Datopotamab Deruxtecan vs Docetaxel in Patients with Non-Small Cell Lung Cancer: Final Overall Survival from TROPION-Lung01

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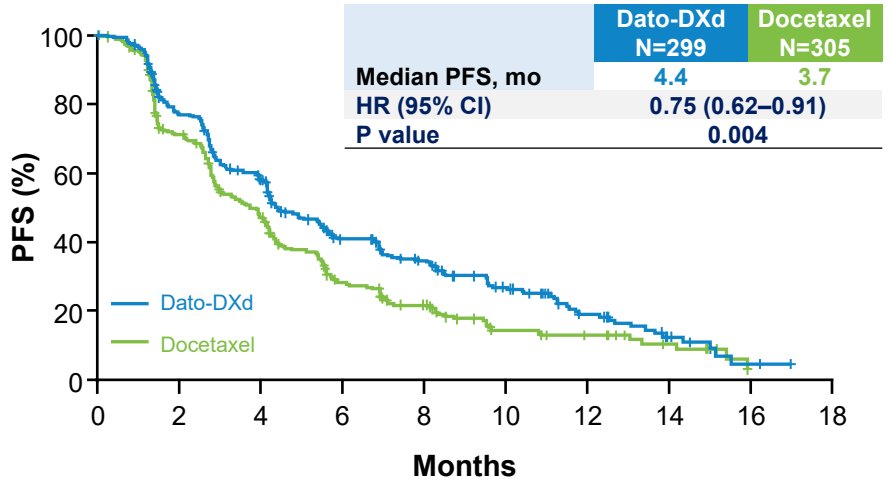
Background

TROPION-Lung01

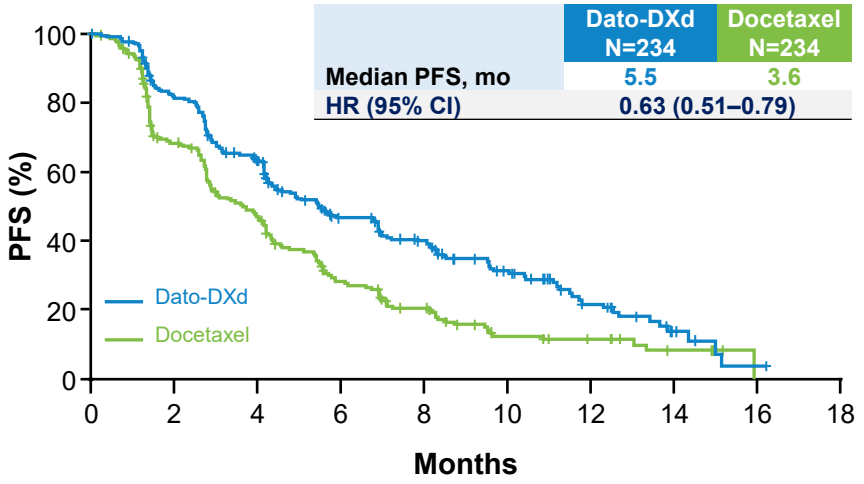
- Survival outcomes for patients with advanced NSCLC on docetaxel-based regimens in the second-line setting and beyond remain poor, and multiple trials of novel treatment regimens have failed in this setting, underscoring a high unmet need[1,2]
- **TROPION-Lung01** met its dual primary endpoint of **PFS with a statistically significant improvement** in favor of **datopotamab deruxtecan** (**Dato-DXd**) vs docetaxel[3]; a 37% reduction in relative risk of progression and more than doubling of response rate were seen in the NSQ subgroup[4]

ITT



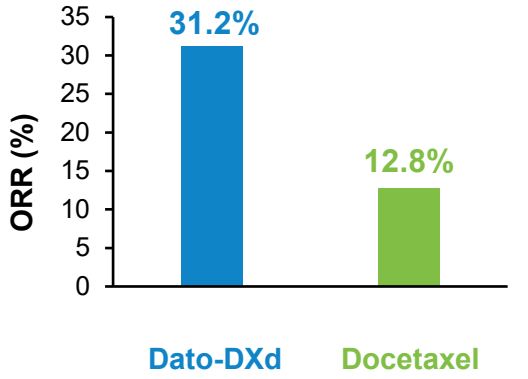
	Dato-DXd N=299	Docetaxel N=305
Median PFS, mo	4.4	3.7
HR (95% CI)	0.75 (0.62–0.91)	
P value	0.004	

