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Intracranial Efficacy of Datopotamab Deruxtecan (Dato-DXd) in Patients With Advanced/Metastatic NSCLC in TROPION-Lung01

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Introduction

- Brain metastases occur in ~50% of patients with NSCLC (~60 to 70% in those with *EGFR*m alterations) and are associated with median survival of ~6 to 11 months in advanced disease[1–9]
- Dato-DXd, a TROP2-directed ADC, has demonstrated intracranial efficacy in patients with advanced NSCLC with actionable genomic alterations and brain metastases in the phase 2 TROPION-Lung05 study[10]
- In TROPION-Lung01, Dato-DXd demonstrated statistically significantly longer PFS and numerically longer OS than docetaxel in patients with previously treated advanced or metastatic NSCLC[11]
- Dato-DXd received accelerated approval by the FDA in June 2025 for patients with locally advanced or metastatic *EGFR*m NSCLC who have received prior EGFR-directed therapy and Pt-CT[12,a]
- We present the intracranial activity of Dato-DXd in patients from TROPION-Lung01 with baseline brain metastases, focusing on those with untreated lesions or progression following radiotherapy

TROPION-Lung01: NCT04656652. TROPION-Lung05: NCT04484142.
[a]Based on data from TROPION-Lung01 and TROPION-Lung05, as well as patients with *EGFR*m NSCLC in TROPION-PanTumor01 (NCT03401385).
ADC, antibody–drug conjugate; FDA, United States Food and Drug Administration; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; Pt-CT, platinum chemotherapy; TROP2, trophoblast cell surface antigen 2.
1. Duma N et al. *Mayo Clin Proc*. 2019;94(8):1623–1640. 2. Waqar SN et al. *Clin Lung Cancer*. 2018;19(4):e373–e379. 3. Lim JH, Um SW. *Ann Transl Med*. 2018;6(suppl 1):S66. 4. Gillespie CS et al. *J Thorac Oncol*. 2023;18(12):1703–1713. 5. Rangachari D et al. *Lung Cancer*. 2015;88(1):108–111. 6. Offin M et al. *Cancer*. 2019;125(24):4380–4387. 7. Barnholtz-Sloan JS et al. *J Clin Oncol*. 2004;22(14):2865–2872. 8. Steeg PS et al. *Nat Rev Cancer*. 2011;11(5):352–363. 9. Bacha S et al. *Tunis Med*. 2018;96(3):165–171. 10. Lisberg A et al. Presented at ASCO Annual Meeting 2024, May 31–June 4, 2024; Chicago, IL. 11. Ahn MJ et al. *J Clin Oncol*. 2025;43(3):260–272. 12. United States Food and Drug Administration. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-datopotamab-deruxtecan-dlnk-egfr-mutated-non-small-cell-lung-cancer. Accessed June 24, 2025.

TROPION-Lung01 Study Design

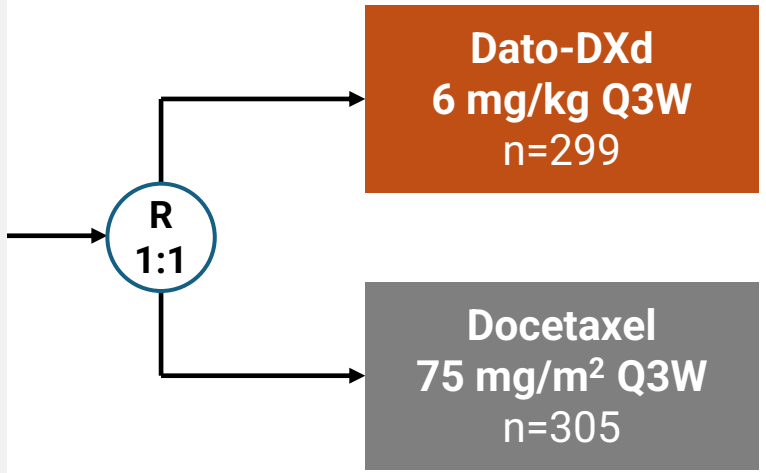
Phase 3, Randomized, Open-Label Study (NCT04656652)

