European Journal of Radiology 194 (2026) 112499

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Review

# Chest computed tomography of trastuzumab-deruxtecan (T-DXd)-related interstitial lung disease: Key points for radiologists

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ARTICLE INFO

*Keywords:*
Trastuzumab-deruxtecan
Interstitial lung disease
Chest computed tomography

ABSTRACT

Trastuzumab-deruxtecan (T-DXd) is an antibody-drug conjugate targeting HER2, increasingly used to treat advanced HER2-positive tumors, including breast, gastric, lung, and colorectal cancers. Like other anticancer agents, T-DXd carries a risk of pneumotoxicity, with interstitial lung disease (ILD) occurring in 10–12% of patients. Early identification, accurate diagnosis, and appropriate management of T-DXd-related ILD are essential to optimize patient outcomes. Radiologists are key in detecting, characterizing, and monitoring ILD on chest computed tomography (CT) within a multidisciplinary care team.

This review aims to familiarize radiologists with the chest CT imaging features of T-DXd-related ILD, drawing from clinical trials and real-world data. Practical guidance is provided for image interpretation and differential diagnosis, with a focus on recognizing key patterns. To support this, the review also outlines the mechanism of action of T-DXd, its clinical indications, and associated adverse events, particularly pneumotoxicity.

Given the expanding use of T-DXd, radiologists must recognize ILD patterns on CT, namely organizing pneumonia (the most common), diffuse alveolar damage, hypersensitivity pneumonitis, and nonspecific interstitial pneumonia, while remaining alert to less frequent findings and differential diagnoses. When available, prior imaging for comparison is essential to differentiate disease progression, infection, and other conditions. CT imaging also supports the assessment of patient eligibility for T-DXd, proactive monitoring during treatment, and ILD reassessment.

Close collaboration between radiologists and oncologists is critical for early ILD detection, accurate diagnosis, and optimal patient management.

## 1. Introduction

Trastuzumab-deruxtecan (T-DXd) is an antibody-drug conjugate (ADC) composed of trastuzumab, a monoclonal antibody targeting HER2, linked to the cytotoxic agent deruxtecan via a chemical linker [1]. T-DXd has been increasingly used for treating various advanced human epidermal growth factor receptor 2 (HER2)-positive tumors, including breast cancer (BC) [2], gastric cancer [3], non-small cell lung cancer (NSCLC) [4], and colorectal cancer [5]. T-DXd has also shown clinical benefit in advanced HER2-expressing tumors of the biliary tract, bladder, cervix, endometrium, ovary, and pancreas [6].

Similarly to other systemic anticancer therapies, T-DXd can yield pneumotoxicity [7]. Indeed, T-DXd-associated interstitial lung disease (ILD) occurs in 10–12 % of patients [8–10], underscoring the need for early identification, accurate diagnosis, and tailored management [11]. A multidisciplinary approach is essential, with radiologists playing a key role in detecting, quantifying, and characterizing ILD on chest computed tomography (CT) [12].

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https://doi.org/10.1016/j.ejrad.2025.112499
Received 15 April 2025; Received in revised form 3 September 2025; Accepted 28 October 2025
Available online 30 October 2025
0720-048X/

**Table 1**
Chest CT roles in managing trastuzumab-deruxtecan-related interstitial lung disease.

| ILD/ pneumonitis CTCAE grade | T-DXd interruption | T-DXd resume | Corticosteroid therapy | Chest CT role |
|---|---|---|---|---|
| 1 | Yes | Possible | Possible | To confirm resolution, ideally within 28 days, or sooner if clinically indicated |
| 2 | Yes | No | Standard dose | To confirm resolution |
| ≥3 | Yes | No | High dose | To confirm resolution and determine the appropriate length of steroid treatment |

*Notes*: ILD, interstitial lung disease; CTCAE, Common terminology criteria for adverse events [23]; T-DXd, trastuzumab-deruxtecan.

This review aims to familiarize radiologists with T-DXd-induced ILD. The first section provides clinical background on T-DXd, including the mechanism of action, clinical indications, and adverse events (AE), emphasizing pneumotoxicity and its clinical diagnosis and management. The second section focuses on chest CT imaging, resuming evidence from clinical trials and real-world practice, and providing guidance on identifying, characterizing, and differentiating CT patterns of T-DXd-induced ILD.

## 2. Clinical background

### 2.1. T-DXd: Mechanism of action and clinical indications

ADCs represent a major advancement in targeted cancer therapy, coupling the specificity of monoclonal antibodies with the potency of cytotoxic agents. Among these, T-DXd has emerged as a highly effective therapeutic option in HER2-driven malignancies [13].

T-DXd consists of a humanized anti-HER2 monoclonal antibody, sharing the amino acid sequence of trastuzumab, linked to a topoisomerase I inhibitor via a cleavable tetrapeptide-based linker. This design allows for a high drug-to-antibody ratio (DAR), approximately 8:1, and ensures plasma stability until internalization by HER2-expressing tumor cells, where lysosomal cleavage releases the cytotoxic payload. The topoisomerase I inhibitor induces DNA damage, leading to replication inhibition, cell cycle arrest, and apoptosis. Due to its membrane permeability, the payload also exerts a bystander effect, killing neighboring tumor cells regardless of HER2 expression, thereby enhancing the ADC's antitumor efficacy [14].

The clinical use of T-DXd has expanded significantly following its regulatory approval for multiple tumor types. In breast and gastric cancers, it is used for HER2-positive tumors, while in NSCLC, it is indicated when activating ERBB2 mutations are detected, regardless of HER2 protein expression [14,15]. More recently, the therapeutic indication has been extended to include HER2-low metastatic BC, defined by an immunohistochemistry (IHC) score of 1 + or 2 + without in situ hybridization-confirmed amplification [16].

