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COMMENTARY

TROPION-Lung01 Results Indicate PFS Benefit with Datopotamab Deruxtecan over Docetaxel in Previously Treated Nonsquamous NSCLC: A Critique and Question

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Abstract

This commentary critically reviews the findings of the TROPION-Lung01 Phase III study, which compared the efficacy and safety of datopotamab deruxtecan (Dato-DXd) with docetaxel in patients with pretreated advanced or metastatic non-small cell lung cancer (NSCLC). The study reported a statistically significant improvement in progression-free survival (PFS) for the overall population, with a pronounced benefit in patients with nonsquamous histology. However, no significant increase in overall survival (OS) was observed. While Dato-DXd exhibited a favorable safety profile, with fewer treatment-related adverse events compared to docetaxel, concerns arose regarding an increased progression risk in patients with squamous histology. This commentary also explores the study's adherence to CONSORT guidelines in presenting absolute and relative risks and reflects on how these findings might be communicated to patients considering Dato-DXd treatment for NSCLC.

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Introduction

The TROPION-Lung01 study, a pivotal research published in September 2024 in the J Clin Oncol, has the potential to significantly impact patient care. This randomized, open-label, global phase III study compared the efficacy and safety of datopotamab deruxtecan (Dato-DXd) versus docetaxel in patients with pretreated advanced/metastatic non-small cell lung cancer (NSCLC)[1]. Our aim is to critically evaluate the key findings from this study, particularly the presentation and interpretation of progression-free survival (PFS) and overall survival (OS) outcomes, and adherence to CONSORT guidelines. Two central questions arise: What would a more rigorous presentation of absolute and relative risks reveal about the study's conclusions? How can these results be effectively communicated to patients, particularly those with NSCLC considering treatment with datopotamab deruxtecan? Do the conclusions of the TROPION-Lung01 study show

any signs of 'spin'?

In early 2024, there were some news regarding the TROPION-Lung01 study results:

Datopotamab Deruxtecan Showed Clinically Meaningful Overall Survival Improvement Versus Chemotherapy in Patients with Advanced Nonsquamous Non-Small Cell Lung Cancer in TROPION-Lung01 Phase 3 Trial. ***BUSSINES Wire***

TROPION-Lung01 Results Indicate PFS Benefit With Datopotamab Deruxtecan Over Docetaxel in Previously Treated Nonsquamous NSCLC. ***ASCO Daily News***

FDA Accepts BLA for Datopotamab Deruxtecan in Pretreated Advanced Nonsquamous NSCLC ***Oncolive***

This is the abstract of the JCO September 2024 publication[1].

“PURPOSE: The randomized, open-label, global phase III TROPION-Lung01 study compared the efficacy and safety of datopotamab deruxtecan (Dato-DXd) versus docetaxel in patients with pretreated advanced/metastatic non–small cell lung cancer (NSCLC).

METHOD: Patients received Dato-DXd 6 mg/kg or docetaxel 75 mg/m2 once every 3 weeks. Dual primary end points were progression-free survival (PFS) and overall survival (OS). Objective response rate, duration of response, and safety were secondary end points.

RESULTS: In total, 299 and 305 patients were randomly assigned to receive Dato-DXd or docetaxel, respectively. The median PFS was 4.4 months (95% CI, 4.2 to 5.6) with Dato-DXd and 3.7 months (95% CI, 2.9 to 4.2) with docetaxel (hazard ratio [HR], 0.75 [95% CI, 0.62 to 0.91]; P 5.004). The median OS was 12.9 months (95% CI, 11.0 to 13.9) and 11.8 months (95% CI, 10.1 to 12.8), respectively (HR, 0.94 [95% CI, 0.78 to 1.14]; P 5.530). In the prespecified nonsquamous histology subgroup, the median PFS was 5.5 versus 3.6 months (HR, 0.63 [95% CI, 0.51 to 0.79]) and the median OS was 14.6 versus 12.3 months (HR, 0.84 [95% CI, 0.68 to 1.05]). In the squamous histology subgroup, the median PFS was 2.8 versus 3.9 months (HR, 1.41 [95% CI, 0.95 to 2.08]) and the median OS was 7.6 versus 9.4 months (HR, 1.32 [95% CI, 0.91 to 1.92]). Grade ≥3 treatment-related adverse events occurred in 25.6% and 42.1% of patients, and any-grade adjudicated drug-related interstitial lung disease/pneumonitis occurred in 8.8% and 4.1% of patients, in the Dato-DXd and docetaxel groups, respectively.

CONCLUSIONS: Dato-DXd significantly improved PFS versus docetaxel in patients with advanced/metastatic NSCLC, driven by patients with nonsquamous histology. OS showed a numerical benefit but did not reach statistical significance. No unexpected safety signals were observed.

What would the results look like if the authors comply with the CONSORT statements[2] recommending the presentation of the relative and absolute risks from the RCT?

These are the estimated Relative and Absolute risks of the study:

PATIENTS	HR	ABSOLUTE RISK OF DEATH	ABSOLUTE RISK OF PROGRESSION
PFS all	**0.75 (0.62 to 0.91)***		0.24% REDUCTION
PFS non-squamous	**0.63 (0.51 to 0.79)***		4.70% REDUCTION
PFS squamous	1.41 (0.95 to 2.08)		**15.47% INCREASE***
OS all	0.94 (0.78 to 1.14),	0.43% INCREASE	
OS non-squamous	0.84 (0.68 to 1.05)	1.28% REDUCTION	
OS squamous	1.32 (0.91 to 1.92)	7.15% INCREASE	

Bold and asterisk: statistically significant. Absolute Risks were calculated with an online calculator: http://araw.mede.uic.edu/cgi-bin/nntcalc.pl

What could be a study spinless conclusion?

Dato-DXd significantly improved PFS versus docetaxel in the whole population of patients with advanced/metastatic NSCLC and in the non-squamous histology patients as well. Overall survival was not significantly increased. No statistically significant changes in absolute risks for progression or death were observed, but a risk increase for progression in the patients with squamous histology. No unexpected safety signals were observed.

A question for oncologists could be: How can these results be explained to a patient with NSCLC who wants to be treated with Datopotamab Deruxtecan?

In summary, Dato-DXd significantly improved PFS compared to docetaxel in the overall patient population, with the greatest benefit observed in non-squamous patients. OS was not significantly increased; concerns about progression risk in squamous histology remain. Presenting absolute and relative risks could enhance transparency, aligning with CONSORT recommendations. We also raise the practical question of explaining these complex findings to patients considering Dato-DXd as a treatment option. Peer feedback on these points would be invaluable in enriching the discussion.

Statements and Declarations

Data and Software Availability

No data are associated with this article.

Competing Interests

The author declare not to have conflicts of interest.

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Author Contribution

The content and ideas expressed in this work are the sole responsibility of the authors.

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2. [^]*Schulz KF, Altman DG, Moher D CONSORT Group. "CONSORT 2010 statement: Updated guidelines for reporting parallel group randomized trials". Ann Intern Med. 2010;152:726–32.*