Poster 42P

TROP2 normalised membrane ratio (NMR) assessed by quantitative continuous scoring (QCS): association with clinical outcomes with datopotamab deruxtecan (Dato-DXd) ± osimertinib in *EGFR*-mutated (*EGFR*m) NSCLC

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Objective

- To evaluate association between TROP2 NMR status, ORR and PFS in patients with *EGFR*m NSQ NSCLC receiving Dato-DXd monotherapy in the TROPION-Lung01 and TROPION-Lung05 studies or receiving osimertinib + Dato-DXd in the ORCHARD study.

Conclusions

- There was no association between TROP2 NMR status and improved clinical outcomes in patients with *EGFR*m NSCLC treated with Dato-DXd in TROPION-Lung01/TROPION-Lung05.
  - Data indicate that Dato-DXd provides clinical benefit for patients with *EGFR*m NSCLC regardless of TROP2 NMR status, suggesting no value in patient selection beyond *EGFR*m for Dato-DXd therapy in this setting.
  - This lack of association between TROP2 NMR status and outcomes was also observed with Dato-DXd + osimertinib in ORCHARD, though interpretation is limited due to small patient numbers.
- This finding is not unexpected; *EGFR*m and non-AGA NSCLC are distinct biological subtypes and TROP2 NMR was optimised in NSQ non-AGA NSCLC only.
- Furthermore, preclinical data indicate that patients with *EGFR*m NSCLC may have enhanced sensitivity to TOP1i payloads.[5]
- Ongoing phase 3 studies in patients with *EGFR*m NSCLC will further elucidate the efficacy of Dato-DXd in this setting (2L Dato-DXd ± osimertinib, TROPION-Lung15, NCT06417814; 1L Dato-DXd + osimertinib, TROPION-Lung14, NCT06350097).

Plain language summary

Why did we perform this research?

- Datopotamab deruxtecan (Dato-DXd) is an antibody-drug conjugate that consists of an antibody (datopotamab) that recognises and attaches to cells with a specific protein called trophoblast cell surface antigen 2 (TROP2), and an anticancer drug (DXd), joined via a cleavable linker.[1,2]
- Dato-DXd received accelerated approval in the United States for the treatment of patients with previously-treated locally advanced (has spread to nearby tissue or lymph nodes) or metastatic (has spread from its original site) non-small-cell lung cancer (NSCLC) whose cancer has an *EGFR* mutation (*EGFR*m).[1–3]
- We previously found that patients with non-squamous (NSQ) NSCLC and no actionable genomic alterations (non-AGA) responded better to treatment with Dato-DXd if they were positive for a marker called TROP2 normalised membrane ratio (NMR), which was measured using a method called quantitative continuous scoring (QCS).[4]
- We wanted to see if patients with *EGFR*m NSQ NSCLC also responded better to treatment with Dato-DXd ± osimertinib if they were positive for the TROP2 NMR marker.

How did we perform this research?

- We looked to see if patients were positive for the TROP2 NMR biomarker by analysing digital images of tumour samples from patients with *EGFR*m NSQ NSCLC receiving Dato-DXd in theTROPION-Lung01 and TROPION-Lung05 studies or receiving Dato-DXd + osimertinib in the ORCHARD study.

What were the findings of this research?

- We found no association between the TROP2 NMR status of samples from patients with *EGFR*m NSQ NSCLC and whether they responded or how long they survived without disease progression when treated with Dato-DXd ± osimertinib.

What are the implications of this research?

- These results suggest that patients with *EGFR*m NSQ NSCLC derive benefit from Dato-DXd irrespective of TROP2 NMR status, suggesting no value of the TROP2 NMR marker in further selecting patients for treatment with Dato-DXd.

Where can I access more information?

- Dato-DXd ± osimertinib is also being investigated in patients with *EGFR*m NSCLC in TROPION-Lung15 (NCT06417814; https://clinicaltrials.gov/study/NCT06417814) and TROPION-Lung14 (NCT06350097; https://clinicaltrials.gov/study/NCT06350097).

1. Ahn M-J, et al. J Thorac Oncol 2025;20:1669–82; 2. Le X, et al. J Thorac Oncol 2025;20(Supplement 1):S2–4;
3. US FDA. DATROWAY® Prescribing Information 2025; 4. Garassino MC, et al. J Thorac Oncol 2024;19(10 Supplement):S2–3.

