IASLC 2023 World Conference on Lung Cancer
SEPTEMBER 9-12, 2023 | SINGAPORE

Datopotamab Deruxtecan (Dato-DXd) + Durvalumab ± Carboplatin in Advanced/Metastatic NSCLC: Initial Results from the Phase 1b TROPION-Lung04 Study

Kyriakos P. Papadopoulos,[1] Debora S. Bruno,[2] Satoru Kitazono,[3] Shuji Murakami,[4] Martin Gutierrez,[5] Kazushige Wakuda,[6] Alexander Spira,[7] Kristof Cuppens,[8,9] Susan Lovick,[10] Adriana Hepner,[11] Gabriel Mak,[11] Saiama N. Waqar[12]

[1]START San Antonio, San Antonio, TX, USA; [2]University Hospitals, Case Comprehensive Cancer Center, Cleveland, OH, USA; [3]The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan; [4]Kanagawa Cancer Center, Yokohama, Japan; [5]John Theurer Cancer Center, Hackensack, NJ, USA; [6]Shizuoka Cancer Center, Shizuoka, Japan; [7]Virginia Cancer Specialists, Fairfax, VA, USA; [8]Jessa Hospital, Hasselt, Belgium; [9]Limburg Clinical Research Center, Hasselt University, Diepenbeek, Belgium; [10]AstraZeneca, Cambridge, UK; [11]AstraZeneca, Gaithersburg, MD, USA; [12]Washington University School of Medicine in St. Louis, St. Louis, MO, USA

Funding

- The TROPION-Lung04 Study (NCT04612751) is sponsored by AstraZeneca. In July 2020, Daiichi-Sankyo entered into a global development and commercialization collaboration with AstraZeneca for datopotamab deruxtecan (Dato-DXd)
- Medical writing support, under the direction of the authors, was provided by Emily Smyth, (Manchester, UK) and Harriet Gallegos, (London, UK) of Ashfield MedComms, an Inizio company, and was sponsored by AstraZeneca
- **Saiama N. Waqar** has the following disclosures:
  - Advisory Board membership for AstraZeneca and Gilead Sciences
  - Research grant support from SWOG Clinical Trials Partnership
  - Research support to institution for clinical trials (site PI) from AbbVie Inc., ARIAD Pharmaceuticals, Genentech, Immunomedics, Inc., Millennium Pharmaceuticals Inc., Roche, Astellas Pharma Inc., Daiichi-Sankyo, Cullinan Pearl, Verastem Inc., GlaxoSmithKline, Janssen Research & Development LLC, Elevation Oncology, Loxo Oncology, Takeda Pharmaceuticals, Ribon Therapeutics Inc., AstraZeneca Pharmaceuticals LP and Advenchen Laboratories
  - Chair of Data and Safety Monitoring Board for a Hoosier Cancer Research Network study

Background

- **Dato-DXd:** An ADC consisting of a humanized anti-TROP2 IgG1 monoclonal antibody covalently linked to a highly potent topoisomerase-I inhibitor payload via a plasma-stable, tumor-selective, tetrapeptide-based cleavable linker[1]
- **Pre-clinical data:** Dato-DXd enhances antitumor response to PD-1/PD-L1 inhibitors[2]
- **Phase 1 data:** Dato-DXd showed encouraging early clinical efficacy and manageable safety in patients with advanced or metastatic NSCLC:[3,4]

TROPION-PanTumor01 study[3,a]

ORR (confirmed): 26%

with Dato-DXd 6 mg/kg monotherapy in heavily pre-treated NSCLC

TROPION-Lung02 study[4,b]

ORR (confirmed and pending): 50% and 57%

with Dato-DXd + pembro and Dato-DXd + pembro + platinum-based chemotherapy, respectively, in 1L NSCLC

- **Phase 3 data:** Dato-DXd 6 mg/kg monotherapy demonstrated a statistically significant improvement in PFS versus docetaxel in previously treated advanced or metastatic NSCLC (TROPION-Lung01 study)[5]

