Abstract # 8263

Analysis of drug-related interstitial lung disease (ILD) in patients treated with datopotamab deruxtecan (Dato-DXd)

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Objective

- Describe the **incidence and severity of adjudicated drug-related ILD** across 5 studies of Dato-DXd in patients with advanced solid tumors

Conclusions

- Across all tumor types, the overall incidence of **adjudicated drug-related ILD cases** seen with Dato-DXd was low
  - The majority of cases were **low grade** (grade 1 or 2)
  - **Grade ≥3 events have been reported**, highlighting the need for careful monitoring and adherence to management guidelines
  - In the NSCLC+BC pool, the median **time to onset** of first adjudicated drug-related ILD event was 48 days and the median **duration** was 39 days
  - **Dato-DXd–related ILD** was more commonly observed in patients with **NSCLC,** and risk factors are currently under investigation
  - These pooled analyses further **support a favorable benefit/risk profile of Dato-DXd** for patients with advanced solid tumors

Background

- **Dato-DXd** is a **TROP2-directed antibody–drug conjugate (ADC)** composed of an anti-TROP2 mAb covalently linked to a highly potent topoisomerase I inhibitor payload via a plasma-stable, tumor-selective, tetrapeptide-based cleavable linker[1]
- Dato-DXd has demonstrated **meaningful clinical activity** in patients across **multiple solid tumor types**, including statistically **significant improvement in PFS** compared with standard chemotherapy in the pivotal TROPION-Lung01 (NSCLC)[2] and TROPION-Breast01 (HR+/HER2– BC)[3] studies
- **ILD** is an important identified risk with many cancer therapies, including both checkpoint inhibitors and ADCs[4]
  - ILD at grade 1 is asymptomatic, underscoring the need for early detection[5]
- Here, we describe **pooled analyses of the incidence and severity of ILD**, across 5 studies investigating Dato-DXd in patients with advanced solid tumors[2,3,6–8]

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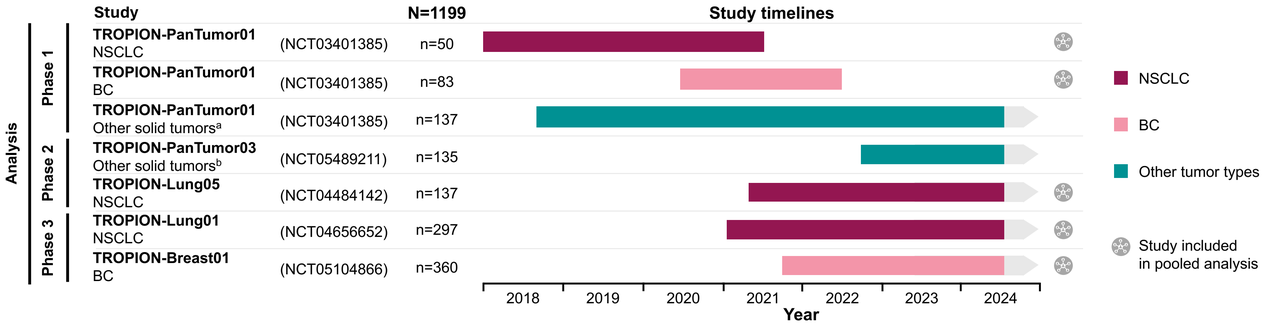
Methods

Patients with NSCLC or BC who received Dato-DXd monotherapy (6 mg/kg) in the phase 1–3 trials TROPION-Lung01, -Lung05, -Breast01, and -PanTumor01 studies were pooled. Additional patients with other solid tumor types (prostate, esophageal, gastroesophageal, pancreatic, small cell lung, urothelial, ovarian, endometrial, colorectal, and biliary tract cancers) receiving Dato-DXd monotherapy as part of newer, ongoing expansion cohorts from the phase I TROPION-PanTumor01 and -PanTumor03 trials were analyzed independently.

An independent adjudication committee retrospectively reviewed all potential ILD cases using imaging and clinical data to assess whether the reported event was a case of ILD and, if such, if it was related to the study drug; only events adjudicated as study drug related are reported. ILD grading is reported by adjudication assessment and may differ from investigator reported grading. In addition, ILD cases with a fatal outcome were assessed to determine if the cause of death was due to study drug-related ILD.



[a]Prostate, esophageal, gastroesophageal, pancreatic, small cell lung, urothelial [b]Prostate, ovarian, endometrial, colorectal, biliary tract cancers.

