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Datopotamab deruxtecan (Dato-DXd) vs docetaxel in previously treated advanced/metastatic (adv/met) non-small cell lung cancer (NSCLC): Results of the randomized phase 3 study TROPION-Lung01

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Declaration of Interests

Myung-Ju Ahn

- **Advisory role** at AstraZeneca, Yuhan, MSD, Merck, Amgen, Daiichi Sankyo, Alpha Pharmaceuticals, Pfizer, Roche, BMS
- **Funding for the current study** provided by Daiichi Sankyo Inc, and AstraZeneca

TROPION-Lung01 Study Design

Randomized, Phase 3, Open-Label, Global Study (NCT04656652)

Dato-DXd is a **TROP2-directed ADC** that selectively delivers a potent topoisomerase I inhibitor payload directly into tumor cells[1]

Key Eligibility Criteria

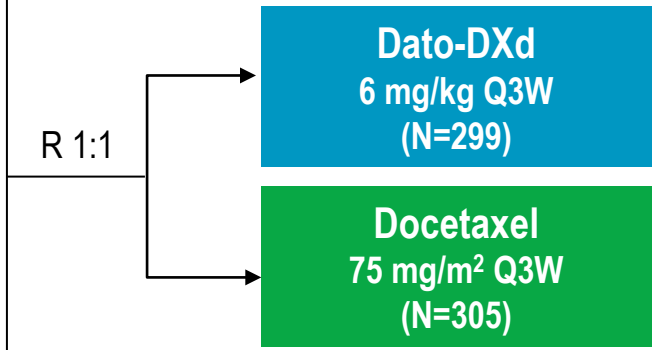
- NSCLC (stage IIIB, IIIC, or IV)
- ECOG PS of 0 or 1
- No prior docetaxel

Without actionable genomic alterations[a]

- 1 or 2 prior lines, 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, or *RET*
- 1 or 2 prior approved targeted therapies + platinum-based CT, and ≤1 anti–PD-(L)1 mAb



Dual Primary Endpoints

- PFS by BICR
- OS

Secondary Endpoints

- ORR by BICR
- DOR by BICR
- Safety

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

Enrollment period: 19 February 2021 to 7 November 2022.

BICR, blinded independent central review; CT, chemotherapy; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed cell death 1 (ligand 1); PFS, progression-free survival; Q3W, every 3 weeks; R, randomized.

[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 non-squamous. [c]Presence vs absence. [d]United States/Japan/Western Europe vs rest of world.

1. Shimizu T, et al. *J Clin Oncol*. 2023;41:4678-4687.

Demographics and Disposition

Characteristic		Dato-DXd N=299	Docetaxel N=305
Age, median (range), years		63 (26-84)	64 (24-88)
Male, n (%)		183 (61)	210 (69)
ECOG PS, n (%)	0	89 (30)	94 (31)
	1	210 (70)	211 (69)
Histology, n (%)	Non-squamous	234 (78)	234 (77)
	Squamous	65 (22)	71 (23)
Actionable genomic alterations, n (%)	Present	50 (17)	51 (17)
	EGFR mutation	39 (13)	45 (15)
Previous systemic therapy, n (%)[a]	Platinum containing	297 (99)	305 (100)
	Anti–PD-(L)1	263 (88)	268 (88)
	Targeted	46 (15)	50 (16)

