Poster 59P

Datopotamab deruxtecan (Dato-DXd) in patients with previously treated advanced non-small cell lung cancer (NSCLC) – Nonsquamous (NSQ) histology in the Phase 3 TROPION-Lung01 trial

Nicolas Girard,[1]* Isamu Okamoto,[2] Aaron Lisberg,[3] Elvire Pons-Tostivint,[4] Robin Cornelissen,[5] Min Hee Hong,[6] Luis Paz-Ares,[7] David Vicente Baz,[8] Shunichi Sugawara,[9] Manuel Cobo Dols,[10] Maurice Pérol,[11] Céline Mascaux,[12] Enriqueta Felip,[13] Yannick Le Guen,[14] Jacob Sands,[15] Michael Chargualaf,[16] Yong Zhang,[16] Paul Howarth,[16] Deise Uema,[16] Myung-Ju Ahn[17]

*Indicates presenting author.

[1]Institut Curie, Paris, France; [2]Kyushu University Hospital, Fukuoka, Japan; [3]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [4]Centre Hospitalier Universitaire de Nantes, Nantes, France; [5]Erasmus MC Cancer Institute, Rotterdam, Netherlands; [6]Yonsei Cancer Center, Severance Hospital, Seoul, Republic of Korea; [7]Hospital Universitario 12 de Octubre, CNIO-H12O Lung Cancer Unit, Universidad Complutense & CiberOnc, Madrid, Spain; [8]Hospital Universitario Virgen Macarena, Seville, Spain; [9]Sendai Kousei Hospital, Sendai, Japan; [10]Medical Oncology Intercenter Unit, Regional and Virgen de la Victoria, University Hospitals, IBIMA, Málaga, Spain; [11]Centre Léon Bérard, Lyon, France; [12]Hôpitaux Universitaires de Strasbourg (CHRU), Strasbourg, France; [13]Hospital Universitario Vall d'Hebron, Barcelona, Spain; [14]Hôpital Pontchaillou, Rennes, France; [15]Dana-Farber Cancer Institute, Boston, MA, USA; [16]Daiichi Sankyo, Inc, Basking Ridge, NJ, USA; [17]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea.

Objective

- Pre-planned subgroup analysis of TROPION-Lung01 evaluating efficacy and safety in patients with advanced/metastatic (a/m) NSCLC with NSQ histology

Conclusions

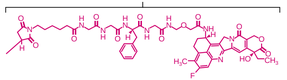
- In TROPION-Lung01, Dato-DXd demonstrated clinically meaningful benefit vs docetaxel in patients with NSQ a/m NSCLC
  - PFS HR, 0.63 (95% CI, 0.51–0.79); median PFS, 5.5 vs 3.6 months
  - Interim OS favors Dato-DXd (OS HR: 0.79, 95% CI: 0.60–1.02; median OS: 13.4 vs 11.4 months)
  - ORR 31% vs 13%; median DoR 7.7 vs 5.6 months
- The safety profile was manageable and consistent with the overall study population[1] enrolled in TROPION-Lung01
  - Fewer grade ≥3 TRAEs, dose reductions and discontinuations occurred in the Dato-DXd vs docetaxel arms
  - While grade ≥3 ILD was observed at similar rates in both treatment arms, the higher overall incidence seen with Dato-DXd highlights the need for careful monitoring and adherence to ILD management guidelines
- These findings support Dato-DXd as a potential new therapeutic option for patients with previously treated, a/m NSQ NSCLC

Background

- **Dato-DXd** is a **TROP2-directed antibody–drug conjugate (ADC)**, composed of a humanized anti-TROP2 IgG1 mAb attached to a highly potent topoisomerase I inhibitor payload via a plasma-stable, tumor-selective, tetrapeptide-based cleavable linker[2]
- In the phase 3 **TROPION-Lung01** trial (NCT04656652), Dato-DXd became the **first, and so far only, ADC** to demonstrate a statistically significant improvement in PFS over docetaxel in patients with previously treated, a/m NSCLC[1]
- **Primary results** from TROPION-Lung01 demonstrated:
  - Statistically significant improvement in PFS by BICR with **Dato-DXd vs docetaxel:** HR 0.75 (95% CI: 0.62–0.91); *P*=0.004
  - OS data not mature, but numerical trend favoring Dato-DXd: HR 0.90 (95% CI: 0.72–1.13)
  - Activity primarily attributed to the subgroup of patients with NSQ histology
  - Manageable safety profile with no new signals observed
- Here, we present **efficacy** and **safety** results from patients with NSQ histology enrolled in TROPION-Lung01

