Abstract # 8617

Datopotamab deruxtecan (Dato-DXd) plus pembrolizumab with or without platinum chemotherapy as first-line therapy for advanced non-small cell lung cancer (NSCLC); subgroup analysis from TROPION-Lung02

Benjamin Levy,[1] Luis Paz Ares,[2] Wu Chou Su,[3] Scott Herbert,[4] Tsung Ying Yang,[5] Anthony Tolcher,[6,7] Yanyan Lou,[8] Yoshitaka Zenke,[9] Diego Cortinovis,[10] Enriqueta Felip,[11] Manuel Domine,[12] Konstantinos Leventakos,[13] Emiliano Calvo,[14] Atsushi Horiike,[15] Edward Pan,[16] Daisy Lin,[16] Xiaoyu Jia,[16] Priyanka Basak,[16] 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 Oncology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan; [4]Quantum, Santa Fe, NM, USA; [5]Division of Chest Medicine, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan; [6]NEXT Oncology, San Antonio, TX, USA; [7]Texas Oncology, San Antonio, TX, USA; [8]Mayo Clinic, Jacksonville, FL, USA; [9]Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [10]Università degli Studi di Milano-Bicocca, Monza, Italy; [11]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [12]Department of Oncology, Hospital Universitario Fundación Jiménez Díaz (IIS-FJD), Madrid, Spain; [13]Mayo Clinic, Rochester, MN, USA; [14]START Madrid-CIOCC, Centro Integral Oncológico Clara Campal, Madrid, Spain; [15]Division of Medical Oncology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan; [16]Daiichi Sankyo, Inc., Basking Ridge, NJ, USA; [17]Merck & Co., Inc., Rahway, NJ, USA; [18]National Cancer Center Hospital, Tokyo, Japan

Objective

- Subgroup analysis of TROPION-Lung02 evaluating Dato-DXd + pembrolizumab ± platinum CT as 1L therapy for patients with advanced/metastatic NSCLC without actionable genomic alterations

Conclusions

- As a 1L therapy for advanced NSCLC, Dato-DXd + pembrolizumab ± platinum CT continues to demonstrate durable antitumor activity across all levels of PD-L1 expression and with both doublet and triplet regimens
  - In this non-randomized study, efficacy outcomes seen with the doublet regimen were not inferior to those seen with the triplet regimen
- Tolerability of the combinations was as expected based on known profiles of the individual agents, with no new safety signals observed
- To date, this is the largest dataset reported for any ADC combined with an anti–PD-1/-L1 agent in the 1L setting for advanced NSCLC
- These data support the evaluation of Dato-DXd + pembrolizumab ± CT vs standard of care therapies in the 1L setting in the pivotal phase 3 TROPION-Lung07 (NCT05555732) and TROPION-Lung08 (NCT05215340) studies

Background

- For patients with advanced/metastatic NSCLC, the standard first-line treatment is pembrolizumab monotherapy for those with high PD-L1 expression and pembrolizumab in combination with platinum-doublet CT for those with low PD-L1 expression; treatment outcomes when using PD-L1 inhibitors are worse in patients with low vs high PD-L1 expression[1]
- **Dato-DXd** is a **TROP2-directed antibody–drug conjugate (ADC)** composed of an anti-TROP2 mAb covalently linked to a highly potent topoisomerase I inhibitor payload via a plasma-stable, tumor-selective, tetrapeptide-based cleavable linker[2]
- Encouraging antitumor activity has been observed in patients with NSCLC receiving Dato-DXd in combination with IO (TROPION-Lung02[3] and TROPION-Lung04[4])
- TROPION-Lung02 (NCT04526691)[5] is the first study evaluating Dato-DXd + pembrolizumab ± platinum CT in advanced NSCLC without actionable genomic alterations
- Here, we report subgroup analyses from TROPION-Lung02 in patients receiving 1L therapy

