Editorial Commentary

The TROP2 paradox: enhancing precision in immunotherapy for advanced non-small cell lung cancer patients—a commentary

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The management of advanced non-small cell lung cancer (NSCLC) has significantly advanced, with guidelines from the American Society of Clinical Oncology (ASCO), and Cancer Care Ontario (CCO) reflecting these changes (1,2). Despite efforts to improve outcomes, metastatic NSCLC still has a poor prognosis, with a 5-year net survival rate of 4% (3,4) Targeted therapies enhance outcomes for those with driver mutations, while immunotherapy, with or without chemotherapy is effective for those without targetable gene alteration. For stage IV NSCLC without driver mutations, first-line treatment options include single-agent immunotherapy like pembrolizumab, atezolizumab, or cemiplimab, based on programmed death-ligand 1 (PD-L1) status (5-7). Studies have reported significant survival benefits for patients with high PD-L1 expression. Dual immune checkpoint inhibitors (ICIs), such as nivolumab and ipilimumab, and combining chemotherapy with immunotherapy, have also shown promising results. Trials like CheckMate 9LA, KEYNOTE-189 and KEYNOTE-407 highlight the benefits of these combinations (8-10). For patients without prior checkpoint inhibitor therapy and no driver mutations, single-agent immunotherapy is more effective than conventional chemotherapy in later treatment stages. However, most advanced NSCLC patients exhibit primary resistance to PD-1/PD-L1 therapies.

In a recent study published in *Clinical Cancer Research* (11), Bessede and associates proposed a significant association of trophoblast cell surface antigen 2 (TROP-2) expression to the primary resistance to PD-L1 blockade in advanced NSCLC patients. Their findings revealed a stark reality. In this study, researchers analyzed transcriptomic data from 891 NSCLC tumors treated with the PD-L1 inhibitor atezolizumab or chemotherapy, revealing that TROP2 overexpression is significantly associated with poorer progression-free survival (PFS) and overall survival (OS) in patients undergoing PD-L1 blockade (11). Using RNA sequencing, multiplex immunofluorescence (mIHF), and plasma proteomic profiling, they suggested that TROP2 overexpression predicts poor outcomes specifically with atezolizumab and not with chemotherapy (11).

The study drew upon data from the POPLAR and OAK trials indicating that atezolizumab improves OS compared to chemotherapy (12,13), regardless of the PD-L1 expression, but high TROP2 expression complicates outcome predictions. Patients with high TROP2 had hazard ratios of 1.31 for PFS and 1.26 for OS when treated with atezolizumab (11). While researchers have made significant strides in demonstrating that TROP2 overexpression may lead to primary resistance to PD-L1 blockade, it is

intriguing that in the majority (>60%) of the patient cohort from the POLAR and OAK trials, PD-L1 status was either unknown or less than 1%. Interestingly, an independent analysis by Bessede and colleagues of a subgroup of patients treated with ICI within the Bergonie Institute Profiling (BIP) program recapitulated a significant association between TROP2 gene expression (TASCTD2) and poor immunotherapy response (11). This finding underscores the need for validation in a larger prospective trial.

TROP2, a protein prominently overexpressed in a range of epithelial tumor including those of the lung, breast, pancreas, gallbladder, urinary bladder, and salivary glands etc. and plays an important role in tumor progression. Its activation involves intramembranous cleavage, resulting in the release of an extracellular domain and an intracellular segment that translocate to the nucleus. In the nucleus, this segment activates the β-catenin pathway, promoting tumorigenic effects through the upregulation of cMyc and cyclin D1 (14). Bessede and researchers highlighted the significance of TROP2 cleavage in predicting responses to ICI. Through gene set enrichment analysis (GSEA), they identified significant upregulation of the MEK signalling pathway in patients with high circulating levels of TROP2 (11). This observation strongly indicates a correlation between TROP2 cleavage and MEK pathway activation. Given this mechanism, targeting TROP2 downregulation could potentially mitigate or even circumvent resistance to immunotherapy.

