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Evaluating risk factors for Trastuzumab-Deruxtecan Pneumonitis in patients with metastatic breast cancer

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Abstract

Background Trastuzumab deruxtecan (T-DXd) is FDA-approved for treatment of patients with HER2 positive and HER2-low metastatic breast cancer. Currently, there is limited understanding of pre-treatment risk factors for pneumonitis associated with T-DXd.

Methods Consecutive breast cancer patients who received at least one dose of T-DXd at a single academic cancer study between January 1, 2019, and February 20, 2024, were identified for analysis. Pneumonitis was documented by the treating oncologist at the time of toxicity and retrospectively independently confirmed by a member of the study team through chart and radiologic review. Pre-treatment variables of interest were collected, including patient demographics, radiation dosimetry variables, and chest imaging abnormalities.

Results Of 179 total patients, 23 (12.8%) had pneumonitis after T-DXd exposure. Patients with pneumonitis had lower baseline oxygen saturation (98% vs. 97%, $p=0.02$) and were more likely to have received abemaciclib (26.1% vs. 9.6%, $p=0.03$) before T-DXd. Multiple pre-treatment variables were not found to be associated with T-DXd pneumonitis, including chest imaging abnormalities (41.9% vs. 47.8%, $p=0.59$), prior immune checkpoint inhibitor treatment (16.0% vs. 8.7%, $p=0.50$) and prior chest or breast radiation (61.5% vs. 47.8%, $p=0.20$). On multivariate analysis, prior treatment with abemaciclib remained significantly associated with T-DXd pneumonitis (OR 3.25 [1.07–9.11], $p=0.04$), while neither pre-treatment chest imaging abnormalities nor prior chest or breast radiation were associated (OR 1.60 [0.62–4.20], $p=0.33$); OR 0.51 [0.20–1.33], $p=0.17$).

Conclusions In this cohort, prior treatment with abemaciclib may be a risk factor for T-DXd pneumonitis. Conversely, pre-treatment chest imaging abnormalities, prior immune checkpoint inhibitor treatment, and prior chest or breast radiation did not increase the risk of T-DXd pneumonitis. Larger studies are warranted to validate these findings toward an improved understanding of risk factors for pneumonitis after T-DXd exposure.

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Keywords Trastuzumab-Deruxtecan, Pneumonitis, Breast cancer

Introduction

Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate consisting of trastuzumab, a monoclonal antibody targeting human epidermal growth factor receptor 2 (HER2), conjugated with deruxtecan, a cytotoxic topoisomerase I inhibitor, to precisely deliver chemotherapy to HER2-expressing cancer cells to enhance therapeutic efficacy. Use of T-DXd has revolutionized the treatment approach for patients with both HER-2 positive and HER-2 low metastatic breast cancer, leading to longer progression-free and overall survival compared to previous standard of care chemotherapy and targeted therapy [1, 2, 3].

However, T-DXd treatment is not without risk. Incidence of T-DXd related interstitial lung disease (ILD), or drug-related pneumonitis, has been reported in up to 15% of breast cancer patients treated with T-Dxd [3–4]. In a pooled analysis of early T-DXd trials, 22% of patients who developed T-DXd pneumonitis required oxygen supplementation and 2% died directly from pulmonary complications of treatment [4]. Though some demographic baseline factors have been identified that may predispose patients to pneumonitis following T-DXd treatment [4], an in-depth analysis of pre-treatment risk factors for T-DXd pneumonitis has not been done. Pre-treatment chest imaging abnormalities and prior cancer treatment modalities have been identified as risk factors for immune checkpoint inhibitor (ICI) pneumonitis [5, 6, 7], but the impact of prior cancer therapies and pre-treatment chest imaging abnormalities on the development of T-DXd pneumonitis is unclear. As T-DXd is increasingly utilized in other solid tumor malignancies [8–9], identifying patients at highest risk for pneumonitis before treatment initiation is of paramount importance.

To address this knowledge gap, we conducted a single-center, retrospective analysis of a cohort of patients with metastatic breast cancer treated with T-DXd to determine whether pre-treatment chest imaging abnormalities and prior cancer treatment modalities are risk factors for the development of T-DXd pneumonitis.

Methods

Data Collection, included patients

We conducted a retrospective cohort study of consecutive patients with breast cancer who received at least one dose of T-DXd at The Ohio State University (OSU) from January 1, 2019, to February 20, 2024. Study data were compiled using REDCap electronic data capture tools at OSU. The study protocol was reviewed and approved by The OSU Institutional Review Board (2023C0104), and a waiver of informed consent was granted due to the retrospective nature of the study.

