PD10-01

Circulating microRNA and cytokine signatures associated with interstitial lung disease in patients treated with trastuzumab deruxtecan

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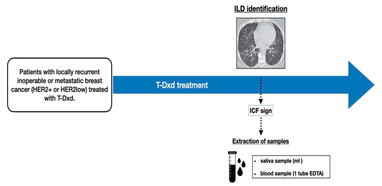
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Background and Objetives:

- **Interstitial lung disease** (ILD) is a clinically relevant adverse event associated with trastuzumab deruxtecan (T-DXd) in HER2-positive and HER2-low metastatic breast cancer.[1-4]
- Most ILD cases are low grade, but severe forms can occur, particularly if diagnosis is delayed.[5]
- To better understand the biology of T-DXd–related ILD, we conducted a translational study analyzing **circulating microRNAs** (miRNAs) and cytokines at the time of ILD diagnosis.
- Other anticancer agents, including mTOR and CDK4/6 inhibitors, have also been linked to ILD, and these therapies are frequently administered sequentially throughout the disease course.[6]
- **Primary objective**: To characterize circulating miRNA and cytokine profiles in patients who developed ILD (cases) on T-DXd compared with those who did not (controls).
- **Exploratory objective:** To compare circulating miRNA profiles in T-DXd–related ILD versus ILD associated with other anticancer agents (everolimus and abemaciclib).

Methods and Materials

- We conducted a prospective, single-center, case–control translational study including patients with HER2-positive or HER2-low metastatic breast cancer treated with T-DXd. Cases of ILD induced by other anticancer agents (everolimus and abemaciclib) were also collected.



- Controls were matched 1:1 based on treatment duration, age and tumor subtype (HER2+ or HER2-low)
- Plasma and saliva samples were obtained at the time of ILD diagnosis or at an equivalent treatment cycle for controls.
- ILD was diagnosed at the investigator's discretion and graded according to CTCAE v5.0.

- miRNA expression was analyzed using the **NanoString nCounter® Human v3 miRNA panel** analyze the expression of 770 miRNAs.
- Cytokine levels were measured using **LEGENDplex™ multiplex immunoassays** targeting immune response and checkpoint markers.

Results

- Seven patients developed T-DXd–related ILD and were matched with controls. Patient and ILD characteristics are summarized in **Table 1/2.**

Primary objective:

- Differential expression of circulating miRNAs in T-DXd–related ILD versus controls is illustrated in Figures 1 and 2.
- In T-DXd–related ILD compared with matched T-DXd controls: Three miRNAs (**hsa-miR-493-3p, hsa-miR-21-5p, hsa-miR-382-5p**) were markedly overexpressed, while six miRNAs (**hsa-miR-107, hsa-miR-92a-3p, hsa-let-7e-5p, hsa-miR-221-3p, hsa-miR-486-3p, hsa-miR-301a-3p**) were underexpressed.

Table 1. Patient characteristics

	n=7
Age, median (range):	56 years (46–84)
Smoking status: Never	7 (100%)
Pulmonary comorbidities:	1 (14%)
Lung metastases:	2 (29%)
T-DXd indication: HER2-low: HER2-positive:	6 (86%) 1 (14%)

Table 1. ILD characteristics

	n=7
T-DXd cycles before ILD, median (range)	6 cycles (4–13)
ILD grade (CTCAE v5.0) G1 G2 ≥ G3	4 (57%) 2 (29%) 1 (14%)
Radiologic ILD pattern - Alveolar - Interstitial - Mix	5 (71%) 1 (14%) 1 (14%)

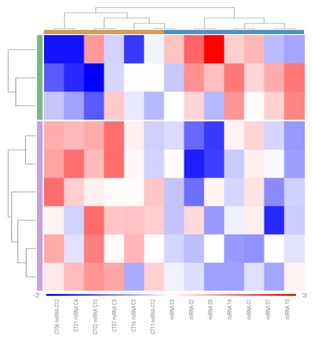


Figure 1. Heatmap of differentially expressed circulating miRNAs in T-DXd–related ILD versus matched controls. Hierarchical clustering shows clear separation between ILD cases and controls based on miRNA expression patterns.

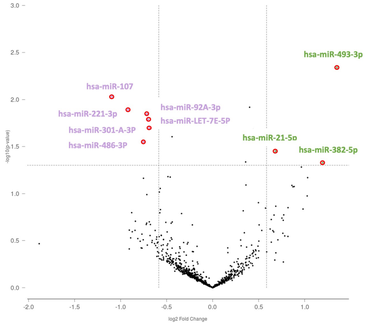


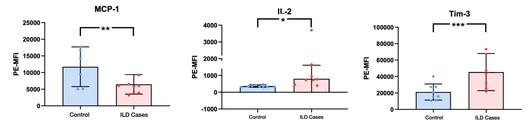
Figure 2. Volcano plot showing differential expression of circulating miRNAs in T-DXd–related ILD versus matched controls. Overexpressed miRNAs are highlighted in the upper right quadrant, and underexpressed miRNAs in the upper left quadrant.

Cytokine profiling:

- ILD cases showed significantly higher levels of IL-6, CXCL10, TIM-3, and IFN-γ, and lower levels of CCL2 ($p < 0.01$).
- Inverse expression patterns were observed between selected miRNAs and cytokines (Figure 3).

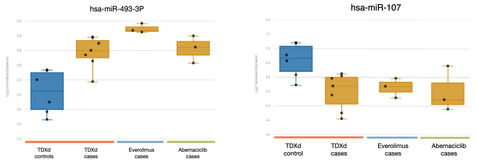
Figure 3: Cytokine levels in T-DXd–related ILD versus controls. Table shows deregulated miRNAs and their predicted targets

	miRNA	Target
UP	hsa-miR-493-3P	MCP-1 (CCL-2)
DOWN	hsa-miR-107	IL-2
	hsa-miR-92A-3P	Tim-3



Exploratory objective:

- In the exploratory cohort, six additional ILD cases were identified (3 everolimus, 3 abemaciclib).
- miRNA expression was descriptively compared with T-DXd–related ILD and controls, without formal statistical testing



Conclusions

- This is the first study to characterize circulating microRNA and cytokine profiles associated with ILD in patients treated with trastuzumab deruxtecan.
- Distinct inflammatory signatures differentiated ILD cases from matched controls, with consistent inverse associations between selected miRNAs and their corresponding immune mediators.
- A subset of these alterations was also observed in ILD cases associated with everolimus and abemaciclib, although comparisons were descriptive and exploratory.
- These findings highlight the potential of circulating biomarkers for characterizing drug-induced ILD and warrant validation in larger cohorts

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