NSQ



	Dato-DXd N=234	Docetaxel N=234
Median PFS, mo	5.5	3.6
HR (95% CI)	0.63 (0.51–0.79)	

	Dato-DXd N=234	Docetaxel N=234
Median DOR, mo	7.7	5.6



- Differential PFS outcomes by histology for Dato-DXd have been independently reported in two other NSCLC trials[5,6]

Here, we report the final analysis of the dual primary endpoint of overall survival for TROPION-Lung01

1. Fossella FV, et al. *J Clin Oncol* 18:2354-2362, 2000; 2. Reck M, et al. *Lancet Oncol* 15:143-155, 2014; 3. Ahn M-J, et al. Presented at ESMO 2023, Madrid, Spain, October 20–24, 2023 (Abstract 509MO);
4. Girard N, et al. Presented at ELCC 2024, Prague, Czech Republic, March 20–23, 2024 (Poster 59P); 5. Planchard D, et al. *J Clin Oncol* 42:8501, 2024; 6. Sun Y, et al. *J Clin Oncol* 42:8548, 2024.
CI, confidence interval; Dato-DXd, datopotamab deruxtecan; DOR, duration of response; HR, hazard ratio; ITT, intention to treat; mo, months; NSCLC, non-small cell lung cancer; NSQ, nonsquamous; ORR, objective response rate; PFS, progression-free survival.

Study Design

TROPION-Lung01

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

Key eligibility criteria

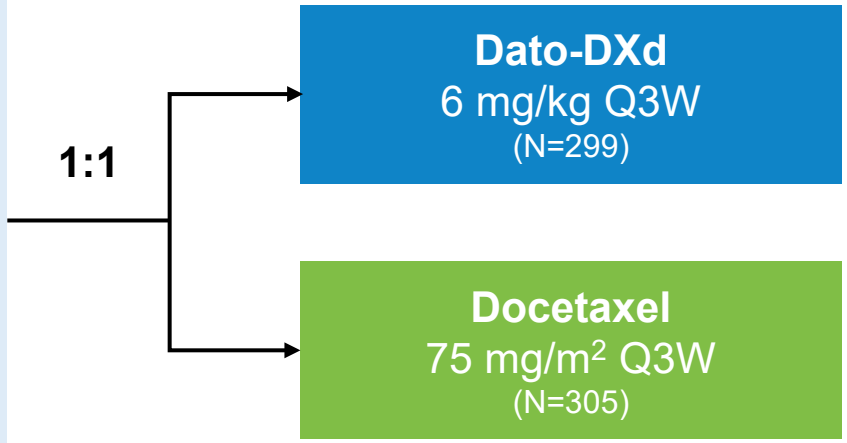
- NSCLC (stage IIIB, IIIC, or IV)
- ECOG PS of 0–1
- No prior docetaxel

Without actionable genomic alterations

- One to two prior lines, including platinum-based 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*
- One to two prior approved targeted therapies + platinum-based CT, and ≤1 anti–PD-(L)1 mAb



Dual primary endpoints

- PFS by BICR[a]
- OS

Secondary endpoints

- ORR[a]
- DOR[a]
- Safety and tolerability

Stratified by histology (nonsquamous vs squamous), actionable genomic alteration status,[b] anti–PD-(L)1 mAb included in most recent prior therapy, and geography[c]

Statistical considerations: Study deemed positive if either of the dual primary endpoints (PFS by BICR or OS) were statistically significant; the pre-specified P-value boundary for the OS analysis was α=0.045

[a]Evaluated per RECIST v1.1. [b]Presence vs absence. [c]United States/Japan/Western Europe vs rest of world.
BICR, blinded independent central review; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; mAb, monoclonal antibody; OS, overall survival; PD-(L)1, programmed cell death 1 (ligand 1); Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours.

