TROPION-Lung02: Datopotamab deruxtecan (Dato-DXd) plus pembrolizumab (pembro) with or without platinum chemotherapy (Pt-CT) as first-line (1L) therapy for advanced non-small cell lung cancer (aNSCLC)

Benjamin P. Levy,[1] Luis G. Paz-Ares,[2] Chien-Chung Lin,[3] Scott Herbert,[4] Tsung-Ying Yang,[5] Anthony W. Tolcher,[6] Yanyan Lou,[7] Yoshitaka Zenke,[8] Diego Cortinovis,[9] Enriqueta Felip,[10] Manuel Domine Sr.,[11] Konstantinos Leventakos,[12] Emiliano Calvo,[13] Atsushi Horiike,[14] Edward Pan,[15] Keisuke Matsubara,[16] Xiaoyu Jia,[15] Rachel A. Chiaverelli,[15] Michael J. Chisamore,[17] Yasushi Goto[18]

[1]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins Medicine, Baltimore, MD, USA; [2]Hospital Universitario 12 de Octubre, CNIO-H12O Lung Cancer Unit, Universidad Complutense & CiberOnc, Madrid, Spain; [3]Department of Internal Medicine, National Cheng Kung University Hospital and Tainan Hospital, Ministry of Health & Welfare, Tainan City, Taiwan; [4]Quantum, Santa Fe, NM, USA; [5]Department of Chest Medicine, Taichung Veterans General Hospital, Taichung, Taiwan; [6]NEXT Oncology, San Antonio, TX, USA; [7]Mayo Clinic, Jacksonville, FL, USA; [8]Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [9]Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy; [10]Vall d'Hebron Hospital Campus, Vall d'Hebron Institute of Oncology, Universitat Autònoma de Barcelona, Spain; [11]Department of Oncology, Hospital Universitario Fundación Jiménez Díaz (IIS-FJD), Madrid, Spain; [12]Mayo Clinic, Rochester, MN, USA; [13]START Madrid-CIOCC, Centro Integral Oncológico Clara Campal, Madrid, Spain; [14]Division of Medical Oncology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan; [15]Daiichi Sankyo, Inc., Basking Ridge, NJ, USA; [16]Daiichi Sankyo Co, Ltd., Tokyo, Japan; [17]Merck & Co., Inc., Rahway, NJ, USA; [18]National Cancer Center Hospital, Tokyo, Japan.

PRESENTED BY: Benjamin P. Levy, MD, FASCO

Key Takeaway Points

1

TROPION-Lung02 is the largest clinical dataset to date evaluating an antibody–drug conjugate combined with an anti–PD-1 agent in patients with a/mNSCLC

2

As 1L therapy, combination Dato-DXd plus pembrolizumab, both with and without Pt-CT, continues to elicit durable antitumor activity across all levels of PD-L1 expression with manageable safety

3

Retrospective testing showed a trend towards improved outcomes in TROP2 NMR positive patients – further demonstrating the potential of this novel predictive biomarker

Background

- Standard 1L treatment for patients with a/mNSCLC lacking actionable genomic alterations is anti–PD-1/L1 monotherapy for those with high PD-L1 expression, and single- or dual-agent checkpoint blockade + Pt-CT for those with low PD-L1 expression[1,2]
- While these regimens have improved outcomes, few patients experience long term disease control and most eventually progress[3,4]
- Dato-DXd, a TROP2-directed ADC bearing a potent topoisomerase I inhibitor payload,[5] extended progression-free survival as monotherapy compared to docetaxel in pretreated patients with a/mNSCLC in the TROPION-Lung01 trial[6]
- TROPION-Lung02 evaluated combination Dato-DXd + pembrolizumab treatment ± Pt-CT in patients with a/mNSCLC without actionable genomic alterations
- Here, we report the final analysis of patients receiving these combination therapies in the 1L setting and the first presentation of outcomes based on TROP2 biomarker analyses using normalized membrane ratio (NMR) measured by quantitative continuous scoring (QCS)

1L, first line; ADC, antibody-drug conjugate; a/mNSCLC, advanced or metastatic non-small cell lung cancer; Dato-DXd, datopotamab deruxtecan; PD-L1, programmed death ligand 1; Pt-CT, platinum-based chemotherapy; TROP2, trophoblast cell surface antigen 2.

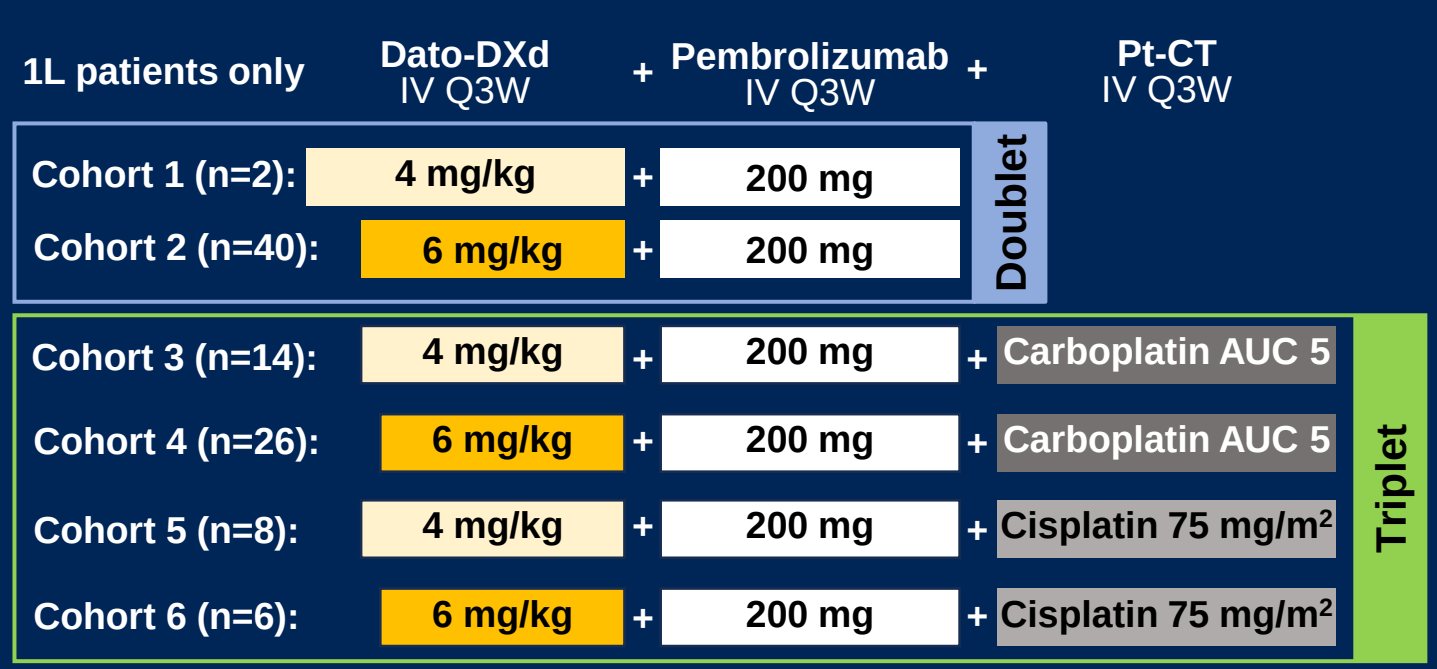
1. Jaiyesimi IA et al. *J Clin Oncol*. 2024;42:e23–e43. 2. Hendriks LE et al. *Ann Oncol*. 2023;34:358–76. 3. Paz-Ares L et al. *J Thorac Oncol.* 2020;15:1657–69. 4. Reck M et al. *J Clin Oncol.* 2021;39:2339–49.
5. Okajima D et al. *Mol Cancer Ther*. 2021;20:2329–2340. 6. Ahn MJ et al. *J Clin Oncol*. 2025;43:260–272.

