Poster 357P

Association of TROP2 quantitative continuous scoring normalised membrane ratio with efficacy in Chinese patients with advanced/metastatic non-small cell lung cancer treated with datopotamab deruxtecan in TROPION-PanTumor02

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Objective

- To assess the association of TROP2 QCS-NMR status with efficacy in Chinese patients with advanced or metastatic NSCLC who received Dato-DXd in the 2L+ setting in the phase 1/2, multicentre, open-label TROPION-PanTumor02 study.

Conclusions

- In this retrospective, exploratory analysis of 38 Chinese patients, those with TROP2 QCS-NMR-positive tumours who received Dato-DXd had a numerically higher ORR and longer median PFS compared with patients with TROP2 QCS-NMR-negative tumours.
- Although the number of patients in the analysis was small, the results from this independent cohort are consistent with TROP2 QCS-NMR data reported for TROPION-Lung01 and further demonstrate the potential of TROP2 QCS-NMR as a predictive biomarker for Dato-DXd in advanced or metastatic NSCLC.
- The association of TROP2 QCS-NMR with efficacy is being assessed as one of the primary endpoints in the ongoing phase 3, randomised, open-label AVANZAR study (NCT05687266) and the ongoing phase 3, randomized, open label TROPION-Lung10 study (NCT06357533).

Plain language summary

Why did we perform this research?

- Datopotamab deruxtecan (Dato-DXd), is a type of drug called an antibody-drug conjugate, which consists of an antibody (datopotamab) and an anticancer drug (DXd), joined via a stable cleavable linker.[1] Dato-DXd has shown activity in clinical studies called TROPION-Lung01 and TROPION-PanTumor02 in patients with a type of lung cancer called non-small cell lung cancer (NSCLC), which had spread from its original site (advanced/metastatic).[2,3]
- In order to work, Dato-DXd must bind to a protein on the surface of cancer cells called trophoblast cell surface antigen 2 (TROP2) and be taken inside the cell.[1] When researchers looked at the amount of TROP2 in tumour cells from patients with NSCLC using a conventional method called immunohistochemistry and manual scoring, the amount of TROP2 did not predict how well Dato-DXd treatment worked.[4,5]
- Researchers designed a new way of looking at the ratio of TROP2 expression both inside the cell and on the cell surface, called quantitative continuous scoring (QCS) normalised membrane ratio (NMR).[6] When they used QCS-NMR to look at tumour samples from patients in a study called TROPION-Lung01 they found that patients who had the best responses to Dato-DXd had tumour cells that had more comparable levels of TROP2 expression inside the cell compared with the cell surface.[7]
- Researchers wanted to look at other studies to see if they could replicate these results.

How did we perform this research?

- Researchers analysed digital images of tumour samples to determine TROP2 QCS-NMR status from Chinese patients with advanced or metastatic NSCLC who received Dato-DXd in the TROPION-PanTumor02 study.

What were the findings of this research?

- Patients whose tumour samples were TROP2 QCS-NMR-positive tended to have better responses and lived longer without their disease getting worse than patients whose tumour samples were TROP2 QCS-NMR-negative.

What are the implications of this research?

- The results from TROPION-PanTumor02 were consistent with the results from TROPION-Lung01 and suggest that TROP2 QCS-NMR may be able to predict which patients may respond best to Dato-DXd in advanced or metastatic NSCLC.

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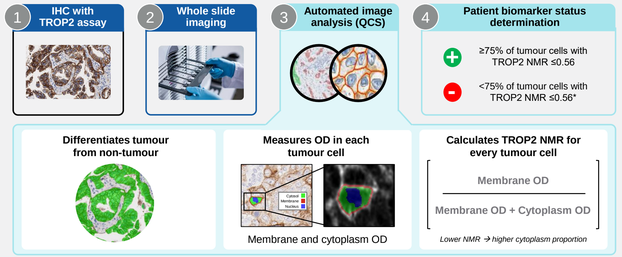
Introduction