### 2.2. T-DXd: Potential pneumotoxicity

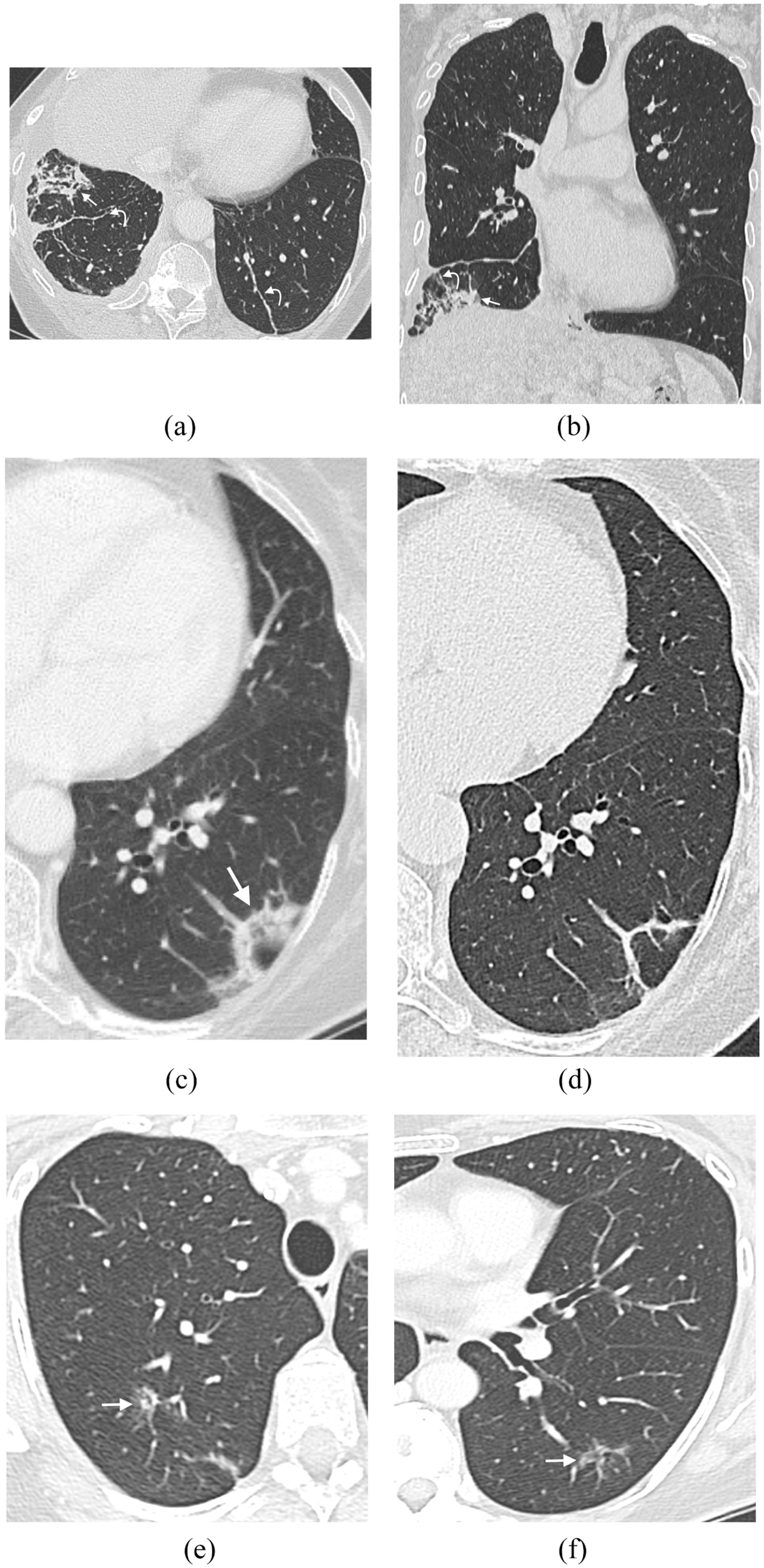
T-DXd demonstrates a generally manageable safety profile, with common AEs including nausea, vomiting, alopecia, and diarrhea. However, ILD has emerged as a serious and potentially life-threatening complication, requiring close monitoring, especially in heavily pretreated patient populations. In the DESTINY-Breast01 trial, which led to the FDA approval of T-DXd at 5.4 mg/m$^2$ for HER2-positive metastatic BC, ILD was reported in 13.6 % of patients, with fatal outcomes in 2.2 % [2]. A comparable incidence (10.5 %), mostly grade 1–2, was reported in DESTINY-Breast03, which demonstrated the superior efficacy of T-DXd over T-DM1 and established it as the standard second-line therapy [17]. The incidence remained notable in the HER2-low population enrolled in DESTINY-Breast04, with ILD occurring in approximately 12 % of cases [16]. At the higher dose used in DESTINY-Gastric01 (6.4 mg/m$^2$), ILD was reported in 12 % of cases [3]. The highest incidence was observed in DESTINY-Lung01, where 26.4 % of patients with HER2-mutant NSCLC developed ILD [18]. Most events (87 %) developed within the first year of treatment, with a median onset of 5.4 months overall (range < 0.1–46.8) and 3.2 months for grade 5 events (range < 0.1–20.8 months) [19].

Despite its significant clinical efficacy, ILD remains a safety concern, particularly among patients with predisposing risk factors such as age ≥ 65 years, underlying pulmonary conditions, prior thoracic radiotherapy, renal impairment, history of smoking, and genetic susceptibility, most prominently observed in East Asian populations, especially among Japanese patients [20].

**Table 2**
Literature overview of trastuzumab-deruxtecan-related interstitial lung disease CT patterns.

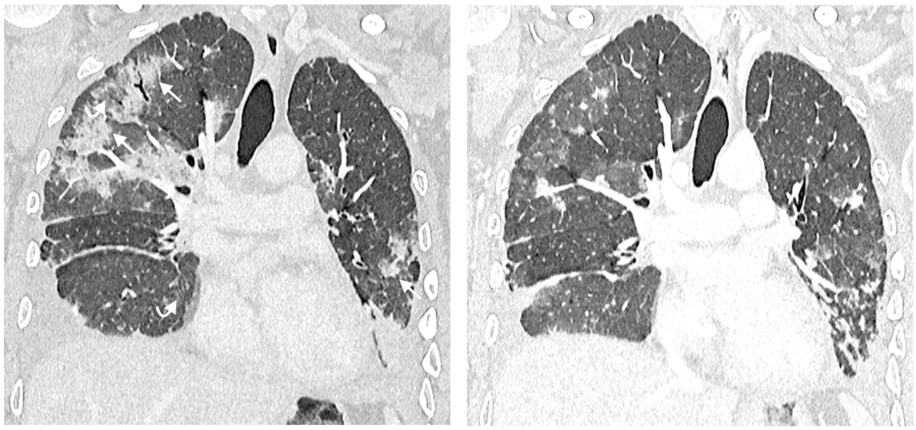
| Study reference | Study type | n. patients | Cancer type | n. patients with ILD/pneumonitis | CT pattern | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | AIP/ ARDS | OP | HP | NSIP | Other |
| Nishino et al. [32] | Retrospective analysis from two studies (DS8201-A-J101 and DESTINY-Breast01) | 542 | Breast, lung, gastric, and other solid cancers | 90 (17 %) | 10 (11 %) | 65 (72 %) | 3 (3 %) | N.A. | OP/HP 12 (13 %) |
| Jang et al. [33] | Retrospective analysis from four studies (NCT03248492, NCT03523585, NCT03529110, and NCT03734029) | 31 | Breast cancer | 4 (13 %) | – | 4 (100 %) | – | – | – |
| Tamura et al. [36] | Open-label, dose-escalation and dose-expansion phase 1 trial | 115 | Breast cancer | 20 (17 %) | N.A. | 6 (30 %) | N.A. | N.A. | ILD or pneumonitis 14 (70 %) |
| Baba et al. [34] | Japanese nationwide post-marketing all-case surveillance | 3000 | Breast and gastric cancers | 130 (4 %) | 19 (15 %) | 82 (63 %) | 22 (17 %) | 4 (3 %) | RRP, PE, ESS 3 (2 %) |
| Canellas et al. [35] | Multicenter French real-world retrospective study | 600 | Breast, lung, and other solid cancers | 67 (11 %) | 6 (9 %) | 35 (52 %) | N.A. | N.A. | N.A. |

*Notes*: ILD, interstitial lung disease; AIP/ARDS, acute interstitial pneumonitis/acute respiratory distress syndrome; OP, organizing pneumonia; HP, hypersensitivity pneumonitis; NSIP, nonspecific interstitial pneumonia; RRP, radiation-recall pneumonitis; PE, pulmonary edema; ESS, extremely slight shadow; N.A., not available.




