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Safe and Effective Use of Trastuzumab Deruxtecan in a Patient with Advanced HER2-Mutant NSCLC and Prior Immune-Related Pneumonitis: Case Report

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Case Report

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Abstract

Trastuzumab deruxtecan (T-DXd) is the first approved therapy for previously treated HER2-mutant advanced non–small cell lung cancer (NSCLC). Although interstitial lung disease (ILD)/pneumonitis remains a major safety concern, evidence regarding its use in patients with prior immune checkpoint inhibitor–related pneumonitis is limited. We report the case of a 69-year-old woman with HER2-mutant advanced NSCLC who developed grade 3 immune-related pneumonitis during first-line carboplatin, pemetrexed, and pembrolizumab, followed by recurrent inflammatory pulmonary episodes requiring prolonged corticosteroids and mycophenolate mofetil. In this context, and after multidisciplinary discussion and informed consent, T-DXd was initiated at 5.4 mg/kg every 3 weeks. The patient achieved a partial radiologic response without recurrence of ILD/pneumonitis. This case suggests that T-DXd may be feasible in highly selected patients with a prior history of immune-related pneumonitis with careful monitoring.

Introduction

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related mortality worldwide, accounting for approximately 18% of all cancer deaths. Within this heterogeneous disease, activating mutations in the human epidermal growth factor receptor 2 (HER2/ERBB2) gene occur in about 2–3% of lung adenocarcinomas, defining a distinct molecular subset of growing therapeutic relevance.[1]

Based on the results of the DESTINY-Lung02 trial, the FDA granted accelerated approval of fam-trastuzumab deruxtecan-nxki (T-DXd) at 5.4 mg/kg for adult patients with previously treated unresectable or metastatic HER2-mutant NSCLC, marking the first approved therapy for this patient subset.[2]

Although the most common adverse events associated with T-DXd are mild and manageable—such as nausea, gastrointestinal disturbances, and bone marrow suppression—interstitial lung disease (ILD)/pneumonitis is a major safety concern and can be life-threatening if not promptly managed. This condition is characterized by inflammation and fibrosis of the pulmonary interstitium and requires immediate discontinuation of therapy and initiation of corticosteroids. In the DESTINY-Lung02 trial, the incidence of drug-related ILD/pneumonitis was 14.9% (2.0% grade ≥ 3). Notably, adjudicated drug-related ILD among patients with prior anti–PD-(L)1 therapy reached 66.7%. Of note, clinical trial protocols allowed reintroduction of treatment only after complete resolution of grade 1 ILD, with or without dose modification based on recovery time, whereas grade ≥ 2 events mandated permanent discontinuation.[2]

Here, we report the case of a patient with HER2-mutant advanced NSCLC and a history of immune-related pneumonitis during first-line treatment, who subsequently received T-DXd and achieved a favorable radiologic and clinical response.

Case Presentation

A 69-year-old patient with a history of light smoking (estimated 4 pack-years) was referred for evaluation of a 2.5-cm right middle-lobe pulmonary nodule detected incidentally on follow-up chest computed tomography (CT). Past medical history included a prior dengue infection and an asymptomatic SARS-CoV-2 infection one year before presentation. Baseline pulmonary function tests showed normal spirometry (forced vital capacity [FVC] 90% predicted; forced expiratory volume in 1 second [FEV_1] 91% predicted).

After PET-CT exclusion of distant metastases, the patient underwent a right middle lobectomy. Histopathological examination revealed a poorly differentiated invasive lung adenocarcinoma positive for CK7, TTF-1, and Napsin A, with a predominant solid pattern (2.0 cm), lymphovascular invasion, and incidental metastases in multiple peribronchial and mediastinal lymph nodes. The final pathological stage was IIIA according to the 9th edition of the TNM classification (pT1bN2bM0). Molecular testing was negative for EGFR mutations and ALK rearrangements, and PD-L1 expression was 15%.

The patient completed four cycles of adjuvant cisplatin plus pemetrexed. Adjuvant immunotherapy was not administered because it was not approved in our country at the time. One year later, she developed systemic relapse, with multiple bilateral pulmonary nodules and an osteolytic lesion of the right sixth rib, which was treated with palliative radiotherapy (30 Gy in 10 fractions).

Comprehensive genomic profiling with the Oncomine Focus Assay, a targeted Next-Generation Sequencing (NGS) panel, identified an oncogenic ERBB2 exon 20 insertion (Y772_A775dup) with a variant allele frequency of 31.9%. First-line systemic treatment for metastatic disease consisted of carboplatin, pemetrexed, and pembrolizumab, was administered every 3 weeks.