Poster

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Poster presented at European Lung Cancer Congress (ELCC) 2026, Copenhagen, Denmark, by Dr Jacob Sands, MD.

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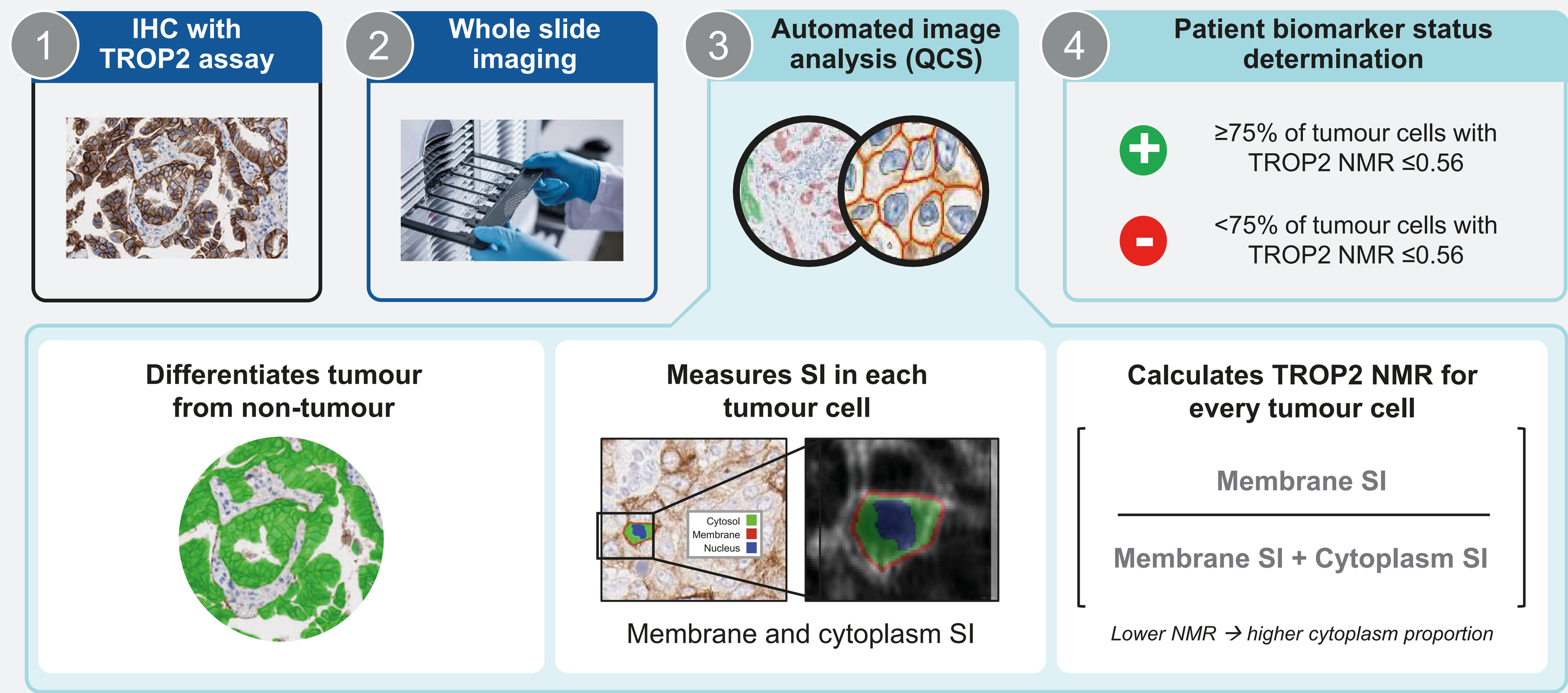
Introduction