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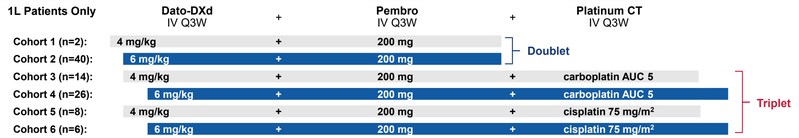
Corresponding author email address: blevy11@jhmi.edu

Methods

- TROPION-Lung02 is a phase 1b, multicenter, open-label study of Dato-DXd + pembrolizumab ± platinum CT in advanced NSCLC without actionable genomic alterations[a]
  - The safety of the Dato-DXd + pembrolizumab doublet was established prior to evaluation of the platinum-containing triplet
  - The safety of Dato-DXd 4-mg/kg combinations was established prior to evaluation of 6-mg/kg combinations
- Patients in the expansion stage were primarily treatment-naive

Key eligibility criteria

- **Advanced/metastatic NSCLC**
- **Dose escalation[b]:** ≤2 lines of prior therapy[c]
- **Dose expansion**
  - ≤1 line of platinum CT (cohorts 1 and 2)[c]
  - Treatment-naive (cohort 2; enrollment after June 30, 2022)[c]
  - Treatment-naive (cohorts 3–6)[c]



- **Primary objectives:** safety and tolerability
- **Secondary objectives:** efficacy, PK, and antidrug antibodies

Data cutoff: October 31, 2023.

[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 (for which enrollment was ongoing at the time of data cutoff). [c]Prior therapy requirements are for treatment in the advanced/metastatic setting.

Results

Demographics and baseline characteristics of 1L patients

	Doublet (n=42)	Triplet (n=54)
Age, median (range), years	66 (49–83)	66 (35–80)
Male, n (%)	32 (76)	34 (63)
Asian race, n (%)	31 (74)	23 (43)
Histology, n (%)		
Adenocarcinoma	31 (74)	35 (65)
Squamous	9 (21)	12 (22)
Stage at study entry, n (%)		
IIIB	1 (2)	0
IIIC	0	1 (2)
IV	2 (5)	8 (15)
IVA	22 (52)	25 (46)
IVB	17 (41)	20 (37)
History of brain metastases, n (%)	4 (10)	10 (19)
ECOG PS 1, n (%)	24 (57)	33 (61)
PD-L1 expression[a], n (%)		
<1%	18 (43)	16 (30)
1–49%	19 (45)	23 (43)
≥50%	5 (12)	15 (28)

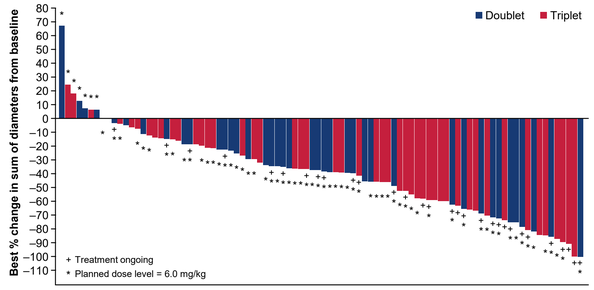
[a]Evaluated locally by tumor proportion score using immunohistochemistry (22C3 assay).

Efficacy outcomes in 1L patients, overall and by PD-L1 status[a,b]