Demographic variables

The following potential risk factors for T-DXd pneumonitis were collected: age, sex assigned at birth, race, body mass index, smoking status, cancer stage, pulmonary involvement of cancer (excluding non-specific pulmonary nodules, chest wall and rib involvement), hormone status (estrogen receptor [ER], progesterone receptor [PR], and HER2), line of therapy, prior systemic therapy, prior chest or breast radiation, total doses of T-DXd, T-DXd concentration, pre-existing lung disease (chronic obstructive pulmonary disease [COPD], asthma, ILD), and baseline SpO2 and oxygen requirements.

Pneumonitis diagnosis and treatment

T-DXd pneumonitis was determined by the treating clinician at the time of toxicity and retrospectively reviewed for agreement by a member of the study team. Attribution of pneumonitis to T-DXd was based on association with T-DXd use, corroborative chest computed topography (CT) findings, and reasonable exclusion of alternate etiologies of lung inflammation including infection and cancer progression. Pneumonitis severity was assigned based on the Common Terminology Criteria for Adverse Events (CTCAE v4), with mild disease defined as grade 1–2 and severe disease as grade 3–5. Pneumonitis treatment course, resolution of pneumonitis, and re-challenge with T-DXd following pneumonitis (if applicable) were recorded.

Radiation dosimetry variables

Prior history of chest and breast radiation preceding T-DXd initiation was recorded for all patients. For patients who had available radiation treatment data, the mean lung dose (MLD), the lung volume receiving ≥ 20 Gy (V20), and regional nodal irradiation (RNI) were recorded. If patients received multiple courses of chest radiation, only the dosimetry variables for definitive treatment of breast cancer were included.

Evaluation of pre-existing chest imaging abnormalities

As previously described [10], we defined the group of patients with chest imaging abnormalities as those who exhibited at least one of the following pre-treatment CT findings in the lung: ground glass appearance, reticular opacity, consolidation (excluding infectious pneumonia), traction bronchiectasis, centrilobular nodularity, and honeycombing. Interstitial changes that were thought to be related to underlying malignancy were not included.

The extent of imaging abnormality was measured on a five-point scale for upper, middle, and lower zones of the lung (0, none, 1 < 5%, 2, 5–25%, 3, 25–50%, 4 > 50%). Determination of imaging abnormality and severity scoring was done by board-certified pulmonologists on the study team who were blinded to all other aspects of the patient history, and interobserver disagreements were resolved by consensus.

Evaluation of Pre-treatment Pulmonary function testing

Spirometry (forced expiratory volume in 1 s [FEV1], forced vital capacity [FVC], FEV1/FVC ratio, bronchodilator responsiveness testing), total lung volume (TLC), residual volume (RV), diffusion capacity (DLCO), diffusion capacity corrected for hemoglobin (DLCO corrected for hemoglobin), 6-min walk test, and oxygen requirement within 12 and 18 months of ICI initiation were recorded by the study team and served as the baseline lung function. Testing that did not meet ATS criteria for acceptability and repeatability were not included [11]. If there were multiple PFTs before ICI treatment, only the PFTs closest to the start of ICI treatment were considered. All values were recorded as raw values (liters for FEV1, FVC, TLC, RV, mmol/min/mmHg for DLCO and DLCO corrected for hemoglobin) or as a percent predicted (pp) adjusted for patient's sex, height, age, and race. When available, post-bronchodilator FEV1/FVC was utilized to determine the presence of obstructive disease [12].

Statistical analysis

Patient characteristics and risk factors were compared between patients with and without T-DXd pneumonitis. Categorical variables were summarized as frequencies (n) and percentages (%) and compared using chi-squared test or fisher exact test as appropriate. Continuous variables were summarized as mean and standard deviation (SD) and compared using two sample t-test if they are normally distributed, otherwise median with interquartile range (IQR, 25th and 75th percentile) is used to describe variable distributions and compared using Wilcoxon rank sum test. Multivariable logistic regressions were used to study the association between potential risk factors and T-DXd pneumonitis, and model selection was based on clinical variables of interest and significant associations found on univariate analysis. The Kaplan-Meier survival curves with log-rank tests were used to compare overall survival between patients with T-DXd pneumonitis and patients without T-DXd pneumonitis, as well as between patients with mild pneumonitis (grade 1–2) and severe pneumonitis (grade 3–5). The statistical analysis was performed using R software (version 4.3.0; R Core Team, R Foundation for Statistical Computing, Vienna, Austria).