[a] N=50 patients in the Dato-DXd 6 mg/kg cohort with an ORR of 26% (95% CI: 14.6, 40.3). [b] N=34 patients in the doublet cohort with an ORR of 50% (95% CI: 32, 68). N=53 patients in the triplet cohort with an ORR of 57% (95% CI: 42, 70).
1L, first-line; ADC, antibody-drug conjugate; CI, confidence interval; Dato-DXd, datopotamab deruxtecan; Ig, immunoglobulin; NSCLC, non-small-cell lung cancer; ORR, objective response rate; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; pembro, pembrolizumab; PFS: progression-free survival; TROP2, trophoblast cell surface protein 2.

1. Okajima D, et al. Mol Cancer Ther 2021;20:2329–40; 2. Okajima D, et al. Poster 2932. Presented at AACR 2023; 3. Shimizu T, et al. J Clin Oncol 2023;10.1200/JCO.23.00059:ePub; 4. Goto Y, et al. Oral 9004. Presented at ASCO 2023; 5. AstraZeneca Press Release. Datopotamab deruxtecan met dual primary endpoint of progression-free survival in patients with advanced non-small cell lung cancer in TROPION-Lung01 Phase III trial. Available at: https://www.astrazeneca.com/media-centre/press-releases.html (accessed July 2023).

TROPION-Lung04 Study Design

Phase 1b, multicenter, open-label, dose escalation/confirmation and expansion study

TROPION-Lung04 is investigating Dato-DXd in combination with different immunotherapy agents ± carboplatin across 11 cohorts. This interim analysis reports the first data from Cohorts 2 and 4

Key eligibility

- Adults (≥18 years) with previously treated or treatment-naïve advanced or metastatic NSCLC[a]
- No actionable genomic alterations
- ECOG PS 0–1

	1 Part 1: Sequential dose escalation[b]	2 Part 2: Dose expansion
Cohort 1 (Doublet)	Dato-DXd 4 mg/kg + durvalumab 1120 mg, Q3W (n=5)	
Cohort 2 (Doublet)	Dato-DXd 6 mg/kg + durvalumab 1120 mg, Q3W (n=3)	Dato-DXd 6 mg/kg + durvalumab 1120 mg, Q3W (n=16)
Cohort 3[c] (Triplet)	Dato-DXd 4 mg/kg + durvalumab 1120 mg + 4 cycles carboplatin AUC 5, Q3W	
Cohort 4 (Triplet)	Dato-DXd 6 mg/kg + durvalumab 1120 mg + 4 cycles carboplatin AUC 5, Q3W (n=6)	Dato-DXd 6 mg/kg + durvalumab 1120 mg + 4 cycles carboplatin AUC 5, Q3W (n=8)

- **Primary endpoint:** Safety and tolerability
- **Key secondary endpoints:** ORR and disease control rate by investigator assessment per RECIST v1.1

Data cut-off: March 6 2023.

[a] Patients in Cohort 1 and one patient in Cohort 2 had received ≥1 platinum-based chemotherapy regimen and anti-PD-1/PD-L1 therapy as per an earlier version of the clinical study protocol. Subsequent patients were treatment-naïve or had ≤1 prior line of systemic chemotherapy without concomitant immune checkpoint inhibitors. [b] Dose escalation was guided by a mTPI-2 design and conducted sequentially from Cohort 1 to 2 (Dato-DXd 4 mg/kg to 6 mg/kg) and Cohort 2 to 4 (doublet to triplet combination). [c] Cohort 3 was skipped as there were sufficient data available from the Dato-DXd development program to conclude that 4 mg/kg Dato-DXd in combination with immunotherapy and carboplatin has an acceptable safety profile.

