Editorial Commentary

Deciding where Trop-2 directed antibody drug conjugates work in non-small cell lung cancer: the not so straightforward road

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Trophoblast cell-surface antigen 2 (Trop-2) is a transmembrane glycoprotein involved in several signaling pathways in carcinogenesis such as calcium signaling, beta-catenin signaling, and fibronectin adhesion (1). In carcinogenesis, Trop-2 promotes cell proliferation, angiogenesis, and metastasis by NF-κB activation and signaling of the extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) kinase MEK signaling pathway (1). Trop-2 immunohistochemical (IHC) expression is overexpressed in 64% adenocarcinomas, 75% squamous cell carcinoma, and 18% of high-grade neuroendocrine tumors in lung cancer, which has led to significant interest in the use of Trop-2 directed therapies in lung cancer (2). Furthermore, Trop-2 directed antibody-drug conjugates (ADCs) have had success in other solid tumors. Sacituzumab govitecan, a Trop-2 ADC that selectively delivers SN-38, an active metabolite of irinotecan, has been United States Food and Drug Administration (FDA) approved in triple-negative breast cancer, hormone-receptor positive (HR^+), human epidermal growth factor receptor 2 negative ($HER2^-$) breast cancer, and advanced urothelial cancer (3-5). Sacituzumab govitecan received approval in triple-negative breast cancer based on the ASCENT study based on pre-treated patients in which the median progression-free survival (PFS) was 5.6 months [95% confidence interval (CI): 4.3–6.3] in patients receiving sacituzumab govitecan compared to 1.7 months (95% CI: 1.5–2.6) in patients receiving single-agent chemotherapy and median overall survival (OS) of 12.1 months (95% CI: 10.7–14.0) and 6.7 months (95% CI: 5.8–7.7) respectively (3). In $HR^+/HER2^-$ breast cancer locally recurrent inoperable or metastatic breast cancer patients who had received at least one previous endocrine therapy, OS was significantly improved with sacituzumab govitecan versus chemotherapy (median 14.4 months (95% CI: 13.0–15.7) *vs.* 11.2 months (95% CI: 10.1–12.7) (4). In urothelial cancer, sacituzumab govitecan was approved after the TROPHY-U-01 study in which patients with metastatic urothelial carcinoma who had progressed on platinum-based combination chemotherapy and checkpoint had median PFS of 5.4 months (95% CI: 3.5–7.2) and OS of 10.9 months (95% CI: 9.0–13.8) (5).

However, finding success in treatment of Trop-2 directed ADCs in non-small cell lung cancer (NSCLC) has proven challenging. The IMMU-132 single-arm multicenter trial for patients with metastatic NSCLC had a modest overall response rate (ORR) of 17% with median PFS of 5.2 months (95% CI: 3.2–7.1) and median OS of 9.5 months

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Table 1 TROPION-Lung 01 and EVOKE-01 studies

Study	N	Indication	Median OS	Median PFS	ORR	Grade 3+ toxicity
TROPION-Lung 01 (7)	299 (Dato-DXd) *vs.* 305 (docetaxel)	Advanced NSCLC having progressed on chemotherapy and immunotherapy	Dato-Dxd *vs.* docetaxel: 12.9 months (95% CI: 11.0–13.9) *vs.* 11.8 months (95% CI: 10.1–12.8), HR 0.94 (95% CI: 0.78–1.14)	Dato-Dxd *vs.* docetaxel: 4.4 months (95% CI: 4.2–5.6) *vs.* 3.7 months (95% CI: 2.9–4.2), HR 0.75 (95% CI: 0.62–0.91)	Dato-Dxd *vs.* docetaxel: 26.4% (95% CI: 21.5–31.8) *vs.* 12.8% (95% CI: 9.3–17.1)	Dato-Dxd *vs.* docetaxel: 25.6% *vs.* 42.1% (any-grade adjudicated drug-related ILD: Dato-Dxd: 8.8% *vs.* docetaxel: 4.1%)
EVOKE-01 (8)	299 (SG) *vs.* 304 (docetaxel)	Metastatic NSCLC with progression on/after platinum-based chemotherapy, anti-PD-(L)1, and targeted treatment for actionable genomic alterations	SG *vs.* docetaxel: 11.1 *vs.* 9.8 months, HR 0.84 (95% CI: 0.68–1.04)	SG *vs.* docetaxel: 4.1 *vs.* 3.9 months, HR 0.92 (95% CI: 0.77–1.11)	SG *vs.* docetaxel: 13.7% (95% CI: 10.0–18.1) *vs.* 18.1% (95% CI: 13.9–22.9)	SG *vs.* docetaxel: 66.6% *vs.* 75.7% (1 patient died from pneumonitis in docetaxel group)