Demographics and Baseline Characteristics

TROPION-Lung01

Characteristic, n (%)		Dato-DXd N=299	Docetaxel N=305
Age, years [median (range)]		63 (26–84)	64 (24–88)
Sex, male		183 (61)	210 (69)
Race	Asian	119 (40)	120 (39)
	White	123 (41)	126 (41)
	Black or African American	6 (2)	4 (1)
	Other/missing	51 (17)	55 (18)
ECOG PS[a]	0	89 (30)	94 (31)
	1	210 (70)	211 (69)
Histology	Nonsquamous	234 (78)	234 (77)
	Squamous	65 (22)	71 (23)

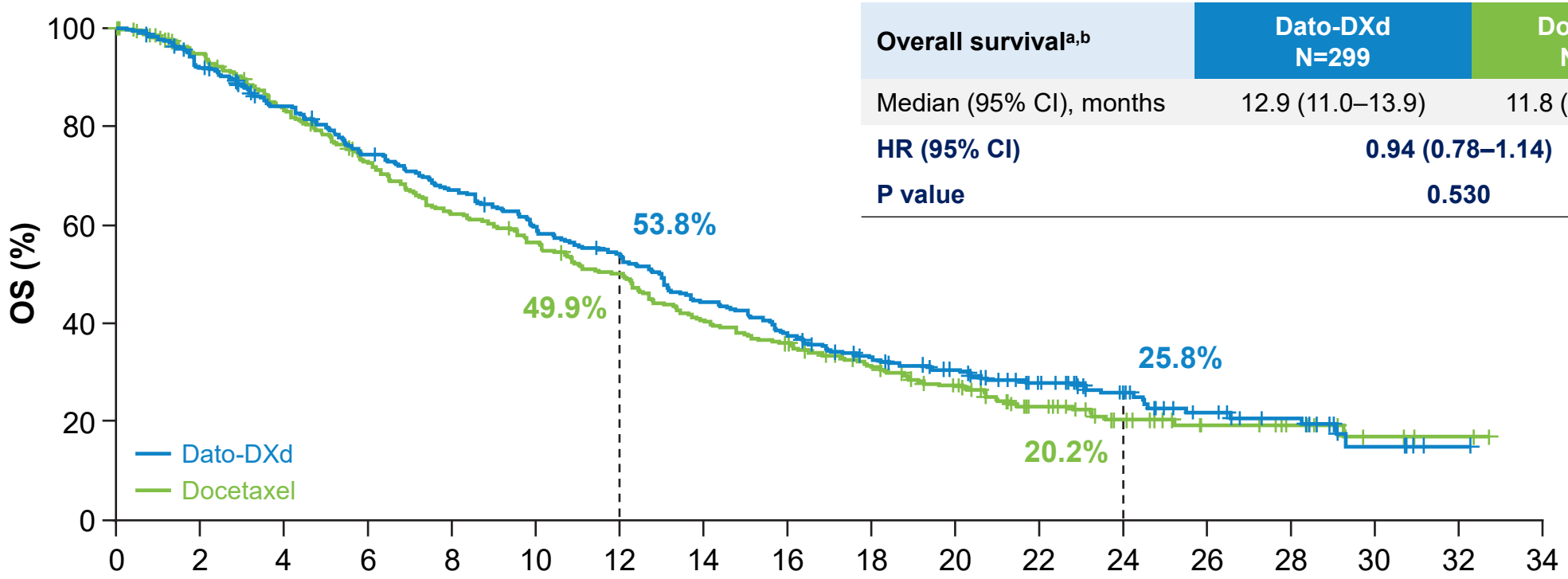
Characteristic, n (%)		Dato-DXd N=299	Docetaxel N=305
Current or former smoker		238 (80)	251 (82)
Actionable genomic alterations present		50 (17)	51 (17)
Brain metastasis at baseline[b]		79 (26)	91 (30)
Prior lines of therapy[c]	1	167 (56)	174 (57)
	2	108 (36)	102 (33)
	3	17 (6)	23 (8)
	≥4	5 (2)	5 (2)
Previous systemic therapy	Platinum containing	297 (99)	305 (100)
	Anti–PD-(L)1	263 (88)	268 (88)
	Targeted	46 (15)	50 (16)

[a]Screening score. [b]Patients with clinically stable brain metastases could be included. Clinically stable defined as asymptomatic, previously treated, or untreated. [c]Two patients in the Dato-DXd treatment group and one patient in the docetaxel treatment group had no prior lines of systemic therapy in the advanced/metastatic setting.
Per investigator reporting, these patients received prior systemic anti-cancer therapy in settings other than the advanced/metastatic setting.

