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REVIEW

A Systematic Review of Mechanisms, Incidence, and Management of Trastuzumab Deruxtecan Induced ILD/Pneumonitis in Solid Tumors

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Abstract: Trastuzumab deruxtecan (T-DXd) has been approved to treat various tumors. While most adverse events (AEs) associated with T-DXd are manageable, interstitial lung disease (ILD)/pneumonitis is a notable AE of special concern. This review describes the incidence, severity, and management of T-DXd-induced ILD/pneumonitis across different tumors. We conducted a systematic search of PubMed, Embase, Cochrane Library, and Web of Science for literature published up to 13 September 2024, regarding the use of T-DXd in the treatment of HER2-positive tumors. Studies included were clinical trials involving HER2-positive tumors with reported ILD/pneumonitis cases.The main data extracted from the full-text articles included the incidence and severity of T-DXd-induced ILD. 18 studies involving 3380 patients with various advanced solid malignancies were included in our review. The overall incidence of adjudicated drug-related ILD/pneumonitis was 12.40%. Although most ILD/pneumonitis cases were low-grade, the risk of ILD/pneumonitis-related death should not be overlooked. Given the prolonged exposure to the drug, careful monitoring and management of T-DXd-induced ILD/pneumonitis are critical. Management strategies include dose reduction, treatment interruption, discontinuation, corticosteroids, and supportive care. Further research is needed to clarify the risk factors and mechanisms underlying T-DXd-induced ILD/pneumonitis. This review highlights critical gaps in understanding the risk factors and mechanisms of T-DXd-induced ILD, underscoring the need for further research.

Keywords: T-DXd, AEs, ILD/pneumonitis, HER2, ADC

Introduction

As a transmembrane glycoprotein receptor, human epidermal growth factor receptor 2 (HER2) belongs to the epidermal growth factor receptor (EGFR) family and exhibits intracellular tyrosine kinase activity.[1,2] The activation of HER2 contributes to cell proliferation, differentiation, invasion, migration, and inhibition of apoptosis.[3] Overexpression, amplification, and other mutations are the most common alterations of HER2, which have been found in various types of solid tumors. Several HER2-targeted agents have been approved for tumor therapy, including anti-HER2 monoclonal antibodies (trastuzumab and pertuzumab) and anti-HER2 antibody-drug conjugate (ADCs) trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd).

T-DXd is a novel ADC that consists of a humanized anti-HER2 monoclonal antibody with the same amino acid sequence as trastuzumab, covalently linked to a novel topoisomerase I inhibitor through a tetrapeptide-based cleavable linker.[4] With its unique design, T-DXd has achieved the highest (approximately 8) drug-to-antibody ratio (DAR) among currently approved ADCs.[5] The linker is stable in plasma and is selectively cleaved after internalization by cathepsins, which are upregulated in tumor cells. The high membrane permeability of the payload allows it to exert cytotoxic effects on neighboring tumor cells via bystander effects, especially in those with low HER2 expression levels.[6,7] Additionally, the

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shorter half-life of the T-DXd cytotoxic payload potentially minimizes systemic exposure and limits off-target toxicity to normal cells.[6,8] Clinical trials have demonstrated that T-DXd exhibits significant antitumor effects across various HER2 expression levels or HER2 mutations, including in gastric, colorectal, breast, and lung cancers.[9] As a result, T-DXd was approved by the FDA for the treatment of unresectable or metastatic HER2-positive breast cancer in 2019[10] and HER2-positive locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma in 2021.[11] More and more indications will be approved of T-DXd basing on an increasing number of clinical trials in the future.

While T-DXd has demonstrated efficacy, its safety profile, particularly concerning ILD/pneumonitis, warrants detailed investigation, and it is listed as a boxed warning on approved labels for T-DXd.[12] ILD can be life-threatening in some instances, posing a challenge in daily clinical treatment.[13] The incidence rate of ILD is higher for T-DXd than for other ADCs.[14]

This review paper focuses on T-DXd-induced ILD in solid tumors. We discuss the etiology, pathophysiology, and mechanism of T-DXd-induced ILD. Recommendations for the diagnosis, monitoring, and management of T-DXd-induced ILD will also be reviewed. A comprehensive understanding and multidisciplinary management of ILD is necessary for the safe use of T-DXd.

Methods

We conducted a systematic search of PubMed, Embase, Cochrane Library, and Web of Science for literature published up to 13 September 2024, regarding the use of T-DXd in the treatment of HER2-positive tumors. All databases were searched for English-language articles only. The search included terms such as "T-DXd", "HER2-positive", and "ILD/pneumonitis", combined using Boolean operators (AND, OR). Excluded studies were non-English publications, case reports, and reviews without original data. The main data extracted from the full-text articles included the incidence and severity of T-DXd-induced ILD. Additional data were retrieved through review of citations published in identified articles. The Cochrane Risk of Bias Tool was used to assess the quality of included studies.

T-DXd-Induced ILD/Pneumonitis in Solid Tumors

18 clinical studies involving 3380 patients with various advanced solid malignancies were included in our review. Most of the patients received intravenous T-DXd at either a 5.4-mg/kg or 6.4-mg/kg dose every 3 weeks. The overall incidence of adjudicated drug-related ILD/pneumonitis was 12.40%, and the incidence of ILD/pneumonitis was different among various tumours. Although most ILD/pneumonitis cases were low-grade, the risk of ILD/pneumonitis-related death should not be overlooked.

