1 g, MMF, infliximab, tacrolimus	Good clinical and radiological response
Present case	47 F, ER−/PR−/HER2+ de novo mBC, hepatic visceral crisis	≈5 weeks (after 2 cycles)	Dyspnoea, dry cough, low-grade fever, SpO_2 88%; bilateral GGO/consolidation, septal thickening, regressing nodules; grade 3	T-DXd discontinued; prednisolone 50 mg/day; piperacillin–tazobactam; O_2	Stable on low-flow O_2; follow-up

BC, breast cancer; GGO, ground-glass opacity; MMF, mycophenolate mofetil; NR, not reported; OP, organising pneumonia; PS, performance status. Cells marked extract must be completed from the full texts.

5. DISCUSSION

This report combines an instructive case with a contemporary quantitative synthesis. Across eight prospective breast cancer trials and more than 3,300 patients, about one in eight patients treated with T-DXd developed drug-related ILD, and approximately 1% of those with metastatic disease died of it. These figures are lower than the 15.4% reported in the early pooled analysis [1], which reflects in part the 2019 introduction of structured ILD monitoring and management guidelines, after which grade ≥3 and fatal events fell substantially [1,3]. They nonetheless remain clinically significant, particularly as T-DXd moves into first-line and curative-intent settings [10,12].

5.1 Timing

Our patient's onset at about 5 weeks lies at the early extreme of the reported distribution (label median 5.5 months; range 0.9–31.5) [2]. Early onset is uncommon but not exceptional: one published patient developed pneumonitis after two cycles (46 days) [19], and post-marketing data show that events occur throughout treatment without a safe window [15]. The DESTINY-Breast03 experience—incidence rising from 10.5% to 15.2% with longer exposure [6]—shows that

surveillance must continue throughout and beyond treatment.

5.2 Diagnosis: discordant radiology

The main diagnostic difficulty in patients with lung metastases is distinguishing drug-induced ILD from lymphangitic progression, infection, and oedema. In our patient, new diffuse bilateral ground-glass and consolidative opacities with septal thickening appeared while pulmonary nodules, the primary, nodes, and bone lesions were all responding. This discordant pattern—similar to the first case of Gocho *et al.,*[16]—is strong circumstantial evidence against tumour progression. BAL cannot confirm drug-induced ILD but is valuable for exclusion: in DESTINY-Breast12, five ILD events co-occurred with opportunistic infection, four of them fatal [11]. Comprehensive microbiological work-up (including bacterial cultures and viral PCR), empirical antimicrobial cover while results are pending, and multidisciplinary review with pulmonology and thoracic radiology are therefore recommended [3,28]. Imaging pattern also carries prognostic weight: organising pneumonia predominates and is usually steroid-responsive, whereas DAD carries the worst prognosis [15].

5.3 Grading and management

Need for supplemental oxygen places this event at CTCAE grade 3 [25]. For any symptomatic (grade ≥2) ILD, labelling mandates permanent discontinuation and prompt systemic corticosteroids (e.g., ≥1 mg/kg/day prednisolone or equivalent) for at least 14 days, followed by a gradual taper over at least 4 weeks [2]. For grade 3–4 events, trial management guidelines and multidisciplinary guidance recommend hospitalisation and empirical high-dose intravenous methylprednisolone (e.g., 500–1,000 mg/day for 3 days) before conversion to ≥1 mg/kg/day oral prednisolone [1,3]. Our patient received prednisolone ≈1 mg/kg/day and stabilised; the subsequent taper should extend over at least 4 weeks with *Pneumocystis* prophylaxis while on prolonged high-dose steroids. For steroid-refractory disease there is no established regimen; published experience is limited to case reports of cyclophosphamide [17], infliximab, mycophenolate, and tacrolimus [18]—none of which can yet be recommended outside multidisciplinary, individualised decisions.