Overall Survival: ITT

TROPION-Lung01

Overall survival[a,b]	Dato-DXd N=299	Docetaxel N=305
Median (95% CI), months	12.9 (11.0–13.9)	11.8 (10.0–12.8)
HR (95% CI)	**0.94 (0.78–1.14)**	
P value	**0.530**	



No. at risk:

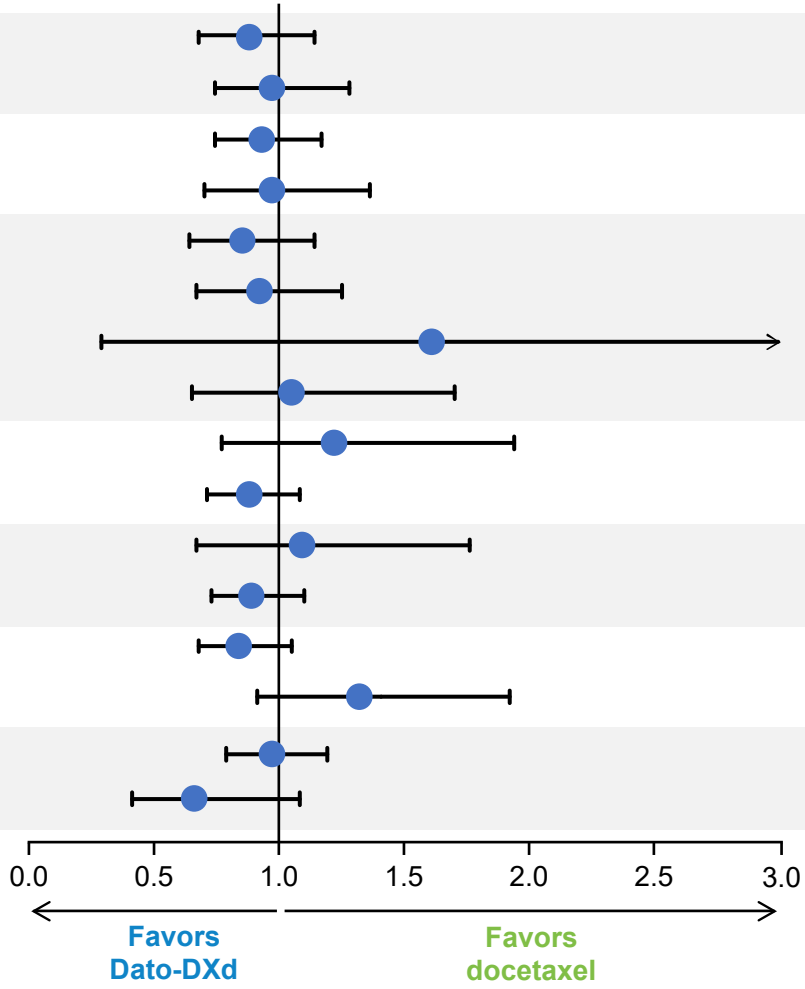
Dato-DXd	299	272	242	213	190	168	151	124	106	84	71	51	35	22	16	5	1	0
Docetaxel	305	273	239	205	175	157	138	112	98	81	63	41	26	15	11	4	2	0

[a]Median (95% CI) OS follow-up was 23.1 (22.0, 24.8) months for Dato-DXd and 23.1 (21.7, 24.2) months for docetaxel. [b]At primary OS analysis (data cutoff: March 1, 2024), 433 OS events (IF) were observed.
IF, information fraction.