Results

Demographic, baseline characteristics, pulmonary function testing

The study demographics and baseline characteristics are summarized in Table 1. A total of 179 breast cancer patients were included, and 23 (12.8%) were found to have T-DXd associated pneumonitis. Of those who developed T-DXd associated pneumonitis, the median (IQR) number of days from T-DXd initiation to pneumonitis was 216 days (119, 369). Patients with T-DXd pneumonitis had lower baseline oxygen saturation (98% vs. 97%, $p = 0.02$) and received prior abemaciclib treatment (26.1% vs. 9.6%, $p = 0.03$) more frequently compared to those who did not develop pneumonitis. We found no statistically significant association between the remaining demographic variables and development of T-DXd pneumonitis, including race, pulmonary involvement of breast cancer, hormonal status of tumor (ER, PR, or HER2 status), prior immune checkpoint inhibitor treatment, prior cyclin dependent kinase (CDK4/6) inhibitors, doses of T-DXd administered, and history of pulmonary disease (COPD, asthma; 0 patients had pre-existing interstitial lung disease [ILD]). As only 23 patients had PFTs performed before T-DXd treatment, we were unable to analyze the impact of abnormalities on PFTs and development of T-DXd pneumonitis (Supplementary Table 1).

History of chest and breast Radiation and Risk of T-DXd Pneumonitis

One hundred and seven (59.8%) patients had prior chest or breast radiation preceding T-DXd treatment. A subset of patients who received chest or breast radiation before T-DXd therapy had radiation dosimetry variables available for review, and their association with the development of T-DXd pneumonitis is summarized in Table 2. There was no statistically significant association between prior chest or breast radiation and development of T-DXd pneumonitis (61.5% vs. 52.2%, $p = 0.21$). None of the queried radiation dosimetry variables were significantly associated with development of T-DXd pneumonitis, including no difference in mean lung dose, V20, V16, V10, and V5 between those with and without pneumonitis.

Pre-treatment chest abnormalities and risk of T-DXd pneumonitis

Seventy-six (42.4%) patients had chest imaging abnormalities preceding T-DXd treatment, and there was no statistically significant association between chest imaging abnormalities and development of T-DXd pneumonitis (41.9% vs. 47.8%, $p = 0.59$). There was no significant association between the presence of emphysema on chest imaging and development of T-DXd pneumonitis (5.2% vs. 8.7%, $p = 0.62$). Due to the relatively small number of

Table 1 Demographic differences in patients with and without Trastuzumab-Deruxtecan Pneumonitis

Variable		No pneumonitis ($n=156$)	Pneumonitis ($n=23$)	*p*-value
Age (median, IQR)		56.0 (46.0, 66.0)	55.0 (47.0, 60.5)	0.38
Gender	Female	154 (98.7%)	22 (95.6%)	0.34
	Male	2 (1.3%)	1 (4.4%)	
Race	White	132 (84.6%)	19 (82.6%)	0.76
	Non-White	24 (15.4%)	4 (17.4%)	
BMI (median, IQR)		25.9 (22.8, 29.3)	27.4 (21.8, 30.1)	0.89
History of Smoking	No	102 (65.4%)	13 (56.5%)	0.41
	Yes	54 (35.6%)	10 (43.5%)	
Pulmonary Involvement	No	91 (58.3%)	14 (60.9%)	0.82
	Yes	65 (41.7%)	9 (39.1%)	
ER (median, IQR, %)		70 (0, 95)	80 (15, 92.5)	0.79
PR (median, IQR, %)		0 (0, 20)	0 (0, 25)	0.78
HER2 (FISH)	Positive	42 (26.9%)	10 (43.4%)	0.10
	Others	114 (43.1%)	13 (56.6%)	
Line of Therapy	1	4 (2.6%)	2 (8.7%)	0.25
	2	17 (10.9%)	3 (13.0%)	
	≥ 3	135 (86.5%)	18 (78.3%)	
Prior Immune Checkpoint Inhibitor Treatment	Yes	25 (16.0%)	2 (8.7%)	0.54
	No	131 (84.0%)	21 (91.3%)	
Prior CDK4/6 inhibitors	Yes	67 (42.9%)	9 (39.1%)	0.73
	No	89 (57.1%)	14 (60.9%)	
Prior abemaciclib	Yes	15 (9.6%)	6 (26.1%)	0.03
	No	141 (90.4%)	17 (73.9%)	
Prior everolimus treatment	Yes	20 (12.8%)	1 (4.3%)	0.32
	No	136 (87.2%)	22 (95.7%)	
Doses of trastuzumab-deruxtecan (median, IQR)		8.0 (3.0, 14.0)	10.0 (7.5, 17.0)	0.13
Pulmonary disease	Yes	21 (13.5%)	3 (13.0%)	> 0.9
	No	135 (86.5%)	20 (87.0%)	
Oxygen saturation (median, IQR, %)		98.0 (96.0, 99.0)	97.0 (96.0, 97.5)	0.02
Oxygen Requirement	Yes	7 (4.5%)	2 (8.7%)	0.33
	No	149 (95.5%)	21 (91.3%)	