Breast Cancer

DESTINY-Breast 01

The DESTINY-Breast01 trial is an open-label, international, multicenter, Phase 2 study evaluating T-DXd in patients with HER2-positive, unresectable, or metastatic breast cancer who have been previously treated with T-DM1. In the first part of the study, patients were randomized to receive T-DXd at doses of 5.4 mg/kg (n=50), 6.4 mg/kg (n=48), or 7.4 mg/kg (n=21) every 3 weeks for pharmacokinetics and dose analysis. In the second part, all patients received the optimal dose (5.4 mg/kg) to assess efficacy and safety.[15] Among the 184 patients in the trial, the T-DXd group achieved a confirmed response rate of 60.9%, with a median progression-free survival (PFS) of 16.4 months. The emergence of ILD/pneumonitis was the leading cause of treatment discontinuation of T-DXd. The final data from the DESTINY-Breast01 trial showed a 15.2% (28 of 184) incidence rate of any grade ILD, with fatal events in 2.7% (5 of 184) of patients.[16] ILD/pneumonitis cases progressively increased during the first 12 months of T-DXd treatment, after which the incidence stabilized. The median time to onset was 193 days, and the median time to recovery was 34 days.

DESTINY-Breast 02

DESTINY-Breast02 is a randomized, open-label, international, multicenter, Phase 3 clinical trial conducted at 227 sites. The trial aimed to compare T-DXd with the treatment of physicians' choice (either trastuzumab plus capecitabine or lapatinib plus capecitabine, on a 21-day schedule) for patients with HER2-positive, unresectable/metastatic breast cancer who had previously been treated with T-DM1.[17] A total of 608 patients were enrolled in this study, with 406 in the T-DXd group and

202 in the physician's choice group. The median PFS, as determined by blinded independent central review, was 17.8 months for the T-DXd group, significantly longer than the 6.9 months observed in the physician's choice group.[18]

In the DESTINY-Breast02 trial, the incidence rate of ILD was 10% (42 of 406) in those receiving T-DXd. Most cases of T-DXd-induced ILD were mild (11 with grade 1 events, 26 with grade 2 events, and 3 with grade 3 events), but there were also 2 grade 5 events leading to death. Interestingly, the incidence of T-DXd-induced ILD was lower in the DESTINY-Breast02 trial compared to the DESTINY-Breast01 trial, and no grade 4 T-DXd-induced ILD was reported in either trial. The median time to onset of T-DXd-induced ILD in the DESTINY-Breast02 trial was 29.9 weeks.[17]

DESTINY-Breast 03

The DESTINY-Breast03 trial is a multinational, randomized, open-label, active-controlled phase 3 trial designed to compare the efficacy and safety of T-DXd versus TDM1 in patients with HER2-positive, unresectable or metastatic breast cancer that has progressed during or after treatment with trastuzumab and a taxane.[19] A total of 524 hER2-positive breast cancer patients (T-DXd group: n=261; T-DM1 group: n=263) from 169 study centers were enrolled in this study. The median PFS was 28.8 months for the T-DXd group, compared to 6.8 months for the T-DM1 group. At data cutoff, 20 November 2023, the median OS was 52.6 versus 42.7 months (HR, 0.73; 95% CI, 0.56–0.94) with T-DXd versus T-DM1.[20] The incidence rate of ILD/pneumonitis was 16.7%, significantly higher than the 3.4% observed in the T-DM1 group. In the T-DXd group, ILD/pneumonitis of any grade was reported in 14 patients (5.4%) within 6 months of the first dose, 12 patients (4.6%) between 6 and 12 months, 11 patients (4.2%) between 12 and 24 months, and 6 patients (2.3%) after 24 months. The severity of ILD/pneumonitis caused by T-DXd still ranges from grade 1 to 3, and there are still no reports of grade 4–5 events. The incidence of T-DXd-induced ILD/pneumonitis increased from 11% in the interim analysis of PFS (data cutoff May 21, 2021) to 16.7% in the present OS interim analysis (data cutoff November 20, 2023). Increased treatment exposure might be a potential risk factor for the development of ILD/pneumonitis. Despite a similar overall incidence of ILD/pneumonitis in the DESTINY-Breast series, the incidence of grade 3 or worse events was lower in the DESTINY-Breast03 trial. A better understanding and multidisciplinary management of T-DXd-induced ILD/pneumonitis may explain the absence of grade 4 or 5 events in this trial.[21]

DESTINY-Breast 04

The DESTINY-Breast04 trial is a randomized, two-group, open-label, phase 3 trial investigating the efficacy and safety of T-DXd versus the physician's choice of treatment (capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel) in patients with HER2-low, unresectable or metastatic breast cancer previously treated with chemotherapy.[22] The median PFS was 9.9 months for the T-DXd group, compared to 5.1 months for the physician's choice group. In the hormone receptor-negative cohort, the median PFS was 8.5 months in the T-DXd group versus 2.9 months in the physician's choice group.[12] The total incidence of T-DXd-induced ILD/pneumonitis in the DESTINY-Breast04 trial was 12.1% (45 of 373), including 13 patients (3.5%) with grade 1 events, 24 patients (6.5%) with grade 2 events, 5 patients (1.3%) with grade 3 events, and 3 patients (0.8%) with grade 5 events. The median time to onset of T-DXd-induced ILD/pneumonitis was 129 days (range, 26 to 710 days).[12]