- Dato-DXd, a TROP2-directed ADC, received accelerated US FDA approval for treatment of patients with advanced or metastatic *EGFR*m NSCLC who received prior *EGFR*-directed therapy and platinum-based chemotherapy[1] based on a pooled analysis of these patients who received Dato-DXd monotherapy in the phase 3 TROPION-Lung01 (NCT04656652) and phase 2 TROPION-Lung05 (NCT04484142) studies.[2]
- The phase 2 ORCHARD study (NCT03944772) demonstrated promising efficacy with Dato-DXd + osimertinib in patients with advanced or metastatic *EGFR*m NSCLC who had progressed on 1L osimertinib.[3]
- Furthermore, in TROPION-Lung01, Dato-DXd showed greatest clinical benefit vs docetaxel in patients with AGA-positive (including *EGFR*m) NSCLC.[2]
  - More broadly, based on preclinical and clinical evidence *EGFR*m tumours have enhanced sensitivity to TROP2 ADCs with TOP1i payloads (including Dato-DXd) due to increased TOP1i sensitivity.[4,5]
  - *EGFR*m cell lines also show enhanced ADC internalisation capacity,[6] and data suggest persistent/upregulated TROP2 expression post-osimertinib/TKI resistance.[6–8]
- The TROP2 NMR biomarker was identified and optimised in NSQ non-AGA NSCLC and was associated with clinical outcomes with Dato-DXd monotherapy in patients with NSQ non-AGA NSCLC who were treated in TROPION-Lung01 and TROPION-PanTumor01 (NCT03401385).[9]
- We therefore evaluated the association of TROP2 NMR status with outcomes in the distinct biological setting of *EGFR*m NSQ NSCLC in patients receiving Dato-DXd ± osimertinib in TROPION-Lung01/ TROPION-Lung05 and ORCHARD.

Methods

- In TROPION-Lung01 and TROPION-Lung05 combined, 115 patients with *EGFR*m NSQ NSCLC received Dato-DXd monotherapy.[2]
- In ORCHARD, 68 patients with *EGFR*m NSQ NSCLC received Dato-DXd + osimertinib.[3]
- Digitised TROP2 IHC-stained whole-slide images from the tumours of these patients were analysed for TROP2 NMR status using QCS.
- QCS distinguishes tumour areas from non-tumour regions, identifies subcellular compartments, and quantifies expression of the target across precise subcellular locations for every tumour cell.
- TROP2 NMR is a measure of TROP2 expression in the membrane relative to TROP2 expression across the membrane and cytoplasm.
- A sample was considered TROP2 NMR+ if ≥75% of tumour cells had a TROP2 NMR ≤0.56.
- Associations between TROP2 NMR status and ORR (best confirmed objective response) and PFS were evaluated.

Figure 1. Determination of TROP2 NMR biomarker status by QCS



Results

Table 1. Baseline characteristics and patient demographics

	TROPION-Lung01/ TROPION-Lung05			ORCHARD		
	Unselected	TROP2 NMR status		Unselected	TROP2 NMR status	
Group	QCS BEP (N=68)	Positive (N=45)	Negative (N=23)	QCS BEP (N=25)	Positive (N=20)	Negative (N=5)
Age, median (range, years)	62.0 (36–75)	62.0 (36–75)	61.0 (39–72)	65.0 (46–78)	64.0 (46–78)	68.0 (51–74)
Male, n (%)	25 (36.8)	12 (26.7)	13 (56.5)	10 (40.0)	7 (35.0)	3 (60.0)
ECOG PS 1, n (%)	45 (66.2)	30 (66.7)	15 (65.2)	11 (44.0)	8 (40.0)	3 (60.0)
Current or former smoker, n (%)	30 (44.1)	16 (35.6)	14 (60.9)	10 (40.0)	6 (30.0)	4 (80.0)
Brain metastasis at study entry, n (%)	17 (25.0)	15 (33.3)	2 (8.7)	11 (44.0)	8 (40.0)	3 (60.0)
≥3 prior regimens, n (%)	2 (2.9)	0 (0)	2 (8.7)	N/A	N/A	N/A