Dato-DXd: Humanized anti-TROP2 IgG1 mAb[3]

Deruxtecan



Cleavable tetrapeptide-based linker

Topo-I inhibitor payload (DXd)

Declaration of Interests

Nicolas Girard reports: research grants/support from AbbVie, Amgen, AstraZeneca, BeiGene, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Gilead, Hoffmann-La Roche, Janssen, LeoPharma, Lilly, Merk Serono, Merck Sharp & Dohme, Novartis, Sanofi, and Sivan; consultative services for AbbVie, Amgen, AstraZeneca, BeiGene, Bristol Myers Squibb, Daiichi Sankyo, Gilead, Ipsen, Hoffmann-La Roche, Janssen, LeoPharma, Lilly, Merck Sharp & Dohme, Mirati, Novartis, Pfizer, Pierre Fabre, Sanofi, and Takeda; participation on a data safety monitoring board for Hoffmann-La Roche; and employment of a family member with AstraZeneca.

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Corresponding author email address: nicolas.girard2@curie.fr

Methods and Results

TROPION-Lung01 study design

Randomized, phase 3, open-label, global study (NCT04656652)

Key eligibility criteria
- NSCLC (stage IIIB, IIIC, or IV)
- ECOG PS 0–1
- No prior docetaxel

Without actionable genomic alterations[a]
- 1–2 prior lines of therapy, including platinum CT and anti–PD-(L)1 mAb therapy

With actionable genomic alterations
- Positive for *EGFR*, *ALK*, *NTRK*, *BRAF*, *ROS1*, *MET* exon 14 skipping, and/or *RET*
- 1–2 prior approved targeted therapies + platinum-based CT, and ≤1 anti–PD-(L)1 mAb

R 1:1

Dato-DXd 6 mg/kg Q3W (N=299)

Docetaxel 75 mg/m² Q3W (N=305)

Dual primary endpoints
- PFS by BICR[e,f]
- OS[f]

Secondary endpoints
- ORR by BICR[e]
- DoR by BICR[e]
- Safety[g]

The analysis presented here includes patients with NSQ histology[b]:
- Dato-DXd: N=234
- Docetaxel: N=234

Data cutoff: 29 March 2023

Stratified by: histology,[b] actionable genomic alteration,[c] anti–PD-(L)1 mAb included in most recent prior therapy, geography[d]

[a]Patients with *KRAS* mutations in the absence of known actionable genomic alterations are eligible; must meet prior therapy requirements for patients without actionable genomic alterations. [b]Squamous vs nonsquamous. [c]Presence vs absence. [d]United States/Japan/Western Europe vs rest of world. [e]Evaluated per RECIST 1.1. [f]PFS and OS by histology were pre-specified subgroup analyses. [g]Safety analyses by histology were post hoc. ᵀCRF-derived.

Patient demographics and clinical characteristics – NSQ population

Characteristic	Dato-DXd (N=234)	Docetaxel (N=234)
Age, median (range), years	63 (26–81)	63 (24–88)
Male, n (%)	134 (57)	150 (64)
Race, n (%)		
White	96 (41)	90 (38)
Asian	92 (39)	96 (41)
Black or African American	4 (2)	3 (1)
Other[a]	36 (15)	39 (17)
ECOG PS, n (%)[b]		
0	73 (31)	79 (34)
1	160 (68)	154 (66)
Current or former smoker, n (%)	177 (76)	184 (79)