DESTINY-Breast 06

The DESTINY-Breast06 is a phase 3, multicenter, open-label trial involving patients with hormone receptor–positive metastatic breast cancer with low HER2 expression (a score of 1+ or 2+ on immunohistochemical analysis and negative results on in situ hybridization) or ultralow HER2 expression (IHC 0 with membrane staining) who had received one or more lines of endocrine-based therapy and no previous chemotherapy for metastatic breast cancer, who were treated with T-DXd, compared with physician's choice of chemotherapy.[23] T-DXd demonstrated a significant improvement in PFS compared to chemotherapy, with a median PFS of 13.2 months in the T-DXd group versus 8.1 months in the chemotherapy group (hazard ratio for disease progression or death, 0.62; P<0.001). The benefits were consistent across the HER2-low and HER2-ultralow populations. The safety profile of T-DXd was manageable, with adverse events occurring in 98.8% of patients treated with T-DXd and 95.2% of those on chemotherapy. Grade 3 or higher adverse events were reported in 52.8% and 44.4% of patients. The most common adverse events included nausea, fatigue, alopecia, and neutropenia. Interstitial lung disease (ILD) or pneumonitis of any grade occurred in 11.3% (49 of 434) of

patients in the T-DXd group, including 7 patients (1.6%) with grade 1 events, 36 patients (8.3%) with grade 2 events, 3 patients (0.7%) with grade 3 events, and 3 patients (0.7%) with grade 5 events. The median time to onset of adjudicated drug-related ILD in the T-DXd group was 141 days (range, 37 to 835). ILD occurred in 1 patient (0.2%) in the chemotherapy group, which was a grade 2 event that resolved after treatment discontinuation.

DESTINY-Breast 12

DESTINY-Breast12 is a phase 3b/4 study, which investigated the efficacy and safety of T-DXd in patients with HER2-positive advanced or metastatic breast cancer (mBC), both with and without brain metastases (BMs).[24] This is the largest prospective study of T-DXd in patients with BMs in this setting. In the BMs cohort, the 12-month PFS was 61.6%, and the 12-month central nervous system (CNS) PFS was 58.9%. In the non-BMs cohort, the ORR was 62.7%. Grade 3 or higher adverse events occurred in 51% of patients in the BMs cohort and 49% in the non-BMs cohort. In the BMs cohort, ILD/pneumonitis was reported in 42 patients (16.0%), with most events being grade 1 (9.9%) and six (2.3%) grade 5 events. In the non-BMs cohort, ILD/pneumonitis occurred in 31 patients (12.9%), with most events being grade 1 (9.1%) and three (1.2%) grade 5 events. The median time to the first onset of ILD/pneumonitis was 168.0 days in the BMs cohort and 169.0 days in the non-BMs cohort. Five cases of opportunistic infection were reported as co-occurring with ILD/pneumonitis (one grade 4 event and four grade 5 events) in the BMs cohort.

Other Clinical Trials

Beyond the DESTINY-Breast series, several clinical trials have investigated the pharmacokinetics, safety, and efficacy of T-DXd in advanced HER2-positive breast cancer, including four Phase I trials and one Phase II trial).[25] In this review, a total of 242 patients from these five clinical trials were analyzed. The incidence rate of adjudicated T-DXd-induced ILD/pneumonitis was 9.1% (22 of 242). Most cases of T-DXd-induced ILD/pneumonitis were grade 1 or 2, with no grade 3 or 4 events reported in these trials. However, three patients did experience grade 5 ILD/pneumonitis in one trial.[22] Unfortunately, data on the median time to onset of lung disease and median time from onset to recovery were not available for these five trials.

Gastric Cancer

DESTINY-Gastric 01

The DESTINY-Gastric01 trial is an open-label, randomized, phase II trial designed to compare the efficacy and safety of T-DXd (6.4 mg/kg, every 3 weeks) compared with physician's choice of chemotherapy (fluoropyrimidine, platinum agent, and trastuzumab or biosimilar) in patients with HER2-positive gastric or gastroesophageal junction cancer who had progressed after two or more prior therapies, including trastuzumab.[26,27] A total of 187 patients were enrolled in this study, with 125 patients T-DXd and 62 patients receiving the physician's choice of therapy. The trial reported a significantly higher objective response rate in the T-DXd group compared to the physician's choice group (51% vs 14%, $p<0.001$). The median OS in the T-DXd group was 12.5 months, significantly better than the 8.4 months observed in the physician's choice group. The median PFS in the T-DXd group was 5.6 months, compared to 3.5 months in the physician's choice group. The incidence rate of T-DXd-induced ILD/pneumonitis in the DESTINY-Gastric01 trial was 10% (12 of 125), with a median time to first onset of 84.5 days (range, 36–638 days).[27,28] As in previous studies, most cases of T-DXd-induced ILD/pneumonitis were mild, including three grade 1 events, six grade 2 events, two grade 3 events, one grade 4 event, and no grade 5 events.[27]

DESTINY-Gastric 02

The DESTINY-Gastric02 trial is an open-label, multicenter, single-arm, phase 2 study aimed at evaluating the efficacy and safety of T-DXd (6.4 mg/kg every 3 weeks) in non-Asian patients with advanced HER2-positive gastric cancer who progressed on trastuzumab. The results are pending.[29] Seventy-nine HER2-positive gastric cancer patients from 24 study sites in the USA and Europe (Belgium, Spain, Italy, and the UK) were enrolled and subsequently treated with T-DXd. As of November 8, 2021, 42% (33 of 79) had a confirmed objective response, including 5% (4 of 79) with a complete response and 37% (29 of 79) with a partial response. The median PFS and median OS by independent central review were 5.6 months and 12.1 months, respectively, as of the November 8, 2021 data cutoff.[30] The incidence of T-DXd-induced ILD/pneumonitis was 10% (8 of 79), with most ILD/pneumonitis events being grade 1 (3%, 2 out of 79 patients)

or grade 2 (5%, 4 out of 79 patients). One patient (1%) died due to ILD, and another (1%) died due to pneumonitis. The median time to first onset of T-DXd-induced ILD/pneumonitis was 80.5 days (range, 56.5–148.0 days), with a median duration of 36.0 days (range, 20.0–56.0 days).[30]

Phase I Trial (NCT02564900)