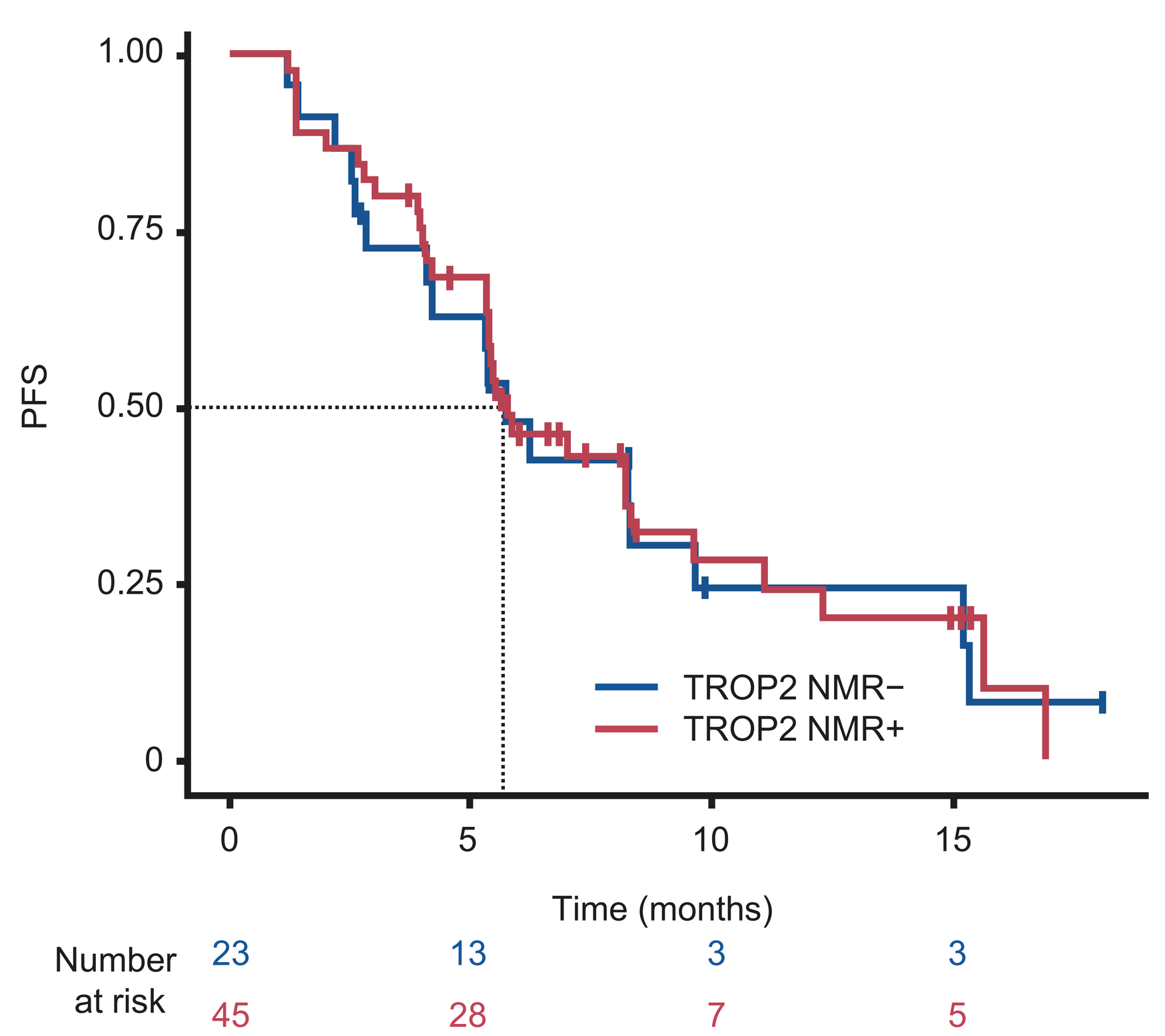
- Overall, 68/115 patients had evaluable samples in TROPION-Lung01/TROPION-Lung05 and 25/68 patients had evaluable samples in ORCHARD (**Table 1**).
- Of these samples, in TROPION-Lung01/ TROPION-Lung05, 66% (45/68) were TROP2 NMR+ and 34% (23/68) were TROP2 NMR–. In the ORCHARD study, 80% (20/25) were TROP2 NMR+ and 20% (5/25) were TROP2 NMR– (**Table 1**).

Table 2. Overall safety

TRAEs, n (%)		TROPION-Lung01/ TROPION-Lung05		ORCHARD	
		TROP2 NMR status		TROP2 NMR status	
		Positive (N=45)	Negative (N=23)	Positive (N=20)	Negative (N=5)
Any TRAE	Any grade	42 (93.3)	23 (100)	18 (90)	5 (100)
	Grade ≥3	12 (26.7)	6 (26.1)	9 (45.0)	2 (40.0)
Treatment-related AESIs, n (%)					
Stomatitis/ oral mucosal inflammation	Any grade	33 (73.3)	16 (69.6)	14 (70.0)	2 (40.0)
	Grade ≥3	6 (13.3)	1 (4.3)	2 (10.0)	0 (0)
Ocular surface events	Any grade	10 (22.2)	10 (43.5)	3 (15.0)	0 (0)
	Grade ≥3	0 (0)	3 (13.0)	0 (0.0)	0 (0)
Adjudicated ILD	Any grade	2 (4.4)	0 (0)	2 (10.0)	0 (0)
	Grade ≥3	0 (0)	0 (0)	1 (5.0)	0 (0)