Results

Demographics and baseline characteristics of NSCLC + BC pool

Characteristic	NSCLC+BC (N=927)
Age, median (range), years	60 (26–86)
≥65 years, n (%)	304 (33)
Female, n (%)	657 (71)
Race, n (%)	
White	421 (45)
Asian	378 (41)
Black	16 (2)
Other	72 (8)
ECOG PS, n (%)	
0[a]	376 (41)
1[a]/2	546 (59)/3 (<1)
Baseline brain metastasis, n (%)	
Yes	143 (15)[a]
Tumor type, n	
NSCLC	484
HR+/HER2– BC	401
TNBC	42
Duration of treatment, n (%)	
>0 to ≤3 months	310 (33)
>3 to ≤6 months	211 (23)
>6 to ≤9 months	181 (20)
>9 to ≤12 months	123 (13)
>12 to ≤18 months	90 (10)
No. of treatment cycles initiated, median (range)	7 (1, 36)

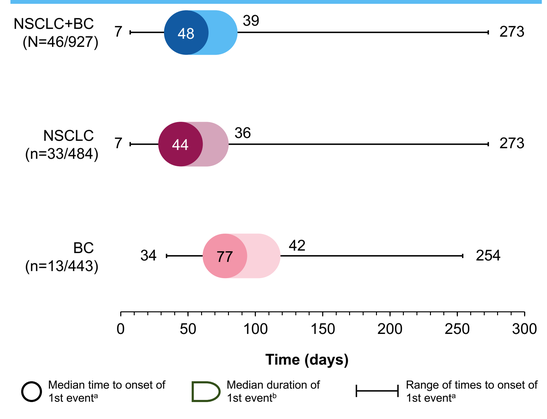
[a]Difference of ≥5% between the TROPION-Breast01 Dato-DXd arm and the NSCLC+BC 6 mg/kg pool.

Pooled analyses of drug-related ILD

Adjudicated drug-related ILD, n (%)	NSCLC+BC (N=927)	NSCLC[a] (N=484)	BC[b] (N=443)	Other tumors[c] (N=272)
Grade 1	9 (1.0)	4 (0.8)	5 (1.1)	1 (0.4)
Grade 2	21 (2.3)	17 (3.5)	4 (0.9)	3 (1.1)
Grade 3	5 (0.5)	2 (0.4)	3 (0.7)	3 (1.1)
Grade 4	2 (0.2)	2 (0.4)	0	1 (0.4)
Grade 5	9 (1.0)	8 (1.7)	1 (0.2)	1 (0.4)[d]
Total	**46 (5.0)**	**33 (6.8)[e]**	**13 (2.9)**	**9 (3.3)**
Associated with dose reduction	3 (0.3)	2 (0.4)	1 (0.2)	0 (0)
Associated with drug interruption	14 (1.5)	11 (2.3)	3 (0.7)	4 (1.5)
Associated with drug withdrawal	26 (2.8)	20 (4.1)	6 (1.4)	3 (1.1)

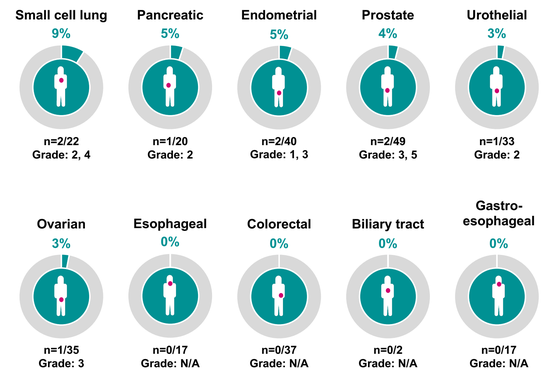
[a]TROPION-Lung01 (n=297); TROPION-Lung05 (n=137); TROPION-PanTumor01 (n=50). [b]TROPION-Breast01 (n=360); TROPION-PanTumor01 (n=83). [c]TROPION-PanTumor01 (n=137); TROPION-PanTumor03 (n=135). [d]One patient with prostate cancer from the TROPION-PanTumor01 trial experienced a grade 5 event. [e]In TROPION-Lung01, 1 additional patient had a drug-related grade 2 ILD event according to the Adjudication Committee. The event was removed from the clinical database by the investigator as the investigator attributed the ILD event to disease progression and is not included in the above analyses.

Time to onset and duration of first adjudicated drug-related ILD event



[a]Assessed by adjudication committee. [b]Assessed by investigator. Median duration of first event is based on resolved cases only.

Incidence of drug-related ILD by other tumor type[a]



[a]TROPION-PanTumor01 (n/N=5/137); TROPION-PanTumor03 (n/N=4/135).