AUC, area under the curve; ECOG PS, Eastern Cooperative Oncology Group performance status; mTPI-2, modified toxicity probability interval-2; Q3W, once every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Baseline Characteristics and Patient Disposition

Characteristic, n (%)		Cohort 2 (doublet) N=19[a]	Cohort 4 (triplet) N=14[a]
Age, median (range), years		63 (49–75)	67 (55–72)
Male		14 (73.7)	9 (64.3)
Dato-DXd combination line of therapy	1L	14 (73.7)	13 (92.9)
	2L+	5 (26.3)[b]	1 (7.1)[b]
Histology	Squamous	5 (26.3)	4 (28.6)
	Non-squamous	14 (73.7)	10 (71.4)
History of brain metastases		4 (21.1)	3 (21.4)
PD-L1 expression	<1%	6 (31.6)	6 (42.9)
	1–49%	6 (31.6)	3 (21.4)
	≥50%	7 (36.8)	5 (35.7)
Tumor stage at study entry	IIIA, IIIB or IIIC	0	2 (14.3)
	IV, IVA or IVB	19 (100)	12 (85.7)

At the time of data cut-off, for Cohort 2 and Cohort 4, respectively:

- Study treatment was ongoing in 31.6% and 50.0% of patients
- Median (range) study treatment duration was 6.0 months (0.7–12.5) and 6.2 months (1.5–11.0)

Data cut-off: March 6 2023.
Patients were enrolled across sites in Japan and the USA only in Cohorts 2 and 4. [a] Includes patients from Part 1 (dose escalation) and Part 2 (dose expansion). Cohort 1 was not expanded. [b] There were 4/5 (80.0%) 2L+ patients in Cohort 2 and 1/1 (100%) 2L+ patients in Cohort 4 who had received prior radiation therapy.
2L+: second line and later.