After four treatment cycles, the patient developed a subacute dry cough and dyspnea. Chest CT showed bilateral patchy consolidations with a bronchiolocentric distribution and associated ground-glass opacities, consistent with immune checkpoint inhibitor–related grade 3 pneumonitis, resembling organizing pneumonia (Fig. 1). Pembrolizumab and chemotherapy were discontinued, and she was treated with prednisone at 1 mg/kg/day, followed by a gradual six-week taper, with complete clinical and radiological improvement.

Subsequent imaging showed partial resolution of the inflammatory infiltrates; however, new ILD and nodular changes in the right lower lobe were observed, consistent with lymphangitic carcinomatosis (progression-free survival of first line was 6 months) (Fig. 1). Second-line treatment with docetaxel was initiated. No objective response was achieved, and disease progression characterized by enlargement of pulmonary nodules, worsening lymphangitic spread, and progression of bone metastases was observed at 5 months. In parallel, recurrent pulmonary infiltrates with clinical suspicion of grade 2 pneumonitis recurrence were noted, requiring reinitiation of corticosteroids and the addition of mycophenolate mofetil for steroid-refractory pneumonitis, with a total combined treatment duration of 33 weeks.

After clinical and radiological recovery and a multidisciplinary discussion at the institutional tumor board, with active patient participation and informed consent, third-line treatment with T-DXd at 5.4

mg/kg every 3 weeks was initiated.

Remarkably, despite her prior history of immune-related pneumonitis, the patient experienced only grade 1 nausea, with no clinical or radiologic evidence of drug-induced interstitial lung disease while receiving tapering low-dose systemic corticosteroids and mycophenolate mofetil. Follow-up CT imaging after four cycles of T-DXd demonstrated a partial response (Fig. 1), with marked reduction in bilateral pulmonary nodules, improvement in parenchymal consolidations previously attributed to lymphangitic spread, and resolution of the pleural effusion. At the most recent evaluation, after 7 months of T-DXd treatment, the patient had bone progression and started a fourth-line regimen with gemcitabine, with no recurrence of pulmonary toxicity.

Discussion

To the best of our knowledge, this is the first report describing the use of T-DXd in a patient with HER2-mutant advanced NSCLC and a history of immune checkpoint inhibitor–related pneumonitis. Despite the well-recognized risk of T-DXd–associated ILD/pneumonitis, treatment was feasible in this carefully selected patient and led to a clinically meaningful antitumor response without recurrence of pulmonary toxicity.

Although prior reports have described successful rechallenge with T-DXd after T-DXd–related ILD in both NSCLC and breast cancer,[3] to our knowledge, no published data specifically address the clinical scenario presented here. This knowledge gap is clinically relevant, as patients with a history of clinically significant pneumonitis or pre-existing ILD are routinely excluded from pivotal T-DXd clinical trials because of concerns about exacerbating pulmonary injury.

Importantly, in the DESTINY-Lung02 trial—which supported the accelerated FDA approval of T-DXd for previously treated HER2-mutant advanced NSCLC—adjudicated drug-related ILD/pneumonitis occurred in approximately 14.9% of patients. Most ILD events occurred within the first three months of treatment initiation. Notably, ILD rates were higher among patients with prior exposure to immune checkpoint inhibitors (66.7%), underscoring the need for careful risk stratification, close monitoring, and prompt management in this subgroup.[2] This observation is particularly clinically relevant because current therapeutic algorithms often place T-DXd after progression on platinum-based chemotherapy, with or without prior immunotherapy.[4]

Mechanistically, T-DXd–associated ILD/pneumonitis appears to differ from immune checkpoint inhibitor–related pneumonitis. Emerging preclinical and translational data suggest that T-DXd lung toxicity is not primarily driven by HER2 expression in pulmonary epithelial cells, but rather by off-target uptake of the antibody–drug conjugate by alveolar macrophages, particularly perivascular niche-resident subsets. After Fc–Fcγ receptor–mediated internalization, cathepsin B–mediated linker cleavage may release the cytotoxic DXd payload locally, promoting direct lung injury and macrophage-driven inflammatory signaling.[5] In contrast, immune checkpoint inhibitor–related pneumonitis is generally considered an immune-mediated toxicity related to disruption of peripheral immune tolerance, T-cell

activation, and inflammatory injury to normal lung tissue. This mechanistic distinction provides a biologic rationale for why prior ICI-related pneumonitis, once clinically and radiographically resolved, may not inevitably predict T-DXd–associated ILD.[5] However, this should not be interpreted as evidence of clinical independence, as prior ICI exposure and preexisting lung injury may still identify patients with increased pulmonary vulnerability.

Beyond treatment sequencing, this case underscores the diagnostic complexity of pneumonitis in patients with lung cancer, in whom respiratory symptoms and imaging abnormalities often have multifactorial etiologies. The differential diagnosis commonly includes immune-related pneumonitis, chemotherapy-related pulmonary toxicity, respiratory infection, exacerbation of underlying ILD, pulmonary embolism, organizing pneumonia (cryptogenic or secondary), and lymphangitic carcinomatosis.[6] Discriminating among these entities requires a systematic evaluation integrating (i) treatment chronology and prior toxicities, (ii) radiologic patterns and their evolution over time, (iii) exclusion of infectious causes, and (iv) clinical course during appropriate interventions—ideally within a multidisciplinary framework involving oncology, pulmonology, and radiology.