(caption on next page)

**Fig. 1.** T-DXd-related ILD/pneumonitis presenting with an organizing pneumonia (OP) pattern in three different female patients with breast cancer, all of them asymptomatic at the time of CT examination. In the first case, axial **(a)** and coronal **(b)** CT images show a peripheral, sharply demarcated consolidation in the right lower lobe *(straight arrows)*, with an irregular shape and air bronchogram. Bilateral parenchymal bands extending to the pleural surfaces of the lower lobes are also visible *(curved arrows)*. In the second case, axial CT image **(c)** demonstrates a left lower lobe consolidation with perilobular distribution and a hazy air bronchogram *(arrow)*, which evolved into a thin, curvilinear perilobular opacity on follow-up CT obtained three weeks later **(d)**. In the third case, the axial CT image in **(e)** demonstrated a poorly marginated, irregularly shaped peribronchovascular consolidation in the right upper lobe *(arrow)*. On follow-up CT performed three months later **(f)**, the initial lesion had regressed (not shown), while a similar consolidation appeared in the left lower lobe *(arrow)*. These findings are consistent with the typical migratory manifestation of OP.



(a) (b)

**Fig. 2.** Extensive organizing pneumonia (OP) pattern in a 57-year-old female patient with breast cancer. One month after initiating T-DXd treatment, the patient presented with intermittent dry cough, progressive exertional dyspnea with desaturation requiring oxygen supplementation, and no fever. Chest CT image in the coronal plane **(a)** shows multiple consolidations involving both upper lobes *(straight arrows)*, characterized by irregular shape, air bronchogram, and peripheral ground-glass opacity components *(curved arrows)*. Following discontinuation of T-DXd, initiation of corticosteroid therapy, and clinical improvement, a follow-up CT performed three weeks later **(b)** demonstrates marked resolution of the consolidations, with no evidence of new lung findings.

### *2.3. T-DXd: The mechanisms underlying ILD*

The mechanisms underlying T-DXd-induced ILD are not fully elucidated. ILD comprises a spectrum of disorders characterized by alveolitis, disruption of alveolar architecture, and interstitial fibrosis, ultimately resulting in impaired gas exchange, typically triggered by acute or chronic lung injury. In the case of T-DXd, uptake of the ADC by alveolar macrophages via Fc receptors may initiate inflammatory and fibrotic responses. This hypothesis is supported by preclinical studies in cynomolgus monkeys, where T-DXd, but not free deruxtecan, induced dose-dependent lung injury. Histological analyses revealed preferential accumulation in alveolar macrophages rather than epithelial cells, suggesting a target-independent, immune cell-mediated mechanism [18,21]. Additionally, the cleavable linker may enable the release of the cytotoxic payload into the lung interstitium, exacerbating local damage through a bystander effect [18]. A key contributor to the T-DXd toxicity profile is its high DAR, significantly greater than the 3.5 of T-DM1, which, while enhancing antitumor efficacy, may also increase off-target toxicity [22].

### *2.4. T-DXd-induced ILD: Diagnosis and management*

Diagnosing T-DXd-induced ILD relies on clinical assessment and CT, the gold standard for detection and monitoring. However, diagnosis is often delayed due to nonspecific symptoms, such as dyspnea, cough, hypoxemia, or entirely asymptomatic presentations with incidental imaging findings. Prompt CT and pulmonary function testing (PFT) are essential in suspected cases. Once ILD is confirmed, treatment with T-DXd should be discontinued, and corticosteroid therapy should be initiated according to the severity of the condition.

The Common Terminology Criteria for Adverse Events (CTCAE), developed by the United States National Cancer Institute, provides a standardized framework for grading the severity of AEs in oncology [23]. It integrates clinical signs, symptoms, and laboratory findings into a five-grade scale (1–5). In cases of drug-induced ILD/pneumonitis, grade 1 refers to an asymptomatic presentation, typically detected on imaging and not requiring treatment. Grades 2 to 4 correspond to increasingly severe symptomatic disease, necessitating medical intervention. Grade 5 denotes fatal pneumonitis. Grade 1 ILD is typically managed with temporary interruption and systemic corticosteroids (prednisolone $\geq$ 0.5 mg/kg/day); if recovery occurs after more than 28 days, treatment may be resumed at a reduced dose. For grade $\geq$ 2 ILD, permanent discontinuation and initiation of high-dose corticosteroids (prednisolone $\geq$ 1 mg/kg/day) are required [19]. Therefore, early recognition and proactive management are critical to minimizing toxicity and preserving the clinical benefit of T-DXd [20].

## 3. The roles of chest CT in T-DXd-related ILD

The radiologist plays a key role within the multidisciplinary team evaluating T-DXd-associated pneumotoxicity. Chest CT is the most valuable imaging modality for characterizing ILD patterns and quantifying the extent of lung involvement. Specifically, CT imaging contributes to three critical areas: assessing patient eligibility for T-DXd treatment, enabling proactive patient monitoring for early detection of pulmonary toxicity, and supporting the reassessment of ILD [11,12,19].

### *3.1. Patient eligibility for T-DXd treatment*

Underlying pulmonary comorbidities may increase susceptibility to T-DXd-induced ILD or pneumonitis or worsen their severity. Therefore, within the framework of clinical trials involving T-DXd treatment, careful assessment of patient eligibility is essential. This process should include a chest CT and a detailed respiratory history to confirm the absence of current and prior ILD or pneumonitis [11]. In real-world clinical practice, such exclusion criteria are not strictly applied. In