Characteristic	Dato-DXd (N=234)	Docetaxel (N=234)
Actionable genomic alterations, n (%)		
Present	48 (21)	50 (21)
EGFR mutation	38 (16)	44 (19)
Brain metastases at baseline,[b] (%)	43 (18)	41 (18)
Prior lines of therapy, n (%)[c]		
1	127 (54)	131 (56)
2	86 (37)	74 (32)
≥3	20 (9)	28 (12)
Previous systemic therapy, n (%)		
Platinum containing	232 (99)	234 (100)
Anti–PD-(L)1	199 (85)	200 (86)
Targeted for indicated actionable genomic alteration	45 (19)	49 (21)

Patients with CRF-derived NSQ histology in the full analysis set. [a]Race data was missing for 6 patients in each arm. [b]Identified by BICR; patients with clinically inactive brain metastases and patients with treated brain metastases who are no longer symptomatic, require no treatment with steroids, and have recovered from radiotherapy may be included in the study. [c]One patient in each group had 0 prior lines of therapy

Patient disposition – NSQ population

Disposition, n (%)	Dato-DXd (N=232)	Docetaxel (N=221)
Treatment status		
Ongoing on study treatment	48 (21)	15 (7)
Discontinued from study treatment	184 (79)	206 (93)
Primary reason for discontinuation		
AE	33 (14)	35 (16)
Progressive disease	131 (57)	138 (62)
Clinical progression	7 (3)	7 (3)
Withdrawal/physician decision	6 (3)	19 (9)
Death	5 (2)	6 (3)

Median study duration: Dato-DXd – **12.9** months; docetaxel – **12.7** months

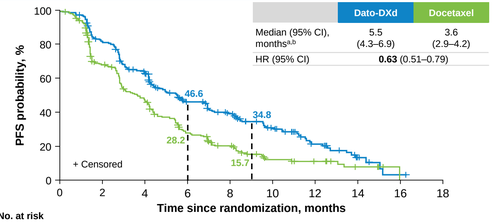
Patients with CRF-derived NSQ histology in the safety analysis set.

Tumor response by BICR – NSQ population

	Dato-DXd (N=234)	Docetaxel (N=234)
ORR,[a] n (%)	73 (31)	30 (13)
(95% CI)	(25–38)	(9–18)
BOR		
CR	4 (2)	0
PR	69 (30)	30 (13)
SD	113 (48)	110 (47)
Non-CR/non-PD	2 (1)	3 (1)
PD	31 (13)	53 (23)
NE	15 (6)	38 (16)
DoR[b]		
Median (95% CI), mo	7.7 (5.6–11.1)	5.6 (5.4–6.0)
DCR[a,c], n (%)	188 (80)	143 (61)
(95% CI)	(75–85)	(55–67)

Patients with CRF-derived NSQ histology in the full analysis set. [a]Two-sided confidence intervals are based on the Clopper-Pearson exact binomial method. [b]Based on the Kaplan-Meier method; 2-sided confidence intervals are computed using the Brookmeyer-Crowley method. [c]CR + PR + SD + [non-CR/non-PD].

PFS by BICR – NSQ population

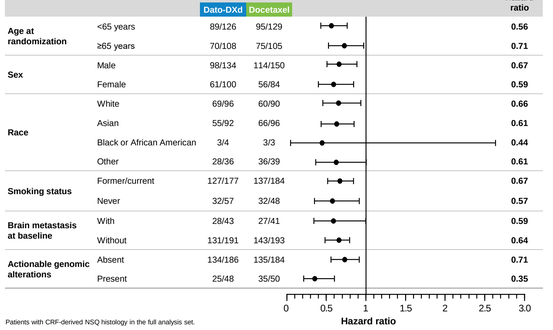


	Dato-DXd	Docetaxel
Median (95% CI), months[a,b]	5.5 (4.3–6.9)	3.6 (2.9–4.2)
HR (95% CI)	**0.63** (0.51–0.79)	

No. at risk											
Dato-DXd	234	181	135	86	67	41	20	7	1	0	
Docetaxel	234	136	91	50	32	14	10	4	0	0	