The NCT02564900 trial was an open-label, dose-escalation (Part 1) and dose-expansion (Part 2) Phase 1 trial conducted at eight hospitals and clinics in the USA and six in Japan.[31] The primary endpoints of the study were safety and preliminary activity. The trial enrolled 44 patients with HER2-positive gastric or gastroesophageal junction cancer, including 3 from Part 1 (dose escalation; 5.4 mg/kg and 6.4 mg/kg cohorts only) and 41 from Part 2b (dose expansion). After a median follow-up of 5.5 months, 43.2% (19 of 44) achieved an objective response, and 79.5% (35 of 44) achieved disease control.[32] The median time to respond was 1.4 months (1.3–1.6), and the median duration of response was 7.0 months (4.4–16.6). The median PFS and OS were 5.6 months and 12.8 months, respectively, at the data cutoff.[32] T-DXd-related ILD, pneumonitis, or organizing pneumonia remains a significant safety concern with this treatment. The incidence of T-DXd-induced ILD/pneumonitis was 9%, with all cases reported as pneumonitis: 7% (3 of 44) experienced grade 1–2 pneumonitis and 2% (1 of 44) had grade 3 pneumonitis.[32]

NSCLC

DESTINY-Lung 01

The DESTINY-Lung01 trial is a multicenter, open-label, two-cohort, phase 2 study designed to evaluate the efficacy and safety of T-DXd (6.4 mg/kg every 3 weeks) in HER2-overexpressing or HER2-mutated advanced, unresectable or metastatic NSCLC.[31] The study enrolled 91 patients with HER2-mutant NSCLC. At the data cutoff (May 3, 2021), 55% of patients (50/91) had a confirmed objective response as assessed by an independent central review, including 1 CR and 49 PR. The median duration of response was 9.3 months, median PFS was 8.2 months and the median OS was 17.8 months.[33]

However, T-DXd-induced ILD/pneumonitis is a significant concern, especially in NSCLC patients. In the DESTINY-Lung01 trial, the incidence of ILD/pneumonitis was 26% (24 of 91), with 3.3% (3 of 91) experiencing grade 1, 16.5% (15 of 91) grade 2, 4.4% (4 of 91) grade 3 and 2.2% (2 of 91) grade 5 ILD/pneumonitis.[33] Of the twenty patients who had previously undergone lung resection in the DESTINY-Lung01 trial, 8 patients developed ILD/pneumonitis. Additionally, most of the patients with ILD/pneumonitis (21 of 24) received at least one dose of glucocorticoids in this trial. Previous studies have reported that the incidence of T-DXd-induced ILD/pneumonitis across different solid tumors is approximately 10%.[34] However, the occurrence of ILD was significantly higher, at 24%. The exact mechanism for this increased occurrence remains unclear, though it is widely accepted that baseline tissue damage caused by the primary lung tumor may be a pivotal factor.[33]

DESTINY-Lung 02

The DESTINY-Lung02 trial is a blinded, randomized, noncomparative, phase 2 trial that aims to evaluate the efficacy and safety of T-DXd (5.4 mg/kg vs 6.4 mg/kg every 3 weeks) in patients with previously treated HER2-mutated metastatic NSCLC.[35,36] As of the December 23, 2022, 101 patients received the 5.4 mg/kg dose, and 50 patients received the 6.4 mg/kg dose. The primary endpoint, the confirmed objective response rate (ORR) by blinded independent central review, was 49.0% in the 5.4 mg/kg group and 56.0% in the 6.4 mg/kg group. T-DXd-induced ILD/pneumonitis was observed in 5.9% of patients in the 5.4 mg/kg group and 14% in the 6.4 mg/kg group.

Phase I Trial (NCT02564900)

The NCT02564900 trial is a dose-expansion, phase I study that evaluates the safety, tolerability, and activity of T-DXd in patients with pretreated, HER2-expressing (IHC ≥1+), non-breast/non-gastric or HER2-mutant solid tumors.[37] Sixty patients were enrolled in this trial, including 20 with colorectal cancer, 18 with NSCLC, and 22 with other tumors. All 18 hER2-mutant NSCLC patients received at least one dose of 6.4 mg/kg T-DXd. In the NSCLC subgroup, the confirmed ORR was 55.6%, the disease control rate (DCR) was 77.8%, the median duration of response was 9.9 months, and the median PFS was 11.3 months.[37] Seven patients across the entire study (4 with NSCLC, 2 with colorectal cancer, and 1

with another type of cancer) experienced ILD or pneumonitis. Among the NSCLC patients who experienced ILD, 3 of the 4 cases were adjudicated as related to T-DXd, and 1 case was adjudicated as unrelated to ILD. One patient experienced respiratory failure associated with a fatal outcome.[37]

Colorectal Carcinoma

Destiny-Crc01

The DESTINY-CRC01 trial is a single-arm, multicenter, open-label, 3-cohort study to evaluate the efficacy and safety of T-DXd (6.4 mg/kg every 3 weeks) in HER2-expressing metastatic colorectal cancer that had progressed on two or more previous regimens.[38] Patients were divided into three cohorts based on HER2 expression: cohort A (HER2-positive, immunohistochemistry IHC 3+ or IHC2+ and in situ hybridization ISH-positive), cohort B (IHC2+ and ISH-negative), and cohort C (IHC1+).

At the data cutoff (December 28, 2020), a total of 86 patients were enrolled (53 in Cohort A, 15 in Cohort B, and 18 in Cohort C), all of whom received at least one dose of T-DXd. In cohort A, a confirmed objective response was observed in 24 patients (45.3%) after a median follow-up of 27.1 weeks.[38] The median PFS, median OS, and duration of response were 6.9, 15.5, and 7.0 months, respectively.