- Dato-DXd is an ADC composed of a humanised TROP2–directed monoclonal antibody linked to a topoisomerase I inhibitor payload via a plasma-stable, cleavable linker.[1]
- In the phase 3 TROPION-Lung01 study, Dato-DXd significantly improved PFS vs docetaxel in patients with advanced or metastatic NSCLC, driven by patients with non-squamous histology. OS showed a numerical benefit but did not reach statistical significance.[2]
- Conventional IHC scoring has not predicted response to TROP2-directed ADCs in patients with NSCLC.[3,4]
- We hypothesised that a more precise and quantitative assessment of TROP2 expression may predict the efficacy of Dato-DXd in NSCLC.
- QCS is a novel, fully supervised computational pathology approach that can precisely quantify targets like TROP2 in individual cells and subcellular components.[5]
- By using QCS to determine TROP2 expression, the NMR can be calculated (a ratio of membrane TROP2 relative to cytoplasm).
- In an exploratory analysis of TROPION-Lung01, patients receiving Dato-DXd who had TROP2 QCS-NMR positive tumours had increased ORR and longer PFS than those with TROP2 QCS-NMR-negative tumours.[6]
- The phase 1/2 TROPION-PanTumor02 study assessed the efficacy and safety of Dato-DXd in Chinese patients with advanced or metastatic solid tumours. In the advanced or metastatic NSCLC cohort, patients with or without AGAs, received Dato-DXd 6 mg/kg intravenously every 3 weeks until disease progression, unacceptable toxicity, withdrawal of consent, or initiation of a new therapy.[7]
  - Dato-DXd demonstrated encouraging preliminary efficacy and no new safety signals were observed.
  - Antitumour activity was more pronounced in patients with non-squamous vs squamous cell carcinoma histology.
- Here, we report the association of TROP2 QCS-NMR status with clinical outcomes in Chinese patients with NSCLC from the TROPION-PanTumor02 study.

Methods

- Digitised TROP2 IHC-stained whole-slide images of tissue samples from patients in TROPION-PanTumor02 were analysed by QCS (**Figure 1**).
- QCS can distinguish tumour cells from normal tissue cells, and can differentiate membrane from cytoplasmic staining in all tumour cells in the digitised image.
- TROP2 staining intensity is determined individually for both membrane and cytoplasm for every tumour cell.
- TROP2 NMR is a measure of TROP2 expression in the membrane relative to total TROP2 in membrane and cytoplasm.
- Samples were considered TROP2 QCS-NMR-positive if ≥75% of tumour cells had NMR ≤0.56.

Figure 1. TROP2 NMR measured by QCS



*Or >25% of tumour cells with TROP2 NMR >0.56.

Results

Patients

- In total, 40 patients were enrolled in the TROPION-PanTumor02 NSCLC cohort and received Dato-DXd; clinical primary analysis data cut-off was 9 October, 2023. A total of 38 patients had tumour images which passed quality control for QCS-NMR determination (biomarker-evaluable population).
- Demographics and baseline characteristics of the biomarker-evaluable population were broadly comparable to those of the total patient population (**Table 1**).

Table 1. Demographics and baseline characteristics of TROPION-PanTumor02 and biomarker-evaluable populations

Demographic or baseline characteristic	Total population (N=40)	Biomarker-evaluable population (n=38)	
		TROP2 QCS-NMR+ (n=20)	TROP2 QCS-NMR– (n=18)
Age, median (range), years	59.0 (33–74)	59.5 (41–74)	59.5 (33–74)
Male, n (%)	29 (72.5)	14 (70.0)	14 (77.8)
ECOG PS 1, n (%)	34 (85.0)	15 (75.0)	17 (94.4)
Smoking history			
Current or former, n (%)	18 (45.0)	10 (50.0)	8 (44.4)
Central nervous system metastasis at study entry, n (%)	3 (7.5)	2 (10.0)	1 (5.6)
≥3 prior lines of therapy at baseline, n (%)	2 (5.0)	2 (10.0)	0 (0)
AJCC staging at baseline, n (%)			
Stage IIIB	3 (7.5)	1 (5.0)	2 (11.1)
Stage IV	37 (92.5)	19 (95.0)	16 (88.9)

AJCC, American Joint Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; NMR, normalised membrane ratio; TROP2, trophoblast cell surface antigen 2; QCS, quantitative continuous scoring.

TROP2 QCS-NMR status by histology

- Of the 38 patient samples for whom QCS was evaluable, 21 had non-squamous histology and 17 had squamous histology.
- In total, 52.6% (n=20/38) were TROP2 QCS-NMR-positive. TROP2 QCS-NMR-positive tumours were numerically higher in patients with non-squamous (76.2%) vs squamous histology (23.5%) (**Table 2**).