TROPION-Lung02

- Phase 1b study of Dato-DXd + pembrolizumab ± Pt-CT in a/mNSCLC without actionable genomic alterations[a]

Key eligibility criteria

- a/mNSCLC
- Dose escalation[b]: ≤2 lines of prior therapy[c]
- Dose expansion
  - ≤1 line of Pt-CT (cohorts 1 and 2)[c]
  - Treatment-naive (cohort 2)[c,d]
  - Treatment-naive (cohorts 3–6)[c]



Objectives

Primary: Safety and tolerability

Secondary: Efficacy

Data cutoff: April 29, 2024. Median study duration was 18.7 months (range, 11–33.8) for doublet and 24.6 months (range, 15.4–32.4) for triplet combinations.

[a]Patients with known actionable genomic alterations in *EGFR*, *ALK*, *ROS1*, *NTRK*, *BRAF*, *RET*, or *MET*, or with alterations in other actionable oncogenic driver kinases were not eligible for this study. [b]The first 3 to 6 patients in each cohort were enrolled to confirm acceptable safety/DLT rate; the remaining patients are considered part of dose expansion. [c]Prior therapy requirements are for treatment in the a/m setting. [d]Enrollment after June 30, 2022.

1L, first line; a/m, advanced or metastatic; CT, chemotherapy; DLT, dose-limiting toxicity; IV, intravenous; NSCLC, non-small cell lung cancer; Pt-CT, platinum-based chemotherapy; Q3W, every 3 weeks.

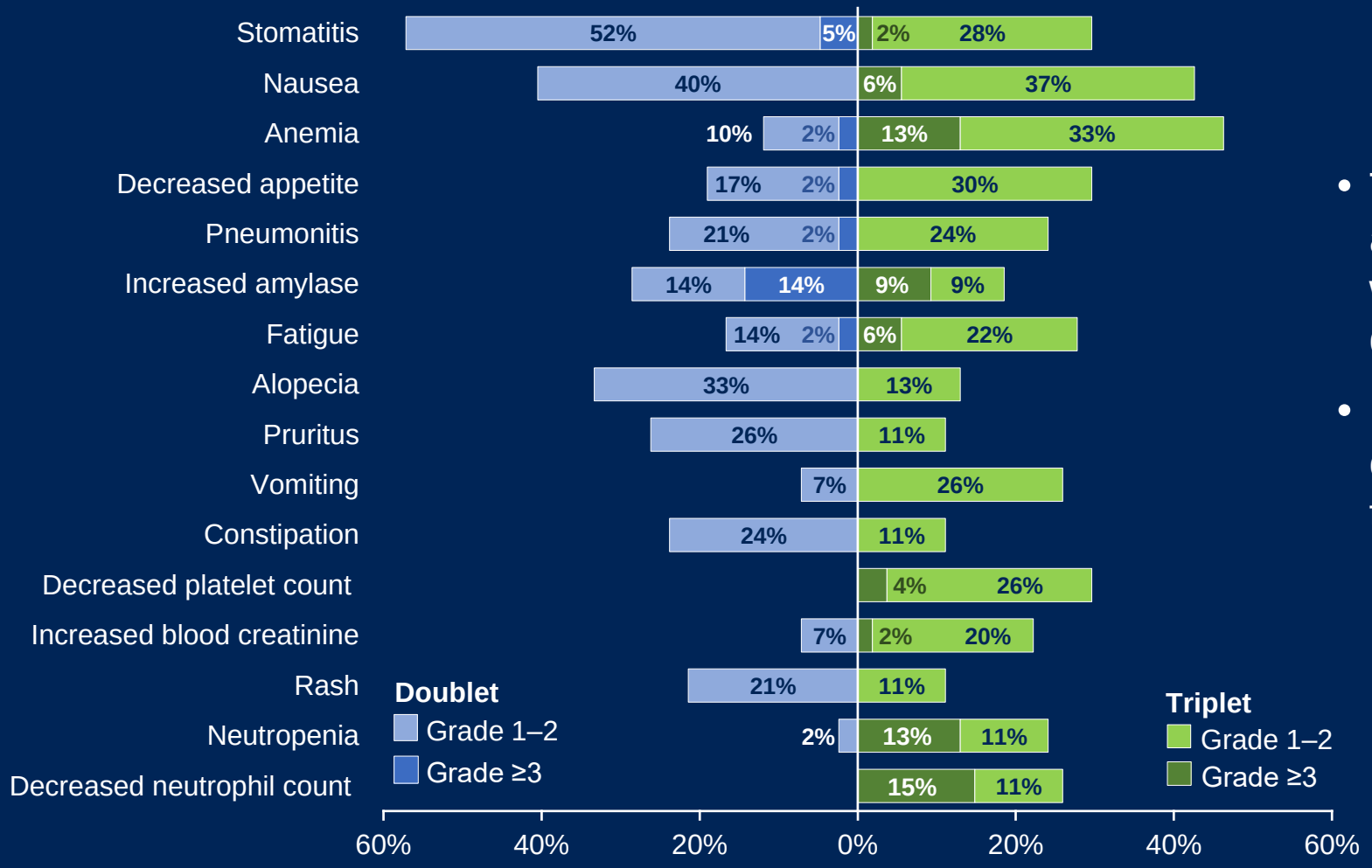
Demographics and Baseline Characteristics, 1L Patients

	All 1L (N=96)	
	Doublet (n=42)	Triplet (n=54)
Age, median (range), years	65 (48–83)	64 (33–78)
Male, n (%)	32 (76.2)	34 (63.0)
Asian race, n (%)	31 (73.8)	23 (42.6)
Histology, n (%)		
Nonsquamous	32 (76.2)	40 (74.1)
Squamous	10 (23.8)	14 (25.9)
History of brain metastases, n (%)	4 (9.5)	10 (18.5)
ECOG PS 1, n (%)	24 (57.1)	33 (61.1)
Dato-DXd dosing, n (%)		
4 mg/kg	2 (4.8)	22 (40.7)
6 mg/kg	40 (95.2)	32 (59.3)
PD-L1 expression[a], n (%)		
<50%	30 (71.4)	40 (74.1)
≥50%	5 (11.9)	10 (18.5)
NE	7 (16.7)	4 (7.4)

Data cutoff: April 29, 2024.

