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A real-world experience of treatment rechallenge after grade 1 trastuzumab-deruxtecan related interstitial lung disease:

clinical outcomes and imaging findings

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Introduction

- Trastuzumab-deruxtecan (T-DXd) is a HER2 directed antibody drug conjugate approved for advanced HER2-positive, low, and ultra-low breast cancer, and multiple other solid tumors.
- T-DXd has a rare, possibly serious risk of interstitial lung disease/pneumonitis (ILD). The incidence of any grade ILD is estimated at 12-15% with a 1-2% risk of fatal ILD, necessitating careful symptom monitoring and imaging.[1]
- For symptomatic ILD (≥ grade 2), T-DXd is permanently discontinued. For grade 1 ILD, T-DXd is held with the option of rechallenge if ILD radiographically improves. [2]
- Pooled analyses of T-DXd related ILD incidence and risk factors have been conducted[1], but limited data exist for T-DXd related ILD imaging findings and clinical outcomes after rechallenge among patients treated in real-world settings.

Methods

- This was a retrospective cohort study of all patients treated with T-DXd at our institution from September 2018-June 2024.
- We identified patients with radiographic evidence of ILD by chart review.
- Adjudication of T-DXd related ILD was based on the treating provider's assessment and graded via CTCAE v5.
- A chest radiologist conducted a blinded review of baseline and all follow-up chest CTs (up to 4 mos post T-DXd) for all patients treated with T-DXd to identify possible cases of drug-related ILD and assess imaging evolution over time.

Results

Figure 1: CONSORT Diagram

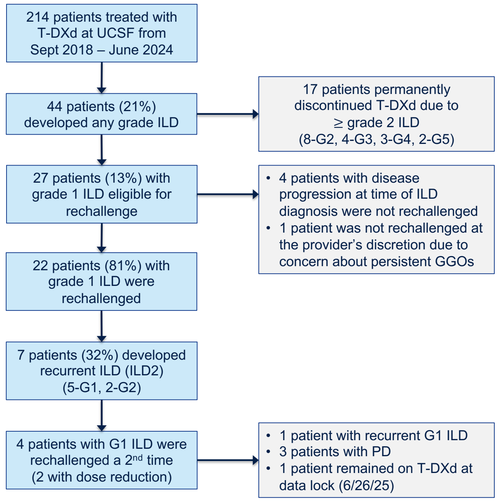


Table 1: Characteristics of patients who developed any-grade ILD (n=44)

Patient Characteristic	n (%) or median (range)
Cancer Type	Breast: 37 (84%) Gastrointestinal: 5 (11%) Lung: 1 (2%) Head and neck: 1 (2%)
Age (yrs)	59 (36-78)
Prior # treatment lines in the advanced/metastatic setting	3 (0-13)
Renal impairment (CrCl < 60 mL/min)	8 (18%)
ILD onset from 1st T-DXd dose (days)	116 (9-833)

Management of Grade 1 ILD (n=27)

- T-DXd treatment was held for all patients
- 21/27 patients (78%) were treated with steroids for a median of 49 days (range 15-149 days)
- Provider-assessed ILD radiographic improvement was seen at a median of 23 days (range 9-79) for patients treated with steroids vs 66 days (range 28-82) for patients who did not receive steroids.
- 2 patients who did not receive steroids were rechallenged with T-DXd.

Outcomes after T-DXd Rechallenge (n=22)

Median time to rechallenge was 42 days from last dose before ILD (range 20-236 days)
- 2 patients received intervening therapy before rechallenge (1 with anastrozole, 1 with tucatinib + trastuzumab)

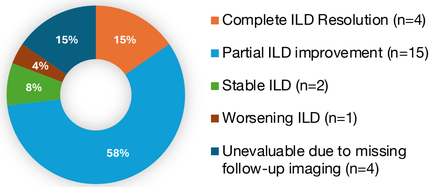
After rechallenge, patients remained on T-DXd for a median of 95 days (range 20-365 days).
- 15 patients remained on T-DXd without recurrent ILD
- 1 patient remained on T-DXd at data lock (6/26/25)