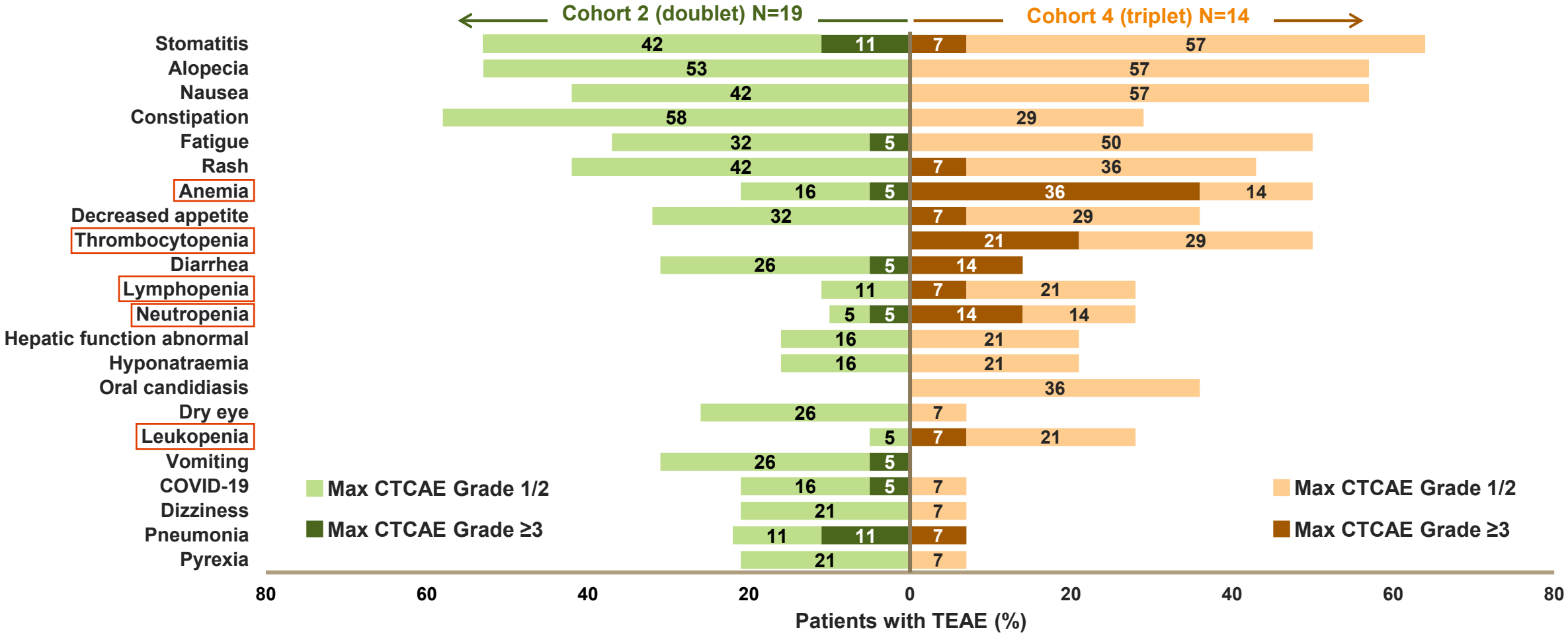
Safety Summary

Events, n (%)		Cohort 2 (doublet) N=19	Cohort 4 (triplet) N=14
TEAEs		**19 (100)**	**14 (100)**
Study treatment-related[a]		19 (100)	14 (100)
Grade ≥3 TEAEs		**8 (42.1)**	**10 (71.4)**
Study treatment-related[a]		6 (31.6)	8 (57.1)
SAEs		**7 (36.8)**	**5 (35.7)**
Study treatment-related[a]		6 (31.6)	5 (35.7)
TEAEs associated with	Death	0	0
	Discontinuation of any drug	4 (21.1)	3 (21.4)
	Discontinuation of Dato-DXd	4 (21.1)	2 (14.3)
ILD adjudicated as drug-related		**3 (15.8)**	**1 (7.1)**
Grade 1		1 (5.3)	0
Grade 2		1 (5.3)	1 (7.1)
Grade ≥3		1 (5.3)[b]	0

- There were **no DLTs** in **Cohort 1** or **Cohort 2** during Part 1 (dose escalation)
- **Two patients** reported DLTs in **Cohort 4** (1 patient had Grade 3 febrile neutropenia and 1 patient had both Grade 3 stomatitis and Grade 3 maculo-papular rash)[c]
- Dose expansion subsequently occurred in Cohort 2 (doublet) and Cohort 4 (triplet)
- There were **no Grade 5 adjudicated ILD events**. There was one Grade 4 adjudicated ILD event in a patient in Cohort 2[b]

Data cut-off: March 6 2023.
TEAEs are defined as AEs with a start date or worsening date on or after the start of study treatment until 97 days after the last dose. [a] Treatment-related TEAEs are related to Dato-DXd, durvalumab or carboplatin. [b] There was one Grade 4 ILD adjudicated as drug-related in a patient who received sotorasib after PD/discontinuation of IP. [C] One patient had Grade 3 stomatitis and Grade 3 maculo-popular rash AEs that reached DLT criteria due to Cycle 2 dosing being delayed by >2 weeks.
AE, adverse event; ILD, interstitial lung disease; IP, investigational product; PD, progression of disease; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

TEAEs in ≥15% of Patients



Data cut-off: March 6 2023.
TEAEs by preferred term/grouped preferred term. TEAEs in ≥15% of patients is based on the total number of safety subjects in Cohort 2 and Cohort 4. Red boxes indicate hematological events.
CTCAE, Common Terminology Criteria for Adverse Events.