Key eligibility criteria

- NSCLC (stage IIIB, IIIC, or IV)
- ECOG PS 0 or 1
- No prior docetaxel
- **Patients with clinically inactive, asymptomatic brain metastases were eligible**

Without actionable genomic alterations:[a]
- 1–2 prior lines, including Pt-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*
- 1–2 prior approved targeted therapies + Pt-CT and ≤1 anti–PD-(L)1 mAb



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

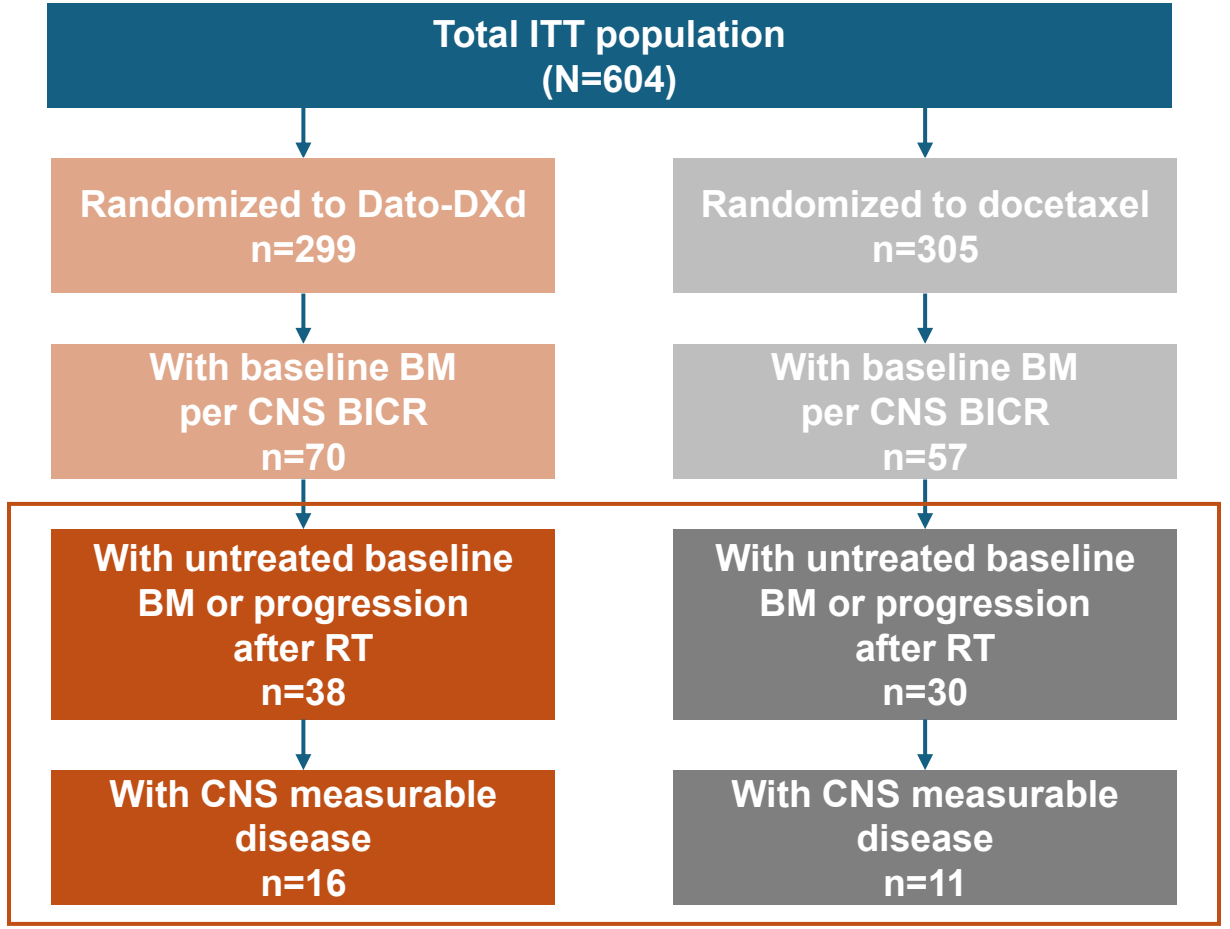
Dual primary end points:
- PFS by BICR per RECIST 1.1
- OS