Overall Survival: Subgroup Analyses

TROPION-Lung01

		No. of events/No. of patients		HR
		Dato-DXd	Docetaxel	
Age at randomization	<65 years	117/162	112/155	0.88
	≥65 years	98/137	106/150	0.97
Sex	Male	136/183	156/210	0.93
	Female	79/116	62/95	0.97
Race	White	90/123	95/126	0.85
	Asian	83/121	79/120	0.92
	Black/African American	4/6	2/4	1.61
	Other	33/43	35/47	1.05
Smoking status	Never	43/60	31/52	1.22
	Former/current	172/239	186/251	0.88
Brain metastases at baseline	With	37/50	31/47	1.09
	Without	178/249	187/258	0.89
Histology	Nonsquamous	160/234	163/234	0.84
	Squamous	55/65	55/71	1.32
Actionable genomic alterations[a]	Absent	182/249	185/254	0.97
	Present	33/50	33/51	0.66



Data cutoff: March 1, 2024.
[a]Regardless of histology.

Overall Survival by Histology

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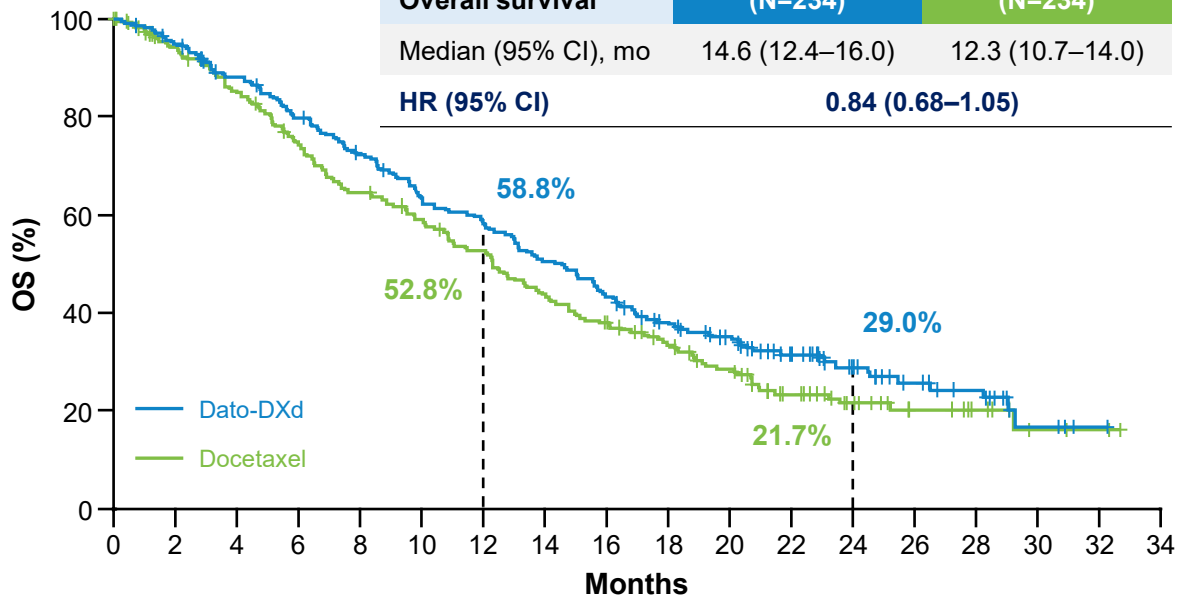
Nonsquamous

Overall survival	Dato-DXd (N=234)	Docetaxel (N=234)
Median (95% CI), mo	14.6 (12.4–16.0)	12.3 (10.7–14.0)
HR (95% CI)	0.84 (0.68–1.05)	