	All 1L (n=96)		1L PD-L1 <1% (n=34)		1L PD-L1 1–49% (n=42)		1L PD-L1 ≥50% (n=20)	
	Doublet (n=42)	Triplet (n=54)	Doublet (n=18)	Triplet (n=16)	Doublet (n=19)	Triplet (n=23)	Doublet (n=5)	Triplet (n=15)
ORR, n (%)	22 (52)	30 (56)	8 (44)	5 (31)	9 (47)	17 (74)	5 (100)	8 (53)
[95% CI]	[36–68]	[41–69]	[22–69]	[11–59]	[24–71]	[52–90]	[48–100]	[27–79]
BOR, n (%)								
CR	1 (2)	1 (2)	1 (6)	0	0	1 (4)	0	0
PR	21 (50)	29 (54)	7 (39)	5 (31)	9 (47)	16 (70)	5 (100)	8 (53)
SD	15 (36)	18 (33)	8 (44)	10 (63)	7 (37)	3 (13)	0	5 (33)
PD	3 (7)	2 (4)	1 (6)	1 (6)	2 (11)	1 (4)	0	0
NE	2 (5)	4 (7)	1 (6)	0	1 (5)	2 (9)	0	2 (13)
DCR, n (%)	37 (88)	48 (89)	16 (89)	15 (94)	16 (84)	20 (87)	5 (100)	13 (87)
[95% CI]	[74–96]	[77–96]	[65–99]	[70–100]	[60–97]	[66–97]	[48–100]	[60–98]
Median TTR, months	1.4	1.4	1.4	1.5	1.5	1.4	1.4	1.5
[Range]	[1.2–7.0]	[1.2–9.6]	[1.2–6.9]	[1.2–9.6]	[1.2–7.0]	[1.2–7.0]	[1.3–2.8]	[1.2–8.3]
Median DoR, months	NE	12.9	NE	12.9	12.0	14.6	NE	18.1
[95% CI]	[9.7–NE]	[5.7–NE]	NE	[4.1–NE]	[4.2–NE]	[4.2–NE]	[5.5–NE]	[4.1–NE]

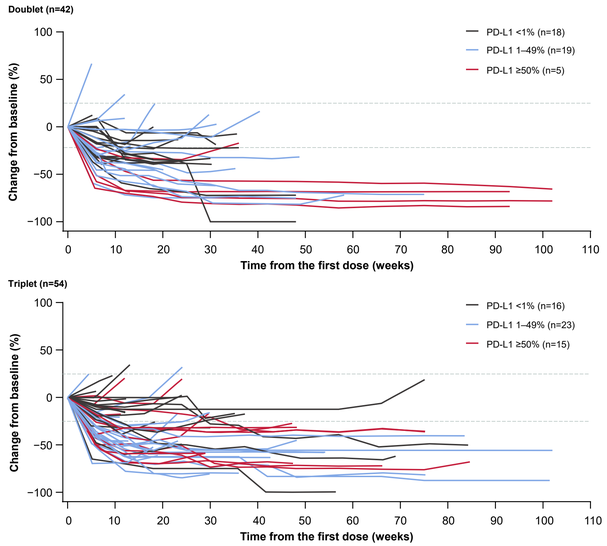
[a]Evaluated locally by tumor proportion score using immunohistochemistry (22C3 assay). [b]Responses with confirmed CR/PR.

Best overall tumor change from baseline in 1L patients



Patients with no baseline target lesions or no postbaseline tumor assessments were excluded from the waterfall plot.

Percent change from baseline in sum of diameter over time in 1L patients by PD-L1 status



Safety summary of 1L patients

Event, n (%)	Doublet (n=42)	Triplet (n=54)
Any TEAE[a]	40 (95)	54 (100)
Study treatment-related[b]	39 (93)	54 (100)
Any grade ≥3 TEAE	24 (57)	41 (76)
Study treatment-related[b]	14 (33)	30 (56)
Any serious TEAEs	16 (38)	24 (44)
Study treatment-related[b]	5 (12)	12 (22)
TEAEs associated with:		
Dose reduction of any drug	9 (21)	10 (19)
Dose reduction of Dato-DXd	9 (21)	7 (13)
Discontinuation of any drug	12 (29)	24 (44)
Discontinuation of Dato-DXd	12 (29)	21 (39)
Death	1 (2)	5 (9)

[a]TEAEs were defined as AEs with a start or worsening date on or after the start of study treatment until 37 days after the end date of study treatment. [b]Drug-related TEAEs may be associated with any component of the study treatment: Dato-DXd, pembrolizumab, cisplatin, or carboplatin.