[a]Evaluated using immunohistochemistry (22C3 assay). 1L, first line; ECOG PS, Eastern Cooperative Oncology Group performance status; NE, not evaluable; PD-L1, programmed death ligand 1.

TRAEs Occurring in ≥20% of 1L Patients



- The most frequent TRAEs of any grade across regimens were stomatitis, nausea, anemia, decreased appetite, and alopecia
- Hematologic toxicities occurred more frequently in the triplet cohorts

Data cutoff: April 29, 2024. 1L, first-line; TRAE, treatment-related adverse event. Current TMGs for Dato-DXd, including prophylaxis recommendations, were not in place at time of study initiation.

Safety Summary, 1L Patients

Event, n (%)	All 1L (N=96)	
	Doublet (n=42)	Triplet (n=54)
TRAEs	39 (92.9)	54 (100)
Grade ≥3	17 (40.5)	30 (55.6)
Associated with death	0	0
TRAEs associated with dose modifications		
Dose reduction of any drug	8 (19.0)	14 (25.9)
Dose reduction of Dato-DXd	8 (19.0)	7 (13.0)
Discontinuation of any drug	14 (33.3)	20 (37.0)
Discontinuation of Dato-DXd	13 (31.0)	16 (29.6)
Serious TRAEs	5 (11.9)	12 (22.2)
Grade ≥3	4 (9.5)	9 (16.7)
AESIs		
Oral mucositis/stomatitis	26 (61.9)	22 (40.7)
Grade 3	2 (4.8)	1 (1.9)
Adjudicated drug-related ILD/pneumonitis	11 (26.2)	14 (25.9)
Grade 3	2 (4.8)	1 (1.9)
Ocular surface events	9 (21.4)	18 (33.3)
Grade 3	1 (2.4)	2 (3.7)

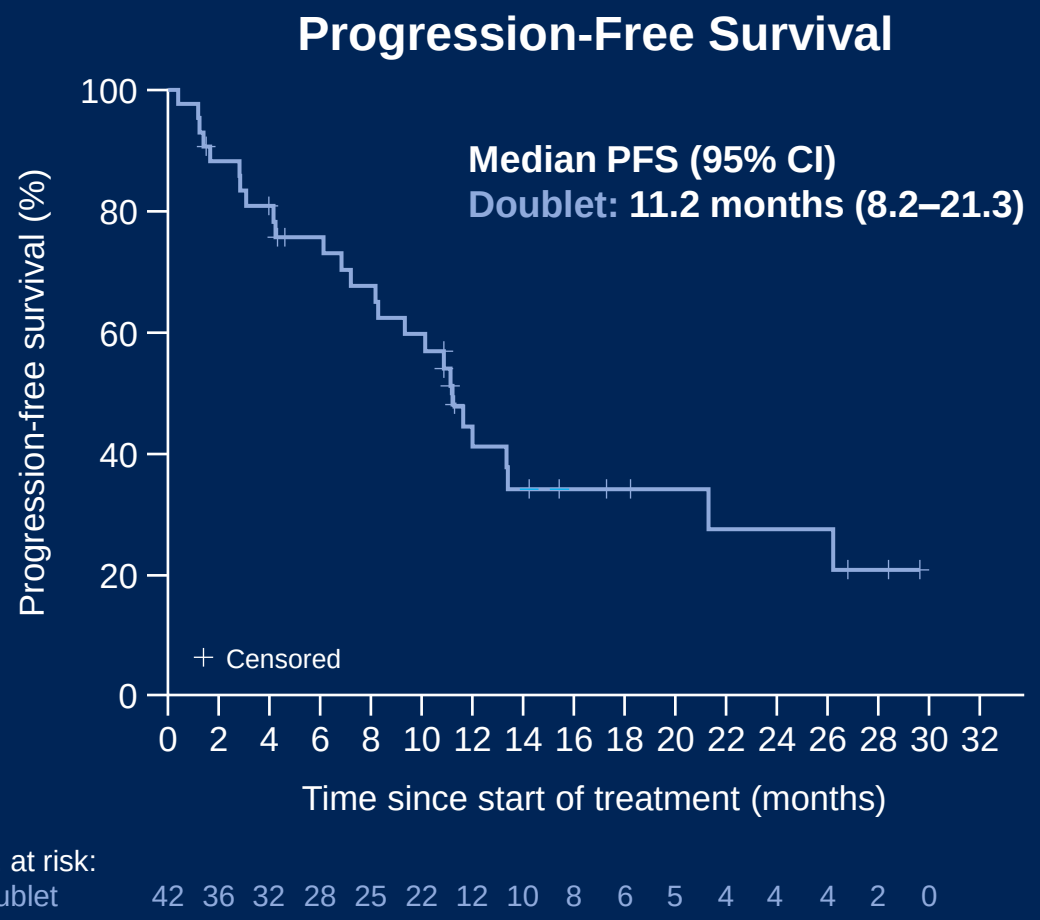
- Median treatment durations for the doublet and triplet combinations were 9.7 and 5.8 months, respectively
- No grade 4 or 5 AESI events were observed

Data cutoff: April 29, 2024.

1L, first line; AESI, adverse event of special interest; ILD, interstitial lung disease; TRAE, treatment-related adverse event. Current TMGs for Dato-DXd, including prophylaxis recommendations, were not in place at time of study initiation.

