# Management of Lung Toxicity with T-DXd in Canada

Subjects: Health Care Sciences & Services

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Ongoing advances in precision cancer therapy have increased the number of molecularly targeted and immuno-oncology agents for a variety of cancers, many of which have been associated with a risk of pulmonary complications, among the most concerning being drug-induced interstitial lung disease/pneumonitis (DI-ILD). As the number of patients undergoing treatment with novel anticancer agents continues to grow, DI-ILD is expected to become an increasingly significant clinical challenge. Trastuzumab deruxtecan (T-DXd) is an antibody–drug conjugate targeting human epidermal growth factor receptor 2 that is gaining widespread use in the metastatic breast cancer setting and is undergoing exploration for other oncologic indications. ILD/pneumonitis is an adverse event of special interest associated with T-DXd, which has potentially fatal consequences if left untreated and allowed to progress. When identified in the asymptomatic stage (grade 1), T-DXd-related ILD can be monitored and treated effectively with the possibility of treatment continuation. Delayed diagnosis and/or treatment, however, results in progression to grade 2 or higher toxicity and necessitates immediate and permanent discontinuation of this active agent. Strategies are, therefore, needed to optimize careful monitoring during treatment to ensure patient safety and optimize outcomes.

trastuzumab deruxtecan | metastatic breast cancer | interstitial lung disease | pneumonitis

## 1. Introduction

A number of systemic agents used for the treatment of cancer have been associated with pulmonary toxicities, one of the most concerning of which is drug-induced interstitial lung disease (ILD)/pneumonitis (DI-ILD). Many novel therapies, including molecularly targeted agents, immune checkpoint inhibitors, and antibody–drug conjugates (ADCs) have been associated with a risk of DI-ILD. As the number of anticancer agents continues to grow, DI-ILD is expected to become an increasingly significant clinical challenge across all types of cancers. The recent approval of trastuzumab deruxtecan (T-DXd), a novel ADC targeting human epidermal growth factor receptor 2 (HER2), for various lines of therapy and indications in breast cancer has highlighted this issue and is the focus of this research.

ILD has been identified as an adverse event of special interest with T-DXd and occurs in approximately 10% to 14% of breast cancer patients treated with the drug [1][2][3][4]. If not effectively identified and treated, T-DXd-related ILD can be fatal. While asymptomatic (grade 1) DI-ILD caused by most drugs does not require specific therapy, T-DXd-related ILD is unique because of the high risk of evolution to serious illness (grades 3–4 ILD) and because

early identification of grade 1 ILD may allow for ongoing treatment, whereas progression to grade 2 or higher ILD necessitates permanent discontinuation of T-DXd.

## 2. Indications for T-DXd in Canada

T-DXd is approved in Canada for the treatment of adult patients with unresectable or metastatic HER2+ breast cancer as a third-line therapy after disease progression following taxanes, trastuzumab + pertuzumab, and trastuzumab-emtansine, as well as for early disease recurrence in the neoadjuvant or adjuvant setting, and for second-line therapy in patients previously treated with taxanes and trastuzumab + pertuzumab [1][2][5]. In 2023, T-DXd was also approved for the treatment of adult patients with unresectable or metastatic HER2-low breast cancer who have received at least two prior lines of endocrine therapy in addition to one line of chemotherapy in the metastatic setting or following disease recurrence during or within 6 months of completion of adjuvant chemotherapy. HER2-low is defined as a score of 1+ on immunohistochemistry (IHC) or an IHC score of 2+ with no HER2 amplification on in situ hybridization [4].

Approvals for these indications were based on significant improvements in all relevant efficacy endpoints compared to standard of care therapy observed in the DESTINY-Breast01 [1][6], DESTINY-Breast02 [2], DESTINY-Breast03 [3], and DESTINY-Breast04 [4] trials.