Abbreviations: ER– estrogen receptor; PR– progesterone receptor; HER2– human epidermal receptor 2; CDK4/6– cyclin dependent kinase 4/6

patients with chest imaging abnormalities and T-DXd pneumonitis, association of the pattern and severity of imaging abnormality and development of T-DXd pneumonitis could not be determined. Full analysis on the association of pre-treatment chest imaging abnormalities and T-DXd pneumonitis, including descriptive analysis on pattern and severity of imaging abnormalities, is summarized in Table 3.

Multivariable analysis on risk factors for T-DXd pneumonitis

In adjusted analyses, there were no significant associations between T-DXd pneumonitis and pre-treatment chest imaging abnormalities or T-DXd pneumonitis and history of prior chest or breast radiation (OR 1.60 [0.62–4.20], $p=0.33$); OR 0.51 [0.20–1.33], $p=0.17$ respectively, Table 4a). However, patients with prior abemaciclib treatment were 3.25 times (95% CI: 1.07–9.11, $p=0.04$) more likely to develop T-DXd pneumonitis compared to patients who never received abemaciclib (Table 4b).

Risk factors for severe pneumonitis, T-DXd pneumonitis and overall survival

There was no significant difference in overall survival between breast cancer patients with and without T-DXd pneumonitis ($p=0.22$, Fig. 1). Of the 23 patients with T-DXd pneumonitis, 15 (8.4% of all treated patients) had mild disease and 8 (4.5% of all treated patients) had severe pneumonitis. Of the 8 patients with severe disease, 4 (2.2% of all treated patients) had grade 5 events. Due to the small number of patients with severe pneumonitis, we were unable to determine risk factors specific for severe disease but outlined differences in demographics and cancer treatment course in patients who developed mild and severe pneumonitis (Supplementary Table 2). When evaluating overall survival between those with mild and severe T-DXd pneumonitis, there was a trend towards lower survival for patients with severe pneumonitis, though this was not statistically significant ($p=0.065$, Fig. 2).

Table 2 Prior chest and breast radiation by pneumonitis

Variables		No Pneumonitis ($n=156$)	Pneumonitis ($n=23$)	p-value
Prior Chest and Breast Radiation	Yes	96 (61.5%)	12 (52.2%)	0.21
	No	60 (38.5%)	11 (47.8%)	
		No Pneumonitis ($n=52$)	Pneumonitis ($n=7$)	
Mean Lung Dose (cGy)*		762 (619, 961)	520 (385, 605)	0.08
		No Pneumonitis ($n=53$)	Pneumonitis ($n=7$)	
Regional node irradiation*		38 (71.7%)	4 (57.1%)	0.42
		No Pneumonitis ($n=51$)	Pneumonitis ($n=6$)	
V20 (median, IQR)*		12 (8, 17)	7 (4, 9)	0.14
V16 (median, IQR)*		15 (10, 19)	8 (6, 11)	0.12
V10 (median, IQR)*		21 (16, 28)	14 (9, 19)	0.15
V5 (median, IQR)*		33 (23, 44)	24 (14, 35)	0.32

*Not all patients had complete radiation treatment variables available for review

Table 3 Pre-treatment chest imaging abnormalities by Pneumonitis

Variables		No Pneumonitis ($n=156$)	Pneumonitis ($n=23$)	p-value
Pre-Treatment Chest Imaging Abnormalities*	Yes	65 (41.9%)	11 (47.8%)	0.59
	No	90 (58.1%)	12 (52.2%)	
Emphysema	Yes	8 (5.2%)	2 (8.7%)	0.62
	No	147 (94.8%)	21 (91.3%)	
Total Severity Score (median, IQR)		2.0 (1.0, 3.0)	3.0 (1.5, 5.5)	0.13
Consolidation	Yes	14 (9.0%)	3 (13%)	0.46
	No	142 (91.0%)	20 (87%)	
Ground glass	Yes	28 (18%)	5 (22%)	0.77
	No	128 (82%)	18 (78%)	
Reticular	Yes	44 (28%)	6 (26%)	0.83
	No	112 (72%)	17 (74%)	
Centrilobular nodules	Yes	1 (0.6%)	3 (13%)	0.01
	No	155 (99.4%)	20 (87%)	
Traction bronchiectasis	Yes	5 (3.2%)	3 (13%)	0.07
	No	151 (96.8%)	20 (87%)	
Honeycombing	Yes	1 (0.6%)	1 (4.3%)	0.24
	No	155 (99.4%)	22 (95.7%)	

