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Assessment of Risk Factors, Monitoring Strategies, Incidence, and Management of Trastuzumab Deruxtecan (T-DXd)-related Interstitial Lung Disease (ILD) in Advanced Breast Cancer with Brain Metastases

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Introduction

- Trastuzumab deruxtecan (T-DXd) is a highly effective antibody-drug conjugate (ADC) indicated for the treatment of unresectable or metastatic HER2-positive or HER2-low/ultra-low breast cancer with objective response rates (ORR) between 50-80% as reported within DESTINY-Breast01, -03, -04, and -06.[1-5]
- T-DXd carries a black box warning for interstitial lung disease (ILD)/pneumonitis with approximately 10-15% risk of ILD development including some reported grade 5 events.[1]
- The DESTINY-Breast12 study found higher rates of ILD in patients with brain metastases (16.0%) than in patients without (12.9%) and 5 patients in the brain metastases group concurrently developed an opportunistic infection and ILD.[6]
- Monitoring guidance for ILD remains limited and variable amongst individual practice.
- As T-DXd use continues to extend across other tumor types, identifying risk factors for developing ILD and monitoring strategies is essential

Materials and Methods

Primary Objective

- Evaluate the incidence of ILD in patients with metastatic breast cancer with brain metastases and/or leptomeningeal disease who have been treated with T-DXd.

Secondary Objectives

- Identify risk factors associated with ILD
- Assess if CT ILD monitoring allows for earlier identification of ILD.
- Assess occurrence of ILD that resulted in discontinuation of T-DXd.
- Evaluate rates of opportunistic infections in patients treated with T-DXd in patients who did versus did not develop ILD.

Methods

- Single center, retrospective, cohort study
- December 2019 – September 2024

Inclusion Criteria

- Age ≥18 years old
- Diagnosed advanced or metastatic HER2-positive, HER2 low, or HER2 ultra-low breast cancer with brain metastases and/or leptomeningeal disease
- Received treatment with T-DXd
- Treatment was received at Duke Cancer Institute with Breast Oncology

Results

Table 1. Patient Demographics.

Patient Demographics	CT-ILD Monitoring (N=23)	Non-CT-ILD Monitoring (N=39)
Age, mean (SD)	55.2 (10.2)	56.2 (13.8)
Sex – no. (%)		
Female	21 (91.3)	39 (100)
Male	2 (8.7)	0 (0)
Hormone receptor positive – no. (%)	12 (52.2)	23 (59.0)
HER2 status – no. (%)		
Positive (IHC 3+, 2+ FISH +)	17 (73.9)	21 (53.8)
Low (IHC 1+, 2+ FISH -)	6 (26.1)	18 (46.2)
Ultra-low (IHC 0+)	0 (0)	0 (0)
Metastases – no. (%)		
Liver	11 (47.8)	18 (46.2)
Bone	10 (43.5)	19 (48.7)
Lung	5 (21.7)	16 (41.0)
Other	5 (21.7)	6 (15.4)
Leptomeningeal	4 (17.4)	5 (12.8)
Brain	23 (100)	39 (100)
Lymphangitic spread	1 (4.3)	1 (2.6)
Peritoneal carcinomatosis	1 (4.3)	1 (2.6)

Figure 1. Type of ILD Monitoring.

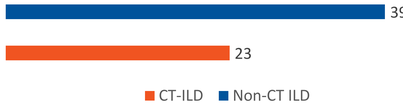


Table 2. Cumulative incidence of ILD at one year.

Population	Cumulative incidence of ILD at one year % (95% CI)
All patients (n=62)	11.9% (4.0%, 24.6%)
CT-ILD Monitoring (n=23)	9.4% (1.5%, 26.4%)
Non-CT-ILD Monitoring (n=39)	14.0% (2.7%, 34.3%)

Table 3. Rate of opportunistic infection during T-DXd treatment.

Duke Cancer Institute - No. (%)	2 (3.6%)
DESTINY-Breast12 BMs – No. (%)	7 (2.7%)

Table 4. ILD Risk Factors.

