v1: 13 November 2024

Commentary

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

Peer-approved: 13 November 2024

Qeios, Vol. 6 (2024)
ISSN: 2632-3834

Leticia Bornstein-Quevedo[1], Alfonso Dueñas-Gonzalez[2,3]

1. Immunohistochemistry and Molecular Biology Laboratory, InmunoQ, Mexico City, Mexico; 2. Departamento de Medicina Genómica y Toxicología Ambiental, Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México, Mexico; 3. Subdirección de Investigación Básica, Instituto Nacional de Cancerología, Tlalpan, Mexico

This commentary aims to point out how the results of the TROPION-LUNG01 study stress the "positive aspects" of the results, specifically the increase in PFS, but hardly mention the potential harm to patients with squamous histology and lack information on binary data (progression-free / progression, alive/death) as per CONSORT guidelines. Here, we also remark on the need for adherence to CONSORT guidelines to inform on the absolute and relative risks of Randomized Controlled Trials (RCT). We emphasize the need for further research to develop a framework for how oncologists might explain the differences between PFS and OS in simple terms for a lay audience to create a more thoughtful decision for patients to embark on any cancer treatment.

Corresponding author: Alfonso Duenas-Gonzalez, alfonso.duenasg@yahoo.com

Introduction

The TROPION-Lung01 study, a pivotal research published in September 2024 in the J Clin Oncol, has the potential to significantly impact advanced NSCLC 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].

The abstract of the JCO September 2024 publication[1] is as follows:

PURPOSE: The randomized, open-label, global phase III TROPION-Lung01 study com- pared 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%

 doi.org/10.32388/1PO7Y7.3

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=0.530). 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".

As is now standard, the publication was highlighted in the press. These are some examples of how these results were announced.

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. BUSINESS Wire.

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

Aims

We aim to comment on two aspects and raise some questions: 1. The presentation and interpretation of progression-free survival (PFS) and overall survival (OS) outcomes, and 2) adherence to CONSORT guidelines regarding the presentation of results, item 17b "for both absolute and relative effect size is recommended". A central question arises: How would a presentation of absolute risks influence the study's conclusions? Do the conclusions of the TROPION-Lung01 study show any signs of 'spin'? Additional questions from this comment are: How can these results be effectively communicated to patients, particularly those with NSCLC considering treatment with datopotamab deruxtecan?

Absolute Risk Analysis

What would the results look like if the authors complied with the CONSORT statements[2] and showed the results on the absolute risks from the RCT? These are the estimated absolute risks of the study for OS and PFS. The Table includes the HR reductions as found in the study.

PATIENTS	HAZARD RISKS	ABSOLUTE RISK OF DEATH (OS)	ABSOLUTE RISK OF PROGRESSION (PFS)
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

PFS all. Dato-DXd: Total n 299/events 213. Docetaxel: Total n 305/events 218.
PFS non-squamous. Dato-DXd: Total n 234/events 159. Docetaxel: Total nr234/events 170.
PFS squamous: Total n 65/events 54. Docetaxel: Total nr 71/events 48.
OS all. Dato-DXd: Total n 299/events 215. Docetaxel: Total n 305/events 218.
OS non-squamous. Dato-DXd: Total n 234/events 160. Docetaxel: Total n 234/events 163.
OS squamous. Dato-DXd: Total n 65/events 55. Docetaxel: Total n 71/events 55.

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."

Open questions and comments

In summary, as evaluated with Hazard Ratios, Dato-DXd significantly improved PFS compared to docetaxel in the overall patient population, with the most significant benefit observed in non-squamous patients. However, the HR results were statistically insignificant for squamous and non-squamous histology subgroups. Likewise, OS was not significantly changed as evaluated by HR in all-comer populations nor in squamous and non-squamous histology subgroups. On the contrary, there was a statistically significant increase in absolute

risk for PFS, while the absolute risk for death (OS) also increased, though not statistically significantly.

From our perspective, this study's conclusions show spin as they do not mention much about the potential negative effects on the subgroup of squamous histology patients, which could significantly impact patient care. Spin refers to reporting practices that distort the interpretation of results and mislead readers so that results are viewed in a more favourable light[3]. This issue underscores the importance of considering all potential outcomes when interpreting study results.

Presenting absolute risks for PFS and OS enhances transparency, aligning with CONSORT recommendations which state that for **binary outcomes, presentation of both absolute and relative effect sizes is recommended**[2]**.** HR is not a binary outcome statistic but rather a measure of the speed of events; however, HR does indeed require binary data (no event/event) on the time curve to calculate the hazards. The question then arises: Could the presentation with absolute risk, in addition to HRs, change the perceptions of oncologists on the benefits of any treatment? How can these results be explained to a patient with NSCLC who wants to be treated with Datopotamab Deruxtecan? These thought-provoking questions highlight the need for further discussion and awareness on the issue of presentation of results in RCTs in oncology.

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.

Grant Information

The author declared that no grants were involved in supporting this work.

Author Contribution

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

References

1. a, b *Ahn MJ, Tanaka K, Paz-Ares L, et al. Datopotamab deruxtecan versus docetaxel for previously treated adv anced or metastatic non-small cell lung cancer: the ra ndomized, open-label phase III TROPION-Lung01 stud y. J Clin Oncol. 2024 Sep 9. doi: 10.1200/JCO-24-01544. Epub ahead of print.*
2. a, b *Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for rep orting parallel group randomized trials. Ann Intern M ed. 2010;152:726-32.*
3. ^ *Chiu K, Grundy Q, Bero L. 'Spin' in published biomedi cal literature: a methodological systematic review. PL oS Biol. 2017;15(9). doi: 10.1371/journal.pbio.2002173.*

Declarations

Funding: No specific funding was received for this work.
Potential competing interests: No potential competing interests to declare.