Bessede and colleagues' current study extends this discussion by investigating the role of the tumor microenvironment (TME) alongside TROP2 in ICI resistance (11). Prior research has elucidated various mechanisms contributing to this resistance. Primary resistance often arises from impaired tumor antigen presentation, epigenetic alterations, persistent WNT (wingless integrated)/β-catenin signalling, and the presence of immunosuppressive cytokines. In contrast, acquired resistance emerging following initial therapeutic success frequently involves the development of resistant strains and compensatory immune checkpoint effects (14,15). In the context of the PD-1/PD-L1 pathway, resistance mechanisms are multifaceted and include immunosuppression, metabolic abnormalities, and shifts in the microbiota. Regulatory T cells (Tregs) and Tumor-associated macrophages (TAMs) in the TME are particularly influential, with Tregs inhibiting effector T cells through molecules such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), while M2-type TAMs suppress T cell activity and support tumor growth (15). Additionally, metabolic dysregulation characterized by heightened aerobic glycolysis and alterations in lipid and amino acid metabolism can enhance PD-L1 expression, aiding tumor evasion from immune surveillance. The gut microbiota also impacts the effectiveness of immunotherapy, and changes in the DNA methylation, particularly involving the PD-L1/DNMT1 axis, contribute to the emergence of drug-resistant strains (15).

Bessede's study further revealed that patients with tertiary lymphoid structures (TLS) exhibit improved responses to PD-L1 blockade, highlighting the crucial role of a robust immune microenvironment. They discovered that the composition of the TME varied markedly between TACSTD2-high and TACSTD2-low tumors. Tumors with low TACSTD2 levels exhibited the highest expression of genes associated with immune cell populations, including T follicular helper (Tfh) cells, T cells, cytotoxic lymphocytes, and B cells (11). Hence, TROP2 gene expression is independently associated with unfavourable outcomes when treated with ICI. Moreover, proteomics analysis which focused on the inflammation, cardiometabolic and neurology proteins via utilizing Proximity Extension Assay (PEA) technology on plasma samples from 74 advanced NSCLC patients indicated that elevated circulating TROP2 levels were associated with significantly lower rates of durable clinical benefit (17.5% *vs.* 52.9%) and reduced PFS and OS (11). These observations suggest a potential role for TROP2 expression as a predictive biomarker for immunotherapy resistance, warranting further exploration and validation.

In 2020, sacituzumab govitecan (SG), an antibody-drug conjugate (ADC) targeting TROP2, became the first FDA-approved anti-TROP2 agent for advanced refractory triple-negative breast cancer (TNBC) (16). Since then, it has also been approved for metastatic hormone receptor-positive and HER2-negative breast cancer, as well as advanced urothelial cancer. Several clinical trials have explored TROP2 ADCs in lung cancer. In the EVOKE-02 trial of metastatic NSCLC patients, the cohort with PD-L1 >50% who received SG and pembrolizumab as 1L therapy, showed promising results with a 67% objective response rate (ORR) and median PFS of 13 months, as presented at ASCO 2024 (17). The larger phase III KEYNOTE D46/EVOKE-03 study, with an expected enrollment of 614 metastatic NSCLC patients, is currently active. This trial compares pembrolizumab alone or in combination with SG in patients with PD-L1 ≥50% (18). The current literature is also consistent with the clinical use of emerging TROP2

ADC in advanced NSCLC (19). Pérol also summarized the exponential role of SG, as per the EVOKE phase III trial results, in the subsequent-line treatment for advanced NSCLC. The study showed an overall survival benefit of 11.8 months with SG compared to 8.3 months with docetaxel chemotherapy in patients who had previously received ICIs and were non-responders. This also explains the potential benefit of TROP2 ADC in post-ICI-resistant patients (20).

Furthermore, a relatively newer TROP2 ADC, sacituzumab tirumotecan (SKB264/MK-2870), developed with a novel linker to conjugate the payload, a belotecan-derivative topoisomerase I inhibitor, is also showing promise. In the phase II study, OptiTROP-Lung01, it demonstrated an ORR of 48.6% (Cohort A) and 77.6 % (Cohort B) and a disease control rate (DCR) of >94% in the entire cohort of metastatic NSCLC patients (21) (*Table 1*). Datopotamab deruxtecan (Dato-DXd), another ADC targeting TROP2, has shown encouraging antitumor activity in advanced NSCLC. Preliminary results from the TROPION-PanTumor01 trial (NSCLC cohort) revealed an ORR of over 23%, with 83% of patients having received prior PD-L1 therapy (22). In addition, the TROPION-Lung02 trial, presented at ASCO 2024, evaluated Dato-DXd plus pembrolizumab with or without platinum chemotherapy as 1L therapy for advanced NSCLC. Both the doublet and triplet regimens showed durable efficacy, with ORRs of 52% and 56%, respectively, and a DCR of 88% across the cohort (23).