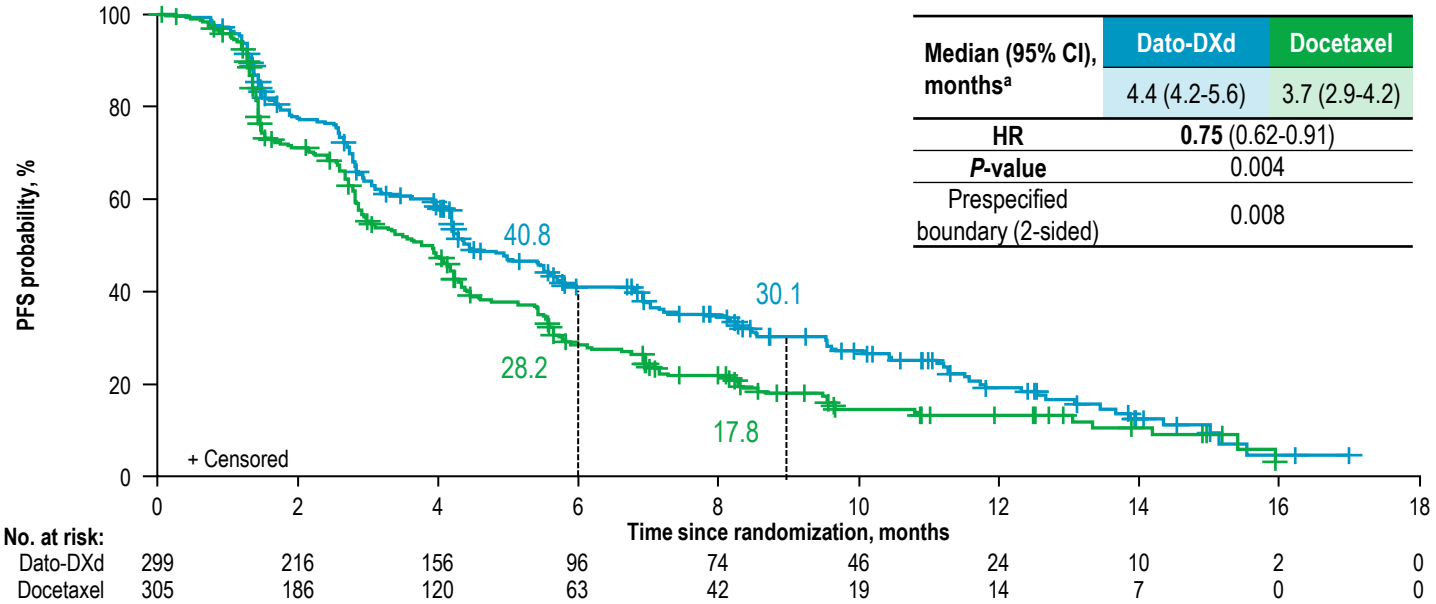
Disposition

- At data cutoff, 18% of patients in the Dato-DXd arm and 6% in the docetaxel arm remained on study treatment
- Treatment duration
  - ≤ 3 months: 40% with Dato-DXd and 58% with docetaxel
  - > 9 months: 20% with Dato-DXd and 8% with docetaxel
- Median study follow-up: Dato-DXd – **13.1** months; docetaxel – **13.0** months

Data cutoff: 29 March 2023.

ECOG PS, Eastern Cooperative Oncology Group performance status; PD-(L)1, programmed cell death 1 (ligand 1).
[a]In the Dato-DXd arm, 2 patients did not receive prior treatment with a platinum-containing therapy and 1 patient with actionable genomic alterations did not receive previous targeted therapy, deviating from the protocol.

Progression-Free Survival: ITT



Median (95% CI), months[a]	Dato-DXd	Docetaxel
	4.4 (4.2-5.6)	3.7 (2.9-4.2)
HR	**0.75** (0.62-0.91)	
P-value	0.004	
Prespecified boundary (2-sided)	0.008	