Post hoc analysis (intracranial activity):
- CNS ORR, DCR, and PFS, assessed by CNS BICR per CNS RECIST
- Percentage change from baseline in SOD in measurable brain metastases

[a]Patients with *KRAS* mutations in the absence of known actionable genomic alterations were eligible; must have met prior therapy requirements for patients without actionable genomic alterations. [b]Squamous vs nonsquamous. [c]Presence vs absence. [d]Yes vs no. [e]United States/Japan/Western Europe vs rest of world.
BICR, blinded independent central review; CNS, central nervous system; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; mAb, monoclonal antibody; ORR, objective response rate; PD-(L)1, programmed death (ligand) 1; Q3W, every 3 weeks; R, randomized; RECIST (1.1), Response Evaluation Criteria in Solid Tumours (version 1.1); SOD, sum of diameters.

Methods and Patient Population

- Brain imaging (MRI or CT) was performed prior to enrollment for all patients, and every 6 weeks thereafter for those with investigator-identified BM at baseline[a]
- Patients with baseline BM identified by CNS BICR (neuroradiologist-reviewed brain imaging) per CNS RECIST were analyzed



Data cutoff: August 30, 2024.

[a]For assessment of CNS response, on-treatment imaging must have been performed using the same modality as at baseline.

BM, brain metastases; CT, computed tomography; ITT, intent-to-treat; MRI, magnetic resonance imaging; RT, radiotherapy.

Baseline Demographic and Clinical Characteristics

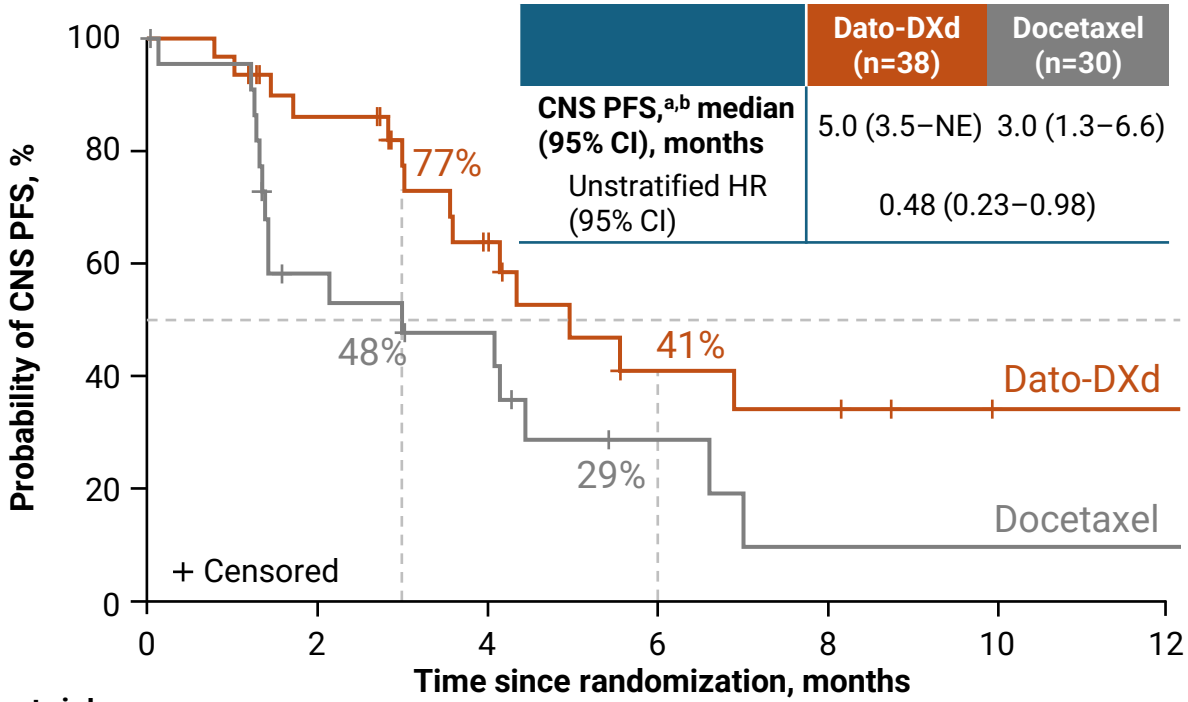
All Patients With Untreated BM or Progression After RT