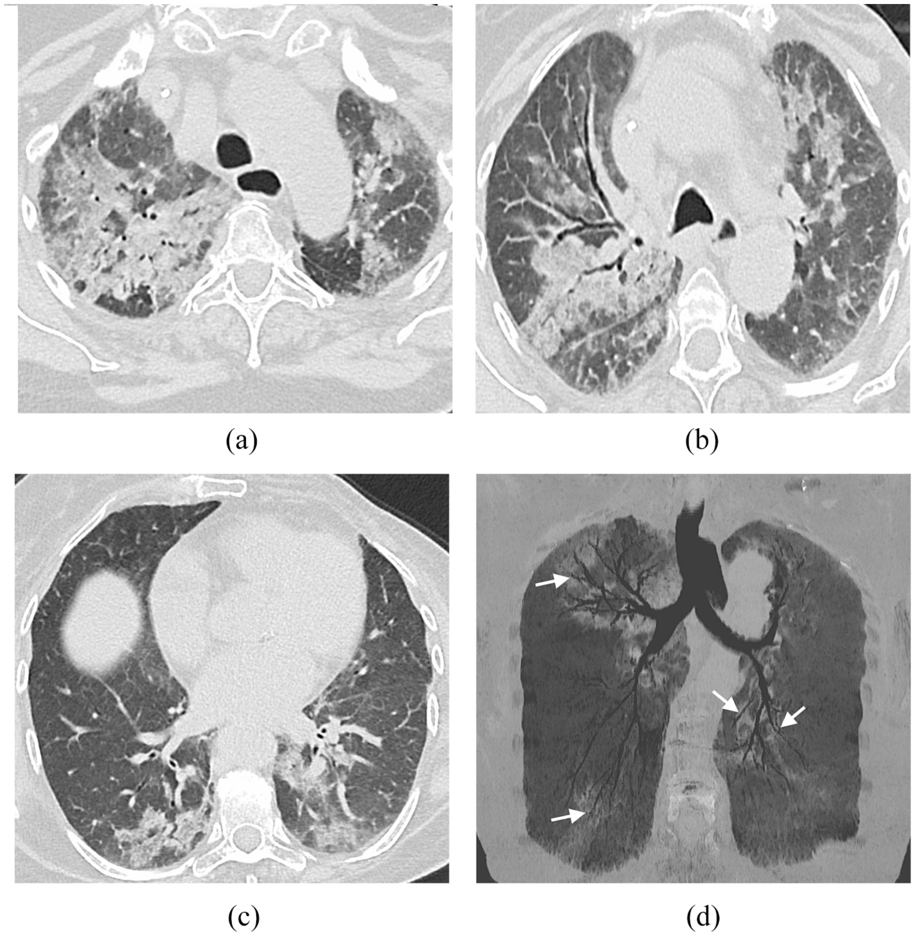



**Fig. 3.** Acute interstitial pneumonitis/acute respiratory distress syndrome (AIP/ARDS) pattern in a 74-year-old female patient with breast cancer. Two years after initiating T-DXd treatment, the patient developed rapidly progressive dyspnea, resulting in respiratory failure requiring admission to the intensive care unit. Despite supportive care, the patient subsequently died. Given the absence of a demonstrated infectious etiology during the clinical course and at autopsy, a T-DXd-related etiology was considered plausible. Axial chest CT images (**a–c**) demonstrate extensive, patchy consolidations and areas of ground-glass opacity (GGO) with a confluent appearance, involving all lobes of both lungs. The coronal image in (**d**), reconstructed with a 25-mm-thick minimum intensity projection algorithm, enhances visualization of mild tractional deformity of the airways within areas of consolidation and GGO *(arrows)*.

patients presenting with pre-existing chronic lung disease, the risks of pulmonary toxicity should be carefully balanced against the potential therapeutic benefits of T-DXd. This assessment is particularly relevant in cases requiring corticosteroid therapy in the previous six months [24].

### *3.2. Proactive patient monitoring*

Close patient monitoring during T-DXd therapy is critical, as the detection of chest CT findings suggestive of ILD (and/or the acute onset or worsening of respiratory symptoms) requires immediate treatment interruption and prompt evaluation to confirm the diagnosis [24]. Evidence from studies on other drugs suggests that delays between ILD onset and treatment withholding are associated with poorer outcomes. In this light, HRCT scans are performed every 6 weeks in T-DXd clinical trials [25], while for real-world clinical practice, performing CT scans every 9–12 weeks has been suggested, with concomitant assessment of tumor response and potential lung toxicity [12]. More frequent imaging, i.e., every 6–9 weeks, is advisable in selected clinical situations, including respiratory symptoms, reduced oxygen saturation, Japanese ancestry, or impaired renal function [24].

In addition to newly identified lung CT findings (see further in the text for details), diagnostic clues pointing toward T-DXd-related ILD include a temporal association of radiologic and/or symptom presentation with T-DXd commencement and exclusion of other causes, e.g., infection or disease progression [26].

### *3.3. Reassessment of ILD*

A follow-up chest CT scan should be performed approximately two weeks after the initial diagnosis of ILD, although the time interval is influenced by the patient's clinical condition, CTCAE grading, and response to therapy [27,28]. Table 1 resumes the role of CT at follow-up according to the CTCAE grade [27].

## 4. CT patterns of T-DXd-related ILD: Evidence from clinical trials and real-world studies

The joint guidelines from the American Thoracic Society (ATS) and European Respiratory Society (ERS) define the chest CT patterns associated with systemic anticancer therapy-related ILD [29]. These patterns include organizing pneumonia (OP), hypersensitivity pneumonitis (HP), acute interstitial pneumonia/acute respiratory distress syndrome (AIP/ARDS), and nonspecific interstitial pneumonia (NSIP) [30]. The term diffuse alveolar damage (DAD) is often used interchangeably with AIP/ARDS; for consistency, we will refer to this entity as AIP/ARDS throughout the manuscript.

In most clinical trials evaluating T-DXd, drug-related pulmonary AE are reported under two overarching terms, "interstitial lung disease" (ILD) and "pneumonitis," as assessed by an independent multidisciplinary adjudication committee [2,3,15,16]. Such drug-related AE terminology aligns with the Standardised Medical Dictionary for

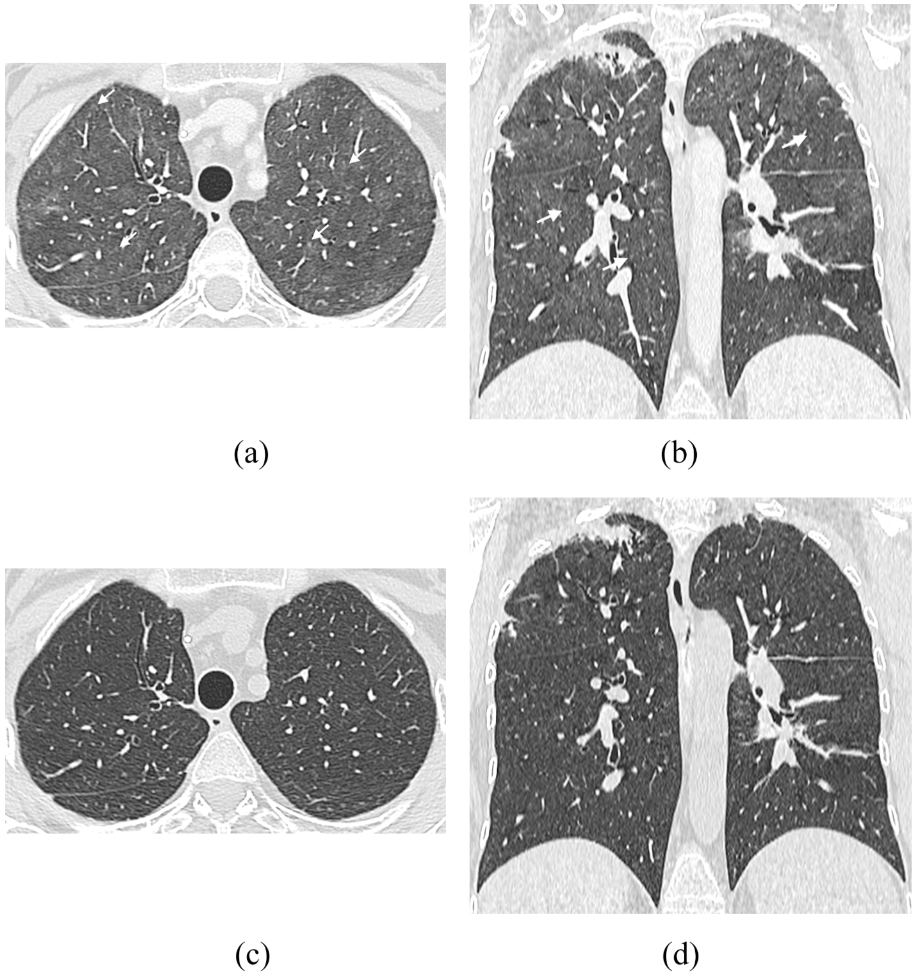



**Fig. 4.** T-DXd-related ILD/pneumonitis presenting with a hypersensitivity pneumonitis (HP) pattern in a 40-year-old female patient with breast cancer, who developed mild dyspnea nine months after initiating T-DXd treatment. Axial **(a)** and coronal **(b)** CT images obtained at full inspiration show diffuse lung mosaic attenuation and numerous small, subsolid centrilobular nodules without tree-in-bud pattern *(arrows)*. These findings nearly resolved on follow-up axial **(c)** and coronal **(d)** CT images acquired three weeks later.