T-DXd-induced ILD/pneumonitis was reported in 8 patients (9.3%), with 4 cases of grade 2, 1 case of grade 3, and 3 cases of grade 5 events.[38] The median time to the adjudicated onset date of ILD/pneumonitis was 66.5 days (range, 7–165 days).[38] A previous study also reported that the time to the onset of ILD was different among different tumors, and ILD occurred relatively early in colorectal cancer.[39] Corticosteroids were administered to these patients, with 4 recovering and 3 succumbing to the disease (1 from disease progression, 1 from pneumonitis, and 1 from interstitial lung disease). The median duration of ILD/pneumonitis events was 23.0 days (range, 7–172 days). Among the three fatal cases, the median time to onset was 22 days, and the median time to death following ILD/pneumonitis diagnosis was 8 days.[38]

Phase I Trial (NCT02564900)

The NCT02564900 trial is a dose-expansion, phase I study evaluating the efficacy and safety of T-DXd (6.4 mg/kg every 3 weeks) in 60 patients with HER2-mutant advanced solid tumors, including 20 patients with colorectal carcinoma.[37] In the colorectal carcinoma subgroup, the confirmed objective response rate (ORR) was 15.0%, the disease control rate (DCR) was 80%, the median duration of response was 7.4 months, and the median PFS was 4.1 months.[37]

Two patients (10%) in this colorectal carcinoma cohort experienced ILD/pneumonitis, contributing to a total of 7 cases of ILD/pneumonitis across the study. The exact number of adjudicated ILD/pneumonitis cases specifically within the colorectal carcinoma group remains unclear.[37,40]

Other Tumors

Biliary Tract Cancer

The HERB trial is an open-label, single-group, multicenter, phase II trial evaluating the efficacy and safety of T-DXd (5.4 mg/kg every 3 weeks) in patients with HER2-expressing unresectable or recurrent biliary tract cancer.[41] A total of 32 patients were enrolled, including 24 with HER2-positive and 8 with HER2-low biliary tract cancer. In the HER2-positive group (22 patients), the confirmed ORR was 36.4%, and the DCR, median PFS, and median OS were 81.8%, 4.4 months, and 7.1 months, respectively. Among the HER2-low patients, the ORR was 12.5%, and the DCR, median PFS, and median OS were 75.0%, 4.2 months, and 8.9 months, respectively. T-DXd-induced ILD/pneumonitis was reported in 25% of patients (8 of 32), including 3 patients with grade 1 events, 1 patient with grade 2, 2 patients with grade 3, and 2 patients with grade 5 events. These AEs were not adjudicated by an independent committee.

Urothelial Carcinoma

NCT03523572 is a phase 1b, 2-part, open-label, multicenter study of T-DXd (5.4 mg/kg every 3 weeks) in combination with nivolumab (360 mg every 3 weeks) in patients with HER2-expressing advanced/metastatic urothelial carcinoma after previous platinum-based chemotherapy.[42] At the primary analysis data cutoff (July 22, 2021), 34 patients (cohort 3, IHC 2+/3+, high expression, 30 patients; cohort 4, IHC 1+, low expression, 4 patients) who received T-DXd and nivolumab were enrolled in this trial. The ORR in cohort 3 was 36.7% (13.3% CR, 23.3% PR), and the median DOR was

13.1 months. The median PFS and median OS were 6.9 months and 11.0 months, respectively.[43] Adjudicated drug-related ILD/pneumonitis occurred in 23.5% of all patients (2 for grade 1; 4 for grade 2; 1 for grade 3; 1 for grade 5).[43]

Uterine Carcinosarcoma

NCCH1615 is a Phase II, multicenter, single-arm, investigator-initiated trial that aims to evaluate the efficacy and safety of T-DXd in patients with advanced or recurrent HER2-expressing uterine carcinosarcoma who had already received standard chemotherapy.[44] A total of 33 patients were enrolled, with 14 receiving 6.4 mg/kg T-DXd and 19 receiving 5.4 mg/kg T-DXd. Due to a lack of measurable disease at baseline by central review, one patient was excluded from the efficacy analysis. Based on HER2 expression, 22 patients were classified as HER2-high, and 10 as HER2-low. In the HER2-high group, the ORR was 68.2% by investigator assessment. In the HER2-low group, the ORR was 70.0% by central review and 60.0% by investigator assessment. The median PFS in the entire efficacy cohort (n =32), the HER2-high group (n=22), and the HER2-low group (n=10) were 6.7 months, 6.2 months, and 6.7 months, respectively. The median OS in the entire efficacy cohort (n=32) and the HER2-high group (n=22) were 15.8 months and 13.3 months, respectively, while the median OS in the HER2-low group (n=10) was not reached at the time of data cutoff.[45] ILD/pneumonitis was also the most common AE leading to drug withdrawal, with an incidence rate of ILD/pneumonitis was 27% (9 of 33), 5 of these patients received an initial dose of 6.4 mg/kg T-DXd, and 4 received an initial dose of 5.4 mg/kg. Most ILD/pneumonitis were grade 1 or 2, with four instances observed in the 6.4 mg/kg group and another four in the 5.4 mg/kg group. It is worth noting that one patient from the 6.4 mg/kg group experienced grade 3 ILD/pneumonitis. No ILD/pneumonitis events were adjudicated by an independent committee.