Drawing on data from the large, randomized controlled trials POPLAR and OAK, Bessede's study offers a robust foundation for analysis, enhancing the reliability of its findings. Moreover, the study provides valuable mechanistic insights, indicating that TROP2 overexpression may lead to reduced T-cell infiltration and contribute to primary resistance to PD-L1 blockade, thus deepening our understanding of ICI resistance. Although the study is based on large RCTs, the analysis is retrospective. This introduces potential biases, and causality cannot be definitively established. While the main cohort is large, some of the validation analyses, particularly those involving mIHF and proteomic profiling, are based on relatively small subsets of patients. This could limit the statistical power and generalizability of these specific findings. The study notes that in the analyzed cohorts, a significant proportion of patients had unknown or low PD-L1 expression (<1%). This heterogeneity might confound the relationship between TROP2 expression and resistance to ICIs, making it difficult to draw clear conclusions. The study itself acknowledges the necessity for further prospective trials to validate the correlation between high TROP2 expression and primary resistance to PD-L1 blockade. Without this, the findings remain preliminary.

To fully validate the role of TROP2 as a predictive biomarker, it would be essential to incorporate it as a stratification factor in RCTs. This would allow researchers to systematically evaluate the impact of TROP2 expression on treatment outcomes. Additionally, TROP2 levels should be consistently measured and reported, whether using a binary classification (high *vs.* low) or as a continuous variable, similar to how PD-L1 is utilized in current clinical practice. This approach would provide a clearer understanding of the correlation between TROP2 expression and resistance to therapies. It's crucial to determine whether the mechanisms behind TROP2 overexpression and its resistance to PD-L1 inhibitors also apply to other ICIs like CTLA-4, LAG-3, or TIM-3 inhibitors. The role of immune cells such as Tregs, TAMs, and cytotoxic T lymphocytes in relation to TROP2 expression could influence the effectiveness of other ICIs. The broader application of these findings will require clinical trials that assess TROP2-targeted therapies in combination with different ICIs across various cancer types. Consistent results in diverse patient groups would suggest that these benefits are not limited to PD-L1 inhibitors alone but may also extend to other checkpoint pathways.

Another notable limitation of Bessede's study is its omission of TROP2 level reporting, both intracellular and circulating, in the docetaxel arm of the trials. This gap hinders a comprehensive evaluation of the relationship between TROP2 expression and treatment efficacy across different therapeutic modalities. Additionally, all patients in the POPLAR and OAK studies had undergone prior chemotherapy, which could have influenced their resistance to ICIs. The study does not address whether previous chemotherapy impacted ICI resistance, leaving a critical question unanswered. Moreover, the prevalent use of combination chemo-immunotherapy or ICI combinations in frontline treatment in recent clinical practice further complicates the assessment of TROP2 as a predictive biomarker for ICI resistance. Understanding how TROP2 expression varies across different NSCLC subtypes, such as adenocarcinoma, squamous cell carcinoma, adenosquamous, and large cell carcinoma, is also vital. Given these complexities, validating and implementing TROP2 as a biomarker in the current therapeutic landscape requires large-scale, prospective RCTs. Such trials must consider not

Table 1 Studies investigating TROP2 ADCs and anti-PD1/PD-L1 in advanced NSCLC patients