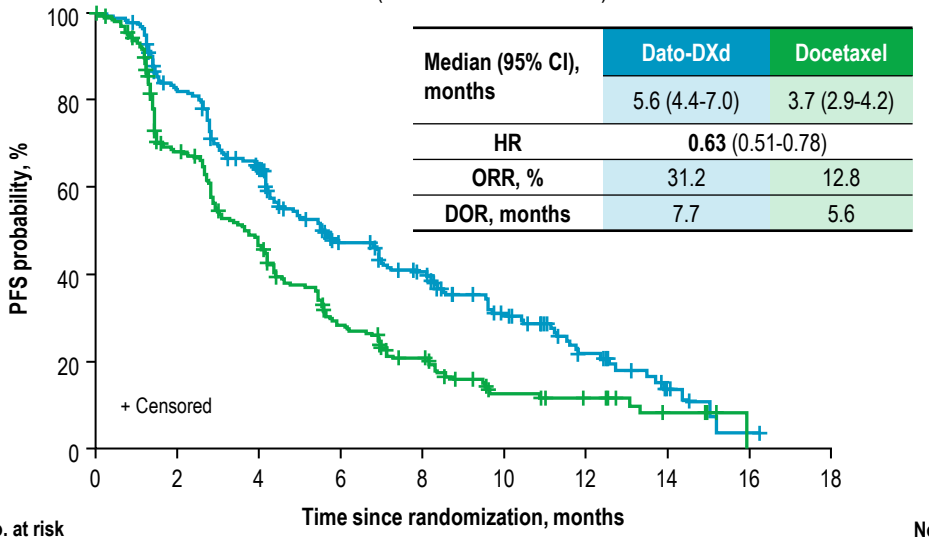
	Dato-DXd	Docetaxel
ORR (95% CI), %[b]	**26.4** (21.5-31.8)	**12.8** (9.3-17.1)
DOR (95% CI), mo	**7.1** (5.6-10.9)	**5.6** (5.4-8.1)

CR, complete response; DOR, duration of response; HR, hazard ratio; ITT, intention to treat; ORR, objective response rate; PFS, progression-free survival; PR, partial response.
[a]Median PFS follow-up was 10.9 (95% CI, 9.8-12.5) and 9.6 (95% CI, 8.2-11.9) months for Dato-DXd and docetaxel, respectively. [b]Included 4 CRs and 75 PRs for Dato-DXd and 39 PRs for docetaxel.

PFS by Histology

Non-squamous

(with and without AGAs)

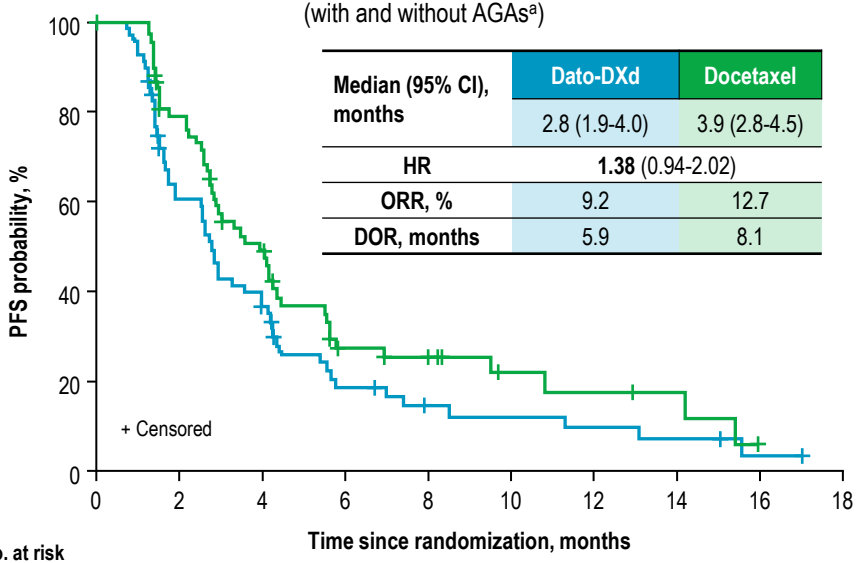


Median (95% CI), months	Dato-DXd	Docetaxel
	5.6 (4.4-7.0)	3.7 (2.9-4.2)
HR	**0.63** (0.51-0.78)	
ORR, %	31.2	12.8
DOR, months	7.7	5.6

No. at risk										
Dato-DXd	229	178	134	86	68	41	20	7	1	0
Docetaxel	232	135	90	50	32	14	10	4	0	0

Squamous

(with and without AGAs[a])