Antitumor Activity

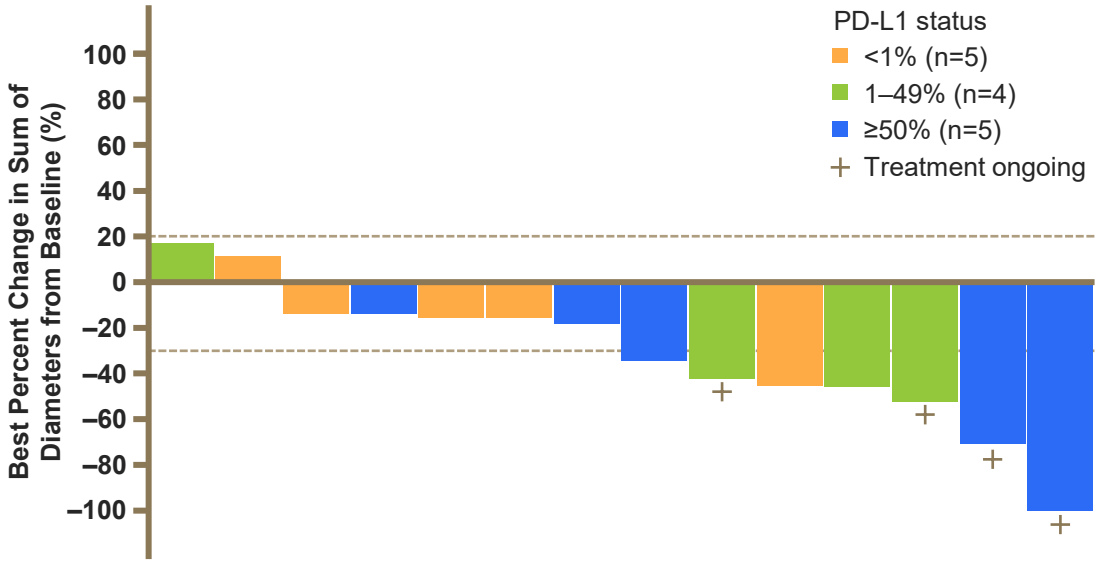
Response in patients in the 1L setting,[a] n (%)		Cohort 2 (doublet) N=14	Cohort 4 (triplet) N=13
Objective response rate (confirmed)		**7 (50.0)**	**10 (76.9)[b]**
[95% CI]		[23.0, 77.0]	[46.2, 95.0]
Best objective response	Complete response	0	0
	Partial response	7 (50.0)	10 (76.9)[b]
	Stable disease	6 (42.9)	2 (15.4)
	Progressive disease	1 (7.1)	1 (7.7)
Disease control rate		**13 (92.9)**	**12 (92.3)**
[95% CI]		[66.1, 99.8]	[64.0, 99.8]

- In the 1L setting, ORRs were **50.0%** for Cohort 2 and **76.9%[b]** for Cohort 4
- In the overall population (1L/2L+), ORRs were **47.4%** for Cohort 2 (N=19) and **71.4%[b]** for Cohort 4 (N=14)
- Responses were numerically higher with the triplet versus doublet combination and were observed across all PD-L1 expression levels

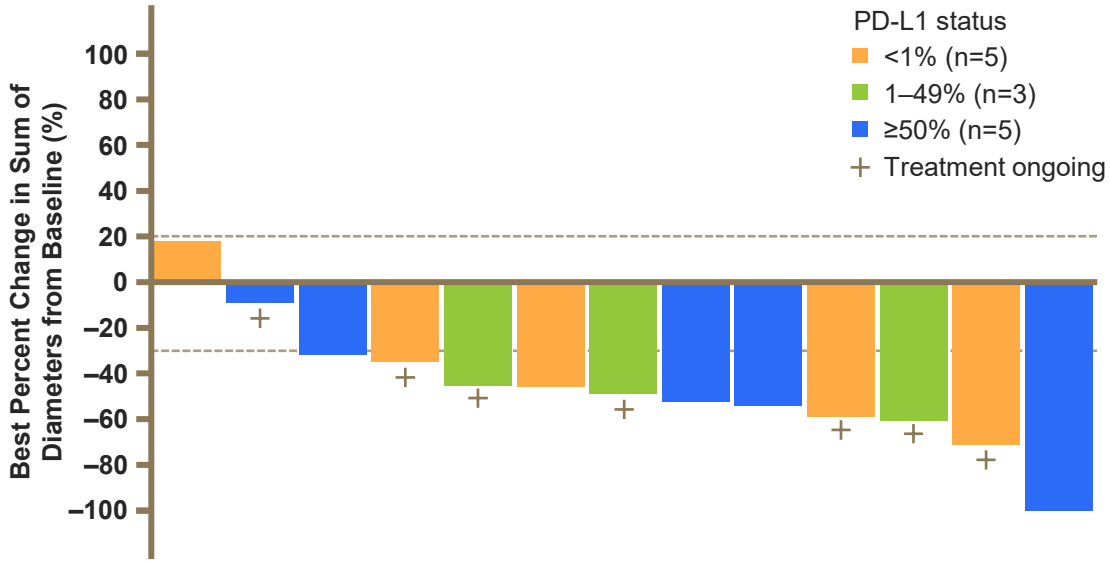
Data cut-off: March 6 2023.
All subjects must have had at least one scan (6 weeks of follow-up) to be included in the ORR interim analysis set. The 2-sided 95% CIs are exact Clopper-Pearson intervals. [a] As assessed by investigator per RECIST v1.1. [b] One of the 10 partial responses in Cohort 4 was confirmed after data cut-off.