Regulatory Activities (MedDRA) Query (SMQ) terminology. According to SMQ, ILD is a broad categorical term encompassing a heterogeneous group of conditions affecting the alveolar walls and perialveolar tissue, possibly resulting in interstitial fibrosis [31]. Pneumonitis is a member term within the SMQ ILD category explicitly referring to an inflammatory condition of the lower respiratory tract [20].

Current data on chest CT patterns associated with ILD primarily derive from a limited number of studies that retrospectively characterized these patterns in subsets of patients enrolled in clinical trials [32,33] or real-world multicentric Japanese [34] and French [35] cohorts. To our knowledge, only one clinical trial has explicitly reported a specific chest CT pattern, i.e., OP, as identified by an independent adjudication committee [36].

Table 2 provides an overview of the CT pattern types described in the current literature [32–36]. The available data suggest OP is the most frequent CT pattern, reported in 52–72 % of cases in the largest patient cohorts [32,34,35]. AIP/ARDS follows OP, observed in 9–15 % of cases. Only two studies have reported cases classified as HP, with reported frequencies ranging from 3-17 % for pure forms and 13 % for mixed OP/HP patterns [32,34]. NSIP has been described in a single real-world study, accounting for a rare occurrence (3 %) [34].

T-DXd–related ILD typically manifests within the first year of treatment, with a reported median time to onset of 184 days from therapy initiation (interquartile range: 115–276 days) [34]. However, the timing and clinical severity of ILD vary markedly depending on the CT pattern, particularly between AIP/ARDS and non-AIP/ARDS presentations. AIP/ARDS cases tend to occur earlier and are associated with higher CTCAE grades compared to non-AIP/ARDS patterns. In the study by Nishino et al., the median time to onset was approximately 18 weeks for AIP/ARDS and 33 weeks for non-AIP/ARDS cases, with 80 % of AIP/ARDS cases graded $\geq$ 3 ILD, compared to only 14 % among non-AIP/ARDS cases [32]. Canellas et al. [35] reported a median onset of 7 weeks for AIP/ARDS cases [34].

The greater clinical severity of AIP/ARDS is further underscored by its prognostic implications: in the series by Baba et al., AIP/ARDS resulted in death in 42 % of patients with this CT pattern [34], and in the study by Canellas et al. two-thirds of fatal ILD cases exhibited an AIP/ARDS pattern on chest CT [35]. Importantly, Nishino et al. also reported that none of the patients who presented with AIP/ARDS were rechallenged with T-DXd following ILD onset [32], highlighting the irreversible and life-threatening nature of this pattern in contrast to other, more indolent forms of drug-induced pneumonitis.

## 5. CT patterns of T-DXd-related ILD: A visual guide

Differentiation between the chest CT patterns encountered in T-DXd-related ILD contributes to clinical diagnosis and decision-making [12]. In imaging, “pattern” refers to a combination of nonspecific findings that suggest one or more specific disease processes [37]. Therefore, provided that standardized terminology is internalized and applied [38], accurate

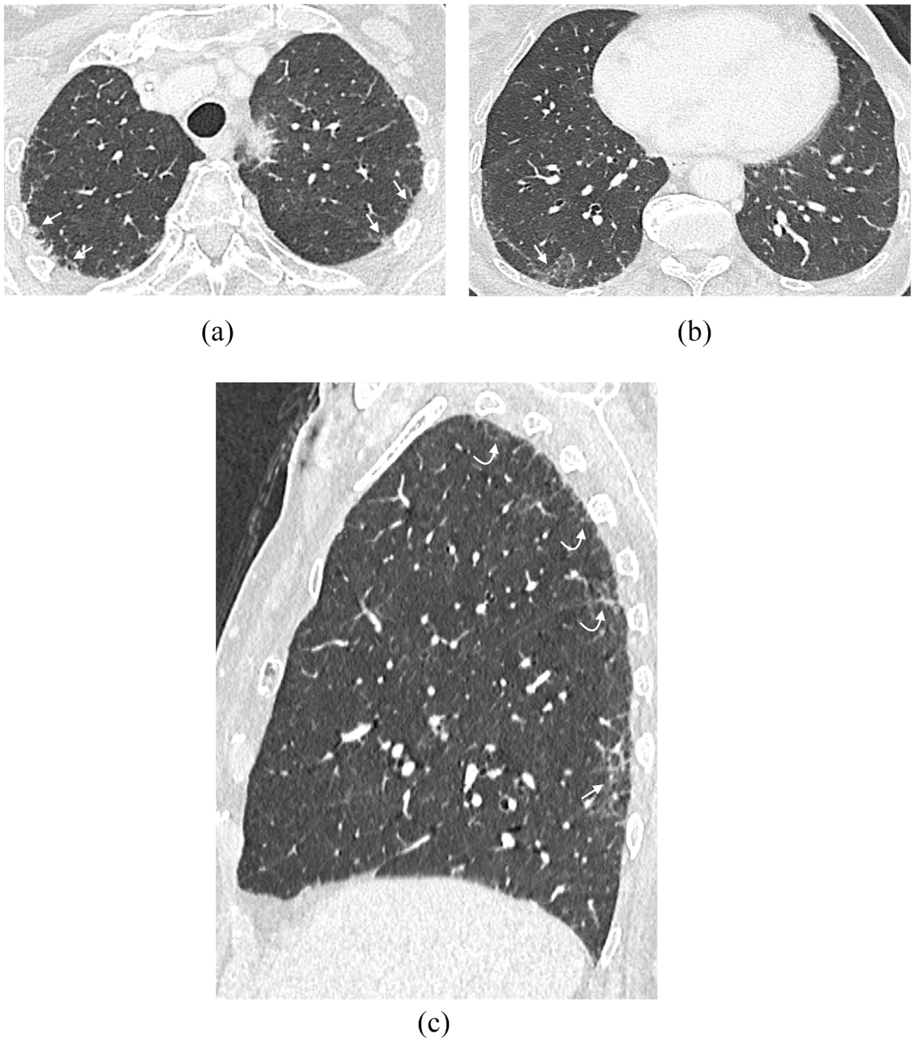



**Fig. 5.** T-DXd-related ILD/pneumonitis presenting with a nonspecific interstitial pneumonia (NSIP) pattern in an 83-year-old female with breast cancer, two months after initiating T-DXd treatment. Axial (**a, b**) and sagittal (**c**) chest CT images show subpleural reticulation superimposed to areas of hazy ground-glass opacity, predominantly affecting the mid-to-lower posterior regions of the lower lobes *(straight arrows)*. Similar but less conspicuous findings are also evident in the dorsal subpleural region of the upper lobes *(curved arrows)* (**c**).

recognition of chest CT patterns depends on a comprehensive understanding of individual findings. Nishino et al. reported ground-glass opacities (GGO) in 100 % of ILD cases, followed by consolidation in 90 %, reticular opacities in 52 %, and traction bronchiectasis in 24 % [32]. These findings are consistent with those Gocho et al. and Jang et al. described in small T-DXd-related ILD case series [33,39].