Organizing pneumonia is particularly relevant in this context. It may be triggered by anticancer therapies, including immune-checkpoint inhibitors and cytotoxic agents, and can present with imaging patterns that overlap with drug-related ILD, such as peripheral or peribronchovascular consolidations and ground-glass opacities. Importantly, organizing pneumonia is often highly responsive to corticosteroids, making timely recognition clinically consequential for guiding management and informing subsequent treatment decisions.[6] In our patient, a history of grade 3 immune-related pneumonitis, subsequent recurrent inflammatory episodes requiring prolonged immunosuppression, and later initiation of T-DXd mandated heightened vigilance. The absence of recurrent pneumonitis/ILD during T-DXd therapy in this case suggests that, after clinical and radiographic recovery and with careful patient selection, T-DXd may be administered safely in exceptional circumstances; however, this single experience should not be interpreted as generalizable evidence of safety.

Conclusions

This case suggests that, with strict monitoring and multidisciplinary decision-making, T-DXd may be a feasible therapeutic option for highly selected patients with HER2-mutant advanced NSCLC who have a history of immune-mediated pneumonitis. It provides clinically relevant evidence for a population typically excluded from pivotal clinical trials. Further real-world data are needed to better characterize the safety of T-DXd in patients with prior immune-related pneumonitis/ILD and to refine patient selection and monitoring strategies.

Declarations

Disclosure

The authors declare no conflicts of interest related to this work and no funding.

Author Contribution

Investigation; Methodology: Fiorella Ferremi, Carlos Palmes, Diego EnricoProject administration: Fiorella Ferremi, Carlos Palmes, Diego Enrico Supervision: Diego EnricoValidation: all authors Writing - original draft; Writing - review & editing: all authors

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Figures

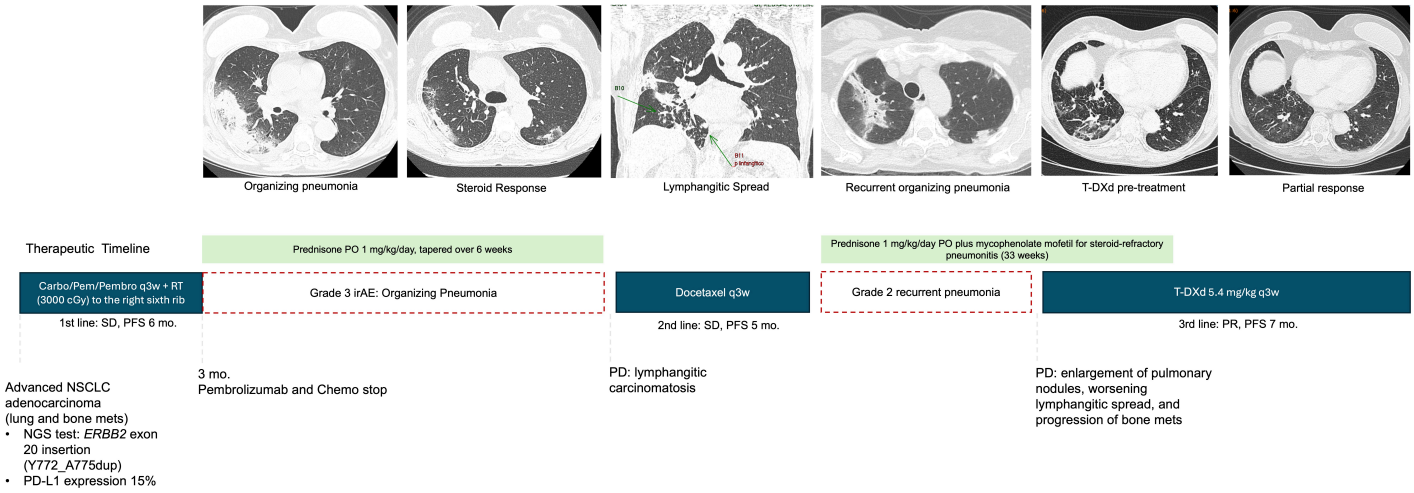


Figure 1

Timeline of the patient's disease course, treatments, and radiologic evolution. SD, stable disease; PR, partial response; PD, progressive disease; NGS, next-generation sequencing; PFS, progression-free survival; mo, months; q3w, every 3 weeks; PO, orally; Carbo/Pem/Pembro, carboplatin, pemetrexed, and pembrolizumab; RT, radiotherapy; irAE, immune-related adverse event; T-DXd, fam-trastuzumab deruxtecan-nxki.