In addition to the indications for metastatic breast cancer, T-DXd is approved in the United States for locally advanced/metastatic HER2-positive gastric cancer, based on the positive results of the DESTINY-Gastric01 and DESTINY-Gastric02 trials [7][8]; for metastatic HER2-positive nonsmall cell lung cancer (NSCLC), based on the DESTINY-Lung01 and DESTINY-Lung02 trials [9][10][11]; and is under investigation for various additional tumor types, including colorectal and other cancers [12][13].

## 3. Known Risk Factors for DI-ILD

The term “ILD/pneumonitis” is broadly used to describe a diverse group of inflammatory lung disorders affecting alveolar structures, pulmonary interstitium, and small airways and is characterized by the presence of inflammation or scarring of lung parenchyma [14]. Identifiable causes include exposure to organic materials, drugs, or toxins that trigger hypersensitivity pneumonitis; exposure to inorganic dusts and other compounds causing pneumoconiosis; autoimmune conditions such as rheumatoid arthritis and scleroderma; uncommon or rare genetic abnormalities (mutations in telomerase enzymes, mucin genes, surfactant proteins, etc.); and exposure to certain drugs [14].

A number of drug classes have been implicated in DI-ILD, including disease-modifying antirheumatic drugs (DMARDs), antiarrhythmics, antimicrobials, and antineoplastic agents [15][16].

Key risk factors that predict for an increased risk of developing DI-ILD include a history of pre-existing lung disease and reduced lung function [16][17][18][19]; poor performance status [20]; smoking [16]; age older than 60 years [16][17][19]; Japanese or African American ethnicity [19][21]; and male sex [16][17]. Specifically related to oncology, prior treatment

with multiple chemotherapy regimens or thoracic radiotherapy; history of radiation recall pneumonitis; presence of lung cancer, lung metastases, or other drug-induced pneumonitides; ongoing therapy with multiple molecularly targeted agents; and treatment with a combination of molecularly targeted and cytotoxic agents have all been identified as risk factors predisposing to DI-ILD [16][19][20]. Factors that increase the risk of poor outcomes and/or mortality from DI-ILD include acute symptomatic disease with rapid symptom onset, hypoxemia, need for mechanical ventilation (associated with a mortality rate > 60%), pre-existing ILD, male sex, age over 65 years, and a diagnosis of nonsmall cell lung cancer [22][23][24][25][26][27]. However, it is important to note that many people who develop DI-ILD have no identifiable pre-existing risk factors, which highlights the need for vigilance.

The identification and monitoring of patients at risk of DI-ILD are crucial for timely intervention; however, there are currently no effective strategies for identifying and monitoring DI-ILD in clinical practice beyond CT imaging and monitoring of oxygen saturation. Prospective clinical trials are on the horizon to determine if there are any helpful screening tools. The authors of this research encourage Canadian clinicians to collect real-world data on the incidence of T-DXd-related ILD and other potential adverse events.

## 4. DI-ILD with Specific Anticancer Treatments

DI-ILD has been recognized as an important toxicity associated with a number of chemotherapeutic and targeted antineoplastic therapies. Bleomycin is the historical example, with a reported incidence of up to 45% and up to a 3% mortality rate [28][29][30]. Contemporary examples include agents targeting mammalian target of rapamycin (mTOR) [31][32], tyrosine kinase/anti-epidermal growth factor receptor (EGFR) inhibitors [33][34][35][36][37][38][39][40], anti-HER2 agents [41][42][43][44][45], *BRAF* inhibitors [46], cyclin-dependent kinase 4/6 inhibitors [47][48][49], and poly (ADP-ribose) polymerase (PARP) inhibitors [50], as well as immune checkpoint inhibitors [51][52][53][54][55][56] and ADCs [28], with case-fatality rates ranging from 0% to 51.3% depending on the drug [16]. DI-ILD has been reported, to a lesser extent, with other widely used conventional chemotherapeutic agents, such as taxanes and gemcitabine, with an incidence of DI-ILD of up to 5% [57][58], and rare but serious events can arise with oxaliplatin [59].