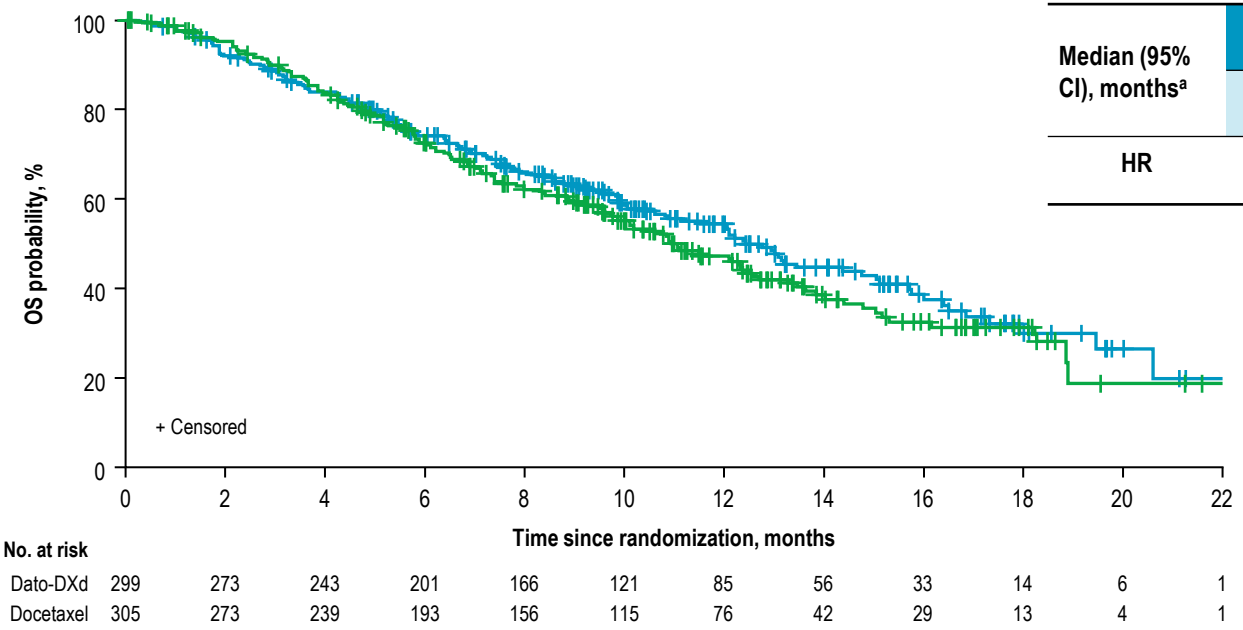
Median (95% CI), months	Dato-DXd	Docetaxel
	2.8 (1.9-4.0)	3.9 (2.8-4.5)
HR	**1.38** (0.94-2.02)	
ORR, %	9.2	12.7
DOR, months	5.9	8.1

No. at risk										
Dato-DXd	70	38	22	10	6	5	4	3	1	0
Docetaxel	73	51	30	13	10	5	4	3	0	0

PFS HR for non-squamous without AGAs: 0.71 (0.56, 0.91)

AGA, actionable genomic alteration; DOR, duration of response; HR, hazard ratio; ORR, objective response rate; PFS, progression-free survival.
[a]Squamous subset included 3 patients with AGAs.

Interim Overall Survival: ITT



Median (95% CI), months[a]	Dato-DXd	Docetaxel
	12.4 (10.8-14.8)	11.0 (9.8-12.5)
HR	**0.90** (0.72-1.13)	

Information fraction at interim analysis (events/total events required): **74%.**

Non-squamous HR (95% CI): **0.77** (0.59-1.01); **Squamous HR** (95% CI): **1.32** (0.87-2.00)

Trial is continuing to final OS analysis

HR, hazard ratio; ITT, intention to treat; OS, overall survival.
[a]Median OS follow-up was 11.8 (95% CI, 11.3-12.7) and 11.7 (95% CI, 10.9-12.9) months for Dato-DXd and docetaxel, respectively.