DESTINY-PanTumor 02

DESTINY-PanTumor02 is an open-label, phase 2 study evaluating the efficacy and safety of T-DXd (5.4 mg/kg every 3 weeks) in patients with HER2-expressing (IHC 3+ or IHC 2+) locally advanced or metastatic tumors that had progressed after at least one prior systemic treatment or had no other treatment options.[46]

A total of 267 patients were enrolled in the trial, which included those with biliary tract, bladder, cervical, endometrial, ovarian, pancreatic, and other tumors (excluding breast cancer, gastric cancer, colorectal cancer, and NSCLC). At the data cutoff (June 8, 2023), all 267 patients had received at least one dose of T-DXd, with a median of two prior lines of treatment. Among these patients, 111 were IHC 3+ expression, 151 were IHC 2+ expression and five with IHC 1+ expression, including cervical tumor (n=40), endometrial cancer (n=40), ovarian cancer (n=40), biliary tract cancer (n=41), pancreatic cancer (n=25), bladder cancer (n=41) and other tumors (n=40). The overall ORR was 37.1%, with a median DOR of 11.3 months. In the endometrial cohort, the ORR was 57.5%, and in its IHC 3+ expression population, the ORR was 84.6%.[46] The incidence rate of adjudicated drug-related ILD/pneumonitis was 10.5% (28 of 267), with 7 cases classified as grade 1, 17 cases as grade 2, 1 case as grade 3, and 3 case as grade 5.[47]

The related information of different clinical trials is summarized in Table 1.

Radiologic Features

Radiological diagnosis is critical in managing T-DXd-induced ILD/pneumonitis, especially when ILD is suspected. High-resolution computed tomography (HRCT) of the chest is commonly used due to its high sensitivity and specificity in detecting drug-induced ILD.[48] Based on previous experience, ILD/pneumonitis can be classified into 5 different patterns: (1)Acute Interstitial Pneumonia (AIP): CT features include areas of ground-glass opacity (GGO), consolidation, and reduced lung volume.[49] (2)Organizing Pneumonia (OP): Characterized by multifocal areas of GGOs and consolidation, typically with a predominantly peripheral distribution.[50] (3)Nonspecific Interstitial Pneumonia (NSIP): Identified by GGOs and predominantly basal and peripheral reticular opacities on CT.[51] (4)Hypersensitivity Pneumonia (HP): CT features include diffuse GGO, centrilobular nodules, and air trapping.[52] (5)Acute Respiratory Distress Syndrome (ARDS): The CT features for ARDS were not detailed in this section but are generally known for severe and diffuse alveolar damage.

Table 1 T-DXd Induced ILD/Pneumonitis in Different Types of Malignancy

Tumor type	Tumor Type	Phase	Sample Size (T-DXd Group), n	Any Grade ILD/ pneumonitis, n (%)	G1 or 2, n (%)	G3, n (%)	G4, n (%)	G5, n (%)	Median Time in Days Until Onset of Lung Disease (Range)
Breast cancer	DESTINY-Breast01	II	184	28(15.2%)	27 (14.7%)	1(0.5%)	0	0	193 days (42–535)
	DESTINY-Breast02	III	406	42(10.3%)	37 (9.1%)	3(0.7%)	0	2(0.5%)	29.9 weeks
	DESTINY-Breast03	III	257	43(16.7%)	41 (16.0%)	2(0.8%)	0	0	14 patients(≤6 months); 12 patients (>6 to ≤12months); 11 patients(>12 to ≤24months); 6 patients(>24 months);
	DESTINY-Breast04	III	373	45(12.1%)	37 (10.0%)	5(1.3%)	0	3(0.8%)	129 days (26–710)
	DESTINY-Breast06	III	434	49(11.3%)	43 (9.9%)	3(0.7%)	0	3(0.7%)	141 days (37–835)
	DESTINY-Breast12	IIIb/IV	263(BMs)	42(16.0%)	34 (12.9%)	1(0.4%)	1 (0.4%)	6(2.3%)	—
			241(non-BMs)	31(12.9%)	28 (11.6%)	0	0	3(1.2%)	—
	Other trails	4 phaseltrails and 1 phaselltrail	242	22(9.1%)	19 (7.9%)	0	0	3(1.2%)	—
Gastric Cancer	DESTINY-Gastric01	II	125	12(10.0%)	9(7.2%)	2(1.6%)	1 (0.8%)	0	84.5days (36–638)
	DESTINY-Gastric02		79	8(10.0%)	6(8.0%)	0	0	2(2%)	80.5 days (56.5–148.0)
	Phaseltrail (NCT02564900)	I	44	4(9.0%)	3(7.0%)	1(2.0%)	0	0	—
Non-small cell lung cancer	DESTINY-Lung01	II	91	24(26.0%)	18 (19.8%)	4(4.4%)	0	2(2.2%)	141 days(14–462)
	DESTINY-Lung02	II	101 (5.4 mg/kg)	6(5.9%)	—	—	—	—	—
			50 (6.4 mg/kg)	7(14.0%)	—	—	—	—	—
	NCT02564900	I	18	3(16.7%)	—	—	—	1(5.6%)	—

(*Continued*)

Table 1 (Continued).

Tumor type	Tumor Type	Phase	Sample Size (T-DXd Group), n	Any Grade ILD/ pneumonitis, n (%)	G1 or 2, n (%)	G3, n (%)	G4, n (%)	G5, n (%)	Median Time in Days Until Onset of Lung Disease (Range)
Colorectal Carcinoma	DESTINY-CRC01	II	86	8(9.3%)	4(4.7%)	1(1.2%)	0	3(3.5%)	66.5 days (7–165)
	NCT02564900	I	20	2(10%)	—	—	—-	—	—
Other tumors	HERB (Biliary Tract Cancer)	II	32	8(25%)	4 (12.5%)	2 (6.25%)	0	2 (6.25%)	—
	NCT03523572 (Urothelial Carcinoma)	Ib	34	8(23.5%)	6 (17.6%)	1(2.8%)	0	1(2.8%)	—
	NCCH1615 (Uterine Carcinosarcoma)	II	33	9(27.3%)	8 (24.2%)	1(3.0%)	0	0	—
PanTumor	DESTINY-PanTumor02	II	267	18(6.7%)	17 (6.4%)	0	0	1(0.3%)	—

ILD/Pneumonitis Mechanism

Although T-DXd-induced ILD/pneumonitis has been widely reported in both clinical studies and real-world practice, the detailed mechanism behind T-DXd-related ILD/pneumonitis remains unclear. Direct cytotoxic lung injury and immune-mediated lung injury are believed to be involved in ADC-induced ILD/pneumonitis. Four possible mechanisms have been proposed: (1) Target-dependent uptake of T-DXd. (2) Target-independent uptake of T-DXd in normal cells. (3) The "bystander effect" is caused by the release of the free cytotoxic payload (DXd) from cancer cells. (4) Circulating free payload resulting from the deconjugation of T-DXd (Figure 1).