As detailed in Table 2, the most frequently encountered chest CT patterns of T-DXd-related ILD include OP, AIP/ARDS, HP, and NSIP. These patterns recall the broader framework of ILD manifestations observed in association with systemic anticancer therapies [7,40] and reflect acute (AIP/ARDS), subacute (OP, HP), or chronic (NSIP) interstitial diseases [41].

### *5.1. Organizing pneumonia (OP)*

T-DXd-related ILD presenting with an OP pattern typically manifests as various combinations of GGO and consolidation. While these findings are relatively nonspecific, OP is characteristically associated with irregularly shaped consolidations, air bronchograms, peribronchovascular and/or peripheral distribution, and lower lobe predominance [40,42,43]. The “reverse halo sign” (RHS), also known as the “atoll sign”, is a supportive CT feature of OP. It is defined as a focal area of ground-glass opacity surrounded by a partial or complete ring of denser consolidation [38]. Although not specific to OP, the RHS can reinforce the diagnostic impression when interpreted alongside the other typical CT findings [42].

On serial CT examinations of the same patient, migratory behavior and changing configuration of lung findings may be observed over time (Figs. 1 and 2) [43]. Compared to other CT patterns, the higher efficacy of steroid therapy in OP highlights the importance of its prompt recognition [27,44]. Notably, although OP and chronic eosinophilic pneumonia (CEP) may share overlapping CT features, CEP typically presents with peripheral, upper lobe-predominant band-like consolidations and is frequently associated with peripheral blood eosinophilia, aiding in the differentiation between the two entities [43]. In T-DXd-related ILD, OP and CEP are frequently regarded as part of the same “umbrella” OP pattern [11].

### *5.2. Acute interstitial pneumonitis/acute respiratory distress syndrome (AIP/ARDS)*

AIP/ARDS, the most severe manifestation of acute lung injury, represents the dominant pattern of grade $>$ 3 drug-induced ILD [27]. On chest CT, the AIP/ARDS pattern observed in T-DXd-related ILD resembles that seen with other drug-related cases [41]. Imaging findings largely depend on the timing of the CT relative to the toxicity effect

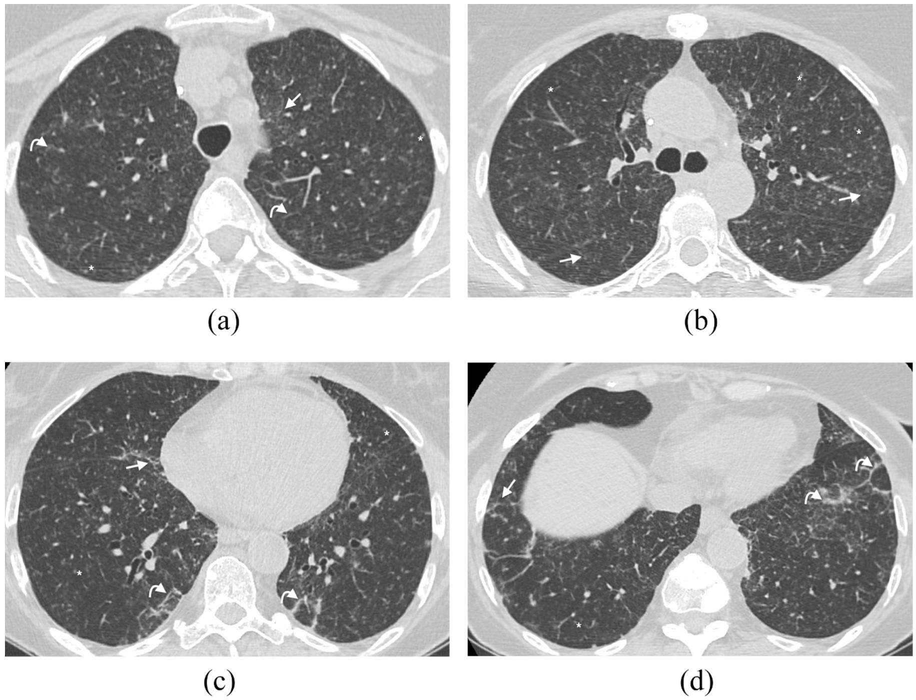


**Fig. 6.** T-DXd-related ILD/pneumonitis presenting with a non-fibrotic overlap pattern in a 66-year-old female patient with breast cancer, six months after initiating treatment. Axial CT images (**a–d**) show bilateral, diffuse pulmonary involvement characterized by patchy areas of hazy ground-glass opacity and fine reticulation, with relative subpleural sparing *(straight arrows)*. These findings are suggestive of a nonspecific interstitial pneumonia (NSIP) pattern. Additionally, diffuse micronodules with an indeterminate distribution are present *(asterisks)*, a feature atypical for NSIP but potentially indicative of hypersensitivity pneumonitis. Perilobular bands with subpleural location, resembling organizing pneumonia, are also evident in images (**a**), (**c**) and (**d**) *(curved arrows)*.

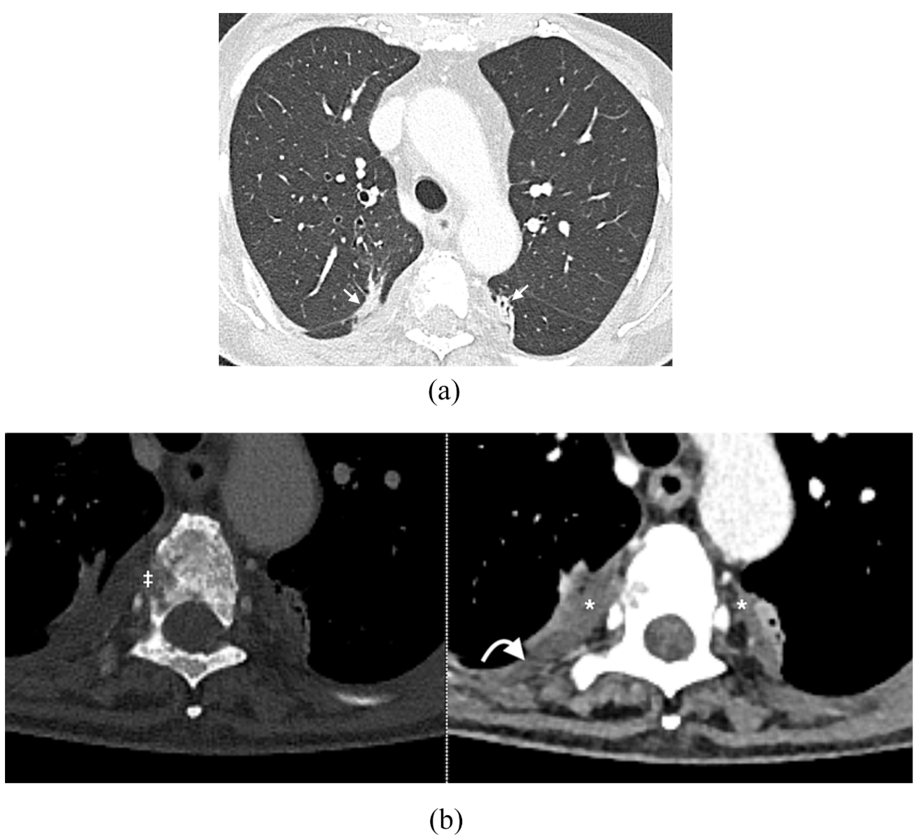


**Fig. 7.** Radiation pulmonary fibrosis in a 78-year-old female with breast cancer who previously underwent radiation therapy to the mid-thoracic spine (25 Gy in 5 fractions). Axial CT image obtained just before initiating T-DXd treatment **(a)** shows bilateral paravertebral irregular lung consolidation bands with air bronchograms *(straight arrows)*. Corresponding axial CT images in bone and soft tissue windows **(b)** reveal lytic bony lesion *(double dagger)*, paravertebral soft tissue thickening *(asterisks)*, and pleural thickening *(curved arrow)*, findings characteristic of a radiation reaction.