- With the caveat of small patient numbers for some events, the safety profile by TROP2 NMR status was generally comparable, except the incidence of ocular surface events which was higher in the TROP2 NMR– group in TROPION-Lung01/TROPION-Lung05 pooled analysis.
- With the caveat of small patient numbers for all events, the safety profile by TROP2 NMR status was generally comparable in ORCHARD analysis; only Dato-DXd-related events are recorded and events exclusively related to osimertinib were not considered.

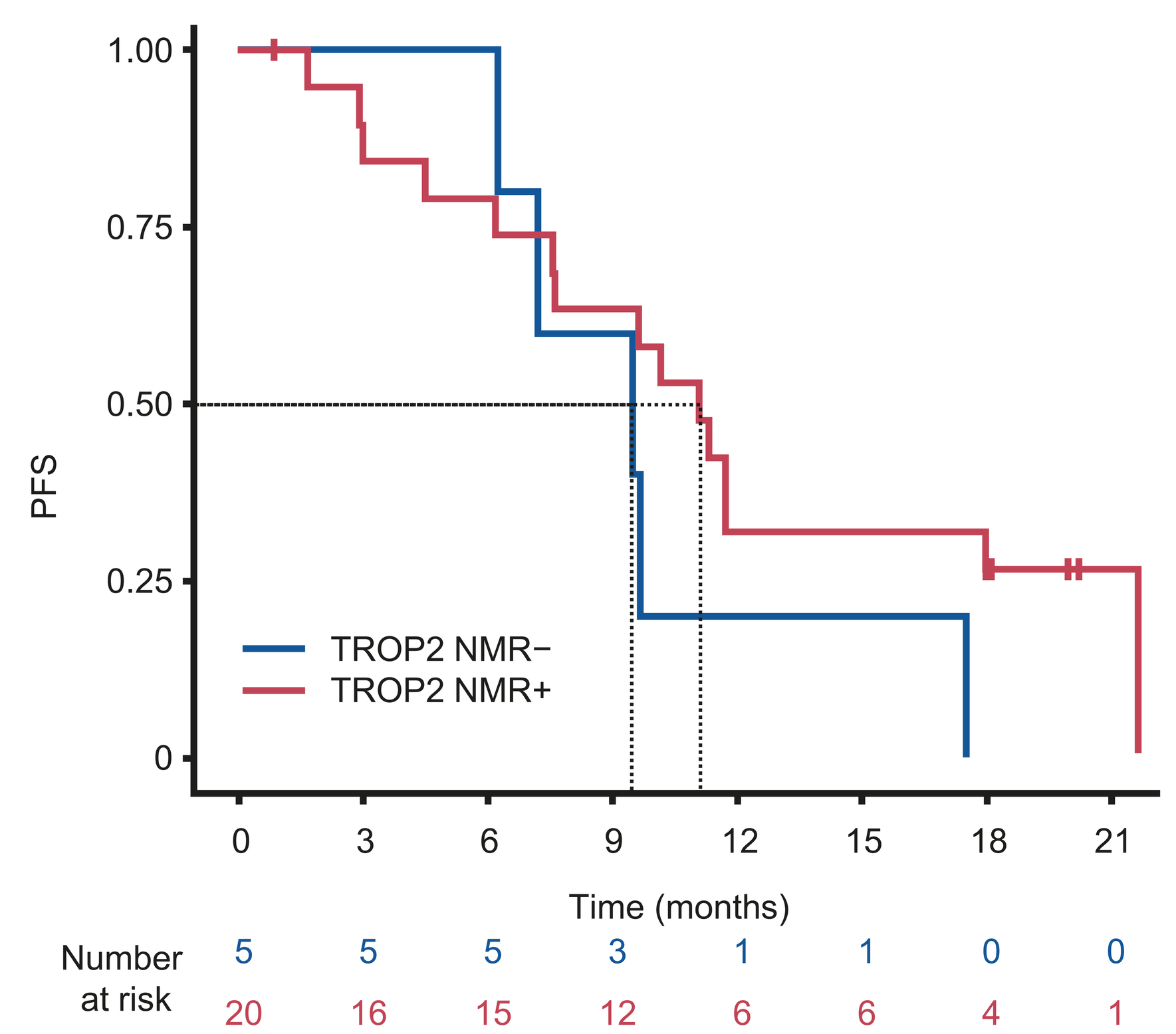
Figure 2. PFS and ORR by TROP2 NMR status in evaluable patients with *EGFR*m NSQ NSCLC receiving Dato-DXd in TROPION-Lung01 and TROPION-Lung05