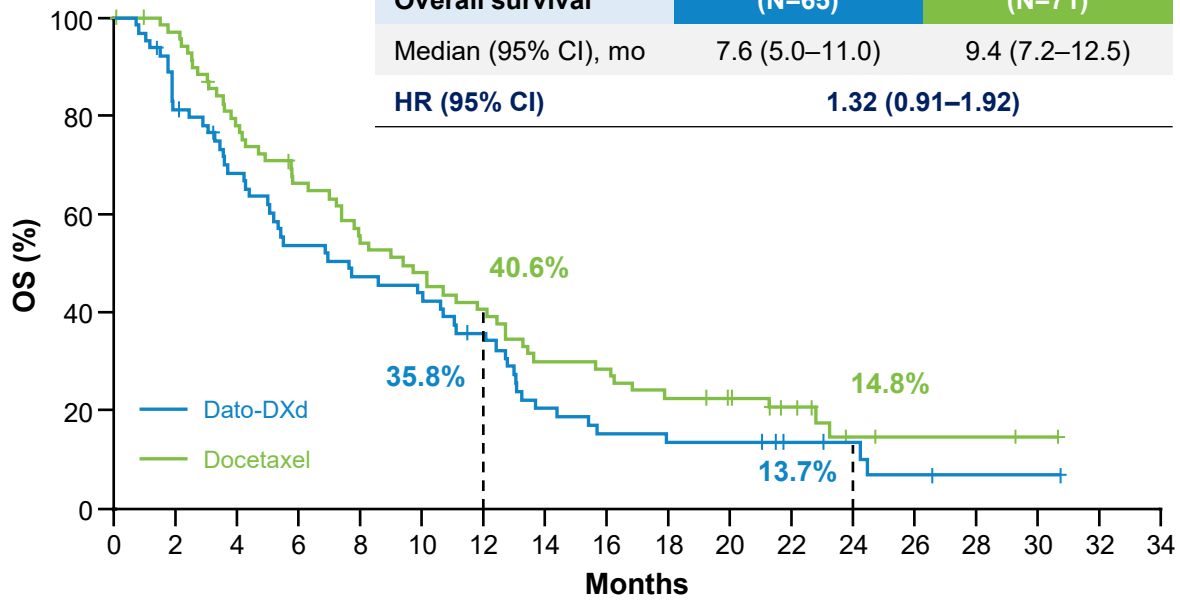


No. at risk:

Dato-DXd	234	220	200	180	161	141	130	112	97	76	63	46	31	20	15	4	1	0
Docetaxel	234	206	186	161	139	125	111	92	79	66	50	32	22	12	8	3	2	0

Squamous

Overall survival	Dato-DXd (N=65)	Docetaxel (N=71)
Median (95% CI), mo	7.6 (5.0–11.0)	9.4 (7.2–12.5)
HR (95% CI)	1.32 (0.91–1.92)	



	65	52	42	33	29	27	21	12	9	8	8	5	4	2	1	1	0	0
	71	67	53	44	36	32	27	20	19	15	13	9	4	3	3	1	0	0

- In patients with NSQ histology, 16% risk reduction for death and 2.3-month improvement in median OS with Dato-DXd
- OS improvements in the NSQ subset were seen regardless of actionable genomic alteration status[a]:
  - **Present**: 15.6 vs 9.8 months (HR [95% CI], 0.65 [0.40–1.08]); **Absent:** 13.6 vs 12.3 months (HR [95% CI], 0.89 [0.70–1.13])

Data cutoff: March 1, 2024.
[a]Based on the number of patients in the respective actionable genomic alteration subsets. Values were calculated based on patient data in the electronic case report forms.

Subsequent Anti-cancer Therapy

TROPION-Lung01

- In the NSQ patient population, **no meaningful impact** on OS by:
  - Removing the effect of subsequent use of docetaxel in the Dato-DXd arm after failure of therapy
  - Removing the effect of all post-treatment anti-cancer therapies in both arms

NSQ population	Dato-DXd (N=234)	Docetaxel (N=234)
Patients receiving any post-treatment anti-cancer therapy, n (%)	125 (**53.4**)	132 (**56.4**)
Median OS (95% CI), months	14.6 (12.4–16.0)	12.3 (10.7–14.0)
HR	0.84 (0.68–1.05)	
Sensitivity analysis[a]: Docetaxel in Dato-DXd arm		
Median OS (95% CI), months	14.8 (12.1–16.9)	12.3 (10.7–14.0)
HR	0.84 (0.66–1.07)	
Sensitivity analysis[a]: All post-treatment anti-cancer therapies in both arms		
Median OS (95% CI), months	12.1 (7.5–17.3)	9.6 (7.5–13.0)
HR	0.79 (0.54–1.15)	

Data cutoff: March 1, 2024.
[a]Analysis was performed using inverse-probability-of-censoring weighting.