Efficacy, 1L Doublet

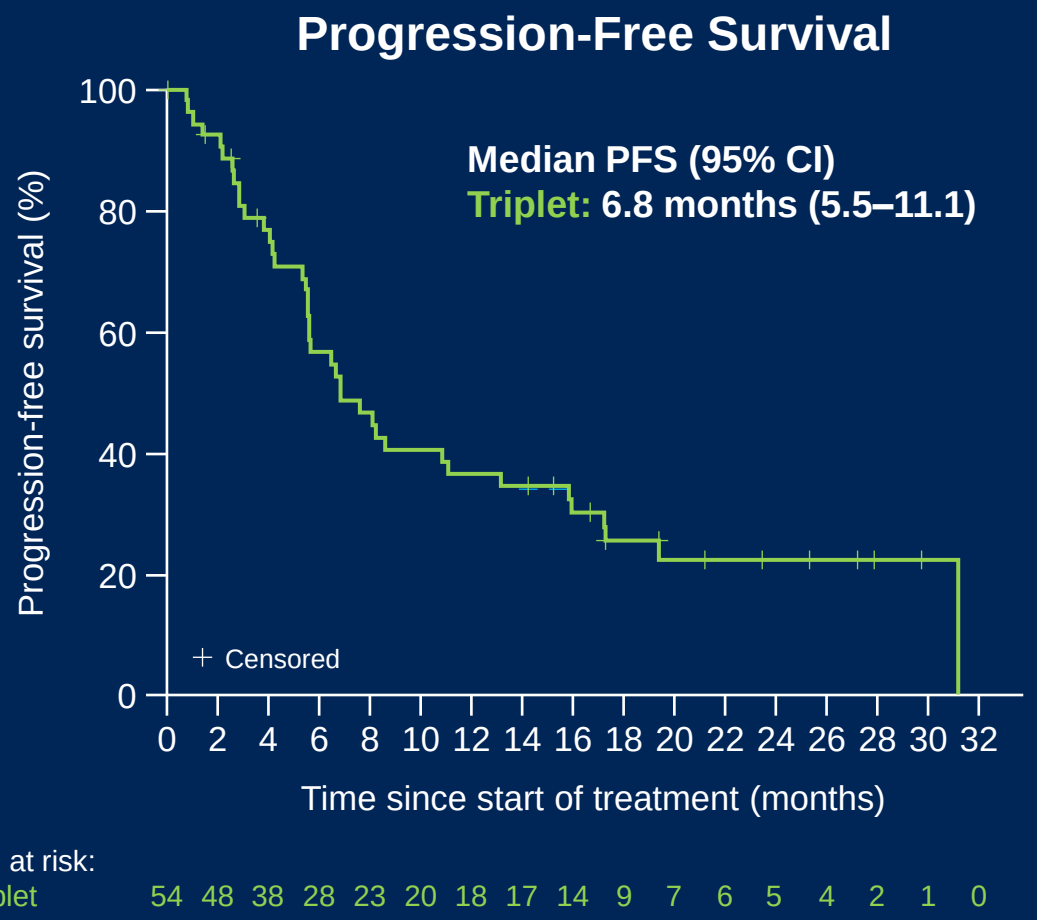
	Doublet (n=42)
Confirmed ORR*, n (%)	**23 (54.8)**
95% CI	38.7–70.2
Median DOR, months	**20.1**
95% CI	9.7–NE
DCR, n (%)	**37 (88.1)**
95% CI	74.4–96.0
Median TTR, months	**1.4**
Range	1.2–7.0
Median PFS, months	**11.2**
95% CI	8.2–21.3
Median OS, months	**NE**
95% CI	19.2–NE



Data cutoff: April 29, 2024. *1 CR, 22 PR. Pooled data including patients who received Dato-DXd 4mg/kg (5%) and Dato-DXd 6 mg/kg (doublet: 95%)
1L, first line; BOR, best overall response; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; NE, not evaluable; ORR, objective response rate; PR, partial response; TTR, time to response.

Efficacy, 1L Triplet

	Triplet (n=54)
Confirmed ORR*, n (%)	**30 (55.6)**
95% CI	41.4–69.1
Median DOR, months	**13.7**
95% CI	5.7–NE
DCR, n (%)	**48 (88.9)**
95% CI	77.4–95.8
Median TTR, months	**1.4**
Range	1.2–9.6
Median PFS, months	**6.8**
95% CI	5.5–11.1
Median OS, months	**17.4**
95% CI	9.1–NE



Data cutoff: April 29, 2024. *2 CR, 28 PR. Pooled data including patients who received Dato-DXd 4mg/kg (41%) and Dato-DXd 6 mg/kg (59%)
1L, first line; BOR, best overall response; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; NE, not evaluable; ORR, objective response rate; PR, partial response; TTR, time to response.

Efficacy by PD-L1 Status

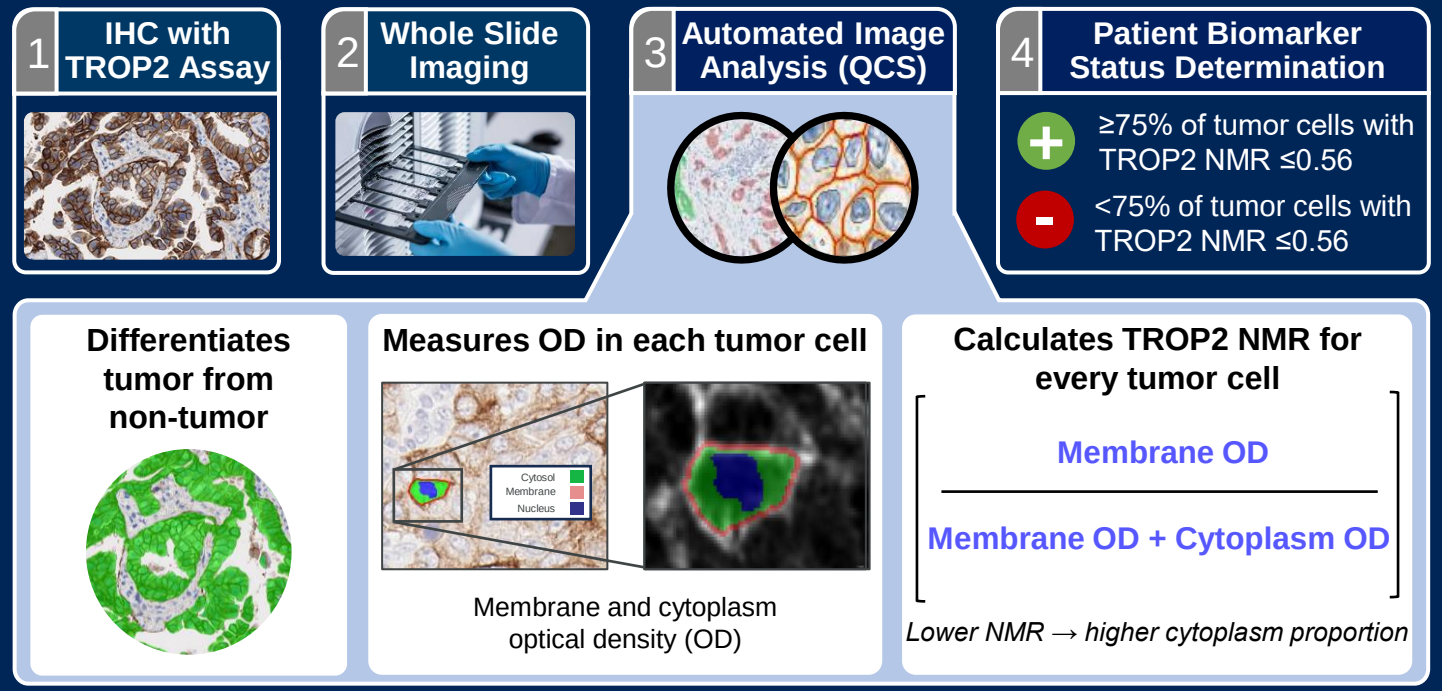
	Doublet		Triplet	
	PD-L1 <50%	**PD-L1 ≥50%**	**PD-L1 <50%**	**PD-L1 ≥50%**
N	30	5	40	10
ORR,% (95% CI)	**53.3%** (34.3–71.7)	**100%** (47.8–100)	**55.0%** (38.5-70.7)	**60.0%** (26.2–87.8)
BoR (%)				
CR	3.3%	0	2.5%	10.0%
PR	50%	100%	52.5%	50.0%
DOR, months (95% CI)	**12.0** (8.0–NE)	**NE** (5.5–NE)	**14.6** (5.3–NE)	**NE** 4.1–NE
DCR (%) (95% CI)	**96.7** (82.8–99.9)	**100** (47.8–100)	**87.5** (73.2–95.8)	**90.0** (55.5–99.7)
Median PFS, months (95% CI)	**11.1** (7.2–13.3)	**NE** (8.3–NE)	**6.4** (5.5–13.2)	**6.8** (0.8–NE)
Median OS, months (95% CI)	**NE** (19.2-NE)	**NE** (12.6-NE)	**13.3** (7.7-NE)	**NE** (0.8-NE)