Best Change in Sum of Diameters of Target Lesions[a]

Cohort 2 (doublet), 1L setting (N=14)
ORR: 50.0%; DCR: 92.9%



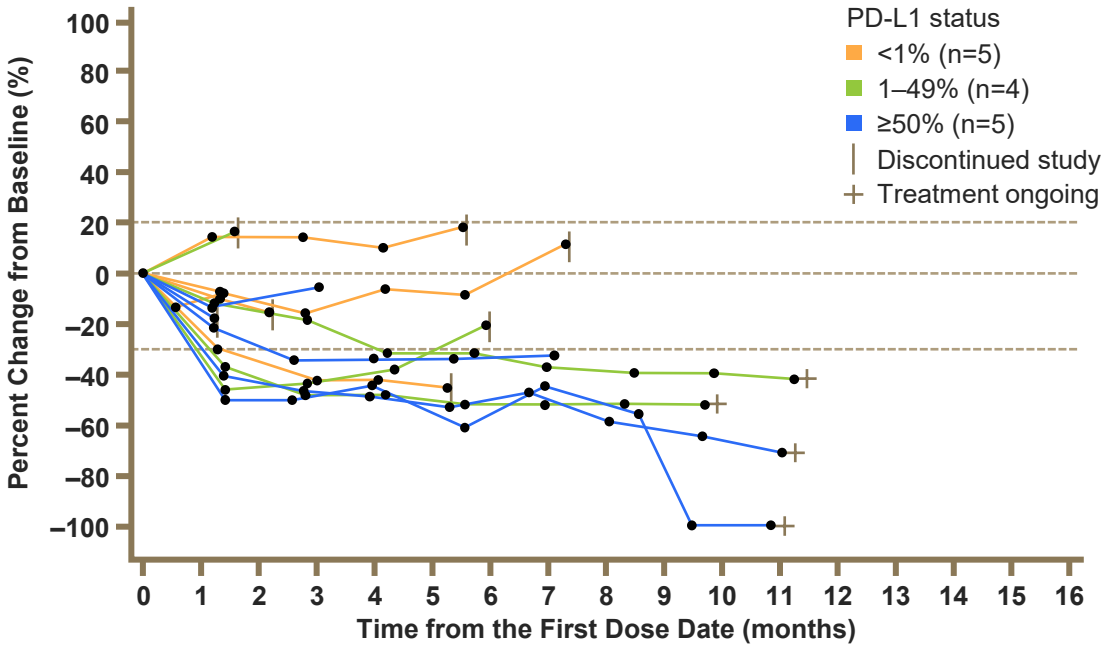
Cohort 4 (triplet), 1L setting (N=13)
ORR: 76.9%;[b] DCR: 92.3%