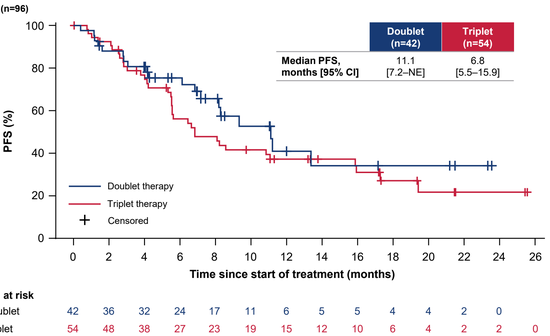
- TEAEs associated with discontinuation of Dato-DXd occurred in 29% of 1L patients receiving the doublet regimen and in 39% of 1L patients receiving the triplet regimen
- The most frequent TEAEs of any grade were stomatitis, nausea, anemia, constipation, and decreased appetite
- Hematologic toxicities such as anemia, platelet count decreased, neutropenia, and neutrophil count decreased occurred more frequently in the triplet cohorts

AESIs in 1L patients

AESI, n (%)	Doublet (n=42)		Triplet (n=54)	
	All grades	Grade 3	All grades	Grade 3
Oral mucositis/stomatitis	26 (62)	2 (5)	22 (41)	1 (2)
Adjudicated drug-related ILD/pneumonitis	10 (24)	2 (5)	14 (26)	1 (2)
Ocular surface events	9 (21)	1 (2)	16 (30)	2 (4)

- Oral mucositis/stomatitis was the most common AESI and was predominantly grade 1/2
- There were no grade 4 or 5 events for any AESI, including adjudicated drug-related ILD/pneumonitis

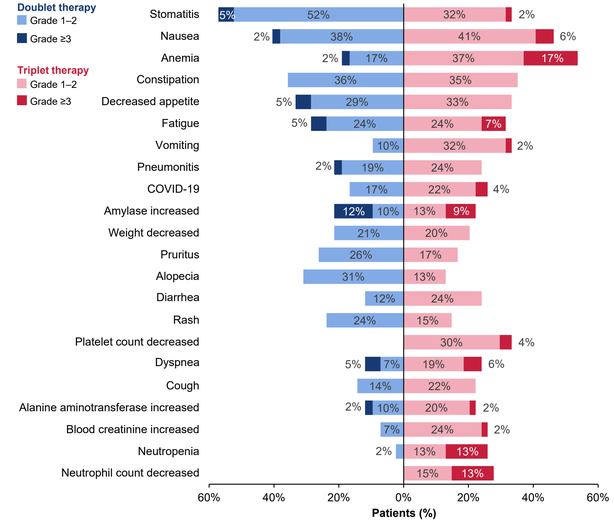
PFS in 1L patients



Median PFS follow-up: 8.5 months (doublet); 17.2 months (triplet).

- More patients treated with the triplet vs doublet regimen received the lower dose of 4 mg/kg Dato-DXd (41% vs 5%)
- A higher proportion of patients treated with the triplet vs doublet regimen had a history of brain metastases (19% vs 10%)

All-cause TEAEs observed in ≥20% of 1L patients



Abbreviations

1L, first-line; ADC, antibody–drug conjugate; AE, adverse event; AESI, adverse event of special interest; AUC, area under the curve; BOR, best overall response; CI, confidence interval; COVID-19, coronavirus disease 2019; CR, complete response; CT, chemotherapy; Dato-DXd, datopotamab deruxtecan; DCR, disease control rate; DoR, duration of response; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; IgG1, immunoglobulin G1; ILD, interstitial lung disease; IO, immuno-oncology; IV, intravenous; mAb, monoclonal antibody; NE, non-evaluable; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death 1; PD-L1, programmed death ligand 1; pembro, pembrolizumab; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; Q3W, every 3 weeks; SD, stable disease; TEAE, treatment-emergent adverse event; TROP2, trophoblast cell surface antigen 2; TTR, time to recurrence.

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