The pathogenesis of DI-ILD is poorly understood, but several mechanisms—both cytotoxic and immune related—may be involved, either alone or in combination, depending on the drug. Direct damage to pneumocytes or alveolar endothelial cells, cell-mediated lung injury, oxidative stress, and systemic cytokine release may all contribute to DI-ILD [60]. In patients treated with immune checkpoint inhibitors, these mechanisms may be compounded by amplified auto-immune processes triggered by the therapy [56]. Further studies are needed to investigate further the cytotoxic and immune-related mechanisms involved in DI-ILD to provide a better understanding of the underlying processes involved and potentially aid in the development of preventive strategies.

## 5. T-DXd and the Risk of ILD

ILD was first identified as an adverse event of special interest in the DESTINY-Breast01 trial, where 13.6% of patients experienced independently adjudicated ILD and 2.2% died because of this complication [1]. Subsequently, guidelines for the identification and management of ILD were incorporated into the DESTINY clinical trial program with a focus on close monitoring and active management including corticosteroids, along with dose interruption/modification and mandatory discontinuation of T-DXd for grade 2 or higher ILD events.

In a pooled analysis of heavily treated patients across 9 phase 1 and 2 T-DXd clinical trials, the incidence of T-DXd-related ILD was 15.4%, with 11.9% experiencing grade 1 or 2 events and a 2.2% incidence of grade 5 events [61]. Rates of ILD ranged from 10.1% in DESTINY-Gastric02 [8] to 26.4% in DESTINY-Lung01 [9]. Most events (87%) occurred during the first 12 months of treatment, with a median time to onset of 5.4 months (range < 0.1 to 46.8 months) overall and of 3.2 months for grade 5 events (range < 0.1 to 20.8 months) [61].

Potential risk factors for DI-ILD in the pooled analysis included baseline oxygen saturation ($SpO_2$) < 95%, T-DXd dose > 6.4 mg/kg q3w, >4 years since initial disease diagnosis, renal dysfunction, age < 65 years, and baseline or prior lung comorbidities (asthma, chronic obstructive pulmonary disease (COPD), prior ILD/pulmonary fibrosis, and radiation pneumonitis) [61]. Treatment in Japan was also identified as a risk factor for DI-ILD in the pooled analysis [61]; however, T-DXd was initially studied in Japan without the monitoring protocols implemented in later trials, which may account for the higher incidence in this population.

As with other anticancer agents, the underlying mechanisms of T-DXd-related DI-ILD are unclear, but the proposed pathogenesis includes target-dependent and/or -independent uptake and catabolism of the ADC or a bystander effect of the cytotoxic payload released from cells following ADC catabolism [62]. Lung epithelial cells express HER2 protein, and off-cancer target mechanisms have been suggested on the basis of animal studies which observed localization of T-DXd in alveolar macrophages rather than pulmonary epithelial cells [63]. The release of the chemotherapy payload and subsequent bystander effect resulting in cytotoxic lung injury is currently the leading hypothesis in the understanding of T-DXd-related ILD [28].

## 6. Diagnosis and Monitoring of T-DXd-Related ILD

Current published recommendations for the early identification and management of T-DXd-related ILD in other jurisdictions do not necessarily fully apply to the Canadian health care environment, with variable timely access to pulmonary function tests (PFTs), high-resolution computed tomography (HRCT), and subspecialty respirology expertise. The steering committee therefore sought to tailor existing recommendations and create a practical approach for the Canadian health care landscape.

Diagnosis of DI-ILD requires timely investigation and multidisciplinary collaboration among the oncologist, respirologist, radiologist, and other allied health care providers. In the case of reasonable causality between T-DXd and development of ILD/pneumonitis, prompt diagnosis and therapeutic intervention is key. Other diagnoses (e.g., bacterial, viral, and fungal infections; alveolar hemorrhage; metastases; heart failure; aspiration pneumonia; radiation-induced lung injury; and pulmonary embolism with infarction [64]) should be kept under consideration for

atypical cases and nonresponding patients. Opportunistic infections such *Pneumocystis jirovecii* (PJP) should be strongly considered for patients on systemic corticosteroids or other immunosuppressive therapies.