Pooled data including patients who received Dato-DXd 4mg/kg (doublet: 5%, triplet: 41%) and Dato-DXd 6 mg/kg (doublet: 95%, triplet: 59%)

TROP2 Normalized Membrane Ratio (NMR) Measured by Quantitative Continuous Scoring (QCS)

QCS is a novel, fully-supervised computational pathology approach that precisely quantifies and locates targets like TROP2

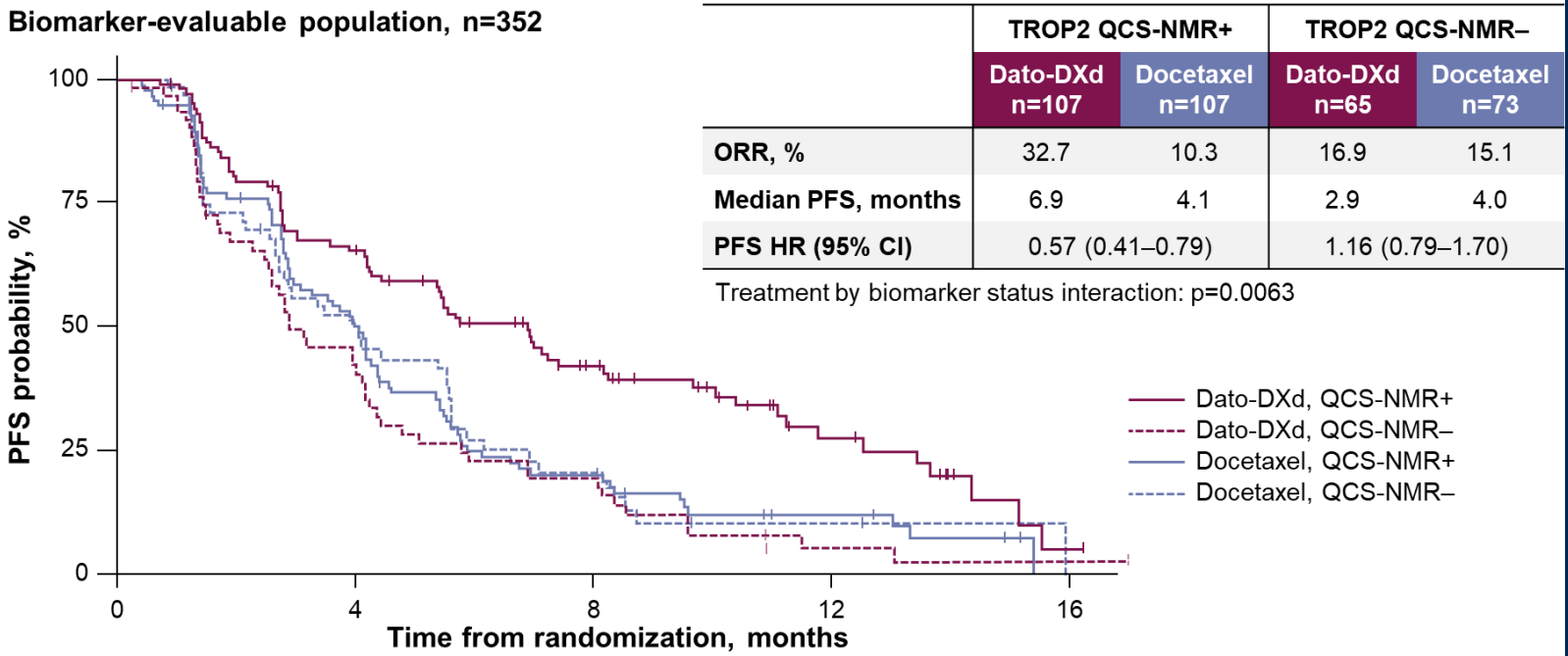
- TROP2 tumor membrane expression using conventional IHC and pathology visual scoring does not enrich for response
- TROP2 NMR as measured by QCS reflects the expression of TROP2 in the membrane relative to total TROP2 (membrane and cytoplasm)



1L, first line; 2L+, second line and beyond; IHC, immunohistochemistry; NMR, normalized membrane ratio; OD, optical density; QCS, quantitative continuous scoring; TROP2, trophoblast cell-surface antigen 2.

TROP2 NMR positivity was predictive for longer PFS with Dato-DXd in TROPION-Lung01[1]

- TROP2 NMR predicted outcomes in an exploratory analysis in the TROPION-Lung01 trial evaluating Dato-DXd as monotherapy in the 2L+ setting[1]



	TROP2 QCS-NMR+		TROP2 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
PFS HR (95% CI)	0.57 (0.41–0.79)		1.16 (0.79–1.70)	

Treatment by biomarker status interaction: p=0.0063

We applied the same cut-off identified for Dato-DXd as 2L+ monotherapy to evaluate enrichment for patient response in the 1L combination setting.

1L, first line; 2L+, second line and beyond; HR, hazard ratio; NMR, normalized membrane ratio; ORR, objective response rate; PFS, progression-free survival; QCS, quantitative continuous scoring; TROP2, trophoblast cell-surface antigen 2.