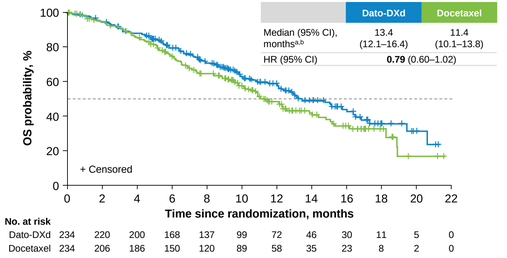
Patients with CRF-derived NSQ histology in the full analysis set. [a]Median PFS follow-up (estimated by inverse Kaplan-Meier) was 10.9 (95% CI, 9.8–12.4) and 9.6 (95% CI, 8.5–12.5) months for patients treated with Dato-DXd and docetaxel, respectively. [b]Based on the Kaplan-Meier method; 2-sided confidence intervals are computed using the Brookmeyer-Crowley method.

PFS by BICR in key subgroups – NSQ population



Patients with CRF-derived NSQ histology in the full analysis set.

OS (interim) – NSQ population



	Dato-DXd	Docetaxel
Median (95% CI), months[a,b]	13.4 (12.1–16.4)	11.4 (10.1–13.8)
HR (95% CI)	**0.79** (0.60–1.02)	

No. at risk												
Dato-DXd	234	220	200	168	137	99	72	46	30	11	5	0
Docetaxel	234	206	186	150	120	89	58	35	23	8	2	0

Patients with CRF-derived NSQ histology in the full analysis set. [a]Median OS follow-up (estimated by inverse Kaplan-Meier) was 12.4 (95% CI, 11.3–13.6) and 12.3 (95% CI, 11.2–12.9) months for patients with NSQ histology treated with Dato-DXd and docetaxel, respectively. [b]Based on the Kaplan-Meier method; 2-sided confidence intervals are computed using the Brookmeyer-Crowley method.

Abbreviations

ADC, antibody–drug conjugate; AE, adverse event; AESI, adverse event of special interest; a/m, advanced/metastatic; BICR, blind independent central review; BOR, best overall response; CI, confidence interval; CR, complete response; CRF, case report form; CT, chemotherapy; Dato-DXd, datopotamab deruxtecan; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IgG1, immunoglobulin G1; ILD, interstitial lung disease; IRR, infusion-related reaction; mAb, monoclonal antibody; MedDRA v26.0, Medical Dictionary for Regulatory Activities version 26.0; NE, non-evaluable; NSCLC, non-small cell lung cancer; NSQ, nonsquamous; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-(L)1, programmed death-(ligand) 1; PFS, progression-free survival; PR, partial response; PT, preferred term; R, randomized; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; Q3W, every 3 weeks; SD, stable disease; SMQ, Standardized Medical Dictionary for Regulatory Activities query; SOC, system organ class; TRAE, treatment-related adverse event; TROP2, trophoblast cell surface antigen 2.

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Safety summary – NSQ population

	Dato-DXd (N=232)	Docetaxel (N=221)
Treatment duration		
Median (range), months	4.9 (0.7–18.3)	2.8 (0.7–18.9)
0–3 months, n (%)	79 (34)	125 (57)
>3 to ≤6 months, n (%)	61 (26)	50 (23)
>6 to ≤9 months, n (%)	40 (17)	26 (12)
>9 to ≤12 months, n (%)	31 (13)	11 (5)
>12 months, n (%)	21 (9)	9 (4)
TRAEs, n (%)		
Any grade	205 (88)	195 (88)
Grade ≥3	51 (22)	90 (41)
Associated with dose reduction	49 (21)	66 (30)
Associated with dose delay	38 (16)	24 (11)
Associated with discontinuation	20 (9)	27 (12)
Associated with death	1 (<1)	2 (1)
Serious TRAEs	19 (8)	25 (11)
Grade ≥3	15 (7)	23 (10)

Patients with CRF-derived NSQ histology in the safety analysis set. AEs were considered related to treatment by the investigator.