Characteristic	Dato-DXd (n=38)	Docetaxel (n=30)
Age, median (range), years	65.5 (35–81)	57.5 (34–77)
Male, n (%)	26 (68)	20 (67)
Race, n (%)		
Asian	13 (34)	10 (33)
White	16 (42)	11 (37)
Black or African American	1 (3)	1 (3)
Other or Missing	8 (21)	8 (27)
ECOG PS, n (%)		
0	11 (29)	11 (37)
1	27 (71)	19 (63)
Histology, n (%)		
Squamous	7 (18)	5 (17)
Nonsquamous	31 (82)	25 (83)
Actionable genomic alterations, n (%)	12 (32)	12 (40)
*EGFR*m	11 (29)	11 (37)
Time from diagnosis to randomization, median (range), months	14.4 (3.0–87.0)	20.6 (3.4–73.1)

Data cutoff: August 30, 2024.

CNS PFS

All Patients With Untreated BM or Progression After RT

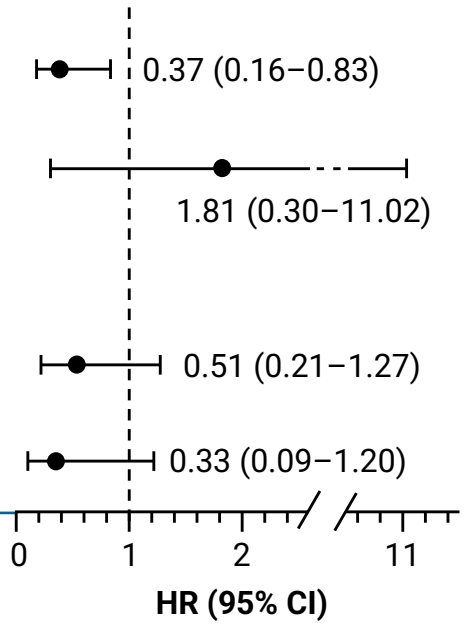


	Dato-DXd (n=38)	Docetaxel (n=30)
CNS PFS,[a,b] median (95% CI), months	5.0 (3.5–NE)	3.0 (1.3–6.6)
Unstratified HR (95% CI)	0.48 (0.23–0.98)	

No. at risk

Dato-DXd	38	23	13	6	5	2	2
Docetaxel	30	11	8	3	1	1	1

Subgroup	Events, n / N: Dato-DXd (n=38)	Events, n / N: Docetaxel (n=30)	HR (95% CI)
Histology			
Nonsquamous (n=56)	11 / 31	13 / 25	0.37 (0.16–0.83)
Squamous (n=12)	3 / 7	3 / 5	1.81 (0.30–11.02)
***EGFR*m**			
Absent (n=46)	9 / 27	10 / 19	0.51 (0.21–1.27)
Present (n=22)	5 / 11	6 / 11	0.33 (0.09–1.20)



Data cutoff: August 30, 2024.

[a]In the Dato-DXd and docetaxel arms, 24 (63.2%) and 14 (46.7%) patients, respectively, were censored. PFS was defined as the time (in months) from randomization to first documentation of PD or death due to any cause, whichever occurred first. In estimations of CNS PFS, patients without PD were not censored or considered to have PD at the start of a subsequent anticancer therapy. [b]Assessed by CNS BICR per CNS RECIST.
CI, confidence interval; HR, hazard ratio; NE, not estimable; PD, progressive disease.