1. Garassino MC et al. *J Thorac Oncol*. 2024;19:S2–S3.

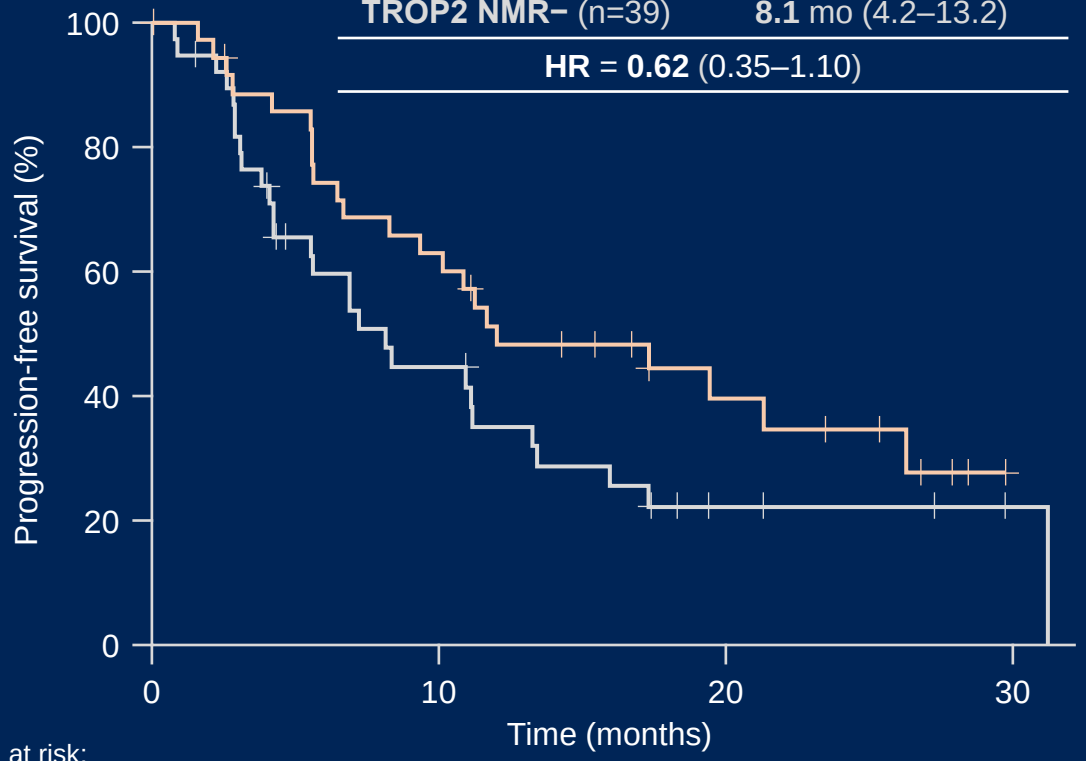
Demographics and Baseline Characteristics, Biomarker Evaluable Population

		TROP2 NMR biomarker evaluable, 1L (n=76)[a]	
	All 1L (N=96)	TROP2 NMR+ (n=37)	TROP2 NMR− (n=39)
Age, median (range), years	64 (33–83)	61 (33–76)	65 (48–82)
Male, n (%)	66 (68.8)	24 (64.9)	27 (69.2)
Asian race, n (%)	54 (56.3)	23 (62.2)	21 (53.8)
Histology, n (%)			
Nonsquamous	72 (75.0)	32 (86.5)	27 (69.2)
Squamous	24 (25.0)	5 (13.5)	12 (30.8)
History of brain metastases, n (%)	14 (14.6)	5 (13.5)	6 (15.4)
ECOG PS 1, n (%)	57 (59.4)	19 (51.4)	26 (66.7)
PD-L1 expression[b], n (%)			
<50%	70 (72.9)	26 (70.3)	31 (79.5)
≥50%	15 (15.6)	8 (21.6)	6 (15.4)
NE	11 (11.5)	3 (8.1)	2 (5.1)

Data cutoff: April 29, 2024.
[a]20 patients from the 1L ITT population were not evaluable for TROP2 NMR analysis. [b]Evaluated using immunohistochemistry (22C3 assay).
ECOG PS, Eastern Cooperative Oncology Group performance status; NE, not evaluable; TROP2 NMR, TROP2 normalized membrane ratio.

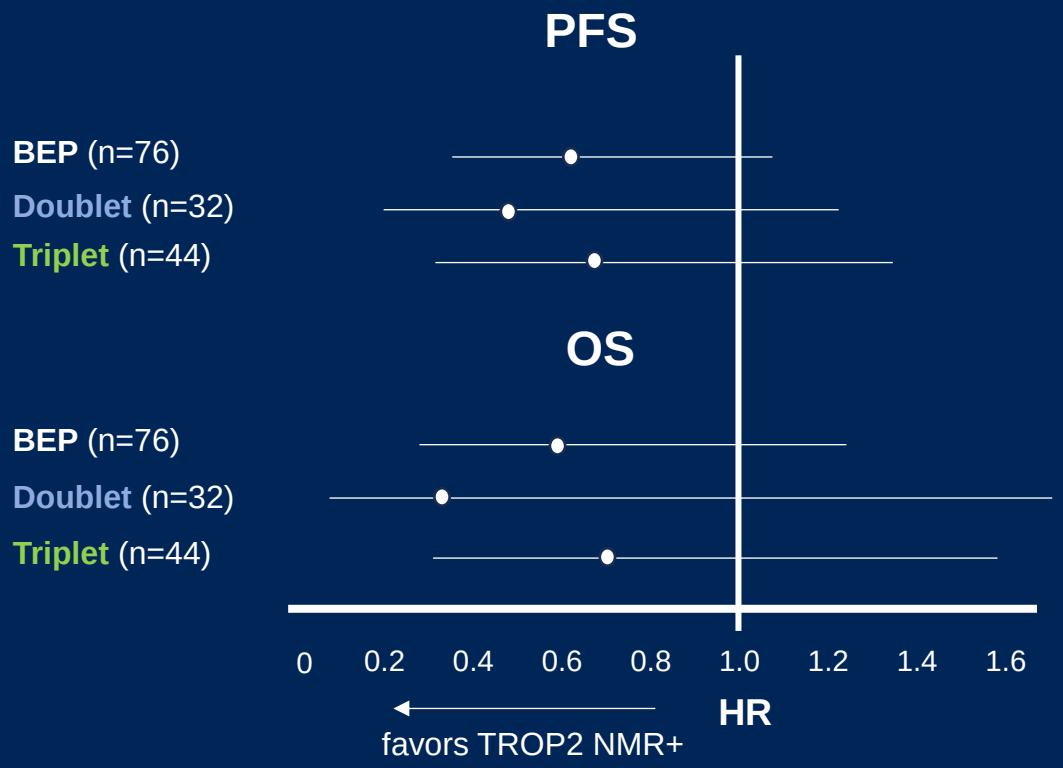
Efficacy by TROP2 NMR, 1L Biomarker Evaluable Population

	Median PFS (95% CI)
TROP2 NMR+ (n=37)	**12.0** mo (8.2–26.2)
TROP2 NMR− (n=39)	**8.1** mo (4.2–13.2)
HR = **0.62** (0.35–1.10)	



No. at risk:

