Incidence and Predictors of Interstitial Lung Disease Associated with Antibody-Drug Conjugates in Breast Cancer: A Systematic Review and Meta-Analysis

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INTRODUCTION

Antibody-drug conjugates (ADCs) have emerged as a transformative therapeutic class in breast cancer, offering targeted cytotoxic delivery with improved efficacy; however, interstitial lung disease (ILD) and pneumonitis have been increasingly recognized as serious, and sometimes fatal, toxicities. Their incidence, severity, and clinical predictors remain incompletely characterized across trials. This meta-analysis quantifies and explores the potential predictors of ILD and pneumonitis in breast cancer patients treated with ADCs.

METHODS

Systematic review and meta-analysis of phase I-III clinical trials evaluating ADCs in breast cancer to estimate the pooled incidence of ILD, including drug-related pneumonitis, and to assess potential contributing factors.

- ILD rates were stratified by CTCAE grade.
- Incidence was pooled using a random-effects proportional meta-analysis.
- Subgroup and meta-regression analyses evaluated the impact of:
  - ADC type
  - Payload
  - Dose
  - Breast cancer subtype
  - Drug-antibody ratio
  - Line of therapy
- Study and subgroup heterogeneity were evaluated using the I2 statistic, with I2 greater than or equal to 50% considered high.

RESULTS

Across the 48 included trials (n = 10607 patients), 664 developed ILD/pneumonitis, yielding a pooled incidence of ILD/pneumonitis of 7.5% (95% CI:4.5%-11.2%; I2 =96.2%, $\tau 2 = 0.0321$, $p < 0.0001$).

- Most events were low-grade (grade 1-2: 6.4%), with fewer high-grade (grade 3-4:0.4%) and fatalities (grade 5: 0.2%) events.
- The ADC, ARX788 had the highest overall ILD incidence (47.6%), largely driven by grade 1-2 events (42.0%).
- Trastuzumab deruxtecan (T-DXd) also demonstrated notable ILD incidence at12.5%, including a fatality rate of 0.93% (grade 5).
- In a mixed-effects meta-regression model, payload type significantly influenced ILD incidence ($R2 = 90.3\%$, $p<0.0001$), accounting for 90.3% of the between-study variance; however, breast cancer subtype, ADC dose, and line of therapy were not significantly associated with the incidence of ILD (all $p > 0.05$).
- ILD incidence by payload was highest with DXd (10.7%), and lower with microtubule inhibitors (3.3%).
- Notably, studies that excluded patients with pre-existing lung disease reported a slightly higher pooled ILD rate (10.0%).
- Treatment modifications due to ILD/pneumonitis (dose reduction, delay, or discontinuation) occurred most frequently with T-DXd, particularly in DESTINY-Breast(DB)-03 (11.9%), DB-02 (9.4%), and DB-01 (9.2%).
- Across studies reporting these outcomes, discontinuation rates ranged from 0.0% to 11.9% (median: 2.8%, IQR: 0.3%-4.8%).

ILD/Pneumonitis Incidence Among 10,607 Patients Who Received an ADC n (%)

Overall Pooled		664 (7.5)
	Grade 1-2	559 (6.4)
	Grade 3-4	62 (0.4)
	Grade 5	43 (0.2)

% of the 664 Patients with ILD/Pneumonitis by ADC & Payload

ARX788	47.6 (Grade 1-2: 42)
T-Dxd	12.5 (Grade 5: 0.93)
Payload: DXd	10.7
Payload: DM1	1.5
Payload: microtubule inhibitors	1.8

CONCLUSION

ILD, including pneumonitis, is a clinically relevant toxicity of ADC therapy in breast cancer. Incidence and severity vary across agents. Payload type emerged as the strongest predictor of ILD risk, underscoring its importance in ADC development and patient selection. ARX788 was associated with the highest ILD risks, while T-DXd had the highest rate of treatment interruptions.

Abstract: 2162
San Antonio Breast Cancer Symposium
December 10-13, 2025