	Unselected	TROP2 NMR status	
Group	QCS BEP	Positive	Negative
Prevalence, n (%)	68 (100)	45 (66)	23 (34)
ORR, n (%) (95% CI)	31 (45.6) (33.5–58.1)	18 (40.0) (25.7–55.7)	13 (56.5) (34.5–76.8)
Median PFS, months (95% CI)	5.8 (5.4–8.3)	5.8 (5.4–9.7)	5.7 (4.2–15.4)
HR (95% CI)	-	0.95 (0.53–1.72)	
p-value	-	0.88	

- ORR was numerically lower in patients with TROP2 NMR+ samples vs TROP2 NMR– samples (**Figure 2**).
- Median PFS was similar between TROP2 NMR+ vs TROP2 NMR– patients (**Figure 2**).

Figure 3. PFS and ORR by TROP2 NMR status in evaluable patients with *EGFR*m NSQ NSCLC receiving Dato-DXd + osimertinib in ORCHARD



	Unselected	TROP2 NMR status	
Group	QCS BEP	Positive	Negative
Prevalence, n (%)	25 (100)	20 (80)	5 (20)
ORR, n (%) (95% CI)	11 (44.0) (24.0–65.0)	7 (35.0) (15.0–59.0)	4 (80.0) (28.0–99.0)
Median PFS, months (95% CI)	9.9 (7.2–11.7)	11.1 (6.2–18.0)	9.5 (6.2–NA)

- ORR appeared numerically lower and PFS curves appeared similar in patients with TROP2 NMR+ samples vs TROP2 NMR– samples (**Figure 3**); however, interpretation is confounded by the very small numbers of patients with TROP2 NMR– samples.

Abbreviations

1L, first-line; 2L, second-line; ADC, antibody-drug conjugate; AESI, adverse event of special interest; AGA, actionable genomic alteration; BEP, biomarker-evaluable population; CI, confidence interval; Dato-DXd, datopotamab deruxtecan; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*m, *EGFR*-mutated; FDA, Food and Drug Association; HR, hazard ratio; IHC, immunohistochemistry; ILD, interstitial lung disease; NA, not available; NMR (+/−), normalised membrane ratio (-positive/-negative); NSCLC, non-small cell lung cancer; NSQ, non-squamous; ORR, objective response rate; PFS, progression-free survival; QCS, quantitative continuous scoring; SI, staining intensity; TKI, tyrosine kinase inhibitor; TOP1i, topoisomerase inhibitor; TRAE, treatment-related adverse event; TROP2, trophoblast cell surface antigen 2; US, United States.

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Disclosures

Jacob Sands has acted as a consultant for AbbVie, Amgen, AstraZeneca, Catalyst, Curadev, Daiichi Sankyo, Fosun, Genetech, Gilead, Jazz Pharmaceuticals, Lilly, Merck, Novartis, PharmaMar, Sanofi and Summit Therapeutics; received research funding to institution from Amgen and Novartis.

References

1. US FDA. DATROWAY® Prescribing Information 2025.
2. Ahn M-J, et al. J Thorac Oncol 2025;20:1669–82.
3. Le X, et al. J Thorac Oncol 2025;20(Suppl 1):S2–4.
4. Wang Z, et al. Acta Pharm Sin B 2023;13:4025–59.
5. Sung M, et al. Poster 449P. Presented at ELCC 2026; Copenhagen, Denmark.
6. Zhao S, et al. Nat Med 2025;31:1976–86.
7. Sands J, et al. J Clin Oncol 2025;43:1254–65.
8. Baldacci S, et al. Cancer Discov 2025;15:2235–50.
9. Garassino MC, et al. J Thorac Oncol 2024;19(10 Suppl):S2–3.