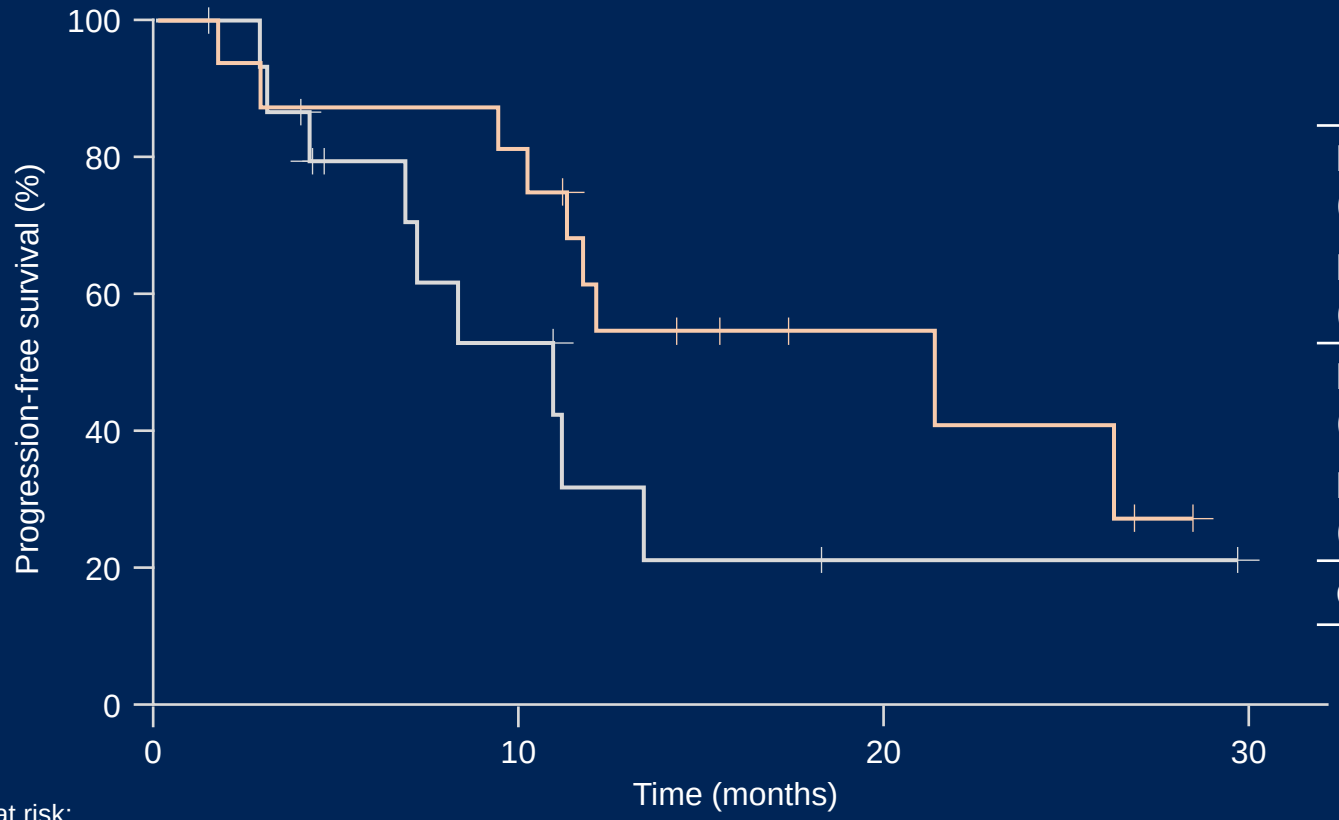
TROP2 NMR+	37	22	8	0
TROP2 NMR−	39	15	4	1



Data cutoff: April 29, 2024. Pooled data including patients who received Dato-DXd 4mg/kg and 6 mg/kg

BEP, biomarker evaluable population;CI, confidence interval; HR, hazard ratio; mo, months; NE, not evaluable; OS, overall survival; PFS, progression-free survival; TROP2 NMR, TROP2 normalized membrane ratio.

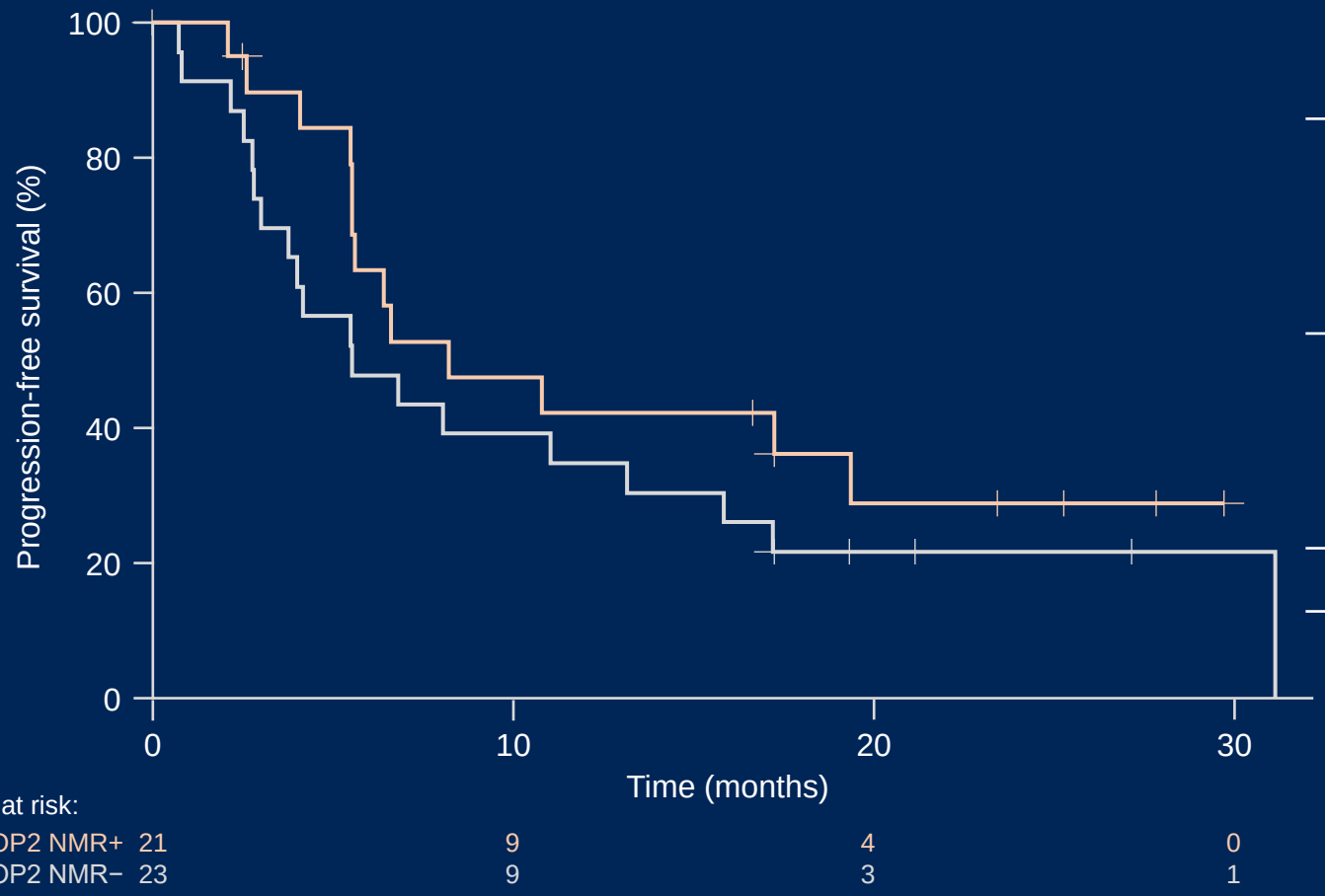
Doublet Efficacy by TROP2 NMR, 1L Biomarker Evaluable