Intracranial Response by CNS BICR

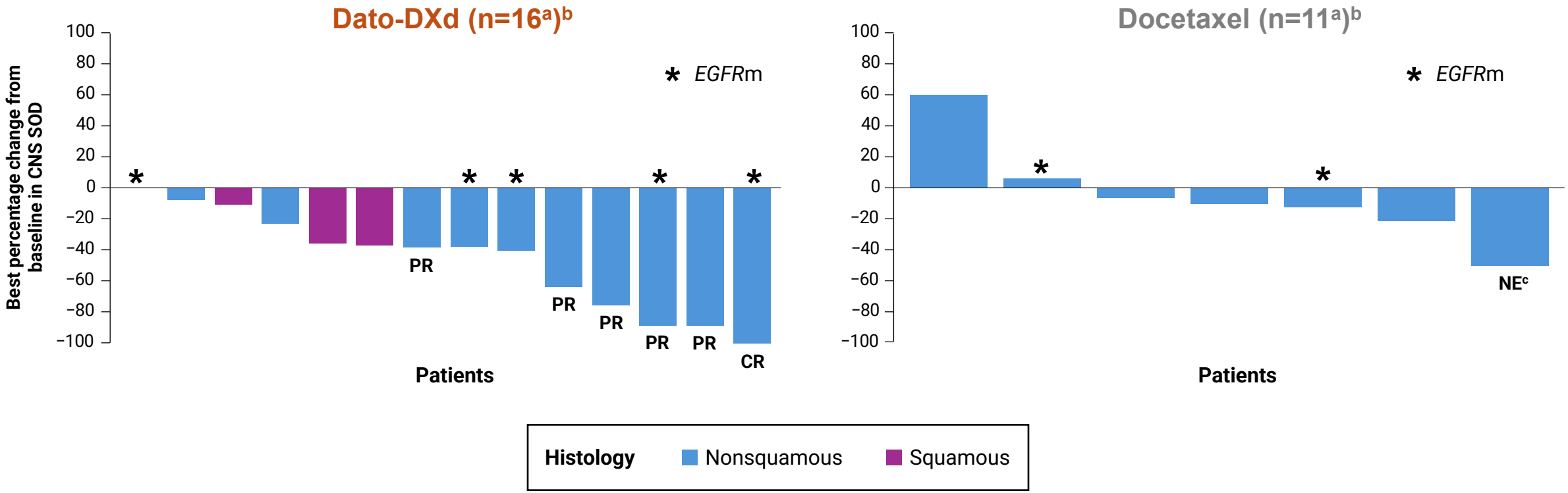
Patients With Untreated BM or Progression After RT, and CNS Measurable Disease

	Dato-DXd (n=16)	Docetaxel (n=11)
CNS confirmed ORR,[a] % (95% CI)	38 (15–65)	0 (0–29)
CNS confirmed BOR,[a] n (%)		
CR	1 (6)	0
PR	5 (31)	0
SD	8 (50)	4 (36)
PD	0	2 (18)
NE	2 (13)	5 (46)
CNS confirmed DCR,[a] % (95% CI)	88 (62–98)	36 (11–69)

Data cutoff: August 30, 2024.
CNS cORR in all patients with untreated BM or progression after RT, including those with non-measurable disease: Dato-DXd (n=38), 16% (95% CI, 6–31); docetaxel (n=30), 0% (95% CI, 0–12).
All lesions were identified by BICR but not necessarily by the investigator. As such, follow-up scans for the majority of non-measurable lesions were not available. These are deemed non-evaluable for intracranial efficacy and limit clinical interpretation of intracranial efficacy.
[a]Assessed by CNS BICR per CNS RECIST.
BOR, best overall response; CR, complete response; PR, partial response; SD, stable disease.