*1 patient did not have pre-treatment chest imaging available to review

Discussion

In this single-center retrospective analysis of consecutive breast cancer patients that received at least one dose of T-DXd, we found that prior abemaciclib treatment increased the risk of development of T-DXd pneumonitis. Pre-treatment chest imaging abnormalities and prior treatment modalities, including prior immune checkpoint inhibitor treatment, prior CDK4/6 inhibitor treatment, and prior chest and breast radiation, were not associated with T-DXd pneumonitis. To our knowledge, our study is the first to fully examine the impact of demographic variables and prior cancer treatment on the development of T-DXd pneumonitis. Our work provides guidance for clinicians considering T-DXd treatment and on the risk of T-DXd pneumonitis for complex metastatic breast cancer patients who have received several modalities of cancer treatment prior to T-DXd.

Table 4 multivariable analysis on risk factors for Trastuzumab-Deruxtecan Pneumonitis

Variable	Odds Ratio	95% Confidence Interval	p-value
A			
Pre-treatment Chest Imaging Abnormalities	1.60	0.62–4.20	0.33
Prior Chest or Breast Radiation	0.51	0.20–1.33	0.17
B			
Prior Abemaciclib Treatment	3.25	1.07–9.11	0.04
Prior Chest or Breast Radiation	0.64	0.26–1.60	0.34

While pre-treatment chest imaging abnormalities and prior chest radiation are risk factors for pneumonitis following ICI treatment [5, 6, 7], there are currently no studies evaluating the impact of chest imaging abnormalities and prior chest radiation on the development of T-DXd pneumonitis in breast cancer patients. In our study, we found no association between pre-TXd chest imaging abnormalities, prior chest radiation, and the development of T-DXd pneumonitis. We also observed no significant relationships between specific radiation dosimetry variables that were predictive of radiation pneumonitis [13] and the development of T-DXd pneumonitis, though our MLD and V20 are well below generally accepted constraints for minimizing risk of radiation pneumonitis [14]. Our results suggest that variables associated with pneumonitis from other cancer treatment modalities (radiation treatment, ICI treatment) may not be applicable in identifying breast patients at the highest risk of developing T-DXd pneumonitis. As patients with confirmed or suspected non-infectious ILD were excluded from the initial T-DXd trials for breast cancer patients [1–2], and none of the patients in our study had a diagnosis of ILD before T-DXd treatment, further studies are needed to determine whether patients with ILD (and not just pre-treatment chest imaging abnormalities) are at higher risk for pneumonitis following T-DXd treatment.

To date, there are no prospective studies evaluating the impact of prior systemic treatment on the development of T-DXd pneumonitis in breast cancer patients. Sequential treatment with cancer therapies known to cause pneumonitis (ICIs, CDK4/6 inhibitor, everolimus) is common in metastatic breast cancer patients being considered for T-DXd, and the risk of T-DXd pneumonitis