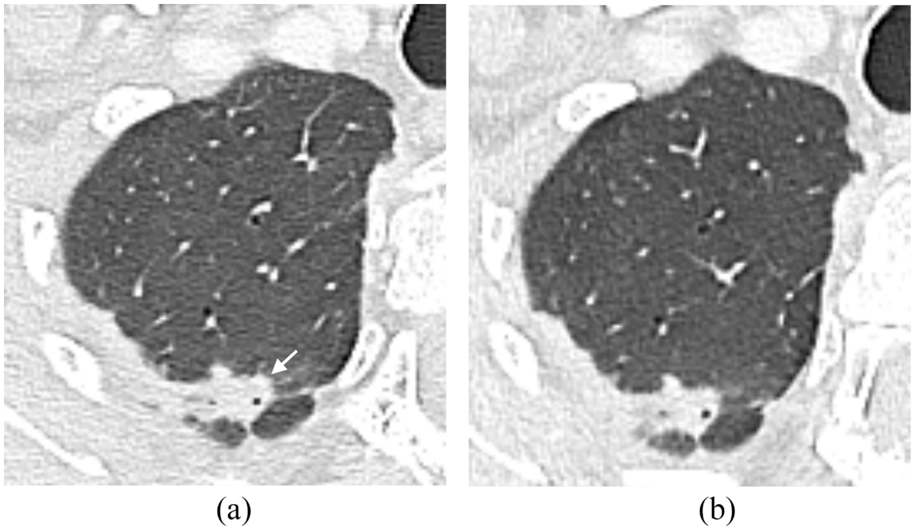


**Fig. 8.** Pleuroparenchymal fibroelastosis–like lesion in a 71-year-old female with breast cancer. **(a)** Axial close-up CT of the right upper lobe, obtained soon after initiating T-DXd treatment, shows an irregular consolidation band, with air bronchogram, abutting the apical pleura, suggestive of organizing pneumonia *(arrow)*. **(b)** A corresponding axial CT image from two years earlier reveals the same finding with identical size and morphology, consistent with aging-related elastotic fibrosis and parenchymal scar.

onset [45]. In the acute phase, preponderant AIP/ARDS findings include GGO and consolidations with diffuse and bilateral distribution, often with areas of lobular sparing (Fig. 3). It has been suggested that OP areas can coexist [46]. When present, the superimposition of thickened inter- and intralobular septa to GGO forms the crazy-paving pattern [11,43]. These findings correspond to the exudative phase of DAD, histologically characterized by edema, hyaline membrane formation, and active inflammation [27]. In the subacute to chronic phases, the extent of consolidation generally decreases, along with the possible emergence of reversed halo sign, irregular reticulation, and traction bronchiectasis. These findings mirror the organizing phase of DAD, with variable fibrosis and type II pneumocyte hyperplasia [11,27]. Eventually, CT findings can resolve, or variable degrees of residual fibrosis persist [27].

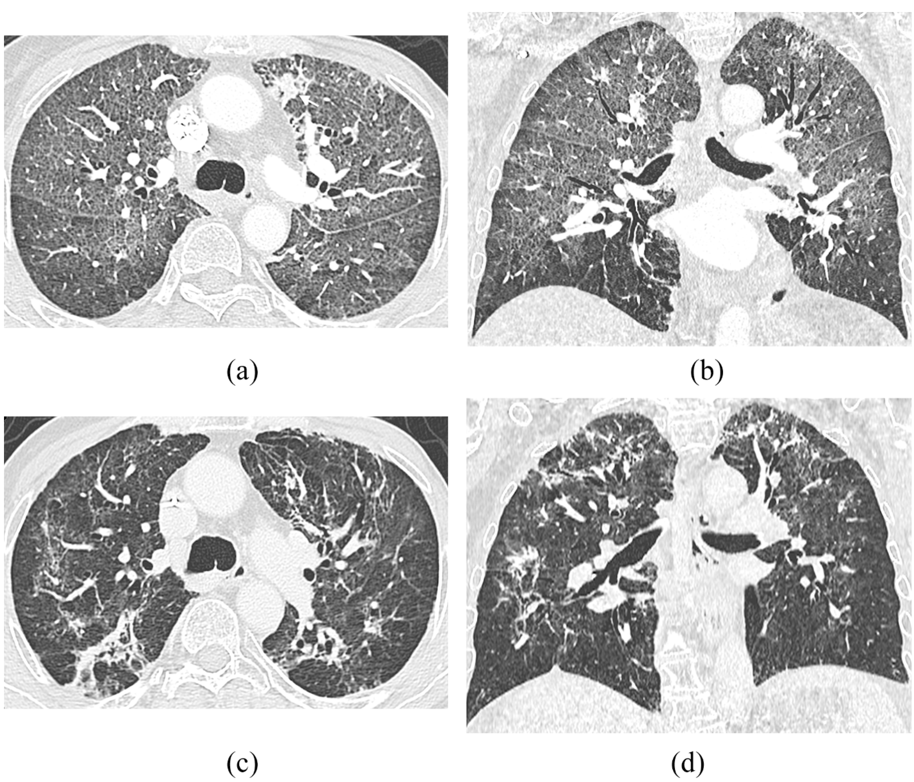
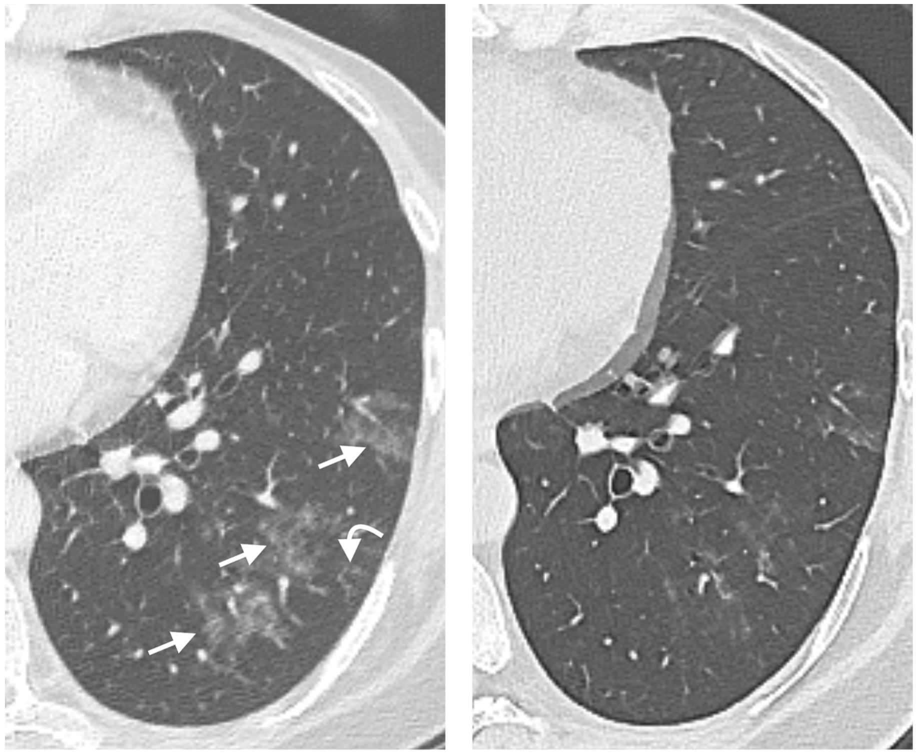