5.4 Hepatic visceral crisis and T-DXd

A distinctive feature of this case is the use of T-DXd in hepatic visceral crisis with a bilirubin of about 22 mg/dL—far above trial eligibility thresholds. Small case reports describe rapid biochemical and radiological responses to full- or reduced-dose T-DXd in severe hepatic impairment [20–22], and our patient's bilirubin normalised within two cycles. However, DXd is hepatically metabolised, and exposure in severe hepatic impairment has not been characterised [2]. Whether higher early payload exposure contributed to the early onset of ILD cannot be determined from a single case, but it is biologically plausible and merits prospective pharmacokinetic study. Other recognised risk factors present were age < 65 years [1];

5.5 Mechanism

The mechanism of T-DXd ILD is incompletely understood. Non-clinical work in monkeys showed dose-dependent interstitial pneumonitis with uptake of the ADC by alveolar macrophages, suggesting target-independent payload delivery to the lung [27]. This aligns with the observation that ILD rates are similar in HER2-positive and HER2-low disease (13.1% vs. 11.7% in our analysis) and with the predominance of macrophage-rich inflammatory patterns.

5.6 Practical implications

The case and the pooled data support a structured approach consistent with current guidance [2,3,30]: baseline chest CT and SpO_2 (with pulmonary function tests where feasible) and risk-factor review; patient education to report cough, dyspnoea, fever, or reduced exercise tolerance immediately; SpO_2 and respiratory symptom review at every visit; repeat chest CT every 6–12 weeks and urgently for new symptoms; interruption of T-DXd at the first suspicion of ILD; and multidisciplinary review. Importantly, an excellent tumour response should never lower vigilance. After grade ≥2 ILD, subsequent anti-HER2 options without T-DXd should be chosen with awareness that ILD can recur or emerge with other HER2-directed agents [18].

5.7 Strengths and limitations

Strengths include a comprehensive set of contemporary phase 3 data spanning metastatic, first-line, and early disease, low heterogeneity in metastatic trials, and an explicit sensitivity analysis for ascertainment method. Limitations include pooling of study-level data with differing follow-up durations and exposure; inclusion of one trial with investigator-reported events; limited case-report detail and probable publication bias toward severe or unusual cases; and, for the index case, the absence of complete microbiology, pulmonary function testing, histology, and long-term radiological follow-up update when available.

6. CONCLUSION

T-DXd–associated ILD affects about 12% of patients with breast cancer in prospective trials and is fatal in about 1% of those with metastatic disease. It may occur early—even within the first two cycles—and in the midst of a striking tumour response. New respiratory symptoms during T-DXd should trigger urgent CT, oxygenation assessment, exclusion of infection and embolism, and multidisciplinary review. Symptomatic (grade ≥2) ILD requires permanent discontinuation and prompt, grade-appropriate corticosteroids. Data on T-DXd in severe hepatic impairment and on steroid-refractory ILD remain limited and warrant prospective study.

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Supplementary Table S1. Search strategies

Database	**Search string**
PubMed/MEDLINE	("trastuzumab deruxtecan"[tiab] OR "T-DXd"[tiab] OR "DS-8201"[tiab] OR "DS8201a"[tiab] OR Enhertu[tiab]) AND ("Lung Diseases, Interstitial"[Mesh] OR "Pneumonia"[Mesh] OR pneumonitis[tiab] OR "interstitial lung disease"[tiab] OR ILD[tiab] OR "organizing pneumonia"[tiab]) AND ("Breast Neoplasms"[Mesh] OR breast[tiab])
Embase (Ovid)	('trastuzumab deruxtecan'/exp OR 'T-DXd':ti,ab OR 'DS-8201':ti,ab OR enhertu:ti,ab) AND ('interstitial lung disease'/exp OR 'pneumonitis'/exp OR 'drug induced lung disease'/exp OR ild:ti,ab) AND ('breast cancer'/exp OR breast:ti,ab)
Cochrane CENTRAL	(trastuzumab deruxtecan OR T-DXd OR DS-8201) AND (pneumonitis OR interstitial lung) AND breast
Scopus	TITLE-ABS-KEY(("trastuzumab deruxtecan" OR "T-DXd" OR "DS-8201") AND (pneumonitis OR "interstitial lung") AND breast)
Congress proceedings	ASCO, ESMO, SABCS 2019–2026: "trastuzumab deruxtecan" AND (ILD OR pneumonitis)