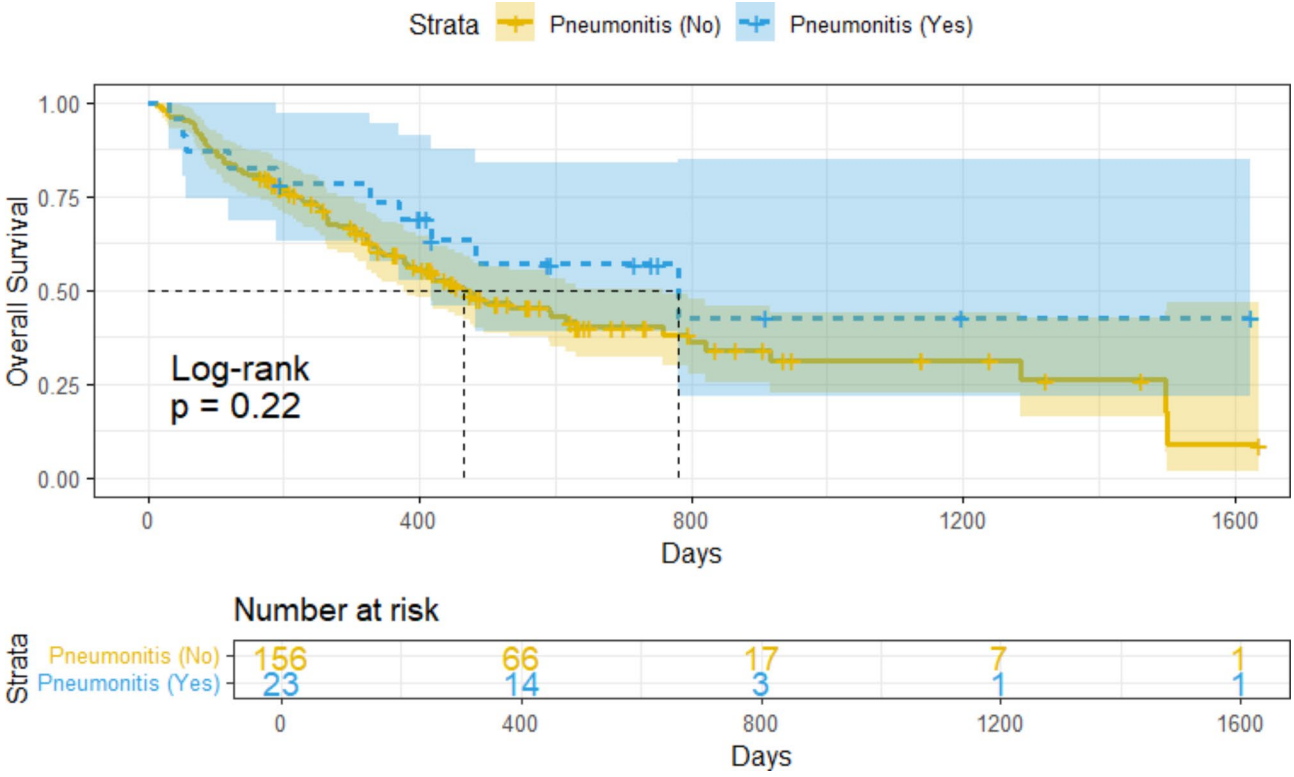

Fig. 1 Survival difference between those with and without pneumonitis

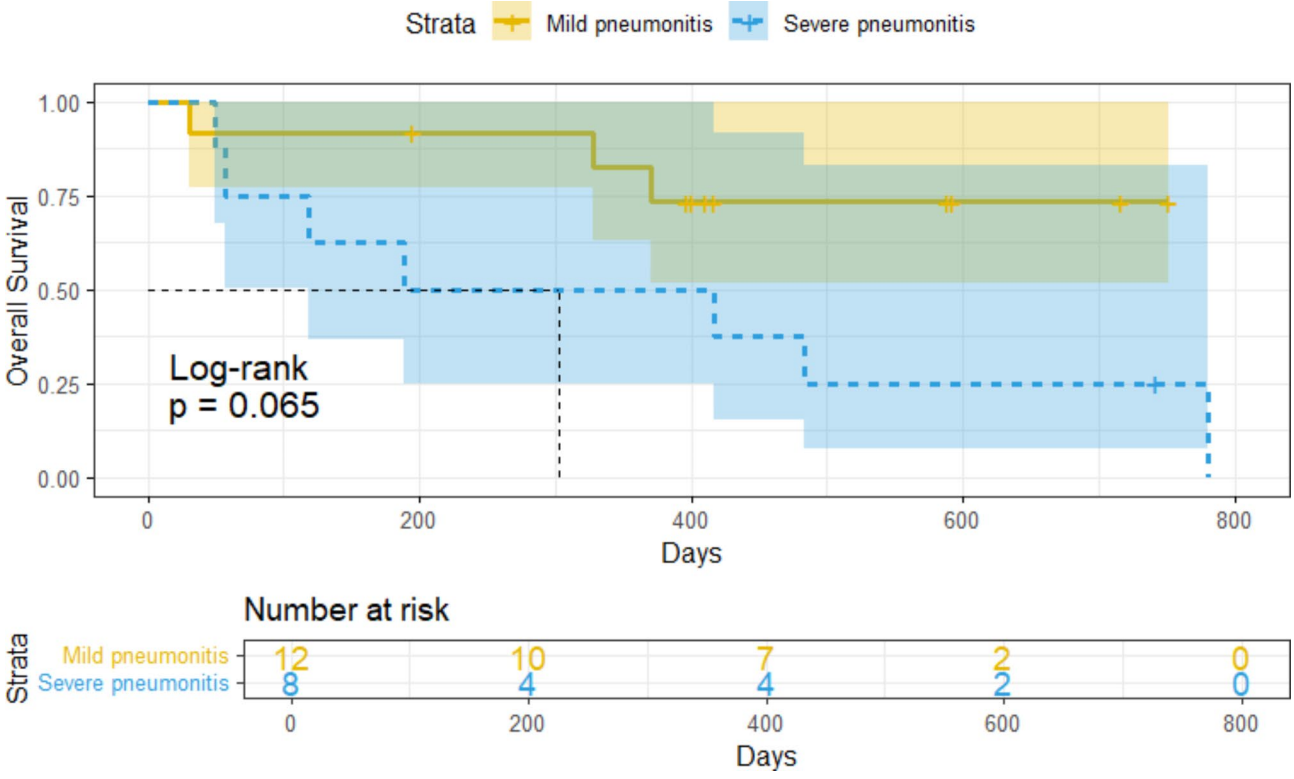

Fig. 2 Survival difference between mild and severe pneumonitis

following these various systemic treatment options is currently unknown. In our study, we did not find a significant association between prior ICI treatment, prior CDK4/6 inhibitor treatment, and prior everolimus treatment with the development of T-DXd pneumonitis. Our results provide some clinical guidance to oncologists weighing the risks of T-DXd treatment for breast cancer patients who have received multiple prior lines of systemic therapy.

Though there were no significant associations between prior treatment with any CDK4/6 inhibitors (abemaciclib, ribociclib, palbociclib) and T-DXd pneumonitis, we found that patients who received abemaciclib before T-DXd had significantly higher rates of pneumonitis compared to those who did not, and this association remained significant in multivariable analysis accounting for prior chest and breast radiation. Abemaciclib has the highest incidence of pneumonitis among the CDK4/6 inhibitors [15] and concurrent treatment with immune checkpoint inhibitors have been associated with higher rates of pneumonitis in breast cancer patients [16]. Prior treatment with abemaciclib may increase the risk of T-DXd pneumonitis by augmenting inflammatory cell recruitment [17], increasing the risk of lung inflammation and pneumonitis following T-DXd treatment. As the number of patients who received abemaciclib and developed pneumonitis was small in our study (6 patients), larger studies will be needed to validate this potential association between abemaciclib and T-DXd pneumonitis.

Most cases of T-DXd pneumonitis are asymptomatic and do not require hospitalization, but a subset of patients develop severe pneumonitis that can result in the need for oxygen supplementation, permanent pulmonary fibrosis, and death [4]. In our study, we found that while most patients had asymptomatic or minor disease, 8 of the 23 patients who developed T-DXd pneumonitis required supplemental oxygen, hospitalization, or