**Fig. 9.** Pneumocystis jirovecii pneumonia in a 73-year-old female patient with breast cancer, presenting with fever and dyspnea nearly one month after initiating T-DXd treatment. Axial **(a)** and coronal **(b)** CT images at clinical onset demonstrate extensive ground-glass opacities (GGO) with a crazy-paving pattern diffusely distributed in both lungs, sparing the basal regions. Focal consolidation is also seen in the left upper lobe *(arrow in a)*. Axial **(c)** and coronal **(d)** follow-up CT images acquired three months later show resolution of GGO and crazy paving, with residual volume loss, irregular bands, and parenchymal distortion consistent with fibrosis.



(a) (b)

**Fig. 10.** Small airway infection in a 42-year-old female patient with breast cancer, presenting with fever and cough at the time of restaging CT performed nine months after initiating T-DXd treatment. Axial CT image in **(a)** demonstrates a cluster of small, centrilobular and peribronchiolar ground glass opacity areas in the left lower lobe *(straight arrows)*, associated with tree-in-bud opacities *(curved arrow)*. These findings largely resolved on close follow-up CT after antibiotic treatment **(b)**.

### 5.3. Hypersensitivity pneumonitis (HP)

Various pharmaceutical agents, including systemic anticancer therapies, have been identified as potential antigens triggering drug-induced HP [47]. In the context of T-DXd treatment, the HP pattern presents as the non-fibrotic type [11]. CT findings include poorly defined, small, centrilobular ground-glass nodules with a diffuse distribution or upper lobe predominance, coupled with mosaic attenuation and air trapping due to bronchiolar obstruction in radiologically typical cases (Fig. 4) [47,48]. Clinically, patients with drug-induced HP usually present with grade 1 ILD and exhibit mild symptoms [43].

### 5.4. Nonspecific interstitial pneumonia (NSIP)

On CT, drug-related NSIP is indistinguishable from idiopathic NSIP [39]. In T-DXd-related ILD, NSIP presents with bilateral, patchy, or diffuse GGO areas, accompanied by varying degrees of reticular opacities. These findings typically show peripheral and basal predominance, along with temporal and spatial homogeneity [11]. Consolidation is generally absent (Fig. 5). The median severity of drug-related NSIP is grade 1 [43].

### 5.5. Other findings and patterns

As previously stated, most reported cases account for the four main T-DXd-related ILD patterns, i.e., OP, AIP/ARDS, HP, and NSIP. Nevertheless, it should be remembered that framework ILD on chest CT within a specific pattern is often more complex than it seems [46]. A few studies reported cases exhibiting mixed imaging patterns, such as coexisting OP and HP [32], as well as rare findings like radiation recall pneumonitis [33] or patterns that remain undefined (Fig. 6) [36]. Additionally, CT patterns may evolve, e.g., from OP to AIP/ARDS or HP to OP [34]. Sarcoid-like reaction is another imaging manifestation observed in patients undergoing systemic anticancer therapy, e.g., immune-checkpoint inhibitors [49]. To our knowledge, no cases of T-DXd-related sarcoid-like granulomatosis have been reported.

### 5.6. Differential diagnoses

When interpreting chest CT during T-DXd treatment, a couple of key rules of thumb should be considered.

First, direct side-by-side comparison with baseline imaging (acquired before T-DXd initiation) is essential to exclude pre-existing ILD or other lung conditions, including previous radiation treatment (Fig. 7) or other benign conditions, e.g., apical cap or pleuroparenchymal fibroelastosis–like lesion (Fig. 8), that could influence the evaluation of new findings [50].

Second, radiological suspicion of T-DXd-related ILD remains a diagnosis of exclusion. Differential diagnoses include infection, pulmonary edema, disease progression (e.g., lung metastases or lymphangitic carcinomatosis), diffuse alveolar hemorrhage, and radiation pneumonitis or fibrosis [27,34]. Pulmonary infections can complicate T-DXd treatment independently or concurrently with ILD [51]. Reported pathogens include bacteria; viruses such as Cytomegalovirus; fungi, including Aspergillus spp. and Pneumocystis jirovecii; and protozoa such as Toxoplasma gondii (Figs. 9 and 10) [27,51,52]. Anecdotal cases of concurrent T-DXd-induced ILD and COVID-19 have also been documented during the pandemic [53].

## 6. Conclusions

The growing use of T-DXd for advanced-stage tumors, particularly breast cancer, requires radiologists to stay informed about T-DXd-related pneumotoxicity in terms of clinical relevance and chest CT role, including patient eligibility for treatment, proactive monitoring, and ILD reassessment. Familiarity with the typical CT patterns – OP (the most common), AIP/ARDS, HP, and NSIP- and recognition of rarer findings is essential.

Since diagnosing T-DXd-related pneumotoxicity requires ruling out other causes, radiologists must consider a broad differential, including disease progression, infections, and other conditions, often aided by side-by-side comparison with prior imaging. Close collaboration with oncologists is crucial for timely T-DXd-related ILD detection, accurate diagnosis, and proper patient management.

*During the preparation of this work the authors used ChatGPT to refine the English language and improve the overall readability of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.*

## CRediT authorship contribution statement

**L. Cereser:** Writing – original draft, Investigation, Conceptualization. **S. Della Rossa:** Writing – original draft, Investigation. **F. Sparascio:** Writing – original draft, Visualization. **L. Gerratana:** Writing – review & editing, Methodology. **A.M. Minisini:** Writing – original draft, Investigation. **F. Puglisi:** Writing – review & editing, Supervision. **R. Girometti:** Writing – review & editing, Supervision. **C. Zuiani:** Writing – review & editing, Project administration.

## Declaration of competing interest

The authors disclosed the following: **L. Cereser:** personal fees from Daiichi-Sankyo and Astra Zeneca, outside the submitted work. **L. Gerratana:** personal fees from AstraZeneca, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Incyte, Novartis, Pfizer, Merck Sharp & Dohme, Menarini Stemline, and AbbVie, outside the submitted work. **A.M. Minisini:** personal fees from Novartis, MSD, BMS, Merk, PierreFabre, Gilead, Seagen, Genomic Health, Regeneron, Sunpharma, Sanophi Regeneron, Astra Zeneca, Daiichi Sankyo, Lilly, and Pfizer, outside the submitted work. **F. Puglisi:** grants from AstraZeneca, Eisai, and Roche; personal fees from AstraZeneca, Roche, Menarini Stemline, Novartis, Eli Lilly, Exact Sciences, Italfarmaco, Daiichi Sankyo, Gilead, Pfizer, and Seagen, outside the submitted work. **S. Della Rossa, F. Sparascio, R. Girometti, and C. Zuiani:** no conflicts of interest to be disclosed.

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