7 patients (32%) had recurrent ILD
- Median time to recurrent ILD was 47 days after rechallenge (range 20-331 days)
- 5 grade 1 and 2 grade 2 recurrent ILD events

4 patients with recurrent grade 1 ILD were rechallenged with T-DXd a second time
- Median duration of 2nd rechallenge was 152 days (range 92-370)
- 2 patients were dose-reduced
- 1 patient (25%) developed recurrent grade 1 ILD
- 3 continued until progression, 1 remained on T-DXd at data lock.

Radiographic outcomes of patients with Grade 1 ILD by blinded imaging review

Figure 1: Best radiographic response after ILD



- Median time from initial ILD response to complete or partial response was 31 days (range 9-209)
- Of the 7 patients who developed recurrent ILD after rechallenge, all had partial imaging responses prior to rechallenge.

Imaging findings not clinically diagnosed as ILD

- Per blinded imaging review, 22 patients had imaging findings consistent with *possible ILD*, but were not clinically diagnosed with T-DXd related ILD.
- Per clinician assessment, imaging findings were attributed to:
  - Progressive disease (n=7)
  - Viral infection (n=5)
  - Aspiration/infection (n=4)
  - Radiation changes (n=2)
  - ILD findings not documented in radiology report (n=4)
- These 22 patients remained on T-DXd for a median of 152 days (range 20-949) and were never clinically diagnosed or treated for ILD.
  - 21 patients stopped at progression and 1 remained on T-DXd at data lock.

Key Findings

81% of patients with G1 ILD were rechallenged

95 days Median duration patients remained on T-DXd *after* rechallenge

32% of patients developed recurrent ILD after rechallenge

58% of patients with G1 ILD had only partial improvement of CT findings

Overall Conclusion:

- **Rechallenge with T-DXd after grade 1 ILD was safe and patients had ongoing clinical benefit from T-DXd with no cases of grade 5 ILD after rechallenge.**
- **Most patients did not have complete resolution of ILD findings on CT. The clinical significance of partial imaging resolution is unknown.**

Conclusions

- High rates of T-DXd rechallenge were seen at our institution after patients had recovered from grade 1 ILD.
- After rechallenge, patients remained on T-DXd for a median of 95 days (range 20-365) , demonstrating sustained clinical benefit after ILD.
- Rates of recurrent ILD (ILD2) were low with no grade 5 events (71% grade 1, 29% grade 2).
- After grade 1 ILD2, 4 patients were successfully rechallenged a 2nd time, with only 1 case of recurrent grade 1 ILD.
- Most patients with grade 1 ILD did not have complete resolution of ILD findings on CT. However, all patients with recurrent ILD had only partial resolution of CT findings. The long-term clinical significance of partial ILD resolution is unknown.
- By imaging review, some patients had imaging findings possibly consistent with ILD, but they were not clinically diagnosed with or treated for ILD, highlighting the challenge of diagnosing T-DXd-related ILD.
- **Future Directions:** A comprehensive imaging review is ongoing to better characterize the imaging findings and sequelae associated with T-DXd-related ILD.

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Conflicts of Interest: Reports an advisory role for AstraZeneca.

References

1. Powell CA, Modi S, Iwata H, Takahashi S, Smit EF, Siena S, Chang DY, Macpherson E, Qin A, Singh J, Taitt C, Shire N, Camidge DR. Pooled analysis of drug-related interstitial lung disease and/or pneumonitis in nine trastuzumab deruxtecan monotherapy studies. ESMO Open. 2022 Aug;7(4):100554.
2. Rugo HS, Bianchini G, Cortes J, Henning JW, Untch M. Optimizing treatment management of trastuzumab deruxtecan in clinical practice of breast cancer. ESMO Open. 2022 Aug;7(4):100553.