died. We also found that while development of T-DXd pneumonitis did not impact overall survival, patients who had severe disease (grade 3–5) had a trend towards lower overall survival compared to those with mild (grade 1–2) T-DXd pneumonitis. As our severe pneumonitis cohort was small, we were unable to evaluate for risk factors for severe disease. As T-DXd is increasingly utilized earlier in the treatment course for patients with metastatic breast cancer, further studies are needed to identify risk factors for severe pneumonitis to ensure selection of patients that would benefit the most from T-DXd treatment.

There are several limitations to our study. This study was conducted at a single center with a large volume of cancer patients and clinical trials, enriching our patient population with those with refractory or progressive malignancy, which may be unique to our center and limit the generalizability of our results. As this was a retrospective study, there may be underrecognized confounders that may misclassify the relationship between chest imaging abnormalities, prior chest or breast radiation, prior systemic cancer treatment, and T-DXd pneumonitis. There were also a relatively low number of number of patients with T-DXd pneumonitis, and larger studies will be needed to fully evaluate the impact of pre-treatment chest imaging abnormalities, prior chest or breast radiation, and prior systemic therapies on the risk of developing T-DXd pneumonitis. Despite these limitations, as there no recommendations on the safety of T-DXd treatment for patients with pre-existing chest imaging abnormalities and who have received prior radiation therapy, our study gives clinicians some guidance on risk stratifying breast cancer patients who may be at increased risk of T-DXd toxicity.

Conclusion

Prior treatment with abemaciclib may be a risk factor for T-DXd pneumonitis. However, we found that pre-treatment chest imaging abnormalities and prior chest or breast radiation did not increase the risk of T-DXd pneumonitis. Larger studies are needed to validate our results.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13058-025-01967-1.