While the risk of T-DXd-related ILD appears to plateau after 12 months [61], it can occur at any time, and long-term monitoring and vigilance are essential.

# 7. Management of T-DXd—Related ILD

Because of the possibility of rapid ILD/pneumonitis progression and because holding treatment is critical in cases of T-DXd-related events, it is important not to delay implementation of the following management steps even when diagnosis may be uncertain.

## 7.1. Grade 1/Asymptomatic ILD

ILD can be fatal if it is left untreated, and progression to grade 2 or higher ILD precludes continued and future treatment with T-DXd [5]. Grade 1 disease will generally be diagnosed and managed by the oncologist or oncology delegate without the need for higher-level investigation or consultation. However, if the patient has a history of previous lung disease or if there is diagnostic uncertainty, assessment by respirology may be warranted.

Grade 1 ILD requires that T-DXd be withheld until recovery to grade 0 (normalization of CT abnormalities), at which point treatment may be resumed, with the dose depending on time to resolution [5]. If resolution occurs in 28 days or fewer from onset, the original dose of T-DXd can be maintained (5.4 mg/kg–6.4 mg/kg for gastric cancer), but dose escalation is not recommended, and some clinicians may choose to dose-reduce out of an abundance of caution. If resolution takes more than 28 days, the dose is reduced to 4.4 mg/kg after a first occurrence (5.4 mg/kg for gastric cancer). If there is a second occurrence, the dose is reduced to 3.2 mg/kg (4.4 mg/kg for gastric cancer). If there is a third occurrence of pneumonitis, or if the grade 1 ILD/pneumonitis event has not resolved within 18 weeks (126 days) from the last infusion, T-DXd must be permanently discontinued.

The Canadian Product Monograph for T-DXd recommends considering corticosteroid treatment for grade 1 DI-ILD (e.g., >0.5 mg/kg/day prednisolone or equivalent until improvement, with a gradual taper over 4 weeks or longer) [5]. Until there are further data to clarify the role of steroids for grade 1 events, the steering committee recommends following this guidance, especially if any DI-ILD-related risk factors are identified. Repeat HRCT should be considered prior to each of the next two doses of T-DXd to ensure no recurrence, after which conventional chest CT scans can resume at an interval of every 9 to 12 weeks.

## 7.2. Grade 2 ILD

Symptomatic ILD that does not interfere with activities of daily living (grade 2) requires permanent discontinuation of T-DXd and prompt initiation of systemic corticosteroid treatment (e.g., ≥1 mg/kg/day prednisolone or equivalent for at least 14 days followed by a gradual taper over at least a 4-week period) [5]. PJP prophylaxis with

trimethoprim/sulfamethoxazole (TMP-SMX) should be considered for all cases and is recommended for patients who are expected to be on corticosteroids at a dose of ≥20 mg for ≥1 month [65].

The patient's symptoms should be monitored closely, with re-imaging conducted as clinically indicated. The steering committee recommends clinical reassessment 7 days after initiation of steroids and early, repeat imaging with low-dose CT scan 7 to 14 days after initiation of steroids for those with nonimproving or worsening symptoms. Precise timing of repeat chest imaging for those who are clearly responding to steroids can be determined by the treating oncologist but should occur within 4 to 6 weeks. If there is clinical or radiographic worsening (especially within 5 days of initiation of therapy), consideration should be given to increasing the dose of steroids (e.g., 2 mg/kg/day of prednisolone or equivalent) or switching to IV administration (e.g., methylprednisolone). A multidisciplinary approach to the management of these patients is indicated. At this point, additional work-up for alternative etiologies and referral to respirology should be considered.