Table 2. TROP2 QCS-NMR status in patients with non-squamous and squamous histology

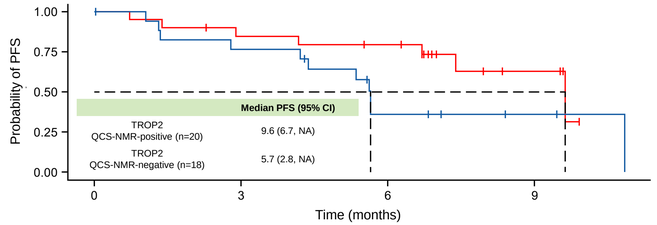
Population	Group	n (%)
Non-squamous samples evaluable for TROP2 QCS-NMR	Overall	21 (100)
	TROP2 QCS-NMR-negative	5 (23.8)
	TROP2 QCS-NMR-positive	16 (76.2)
Squamous samples evaluable for TROP2 QCS-NMR	Overall	17 (100)
	TROP2 QCS-NMR-negative	13 (76.5)
	TROP2 QCS-NMR-positive	4 (23.5)

NMR, normalised membrane ratio; QCS, quantitative continuous scoring; TROP2, trophoblast cell surface antigen 2.

PFS by TROP2 QCS-NMR status

- Median PFS was longer for patients with TROP2 QCS-NMR-positive tumours than for patients with TROP2 QCS-NMR-negative tumours (**Figure 2**).

Figure 2. PFS by TROP2 QCS-NMR status



Number at risk (number censored)

TROP2 QCS-NMR-negative	18 (0)	13 (1)	5 (3)	2 (6)
TROP2 QCS-NMR-positive	20 (0)	16 (1)	14 (2)	4 (10)

ORR by TROP2 QCS-NMR status

- ORR was numerically higher for patients with TROP2 QCS-NMR-positive tumours vs TROP2 QCS-NMR-negative tumours (**Table 3**).

Table 3. ORR by TROP2 QCS-NMR status

	Biomarker-evaluable population (n=38)	
TROP2 QCS-NMR status	Positive (n=20)	Negative (n=18)
ORR, % (95% CI)	55.0 (32, 77)	27.8 (10, 53)

NMR, normalised membrane ratio; ORR, objective response rate; QCS, quantitative continuous score; TROP2, trophoblast cell surface antigen 2.

Limitations

- This was a post hoc exploratory analysis.
- The samples size was small and there were insufficient patient numbers to perform an analysis of PFS by histology.

Safety by TROP2 QCS-NMR status

- With the caveat of small patient numbers for some events, the safety profile by TROP2 QCS-NMR status was generally comparable, except the incidence of stomatitis which was higher in the TROP2 QCS-NMR positive group (**Table 4**).

Table 4. Safety by TROP2 QCS-NMR status

TRAEs, n (%)		TROP2 QCS-NMR+ (n=20)	TROP2 QCS-NMR– (n=18)
Any TRAE	All grades	20 (100.0)	15 (83.3)
	Grade ≥3	8 (40.0)	6 (33.3)
Treatment-related AESIs*			
Stomatitis/oral mucosal inflammation	All grades	17 (85.0)	6 (33.3)
	Grade ≥3	3 (15.0)	2 (11.1)
Ocular surface events	All grades	5 (25.0)	4 (22.2)
	Grade ≥3	0	0
Adjudicated ILD†	All grades	0	0

The relationship between treatment and events were assessed by the investigator. *AESIs are grouped terms using preferred terms selected from relevant standardised MedDRA query, MedDRA V26.0. †Adjudicated ILD; CTCAE grade and relationship with study drug were assessed by the adjudication committee. AESI, adverse event of special interest; ILD, interstitial lung disease; NMR, normalised membrane ratio; QCS, quantitative continuous scoring; TRAE, treatment-related adverse event; TROP2, trophoblast cell surface antigen 2.

Abbreviations

1L/2L, first/second line; AESIs, adverse event of special interest; ADA, antibody-drug conjugate; AGA, actionable genetic alterations; AJCC, American Joint Committee on Cancer; Dato-DXd, datopotamab deruxtecan; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; ILD, interstitial lung disease; MedDRA, Medical Dictionary for Regulatory Activities; NMR, normalised membrane ratio; NSCLC, non-small cell lung cancer; OD, optical density; OS, overall survival; ORR, objective response rate; PFS, progression-free survival; QCS, quantitative continuous scoring; TRAE, treatment-related adverse event; TROP2, trophoblast cell surface antigen 2.

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Disclosures

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