Overall Safety Summary

TRAEs, n (%)	Dato-DXd N=297	Docetaxel N=290
All grades	257 (87)	252 (87)
Grade ≥3	73 (25)	120 (41)
Associated with dose reduction	58 (20)	85 (29)
Associated with dose delay	49 (17)	31 (11)
Associated with discontinuation	23 (8)	34 (12)
Associated with death[a]	3 (1)	2 (1)
Serious TRAEs	30 (10)	36 (12)
Grade ≥3	25 (8)	33 (11)

- The median treatment durations for Dato-DXd and docetaxel were **4.2** and **2.8** months, respectively
- Stomatitis (47%; Grade ≥3, 6%) and nausea (34%; Grade ≥3, 2%) were the most frequent TRAEs seen with Dato-DXd and were predominantly grade 1 or 2[b]
- Hematologic toxicities were more common with docetaxel, including neutropenia (Grade ≥3, 23% vs 1%) and febrile neutropenia (all grades, 7% vs 0.3%)
- No new safety signals were observed with Dato-DXd

ILD, interstitial lung disease; TRAE, treatment-related adverse event.
[a]Investigator assessed. Dato-DXd: 2 cases of ILD/pneumonitis and 1 case of sepsis; docetaxel: 1 case of ILD/pneumonitis and 1 case of septic shock. [b]Incidences of stomatitis and nausea for docetaxel were 16% (Grade ≥3, 1%) and 17% (Grade ≥3, 1%), respectively.
The safety analysis set included all randomized patients who received ≥1 dose of the study drug.

Adverse Events of Special Interest

AESI, n (%)	Dato-DXd N=297	Docetaxel N=290
Stomatitis/oral mucositis[a]		
All grades	160 (54)	59 (20)
Grade ≥3	19 (6)	4 (1)
Ocular events[b]		
All grades	57 (19)	27 (9)
Grade ≥3	5 (2)[c]	0
Adjudicated drug-related ILD[d]		
All grades	25 (8)	12 (4)
Grade ≥3	10 (3)	4 (1)
Grade 5	7 (2)	1 (0.3)

- Stomatitis/oral mucositis associated with Dato-DXd resulted in a low rate of discontinuation (0.7%)
- Dry eye was the most common ocular event seen with Dato-DXd (6.1%; primarily grade ≤2), followed by increased lacrimation (5.4%)
- Seven adjudicated drug-related grade 5 ILD events
  - Primary cause of death in 4 out of 7 was attributed to disease progression by investigator
  - Non-squamous: 4 of 232 patients (1.7%); Squamous: 3 of 65 patients (4.6%)[e]
- IRRs were observed in 8% of patients in each arm, all were grade ≤2 with the exception of 1 grade 3 event with Dato-DXd

AESI, adverse event of special interest; ILD, interstitial lung disease; IRR, infusion-related reaction; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SMQ, standardized MedDRA query; SOC, system organ class. AESIs listed in this slide are treatment emergent and include all PTs that define the medical concept.

[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]Included 4 cases of keratitis and 1 case of ulcerative keratitis. [d]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). [e]Among treated patients, histology information per the case report form.

Conclusions

- Dato-DXd is the first ADC to demonstrate a statistically significant improvement in PFS over docetaxel in patients with previously treated, locally advanced or metastatic NSCLC
- PFS benefit was primarily driven by patients with non-squamous histology
- Fewer grade ≥3 TRAEs and no new safety signals were observed with Dato-DXd
- Grade ≥3 ILD was seen, highlighting the need for careful monitoring and adherence to ILD management guidelines
- The interim OS findings favor Dato-DXd, and the trial is continuing to final analysis

Dato-DXd is a potential new meaningful therapy for patients with previously treated non-squamous NSCLC

ADC, antibody-drug conjugate; ILD, interstitial lung disease; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; TRAE, treatment-related adverse event.

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