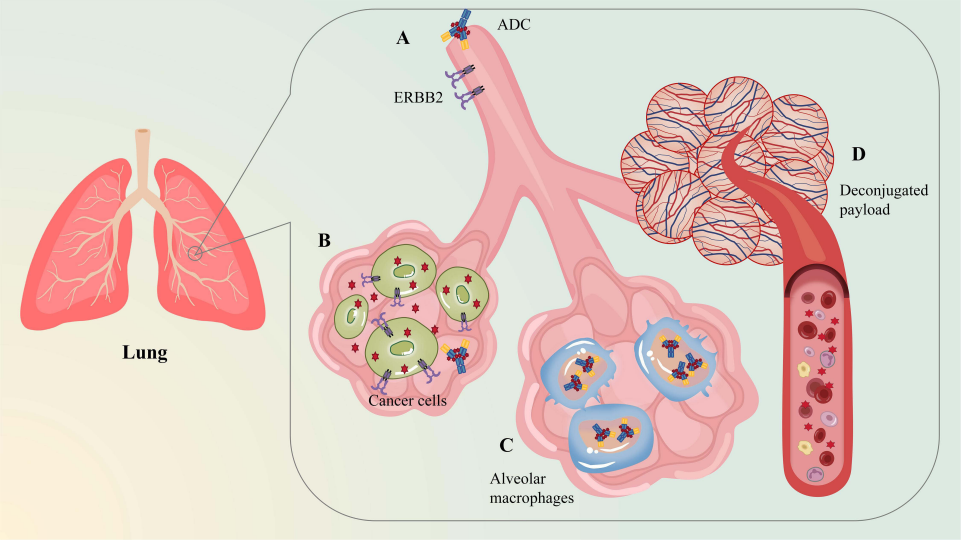

Figure 1 Possible mechanism of T-DXd-induced ILD/pneumonitis. (**A**) ERBB2 target-dependent uptake of T-DXd, (**B**) target-independent uptake of T-DXd in normal cells, (**C**) a "bystander effect" caused by the free cytotoxic payload (DXd) released from cancer cells, (**D**) circulating free payload resulting from deconjugation of T-DX.

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Because of the most abundant blood flow and the longest retention time in lung, the undesirable uptake of the ADC and the free payloads in blood most occurred is in lung to induce ILD. HER2 protein expression in human lungs is primarily limited to the bronchial and bronchiolar epithelium, not the alveolar epithelium.[53] Recent studies increasingly suggest that the target-independent uptake of T-DXd by immune cells is a key contributor to the development of ILD/pneumonitis. In animal studies, T-DXd or DXd was administered at increasing doses in monkeys over up to 3 months, and the results showed that lung damage occurred at the HER2-negative alveolar level but not in the HER2-positive bronchial epithelium.[54,55] These findings highlight that T-DXd-induced lung toxicity in monkeys is dose-dependent and dose-frequency-dependent, and is unrelated to HER2 uptake in pulmonary epithelial cells. Additionally, circulating unconjugated DXd does not appear to explain the observed lung toxicity associated with T-DXd.

Although the target organs of toxicity by ADC depend on the payload and linker technology, it is believed that most adverse events would be caused by off-target effects originating from target-independent uptake. The primary target-independent mechanism for T-DXd-induced lung toxicity involves macrophage uptake in the lungs. Cathepsin B, constitutively expressed in human alveolar macrophages, catalyzes the cleavage of the linker in T-DXd.[56,57] This process has been implicated in T-DXd-induced lung toxicity in animal models.[55] Previous animal study has showed that T-DXd induces lung injury through direct cytotoxicity rather than an immune-mediated action. Moreover, a high incidence of ILD/pneumonitis has been observed with another deruxtecan-based ADC, datopotamab deruxtecan, which targets TROP2 and has shown relatively high rates of ILD (8%, including 3 fatal cases) in NSCLC patients.[58] Due to the high drug-to-antibody ratio (DAR) of T-DXd and the permeability of DXd, even a small amount of trastuzumab deruxtecan attached to cells with low HER2 expression can release enough cytotoxic payload to induce lung injury. Comparative studies with other ADCs are needed to contextualize the safety profile of T-DXd.

Risk Factors

Given the serious nature of ILD/pneumonitis, it is crucial to evaluate potential risk factors before initiating T-DXd therapy. A previous study was analyzed from the DS8201-A-J101 study and the DESTINY-Breast01 trial to identify possible risk factors for T-DXd-induced ILD. A total of 542 patients participated in these two trials, with the majority being breast cancer patients (80.6%) and 234 patients from Japan.[34] The analysis revealed that the incidence rate of ILD/pneumonitis was significantly lower in patients with non-breast cancer compared to those with breast cancer (11.4% vs 18.1%). Additionally, Japanese individuals were found to be at a higher risk of ILD compared to non-Japanese individuals (24.4% vs 11%), although race and country did not appear to be risk factors for the incidence of high-grade ILD.[34] Other factors that may increase the risk of ILD with T-DXd include dosage, age, kidney dysfunction, smoking history, lung comorbidities, oxygen saturation, concomitant radiotherapy, and the time since the initial diagnosis. These factors may contribute to the development of T-DXd-related ILD. Further studies should explore genetic predispositions and biomarkers predictive of ILD risk. In addition, it is also necessary to design prospective studies to identify high-risk patients or testing dose optimization strategies.