Safety Summary: All Treated Patients

TROPION-Lung01

TRAEs, n (%)	Dato-DXd N=297	Docetaxel N=290
Any	260 (88)	252 (87)
Grade ≥3	76 (26)	122 (42)
Associated with:		
Dose reduction	60 (20)	86 (30)
Treatment discontinuation	24 (8)	35 (12)
Death[a]	3 (1)	2 (<1)
Serious	33 (11)	37 (13)
Grade ≥3	28 (9)	34 (12)

- Compared with the prior PFS data cutoff, with an additional ~11 months follow-up:
  - Overall safety profile was consistent
  - No late-onset toxicities were observed
- Fewer grade ≥3 TRAEs were observed with Dato-DXd compared with docetaxel
- Fewer TRAEs leading to dose reductions or discontinuations were seen with Dato-DXd compared with docetaxel

The median treatment durations for Dato-DXd and docetaxel were 4.2 and 2.8 months, respectively

Data cutoff: March 1, 2024.
[a]Two cases of ILD/pneumonitis and one of sepsis (Dato-DXd), and one case of ILD/pneumonitis and one of septic shock (docetaxel).
ILD, interstitial lung disease; TRAE, treatment-related adverse event.

TRAEs ≥15% and Adjudicated Drug-Related ILD

TROPION-Lung01

TRAEs,[a] n (%)	Dato-DXd (N=297)		Docetaxel (N=290)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Stomatitis	141 (47)[b]	20 (7)	45 (16)	3 (1)
Nausea	101 (34)	7 (2)	48 (17)	3 (1)
Alopecia	95 (32)	0	101 (35)	1 (<1)[c]
Decreased appetite	68 (23)	1 (<1)	46 (16)	1 (<1)
Asthenia	56 (19)	8 (3)	56 (19)	5 (2)
Anemia[d]	44 (15)	12 (4)	60 (21)	12 (4)
Diarrhea	30 (10)	1 (<1)	55 (19)	4 (1)
Neutropenia[e]	14 (5)	2 (1)	76 (26)	68 (23)
Leukopenia[f]	9 (3)	0	45 (16)	38 (13)
Adjudicated drug-related ILD or pneumonitis	26 (9)[g]	11 (4)	12 (4)	4 (1)

- Stomatitis events, the most common TRAE with Dato-DXd, were primarily grade 1 (23%) or grade 2 (18%)
- Hematologic toxicities, including neutropenia and febrile neutropenia[h], were more common with docetaxel
- No new adjudicated drug-related ILD events or deaths occurred since the PFS database lock
- Similar safety profiles were seen for the full safety analysis set and the NSQ subgroup

Data cutoff: March 1, 2024.
[a]Occurring in ≥15% of patients in either treatment group, plus all events of adjudicated drug-related ILD or pneumonitis. [b]Due to rounding, summed rates may not reflect total percentage of TRAEs. [c]Includes an event incorrectly reported as grade 3. [d]Grouped preferred terms of anemia, hemoglobin decreased, and red blood cell count decreased. [e]Grouped preferred terms of neutropenia and neutrophil count decreased. [f]Grouped preferred terms of leukopenia and white blood cell count decreased. [g]Includes one patient in the Dato-DXd group who experienced a grade 2 event that was adjudicated to be drug-related ILD by the adjudication committee. The investigator attributed the event to disease progression and removed the patient from the clinical database. [h]0.3% vs 6.9% for Dato-DXd and docetaxel, respectively.

Conclusions

TROPION-Lung01

- TROPION-Lung01 **met its dual primary endpoint of PFS** with a statistically significant improvement for Dato-DXd over docetaxel in the overall population
- The dual primary endpoint of **OS showed a numerical improvement** but **was not statistically significant**
- Consistent benefit seen with Dato-DXd across all efficacy endpoints in patients with **NSQ histology**
- The tolerability profile remains manageable and **no new safety signals** were identified
- TROP2 normalized membrane ratio as measured by quantitative continuous scoring has been shown to predict clinical response to Dato-DXd in an exploratory TROPION-Lung01 analysis[1]

The results of TROPION-Lung01 support the use of Dato-DXd as a potential new therapeutic option for patients with previously treated NSQ NSCLC eligible for subsequent therapy

1. Garassino M, et al. Presented at WCLC 2024, San Diego, CA, USA, September 7–10, 2024 (Abstract PL02.11).

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Datopotamab Deruxtecan Versus Docetaxel for Previously Treated Advanced or Metastatic Non–Small Cell Lung Cancer: The Randomized, Open-Label Phase III TROPION-Lung01 Study

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