## 7.3. Grade 3 or 4 ILD

Patients with grade 3 or higher ILD need to be hospitalized because of supplemental oxygen requirements and ventilator support. Empiric high-dose methylprednisolone IV should be promptly initiated (e.g., 500 to 1000 mg/day for 3 days), followed by at least 1.0 mg/kg/day of prednisolone (or equivalent) for at least 14 days, followed by a gradual taper over at least 4 weeks. PJP prophylaxis with TMP-SMX should be considered for all cases and is recommended for patients who are expected to be on corticosteroids at a dose of ≥20 mg for ≥1 month [65].

A multidisciplinary approach to the management of these patients is indicated. In-patient respirology consultation along with involvement of other relevant specialists should be considered, including but not limited to radiologists, intensivists, internists, and infectious disease specialists. The patient's symptoms should be monitored closely, with re-imaging conducted as clinically indicated. The steering committee recommends daily clinical reassessment after initiation of steroids and early, repeat imaging with low-dose CT scan 7 to 14 days after initiation of steroids for those with nonimproving or worsening symptoms. Precise timing of repeat chest imaging for those who are clearly responding to steroids can be determined by the treating oncologist but should occur within 4 to 6 weeks. If there is clinical or radiographic worsening (especially within 5 days of initiation of therapy), additional work-up should be considered to explore alternative etiologies. Consider other immunosuppressants and/or treat per local practice.

- **Summary: Management of T-DXd-Related DI-ILD**
- *Grade 1 DI-ILD*

- Interrupt T-DXd until resolved to grade 0 (resolution of CT abnormalities), then:
    - If resolved in ≤28 days from date of onset, maintain dose (starting dose is 5.4 mg/kg (6.4 mg/kg for gastric cancer));
    - If resolved in >28 days from date of onset, reduce dose one level:

- Dose reduction with first occurrence: 4.4 mg/kg (5.4 mg/kg for gastric cancer);
- Dose reduction with second occurrence: 3.2 mg/kg (4.4 mg/kg for gastric cancer).
    - Permanently discontinue T-DXd if there is a third recurrence;
    - Permanently discontinue T-DXd if the grade 1 ILD/pneumonitis event has not resolved within 18 weeks (126 days) from the last infusion.
- Consider prednisolone ≥ 0.5 mg/kg/day or equivalent with a gradual taper over ≥4 weeks, until improvement; *
- Monitor and closely follow up in 2–7 days for onset of clinical symptoms and $SpO_2$;
- Consider follow-up imaging in 1–2 weeks or as clinically indicated.

- *Grade 2 DI-ILD*

- Permanently discontinue T-DXd;
- Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected: *
    - A total of 1 mg/kg/day of prednisolone or equivalent for ≥14 days;
    - Gradually taper over ≥4 weeks.
- Monitor symptoms closely;
- Re-image with HRCT within 7–14 days to confirm improvement and then re-image as clinically indicated;
- If clinical or radiographic worsening or still no improvement (especially within 5 days):
    - Consider increasing dose of steroids (e.g., 2 mg/kg/day of prednisolone or equivalent), switching administration to i.v. (e.g., methylprednisolone); *
    - Reconsider additional work-up for alternative etiologies, as described above;
    - Escalate care as clinically indicated.

- *Grade 3+ DI-ILD*

- Permanently discontinue T-DXd;
- Hospitalization required;

- Promptly initiate empirical high-dose methylprednisolone IV treatment: *
  - Give 500–1000 mg/day for 3 days followed by ≥1 mg/kg/day of prednisolone (or equivalent) for ≥14 days;
  - Gradually taper over ≥4 weeks
- Re-image with HRCT within 7–14 days to confirm improvement and then re-image as clinically indicated;
- If clinical or radiographic worsening or still no improvement (especially within 5 days):
  - Reconsider additional work-up for alternative etiologies, as described above;
  - Consider other immunosuppressants and/or treat per local practice.
- Consider involvement of respirology or internal medicine.

* Consider PJP prophylaxis with TMP-SMX for all patients—recommended for patients who are expected to be on corticosteroids at a dose of ≥20 mg for ≥1 month.

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