Adjudicated drug-related ILD events with outcome of death

- In the NSCLC+BC pool, there were 9 grade 5 adjudicated drug-related ILD events (7 in TROPION-Lung01, 1 in TROPION-Lung05, 1 in TROPION-Breast01)
  - Of the 8 fatal events in patients with NSCLC, 5 were attributed to disease progression by investigator
  - The 1 fatal event in the patient with BC was also attributed to disease progression by investigator

Guidelines for ILD management

STEP 1: Monitor

Suspected ILD/pneumonitis → Hold Dato-DXd

Rule out ILD/pneumonitis if a patient develops radiographic changes potentially consistent with ILD/pneumonitis or develops an acute onset of new or worsening pulmonary or other related signs/symptoms, such as dyspnea, cough, or fever

STEP 2: Confirm

All ILD/pneumonitis events, regardless of severity or seriousness, must be followed until resolution, including after discontinuation of Dato-DXd

Evaluations should include:

- High-resolution computed tomography
- Pulmonologist consultation (infectious disease consultation as clinically indicated)
- Blood culture and complete blood count, and other blood tests as needed
- Bronchoscopy and bronchoalveolar lavage, if clinically indicated and feasible
- Pulmonary function tests
- Pulse oximetry (SpO_2)
- Arterial blood gases, if clinically indicated
- One blood sample collection for PK analysis as soon as ILD/pneumonitis is suspected, if feasible

STEP 3: Manage

Hold Dato-DXd for any ILD/pneumonitis events, regardless of grade

Grade 1

- Monitor symptoms and closely follow-up in 2–7 days for onset of clinical symptoms and SpO_2
- Consider follow-up imaging in 1–2 weeks (or as clinically indicated)
- Consider starting systemic steroids[a]
- Hold Dato-DXd until fully resolved,[b] then
  - If resolved in ≤28 days from onset date, maintain dose
  - If resolved in >28 days from onset date, reduce dose 1 level
  - If the grade 1 ILD/pneumonitis event does not resolve within 84 days from the last infusion, permanently discontinue Dato-DXd

Grade 2

- Permanently discontinue Dato-DXd
- Monitor symptoms closely and re-image as clinically indicated
- Promptly start treatment with systemic steroids[c]
- If worsening or no improvement is observed in ≤5 days, then
  - Consider increasing the dose of steroids[d]
  - Re-consider work-up for alternative etiologies (return to **Step 2**)
  - Escalate care as clinically indicated

Grade 3–4

- Permanently discontinue Dato-DXd
- Hospitalization required
- Promptly initiate high-dose systemic steroids[c]
- Re-image as clinically indicated
- If no improvement within 3–5 days, then
  - Re-consider work-up for alternative etiologies (return to **Step 2**)
  - Consider other immunosuppressants and/or treat per local practice

These guidelines reflect those which were in place in the clinical development program from December 5, 2022 and are continually updated with the emergence of new safety data. ILD grading is based on investigator assessment, per the guidelines. [a]Prednisone ≥0.5 mg/kg/day or equivalent until improvement, followed by a gradual taper over ≥4 weeks. If events worsen despite corticosteroid treatment, follow guidelines for grade 2 events. [b]Full resolution (grade 0) of ILD/pneumonitis includes the disappearance of radiological findings associated with active ILD/pneumonitis; residual scarring or fibrosis following recovery of ILD/pneumonitis is not considered to be active disease. [c]Grade 2 events: prednisone ≥1.0 mg/kg/day or equivalent; grade 3–4 events: empiric high-dose methylprednisolone IV treatment (e.g., 500–1000 mg/day for 3 days) followed by prednisone ≥1.0 mg/kg/day or equivalent. Corticosteroid treatment should be administered for ≥14 days or until complete resolution of clinical and chest computed tomography findings, followed by a gradual taper over ≥4 weeks. [d]Prednisone 2 mg/kg/day or equivalent or switch to IV administration of methylprednisolone.

Abbreviations

ADC, antibody-drug conjugate; BC, breast cancer; Dato-DXd, datopotamab deruxtecan; ECOG PS, Eastern Cooperative Oncology Group performance status; HR+/HER2–, hormone receptor positive/human epidermal growth factor receptor 2 negative; ILD, interstitial lung disease; IV, intravenous; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; PK, pharmacokinetic; SpO_2, blood oxygen level; PFS, progression-free survival; TNBC, triple negative breast cancer; TROP2, trophoblast cell surface antigen 2.

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