Exposure and ILD/Pneumonitis

Exploring the relationship between T-DXd exposure and the emergence of ILD/pneumonitis is crucial for supporting its clinical use. A population pharmacokinetic model was developed using data from patients with gastric cancer, breast cancer, or other tumors enrolled in T-DXd clinical trials, primarily conducted in Asia. Univariate Cox regression analysis revealed that the steady-state area under the concentration-time curve of T-DXd was significantly associated with the incidence of any grade ILD. Additionally, a statistically significant relationship was observed between the steady-state Cmax of T-DXd and the grade ≥3 ILD.[59] Ma et al[60] reported a higher proportion of ILD events in patients receiving 6.4 mg/kg of T-DXd compared to the 5.4 mg/kg dose group. Similarly, Powell et al[34] found that the incidence of ILD/pneumonitis was significantly lower in patients treated with a lower dose of T-DXd, consistent with previous studies. In a study involving 1,193 patients with various advanced solid malignancies, the incidence rate of ILD/pneumonitis was 12.6% (70 of 562 patients) among those who received T-DXd at 6.4 mg/kg every three weeks. However, for those who received T-DXd at 5.4 mg/kg every three weeks, the incidence rate was 12.2% (25 of 205 patients).[40]

Management and Monitoring of ILD/Pneumonitis

Effective management and monitoring of ILD/pneumonitis are crucial for minimizing the risk of fatal outcomes during T-DXd therapy. Numerous studies have outlined guidelines for managing and monitoring suspected T-DXd-induced ILD/pneumonitis adverse events.

Prevention

Before initiating T-DXd treatment, several preventive measures are recommended: (1) Thorough assessment of individual risk factors. (2) Baseline evaluation of respiratory function, including vital signs, physical examination, and chest imaging. (3) Educating patients about the risks of ILD and its clinical manifestations. Patients should be informed about the signs and symptoms of ILD/pneumonitis to facilitate early identification and treatment. In addition to monitoring for symptoms, CT scans should be performed every 9–12 weeks during treatment.

Management

If ILD/pneumonitis is suspected or confirmed, treatment should be tailored based on the CTCAE grade of the event: (1) Treatment interruption: T-DXd must be interrupted at the onset of ILD/pneumonitis, regardless of grade. (2) Corticosteroids: For grade 2 ILD/pneumonitis, prompt initiation of corticosteroids is recommended. For grade 1 events, corticosteroid treatment should be considered. Corticosteroids can help prevent the progression to higher-grade ILD/pneumonitis.

Monitoring

Clinical symptoms and pulse oximetry should be closely monitored. Systemic corticosteroids (≥0.5 mg/kg/day of prednisone) should be administered until improvement, followed by a gradual taper over at least four weeks.

Discontinuation

For patients who develop grade ≥2 ILD/pneumonitis, permanent discontinuation of T-DXd is recommended.

Severe Cases

For grade 3 ILD/pneumonitis, hospitalization and the prompt administration of high-dose pulse corticosteroids (eg, methylprednisolone 500–1,000 mg/day for three days, followed by ≥1 mg/kg/day of prednisone or equivalent) are recommended.[61]

Frequent Imaging

Patients with ILD/pneumonitis should undergo frequent CT scans (every 1–2 weeks or as clinically indicated).

Rechallenge

In cases where grade 1 ILD/pneumonitis resolves, rechallenging with T-DXd could be considered, particularly for patients who have shown significant benefit from the treatment.[40]

Limitations

This review has several limitations. At first, some trials included in this review were open-label, where participants and investigators were aware of the treatment allocation. This awareness could have introduced bias in the reporting of ILD/pneumonitis. Secondly, in some trials, the investigators reported the emergence of ILD/pneumonitis rather than an independent committee, potentially affecting the objectivity of the findings. The underlying studies have potential limitations, such as regional biases or differences in clinical settings. Thirdly, as clinical trials of T-DXd for certain tumors are ongoing, the reported ILD/pneumonitis cases are interim results. Outcomes should be tracked for a comprehensive understanding. Finally, the lack of available information on prior treatment histories in some cases makes it difficult to assess whether sequential treatments may have increased the patient's risk for ILD/pneumonitis.

Conclusion

T-DXd has shown significant efficacy against various tumors, including breast cancer, gastric cancer, NSCLC, and colorectal carcinoma. However, ILD/pneumonitis remains a serious adverse event (AE) associated with T-DXd, which can be life-threatening and presents challenges in clinical practice. Due to the prolonged drug exposure required, the careful monitoring and management of ILD/pneumonitis are essential. Clinicians should prioritize early detection and management of ILD in patients receiving T-DXd, and researchers should investigate dose optimization strategies. The contributions of our present study is the synthesis of data across tumor types, recommendations for clinical management and prevention of T-DXd induced ILD/pneumonitis, which is meaningful for safety use of T-DXd. Future studies should continue to explore the risk factors, the better biomarkers and underlying mechanisms of T-DXd-induced ILD/pneumonitis, it is also important to investigate tailored therapeutic regimens. These findings are based on a systematic review of limited trials; thus, conclusions should be interpreted cautiously.

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Consent to Participate and Consent for Publication

All authors have contributed to review and enhancement of the quality of this paper and have reviewed and approved the final version of the manuscript.

Disclosure

All authors declare no competing interests.

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