ILD Risk Factors	ILD	No ILD
Age ≥60 years old (n=23) – no. (%)	3 (13.0)	20 (87.0)
Age <60 years old (n=39) – no (%)	5 (12.8)	34 (87.2)
History of smoking tobacco (n=18) – no. (%)	3 (16.7)	15 (83.3)
Active smoker (n=2) – no. (%)	0 (0)	2 (100)
Lung Disease – no. (%)		
Asthma (n=5)	0 (0)	5 (100)
Other (n=1)	1 (100)	0 (0)
COPD (n=0)	0 (-)	0 (-)
Hispanic ethnicity (n=2) – no. (%)	0 (0)	2 (100)
Chronic kidney disease (n=2) – no. (%)	0 (0)	2 (100)
History of ILD (n=0) – no. (%)	0 (-)	0 (-)

Figure 2. Cumulative Incidence of ILD Stratified by Monitoring Type.

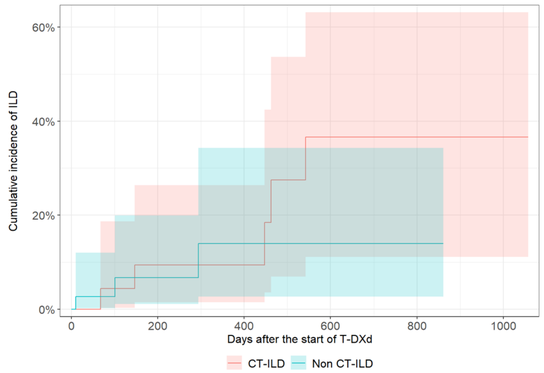


Table 5. Monitoring Type and ILD Grade.

ILD Grade	CT-ILD Monitoring (N=23)	Non-CT ILD Monitoring (N=39)
Any Grade ILD no. (%)	5 (21.7)	3 (7.6)
Grade 1 – no. (%)	2 (8.7)	0 (0)
Grade 2 – no. (%)	3 (13.0)	2 (5.1)
Grade 3 – no. (%)	0 (0)	1 (2.6)

Table 6. Trastuzumab deruxtecan treatment

T-DXd Treatment and ILD	CT-ILD (n=23)	Non-CT-ILD (n=39)
Total number of T-DXd cycles – mean (SD)	22.9 (18.1)	7.6 (7.0)
Days on T-DXd therapy – mean (SD)	399.5 (311.8)	151.9 (171.9)
Hold due to suspected ILD – no. (%)	8 (34.8)	2 (5.1)
Dose modification due to adverse event – no. (%)	15 (65.2)	13 (33.3)
T-DXd discontinuation due to ILD – no. (%)	0 (0)	3 (7.7)

Table 7. ILD evaluation and treatment

ILD Evaluation and Treatment	CT-ILD (n=23)	Non-CT-ILD (n=39)
Time to ILD onset – mean (SD)	333.2 (211.0)	135.0 (145.0)
Pulmonology consults – no. (%)	1 (4.8)	1 (2.6)
Bronchoscopy – no. (%)	2 (8.7)	0 (0)
Treatment for ILD with steroids – no. (%)	5 (21.7)	3 (7.7)
Steroid dose – no. (%)		
0.5 mg/kg	2 (8.7)	1 (2.6)
1 mg/kg	3 (13.0)	2 (5.1)
Steroid duration – mean (SD)	45.4 (26.1)	40.7 (19.4)

Conclusions

- Any grade ILD rates were higher with CT ILD monitoring vs Non-CT ILD monitoring. The ILD cumulative incidence at one year of 11.9% is within the range of rates seen within previous DESTINY-Breast studies which have reported ILD rates between 10-15%.[2-5]
- Two patients who received monitoring for ILD with CT-ILD were found to have grade 1 ILD, compared to no patients who did not have CT-ILD monitoring. This suggests that CT-ILD monitoring may allow for identification of ILD at a lower grade.
- The results did not demonstrate a relationship between ILD risk factors and the rate of ILD, however this study contained a small sample size.
- Two patients (3.6%) developed an opportunistic infection during treatment with T-DXd, which is numerically slightly higher than the rate of opportunistic infection in the DESTINY-Breast12 study (2.7%).[6]
- Limitations of this study include it was a retrospective study and included a small sample size.

Abbreviations: T-DXd: trastuzumab deruxtecan; ILD: interstitial lung disease; BM: brain metastases

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