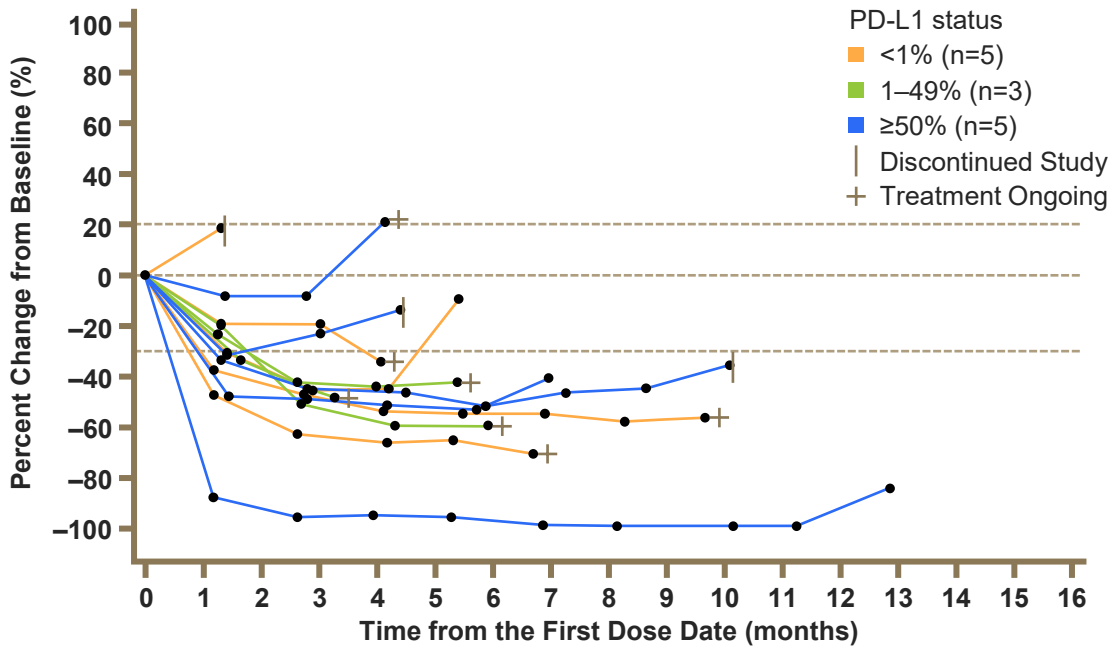
Data cut-off: March 6 2023.
[a] As assessed by investigator per RECIST v1.1. [b] One of the 10 partial responses in Cohort 4 was confirmed after data cut-off.
DCR, disease control rate.

Depth and Durability of Response[a]

Cohort 2 (doublet), 1L setting (N=14)



Cohort 4 (triplet), 1L setting (N=13)



Data cut-off: March 6 2023.
[a] As assessed by investigator per RECIST v1.1.

Conclusions

Safety	No new safety signals were observed in Cohort 2 and Cohort 4 investigating Dato-DXd in combination with durvalumab ± carboplatin, throughout dose escalation and dose expansion
	The most frequent TEAEs of any grade were stomatitis, alopecia and nausea. In general, Grade ≥3 TEAEs were more frequently observed with the triplet versus the doublet combination, which was mainly driven by more hematological events. There were four cases of ILD adjudicated as drug-related; three cases were Grade 1 or 2 and none were Grade 5
Efficacy	Interim efficacy analyses demonstrated promising ORRs with durable responses for both the doublet and triplet combination, both in the 1L setting and the overall population
	Responses were numerically higher with the triplet versus doublet combination and were observed across all PD-L1 expression levels

The Phase 3 AVANZAR (NCT05687266), TROPION-Lung07 (NCT05555732) and TROPION-Lung08 (NCT05215340) trials are evaluating Dato-DXd and immune checkpoint inhibitor combinations as potential 1L treatment options in patients with advanced or metastatic NSCLC[1–3]

1. Aggarwal C, et al. Poster P2.04-02. Presented at WCLC 2023; 2. NCT05555732. Available at: https://clinicaltrials.gov/ct2/show/NCT05555732 (accessed August 2023); 3. NCT05215340. Available at: https://clinicaltrials.gov/ct2/show/NCT05215340 (accessed August 2023).

Acknowledgements

- The authors would like to thank the patients, their families and caregivers, as well as the TROPION-Lung04 investigators and site personnel

- Contact email: saiamawaqar@wustl.edu