Supplementary Material 1

Supplementary Material 2

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Not applicable.

Author contributions

JH, TH, OA, and RA performed data abstraction. JH and TH wrote the initial draft of the manuscript. JS, PK, and SJ collected the radiation dosimetry variables. TH, JW, MW, VE, IB, and KH performed chest imaging review. JM performed statistical analysis. KJ, DS, and MM critically appraised the manuscript. KH and MM were responsible for conception of the research. All authors read and approved the final draft of the manuscript.JH and TH are co-first authors.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics statement

The study protocol was reviewed and approved by The OSU Institutional Review Board (2023C0104), and a waiver of informed consent was granted due to the retrospective nature of the study.

Consent for publication

Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Modi S, Saura C, Yamashita T, et al. Trastuzumab Deruxtecan in previously treated HER2-Positive breast Cancer. N Engl J Med. 2020;382(7):610–21.
2. Modi S, Jacot W, Yamashita, et al. Trastuzumab Deruxtecan in previously treated HER2-Low advanced breast Cancer. N Engl J Med. 2022;387(1):9–20.
3. Hurvitz SA, Hegg R, Chung WP, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. Lancet. 2023;401(10371):105–17.
4. Powell CA, Modi S, Iwata H, et al. Pooled analysis of drug-related interstitial lung disease and/or pneumonitis in nine trastuzumab deruxtecan monotherapy studies. ESMO Open. 2022;7(4):100554.
5. Shimoji K, Masuda T, Yamaguchi K, et al. Association of Preexisting Interstitial Lung Abnormalities with Immune Checkpoint inhibitor-Induced interstitial lung disease among patients with Nonlung Cancers. JAMA Netw Open. 2020;3(11):e2022906.
6. Wong A, Riley M, Zhao S, et al. Association between pre-treatment chest imaging and pulmonary function abnormalities and immune checkpoint inhibitor pneumonitis. Cancer Immunol Immunother. 2023;72(6):1727–35.
7. Wong A, Riley M, Zhao S, et al. Association between Pretreatment Chest Imaging and Immune checkpoint inhibitor pneumonitis among patients with Lung Cancer. J Natl Compr Canc Netw. 2023;21(11):1164–e11715.
8. Li BT, Smit EF, Goto Y, et al. Trastuzumab Deruxtecan in *HER2*-Mutant non-small-cell Lung Cancer. N Engl J Med. 2022;386(3):241–51.
9. Meric-Bernstam F, Makker V, Oaknin A, et al. Efficacy and safety of Trastuzumab Deruxtecan in patients with HER2-Expressing solid tumors: primary results from the DESTINY-PanTumor02 phase II trial. J Clin Oncol. 2024;42(1):47–58.
10. Kanai O, Kim YH, Demura Y. Efficacy and safety of nivolumab in non-small cell lung cancer with preexisting interstitial lung disease. Thorac Cancer. 2018;9(7):847–55.
11. Graham BL, Steenbruggen I, Miller MR, et al. Standardization of Spirometry 2019 Update. An official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med. 2019;200(8):e70–88.
12. Sterk PJ. Let's not forget: the GOLD criteria for COPD are based on post-bronchodilator FEV1. Eur Respir J. 2004;23(4):497–8.
13. Kabolizadeh P, Kalash R, Huq MS, et al. Dosimetric definitions of total lung volumes in calculating parameters predictive for radiation-induced pneumonitis. Am J Clin Oncol. 2015;38(4):401–4.
14. Marks LB, Bentzen SM, Deasy JO, et al. Radiation dose-volume effects in the lung. Int J Radiat Oncol Biol Phys. 2010;76(3 Suppl):S70–6.
15. Raschi E, Fusaroli M, Ardizzoni A, et al. Cyclin-dependent kinase 4/6 inhibitors and interstitial lung disease in the FDA adverse event reporting system: a pharmacovigilance assessment. Breast Cancer Res Treat. 2021;186(1):219–27.
16. Rugo HS, Kabos P, Beck JT, et al. Abemaciclib in combination with pembrolizumab for HR+, HER2- metastatic breast cancer: phase 1b study. NPJ Breast Cancer. 2022;8(1):118.
17. Birnhuber A, Egemnazarov B, Biasin V, et al. CDK4/6 inhibition enhances pulmonary inflammatory infiltration in bleomycin-induced lung fibrosis. Respir Res. 2020;21(1):167.

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