Intracranial Activity

Patients With Untreated BM or Progression After RT, and CNS Measurable Disease



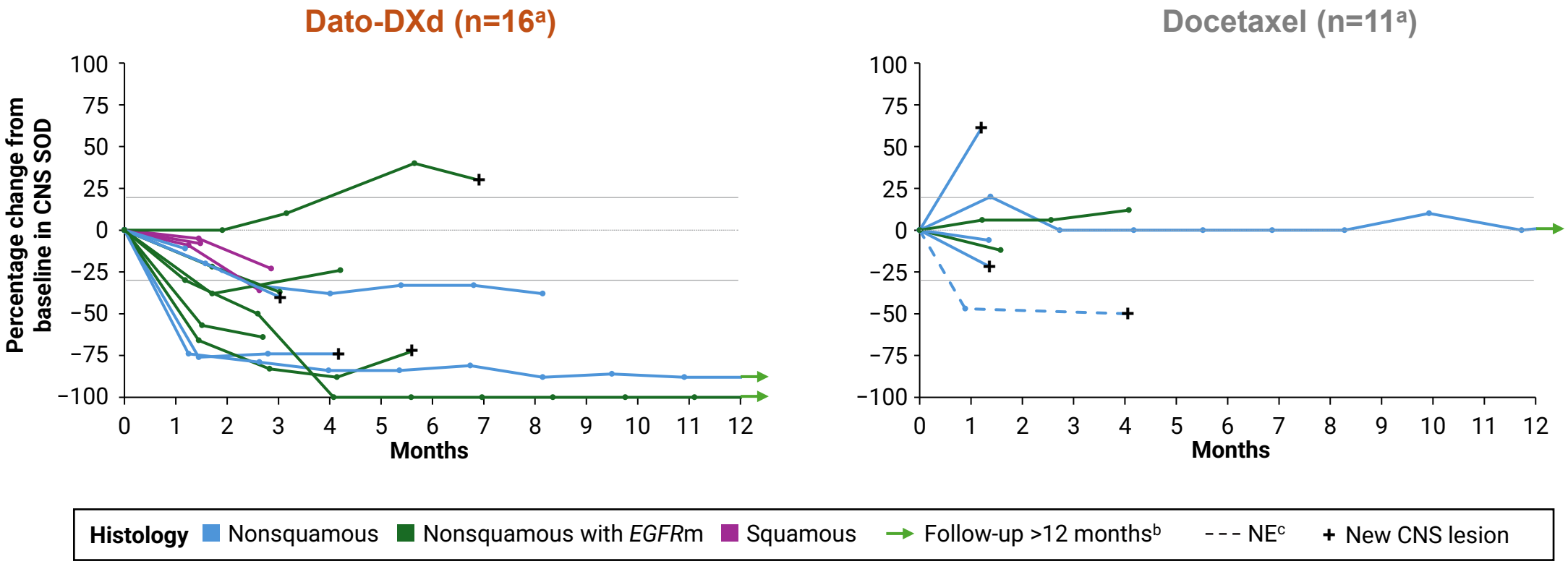
Data cutoff: August 30, 2024.

[a]Two patients in the Dato-DXd arm and 4 patients in the docetaxel arm did not have adequate post-baseline tumor assessments and were excluded from the waterfall plots. [b]CNS BOR assessed by CNS BICR per CNS RECIST is presented underneath bars for patients with CNS BOR of PR, CR, or NE. [c]This patient had an initial CNS assessment that was <5 weeks after randomization and a subsequent assessment of PD due to new brain lesions, resulting in a CNS BOR of NE.

NE, not evaluable.