N, number of subjects; OS, overall survival; PFS, progression free survival; ORR, overall response rate; Dato-DXd, datopotamab deruxtecan; NSCLC, non-small cell lung cancer; HR, hazard ratio; CI, confidence interval; SG, sacituzumab govitecan; ILD, interstitial lung disease; PD-(L)1, programmed cell death (ligand) 1.

(95% CI: 5.9–16.7) (6). Of note, more than 90% of the 26 assessable archival tumor samples in the study had Trop-2 IHC specimens that were highly positive (2+, 3+) suggesting that Trop-2 IHC positivity was not a predictive biomarker for response. (6) Subsequently, Trop-2 ADCs have been studied with datopotamab deruxtecan (Dato-DXd), a Trop-2 monoclonal antibody linked to a topoisomerase I inhibitor. In the TROPION-Lung 01 phase 3 study comparing Dato-DXd versus docetaxel in patients with advanced NSCLC who progressed on chemotherapy and immunotherapy, there was a statistically significant though numerically modest PFS improvement in Dato-DXd compared to docetaxel chemotherapy (7) (*Table 1*). On further inspection, this appeared to be driven by non-squamous cases, as non-squamous cases had a significantly improved survival histology [PFS: 5.6 months (95% CI: 4.4–7.0) *vs.* 3.7 months (95% CI: 2.9–4.2); hazard ratio 0.63 (95% CI: 0.51–0.78)] while squamous cases did not have any survival benefit [median PFS 2.8 months (95% CI: 1.9–4.0) in Dato-DXd *vs.* median PFS 3.9 months (95% CI: 2.8–4.5) in docetaxel; hazard ratio 1.38 (95% CI: 0.94–2.02)] (7). Grade ≥3 treatment-related adverse events (TRAEs) occurred at rates of 25.6% and 42.1%, serious TRAEs at 11.1% and 12.8%, dose reductions at 20.2% and 29.7%, and treatment discontinuations at 8.1% and 12.1% for Dato-DXd and docetaxel, respectively (7). The EVOKE-01 study was another phase 3 study looking at measurable stage IV patients with progression after platinum-based and anti-PD-(L)1-containing regimen to either receive sacituzumab govitecan or docetaxel (8). The study did not meet its primary endpoint of OS. Subgroup analysis did not show OS benefit in either the non-squamous group [hazard ratio 0.87 (95% CI: 0.68–1.11)] or the squamous group [hazard ratio 0.83 (95% CI: 0.56–1.22)] that was seen in the Dato-DXd TROPION-Lung 01 study (8).

These disappointing results truly brought into question how to best evaluate which patients in NSCLC would benefit from Trop-2-directed therapy. The ICARUS-LUNG 01 study was a phase 2 investigator-initiated study evaluating patients receiving Dato-DXd who had progressed on 1–3 lines of therapy in trying to see if there were specific biomarkers or mechanisms of actions that could differentiate between responders and non-responders (9). Similar to the TROPION-Lung 01 study, Dato-DXd appeared to show benefit in tumors with non-squamous histology (9). Regarding H-score, there was more survival benefit in patients with an H-score of ≥100 but patients with a wide range of Trop-2 expression by H-score benefitted from Dato-Dxd therapy (9). There also were no driver alterations with a significant association with response or resistance to Dato-DXd (9). The study did show that activation of DNA repair and suppression of immune-mediated pathways after 1–2 cycles of Dato-DXd could be associated with treatment resistance (9).