TRAEs occurring in ≥10% – NSQ population

System organ class	Dato-DXd (N=232)		Docetaxel (N=221)	
Preferred term, n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3
Blood and lymphatic system				
Anemia	37 (16)	10 (4)	46 (21)	8 (4)
Neutropenia[a]	9 (4)	1 (<1)	56 (25)	49 (22)
Gastrointestinal				
Stomatitis	114 (49)	16 (7)	35 (16)	3 (1)
Nausea	83 (36)	5 (2)	45 (20)	3 (1)
Vomiting	28 (12)	2 (1)	21 (10)	1 (<1)
Diarrhea	24 (10)	1 (<1)	45 (20)	3 (1)
Constipation	23 (10)	0	26 (12)	0
General				
Asthenia	45 (19)	7 (3)	42 (19)	5 (2)
Fatigue	30 (13)	0	30 (14)	4 (2)
Malaise	14 (6)	1 (<1)	22 (10)	2 (1)
Edema peripheral	1 (<1)	0	26 (12)	1 (<1)
Metabolism and nutrition				
Decreased appetite	54 (23)	1 (<1)	34 (15)	1 (<1)
Skin and subcutaneous				
Alopecia	83 (36)	0	82 (37)	1 (<1)
Rash	27 (12)	0	14 (6)	0

Patients with CRF-derived NSQ histology in the safety analysis set. AEs were considered related to treatment by the investigator. [a]Includes the PTs "neutropenia" and "neutrophil count decreased". Febrile neutropenia occurred in 15 (7%) patients treated with dotadexel; no cases were observed in patients treated with Dato-DXd.

- Stomatitis, nausea, and alopecia were the most frequent TRAEs seen with Dato-DXd
- Hematologic toxicities, including neutropenia and anemia, were more common with docetaxel. No febrile neutropenia was seen with Dato-DXd (docetaxel, 7%)

Adverse events of special interest – NSQ population

AESI, n (%)	Dato-DXd (N=232)	Docetaxel (N=221)
Stomatitis/oral mucositis[a]		
All grades	131 (57)	49 (22)
Grade ≥3	16 (7)	4 (2)
Ocular events[b]		
All grades	46 (20)	25 (11)
Grade ≥3	5 (2)	0
Adjudicated drug-related ILD[c]		
All grades[d]	19 (8)	7 (3)
Grade ≥3	5 (2)	4 (2)
Grade 5	4 (2)	1 (1)

Patients with CRF-derived NSQ histology in the safety analysis set. [a]Events included the selected PTs oral mucositis/stomatitis: oropharyngeal pain, mouth ulceration, odynophagia, dysphagia, oral pain, glossitis, pharyngeal inflammation, aphthous ulcer, and oral mucosa erosion. [b]Ocular events included selected PTs from the corneal disorder SMQ and selected relevant PTs from the eye disorder SOC. [c]ILD includes events that were adjudicated as ILD and related to use of Dato-DXd or docetaxel (includes cases of potential ILD/pneumonitis based on MedDRA v26.0 for the narrow ILD SMQ, selected terms from the broad ILD SMQ, and PTs of respiratory failure and acute respiratory failure). [d]One additional patient in the Dato-DXd arm had grade 2 adjudicated drug-related ILD ('pneumonitis'), but this event was not an AE in the clinical database as determined by the investigator.

- Stomatitis/oral mucositis events with Dato-DXd were predominantly grade 1 (28%) or 2 (22%) and associated with a low rate of discontinuation (1%)
- Lacrimation increased was the most common ocular event seen with Dato-DXd (8%), followed by dry eye (7%); all cases were grade ≤2
- 4 adjudicated drug-related grade 5 ILD events (2%) were seen with Dato-DXd; primary cause of death in 2/4 patients was attributed to disease progression by investigator
- IRRs were observed in 8% and 9% of patients treated with Dato-DXd and docetaxel, respectively; no grade ≥3 events in either arm were reported

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References

1. Ahn M-J, et al. Presented at ESMO 2023, October 20–24, 2023, Madrid, Spain. 2. Okajima D, et al. *Mol Cancer Ther*. 2021;20:2329–2340.
3. Dent RA, et al. *Future Oncol*. 2023;19(35):2349–2359.