	TROP2 NMR+ (n=16)	TROP2 NMR− (n=16)	1L ITT (n=42)
Median PFS (95% CI)	**21.3 mo** (10.2–NE)	**10.9 mo** (4.2–13.4)	**11.2 mo** (8.2–21.3)
HR (95% CI)	**0.50** (0.19–1.29)		-
Median OS (95% CI)	**NE** (26.2–NE)	**NE** (14.3–NE)	**NE** (19.2–NE)
HR (95% CI)	**0.35** (0.07–1.72)		-
ORR	68.8%	62.5%	54.8%

Data cutoff: April 29, 2024. Pooled data including patients who received Dato-DXd 4mg/kg and 6 mg/kg.
CI, confidence interval; HR, hazard ratio; NE, not evaluable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TROP2 NMR, TROP2 normalized membrane ratio.

Triplet Efficacy by TROP2 NMR, 1L Biomarker Evaluable



	TROP2 NMR+ (n=21)	TROP2 NMR− (n=23)	1L ITT (n=54)
Median PFS (95% CI)	**8.2 mo** (5.6–NE)	**5.5 mo** (3.0–13.2)	**6.8 mo** (5.5–11.1)
HR (95% CI)	**0.67** (0.33–1.36)		-
Median OS (95% CI)	**26.9 mo** (7.1–NE)	**13.3 mo** (6.4–NE)	**17.4 mo** (9.1–NE)
HR (95% CI)	**0.71** (0.31–1.59)		-
ORR	61.9%	52.2%	55.6%

Data cutoff: April 29, 2024. Pooled data including patients who received Dato-DXd 4mg/kg and 6 mg/kg.
CI, confidence interval; HR, hazard ratio; NE, not evaluable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TROP2 NMR, TROP2 normalized membrane ratio.

Conclusions

- At TROPION-Lung02 final analysis, the combination of Dato-DXd + pembrolizumab ± Pt-CT continued to elicit durable antitumor activity in patients with a/mNSCLC, with efficacy observed in both high and low PD-L1 expression subgroups
- Tolerability of the combinations was as expected based on known profiles of the individual agents
- These data support the evaluation of Dato-DXd + pembrolizumab ± Pt-CT vs standard-of-care therapies in the 1L setting in the ongoing pivotal phase 3 TROPION-Lung07 and TROPION-Lung08 studies
- In this nonrandomized study, exploratory retrospective TROP2 NMR testing showed a trend towards prolonged PFS and OS in biomarker positive patients

Limitations

- TROPION-Lung02 was nonrandomized and comparisons cannot be made between the doublet and triplet cohorts due to differences in baseline characteristics
- Limited sample sizes to clearly interpret the various subgroups of the study (including by PD-L1 status)
- TROP2 biomarker analyses were conducted retrospectively with the evolving development of QCS as a novel computational approach to assess TROP2 expression patterns in NSCLC

Acknowledgments

- The authors would like to thank the patients, their families, and all investigators involved in this study
- This study was sponsored by Daiichi Sankyo, Inc. In July 2020, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for datopotamab deruxtecan (Dato-DXd)
- Pembrolizumab is being provided under agreement by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA
- Medical writing support, including assisting authors with development of the presentation, incorporation of comments, referencing, and figure preparation was provided by Michelle Jenvey, PhD, and editorial support by Jess Galbraith, BSc, and Isobel Markham, MSc, all of Core (a division of Prime, London, UK), supported by Daiichi Sankyo, Inc., according to Good Publication Practice guidelines

Lay Summary

What does this research tell us?

There is a need for better treatment options for patients with non-small cell lung cancer (NSCLC) that has spread to other parts of the body (advanced or metastatic), as well as methods to help predict how patients will respond to potential new cancer treatments.

Datopotamab deruxtecan (Dato-DXd) is a type of drug called an antibody-drug conjugate, which is made up of an antibody (datopotamab) linked to a chemotherapy drug (DXd). The antibody attaches to a protein found on the surface of cancer cells called TROP2 and then is taken inside the cell, where it releases the chemotherapy to kill the tumor cells. Dato-DXd has shown activity when given to patients with advanced or metastatic NSCLC who had previously received other treatments for their disease.

TROPION-Lung02 is a clinical trial testing Dato-DXd given together with the immunotherapy drug pembrolizumab, both with and without chemotherapy. This analysis included patients from TROPION-Lung02 who had never received any treatment for their advanced cancer before. One group of patients was treated with Dato-DXd and pembrolizumab (doublet group), and the other group was treated with Dato-DXd, pembrolizumab, and chemotherapy (triplet group). The researchers wanted to find out what side effects occurred, whether the patients' tumors shrank or disappeared, and how long patients received Dato-DXd for before their cancer got worse. Researchers also wanted to find out whether a new way of measuring the ratio of TROP2 expression both inside the cell and on the cell surface, called quantitative continuous scoring (QCS) normalized membrane ratio (NMR), could predict the patients' response to treatment with Dato-DXd doublet and triplet combinations.

Treatment made tumors shrink in approximately 55% of patients in both the doublet and triplet groups. In patients whose tumors shrank, treatment continued to work for an average of 20 months in patients in the doublet group and 14 months in patients in the triplet group. Patients whose tumor samples were TROP2 QCS-NMR-positive tended to live longer without their disease getting worse than patients whose tumor samples were TROP2 QCS-NMR-negative. Side effects caused by these combinations were as expected, with stomatitis (an inflamed and sore mouth) seen most often. Nobody in the study died or had life-threatening side effects because of treatment with Dato-DXd.

Who does this research impact?

This research impacts patients with advanced or metastatic NSCLC who have not received any treatment for their cancer before, and specifically, those patients lacking certain genetic mutations for which targeted therapy is available.

What does this mean for patients right now?

These results suggest that, in the future, patients could potentially receive Dato-DXd in combination with pembrolizumab with or without chemotherapy as their first line of treatment for advanced or metastatic NSCLC.

The potential of TROP2 QCS-NMR to act as a biomarker (a biological molecule which can be used to predict how well the tumor is likely to respond to a treatment) was previously shown in patients with NSCLC who received Dato-DXd alone following previous treatment(s) for their cancer. While further validation is needed, it is encouraging to see that responses to these new Dato-DXd combinations could also be predicted by the same method.