Table 2 Efficacy by Trop-2 QCS-NMR status

Efficacy endpoint	Trop-2 QCS-NMR$^+$		Trop-2 QCS-NMR$^-$	
	Dato-DXd (n=107)	Docetaxel (n=107)	Dato-DXd (n=65)	Docetaxel (n=73)
ORR, %	32.7	10.3	16.9	15.1
Median PFS, months	6.9	4.1	2.9	4.0
HR of PFS (95% CI)	0.57 (0.41–0.79)		1.16 (0.79–1.70)	

Trop-2, trophoblast cell-surface antigen 2; QCS-NMR, Quantitative Continuous Scoring-Normalized Membrane Ratio; QCS-NMR$^+$, Quantitative Continuous Scoring-Normalized Membrane Ratio positive (defined as ≥75% of tumor cells with Trop-2 NMR ≤0.56); QCS-NMR$^-$, Quantitative Continuous Scoring-Normalized Membrane Ratio negative (defined as <75% of tumor cells with Trop-2 NMR ≤0.56); Dato-DXd, datopotamab deruxtecan; n, number of subjects; ORR, overall response rate; PFS, progression free survival; HR, hazard ratio; CI, confidence interval.

Bessede *et al.* provided an alternative perspective to understanding Trop-2 expression in NSCLC treatment response that may better select the patients (10). In this study, the investigators collected gene expression data from the phase II POPLAR and phase III OAK trials which evaluated atezolizumab versus docetaxel in NSCLC patients who progressed on platinum-based chemotherapy and performed multiplex immunofluorescence, RNA sequencing, and plasma proteomics (10). Notably, it was found that high Trop-2 encoding gene (TACSTD2) expression was associated with worse OS (median 12.6 *vs.* 16.3 months, P=0.007) in patients treated with atezolizumab but not with chemotherapy (10). It also showed that specifically the intracellular domain of Trop-2 was associated with worse outcomes in patients treated with atezolizumab in which high TACSTD2 intracellular expression was significantly associated with worse PFS (median PFS 1.4 *vs.* 13.4 months, P=0.038) and OS (median 6.9 *vs.* 30.8, P=0.226) in patients treated with atezolizumab (10). High circulating Trop-2 levels were associated with worse outcomes in PFS (median 8.5 *vs.* 24.6 months, P=0.045) (10). These results showed that Trop-2 gene expression as we know it may not be predictive for Trop-2 directed ADCs but instead predictive for immunotherapy resistance (10). These results align with subgroup analysis from the EVOKE-01 of which non-responders (defined as those with best response to therapy as stable disease or progressive disease) had a significant OS improvement [11.5 months (95% CI: 9.6–12.5) in sacituzumab govitecan *vs.* 8.3 months (95% CI: 7.0–10.6) in docetaxel] not seen in patients with complete or partial response to programmed cell death (ligand) 1 [PD-(L)1] containing response [median OS 9.6 months (95% CI: 8.1–14.4) in sacituzumab govitecan *vs.* 10.6 months (95% CI: 8.9–12.8) in docetaxel] (8). These studies could dictate which patients should either be candidates for a combination of Trop-2 ADC and immunotherapy or candidates who may have significant benefit for a Trop-2 ADC over immune checkpoint inhibitor.

More recently, a study was presented that evaluated Trop-2 expression by quantitative continuous scoring (QCS) utilizing digitalized Trop-2 IHC stained whole-slide images from NSCLC patients and using machine learning to identify tumor areas and cellular components (membrane and cytoplasm) within the whole-slide images (11). The automated image analysis evaluated the optical density between membrane and cytoplasm. Subsequently, we then calculated Trop-2 expression in the membrane relative to the cytoplasm producing a normalized membrane ratio (NMR) measured by QCS. A sample was considered NMR positive if ≥75% of tumor cells with Trop-2 have an NMR ≤0.56, suggestive of higher Trop-2 expression in the cytoplasm (11). The investigators used samples from the TROPION-Lung01 study of which 352 were biomarker evaluable. Among biomarker evaluable patients, 63% had Trop-2 QCS-NMR$^+$ (11). The highest prevalence of Trop-2 QCS-NMR$^+$ was observed in non-squamous/actionable mutations subgroup (75%) followed by non-squamous/non-actionable mutation, and squamous (43%) subgroup. When evaluating efficacy based on Trop-2 QCS-NMR$^+$, ORR and PFS efficacy was significantly improved in the Dato-DXd group compared to the docetaxel group (11). However, in the Trop-2 QCS-NMR$^-$, ORR and PFS efficacy were not predictive (11) (*Table 2*). The rates of adverse events were similar regardless of Trop-2 QCS-NMR status.