S. No	Study	No. of patients	Treatment regimen and line of treatment	Molecular target	Brief description/ outcomes	References
1	Evoke-2/Phase II trial	Cohort A (PD-L1 TPS ≥50%) =30, Cohort B (PD-L1 TPS <50%) =33 (squamous and non-squamous)	sacituzumab govitecan (SG) + Pembrolizumab (with or without platinum 1L therapy	TROP2, PD1	Cohort A results revealed an ORR of 67%, median PFS was 13 months (data cut off December 2023)	(17)
2	KEYNOTE D46/ EVOKE-03 Study/Phase III	614 (expected), stage IV squamous and non-squamous	Pembrolizumab alone or in combination with SG 1L therapy	TROP2, PD1	Ongoing trial for PD-L1 ≥50% stage IV NSCLC, to measure outcomes in terms of PFS, OS, ORR and DOR	(18)
3	OptiTROP-Lung01/Phase II	As of January 2, 2024, 40 patients have been enrolled in cohort 1A and 63 in cohort 1B of the study evaluating SKB264 and KL-A167 at different dosing schedules	Sacituzumab tirumotecan (SKB264/MK-2870) and KL-A167 (anti-PD-L1) 1L therapy	TROP2, PD-L1	Cohort 1A = the ORR was 48.6%, and the DCR was 94.6% with a median PFS of 15.4 months Cohort 1B = the ORR was 77.6%, the DCR was 100%, with median PFS not yet reached	(21)
4	TROPION-PanTumor01 Trial/Phase I (NSCLC Cohort)	180 squamous and non-squamous advanced NSCLC patients	Datopotamab deruxtecan (Dato-DXd), subsequent line treatment	TROP2	23% ORR, 83% of patients had previously received PD-L1 therapy	(22)
5	TROPION-Lung02 Trial/ Phase I	A total of 96 patients of squamous and non-squamous advanced NSCLC were treated (n=42 in doublet, 54 in triplet)	Dato-DXd + pembrolizumab with/without platinum chemotherapy (doublet v/s triplet) 1L therapy	TROP2, PD1	52% ORR (doublet), 56% ORR (triplet), 88% DCR in entire cohort	(23)
6	TROPION-Lung04 Trial/ Phase I (NCT04612751)	Not specified	Dato-DXd + immunotherapy with/without carboplatin 1L and subsequent line treatment	TROP2, PD1, PD-L1, CTLA4, TIGIT, TIM-3	This study aims to evaluate the safety, tolerability, and treatment efficacy of Dato-DXd in combination with various immunotherapies (durvalumab, AZD2936, MEDI5752, or AZD7789), with or without four cycles of carboplatin, across 14 study cohorts	(24)
7	TROPION-Lung10 Study/ Phase III (NCT06357533)	Not specified	Dato-DXd + rilvegostomig or rilvegostomig monotherapy, or pembrolizumab monotherapy 1L therapy	TROP2, PD1, TIGIT	Phase III study, focusing on PFS and OS in both TROP2 biomarker-positive and ITT populations with high PD-L1 (>50%) population	(25)

TROP2, trophoblast cell surface antigen 2; ADC, antibody drug conjugate; PD1, programmed death 1; PD-L1, programmed death-ligand 1; NSCLC, non-small cell lung cancer; TPS, tumour proportion score; ORR, objective response rate; 1L, first line; PFS, progression-free survival; OS, overall survival; DOR, duration of response; DCR, disease control rate; TIGIT, T-cell immunoreceptor with Ig and ITIM domains; TIM-3, T-cell immunoglobulin and mucin domain 3, CTLA4, cytotoxic T lymphocyte-associated antigen 4; ITT, intent-to-treat.

only the biomarker's predictive value but also its interaction with various treatment combinations and cancer subtypes.

Consequently, the TROPION-Lung04 trial (NCT04612751) is evaluating the safety and tolerability of Dato-DXd in combination with immunotherapy, with or without four cycles of carboplatin, in patients with advanced or metastatic NSCLC (24). Similarly, TROPION-Lung10 (NCT06357533) is a global study comparing Dato-DXd in combination with rilvegostomig, rilvegostomig monotherapy, and pembrolizumab monotherapy for first-line treatment of locally advanced or metastatic non-squamous NSCLC with high PD-L1 expression (25). The results of these prospective studies are eagerly anticipated and could provide valuable insights. These findings underscore the importance of targeting TROP2 through ADCs, highlighting the potential for TROP2 testing as a biomarker for predictive response. Hence, combining TROP2 ADCs with ICIs could be a more effective treatment strategy than the traditional platinum doublet with ICI for metastatic NSCLC patients without actionable genomic alterations, because of TROP2's potential role in immunotherapy resistance but it requires further validation. *Table 1* provides an overview of studies exploring TROP2 ADCs. These might explain the potential role of TROP2 as a biomarker for immune checkpoint resistance in metastatic NSCLC.

We commend Bessede and colleagues for their insightful elucidation of the relationship between TROP2 gene expression, intracellular TROP2 expression, circulating TROP2 levels, and patient outcomes. Their findings advocate for a biomarker-driven paradigm that could facilitate noninvasive diagnostics via blood assays. The observed linkage between TROP2 overexpression and inherent resistance to PD-L1 blockade in NSCLC highlights the imperative for precision medicine. By customizing treatment protocols based on TROP2 expression and other pertinent biomarkers, we edge closer to the advent of personalized oncology care, poised to markedly enhance outcomes for individuals battling advanced NSCLC and beyond to other cancer sites where ICI and ADCs can be used.

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Footnote

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