Thus, these two recent developments suggest that we can find the right NSCLC patients who will benefit from Trop-2 ADCs but this will require a more complex approach than IHC expression. There will need to be more

validation towards studying the role of Trop-2 expression both in the membrane and the cytoplasm and seeing which aspects of the cell will be predictive towards Trop-2 response. For example, Garassino *et al.* suggested that a higher ratio of Trop-2 cytoplasm to membrane expression was predictive of better ORR and longer PFS (11). On the other hand, Bessede *et al.* showed that increased intracellular Trop-2 expression was associated with worse immune checkpoint inhibitor response (10). The Trop-2 QCS-NMR biomarker is being used in the phase III AVANZAR trial evaluating Dato-DXd, durvalumab, and carboplatin as first-line treatment of advanced NSCLC without actionable mutations (NCT05687266) and biomarker analysis of Trop-2 QCS-NMR in patients from this study will serve a key validator towards the initial findings seen in retrospective analysis of TROPION-Lung 01. Overall, replication of these results is important given that there is no current gold standard for Trop-2 biomarkers.

Furthermore, more remains to be seen with the use of Trop-2 ADCs as combination therapies. There are multiple ongoing studies combining Trop-2 ADCs and immunotherapy in the front-line such as the EVOKE-02 study combining sacituzumab govitecan which showed ORR of 67% (95% CI: 47–83%) and median PFS of 13.1 months (95% CI: 5.5–not reached) in PD-L1 TPS ≥50% patients and the TROPION-Lung02 study in which front line Dato-DXd with chemotherapy and pembrolizumab had an ORR of 60% (95% CI: 36–81%) and Dato-DXd and pembrolizumab had an ORR of 55% (95% CI: 39–70%) (12,13). Further maturation of the data and retrospective analysis of viable biopsy samples obtained from these studies will help determine whether adding immunotherapy or chemotherapy to Trop-2-directed ADCs may be beneficial to a subset of NSCLC patients based on biomarker testing.

Another key aspect to implementing Trop-2 biomarkers into practice will be to see how easy it will be for pathology to replicate these studies for many patients without delaying treatment to care and how much it will cost. If the ability to create digital slides and utilize machine learning required for each patient will be time-consuming and costly then it will not be replicable in many places outside of cancer centers with specialized pathologists and only worsen the barriers to cancer healthcare equity. The computational methods towards creating these slides involve pre-processing an image, segmentation into separating the nucleus and cytoplasm portion of the cell, hematoxylin and eosin (H&E) based phenotyping, spatial analysis (involving interactions between immune cells and tumor, heterogeneity of cell types across tumor, clustering of co-occurring cell groups in a certain space within the cell) to capture the patterns of cellular distributions within the tumor microenvironment, and spatiotemporal pathology to evaluate spacing and location at different timepoints of cancer (14). Projects involving machine learning/artificial intelligence have vastly variable but significantly greater costs, as a biomarker implementing artificial intelligence can cost USD $60,000–$100,000 (15). Compared to biomarker testing in NSCLC that costs an average USD $2,259 per patient, this is a significant difference that will need to be considered before reproducing such a biomarker test for wide use (16). While these methods are far more in-depth compared to standard biomarker studies and can provide a much more accurate picture of the tumor microenvironment to predict response, it will be challenging for it to be practice changing if it is not reproducible for many patients at once and costly that most patients would be unable to afford such testing.

Moving forward, there may be a role in Trop-2 ADCs particularly with the advances recently from Bessede *et al.* suggesting the role of Trop-2 expression reflecting resistance to immunotherapy and Garassino *et al.* demonstrating that NMR could be predictive of survival and efficacy (10,11). Further work will involve looking at the efficacy of combination therapies, validation of developing biomarkers, and evaluating the reproducibility of such biomarkers to patients including those from resource-limited healthcare settings.

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Footnote

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