Intracranial Activity Over Time

Patients With Untreated BM or Progression After RT, and CNS Measurable Disease

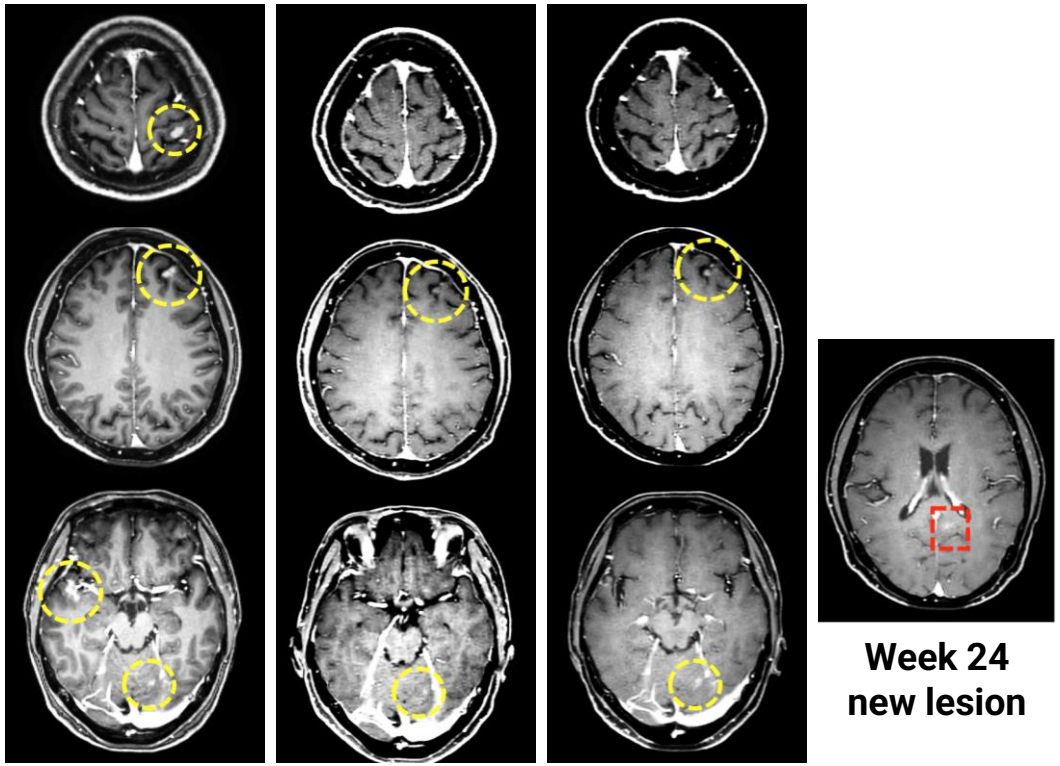


Data cutoff: August 30, 2024.

[a]Two patients in the Dato-DXd arm and 4 patients in the docetaxel arm did not have adequate post-baseline tumor assessments and were excluded from the spider plots. [b]Dato-DXd: One patient with a CNS CR up to ~19.5 months (systemic BOR: SD) and 1 patient with a CNS PR up to ~27.5 months (systemic BOR: PR); docetaxel: CNS SD up to ~27.0 months (systemic BOR: PR). [c]This patient had an initial CNS assessment that was <5 weeks after randomization and a subsequent assessment of PD due to new brain lesions, resulting in a CNS BOR of NE.

Patient Case

Female Patient With Stage IVB Adenocarcinoma NSCLC With EGFR L858R



Baseline **Week 6** **Week 24**

Baseline lesion New lesion

Week 24 new lesion

Case summary	
Prior RT or surgery	• None
Previous anticancer therapy	• Osimertinib[a] (~3.5 years) • Carboplatin + pemetrexed[b] (22 days)
Dato-DXd treatment[c]	• First dose of Dato-DXd received ~5 weeks after last dose of carboplatin + pemetrexed • Remained on treatment for ~36 weeks (12 cycles) • Patient experienced PD 6 days after the last dose of Dato-DXd and died 32 weeks later, with cause of death reported as disease progression
Intracranial response to Dato-DXd	• **CNS BICR PR** starting at week 6 • **CNS BICR PD** at week 24 (new lesion in left occipital lobe)

CNS BICR chosen lesions: T01: Right temporal lobe 17 mm; T02: Left frontal lobe 13 mm; T03: Left parietal lobe 11 mm; NT01: Left cerebellum.

[a]Osimertinib, started 20 days after diagnosis. [b]Carboplatin + pemetrexed, started 6 days after the last dose of osimertinib. [c]Reported adverse events included grade 1 nausea, alopecia, and hyperuricemia, and grade 2 oral mucositis, laryngopharyngitis, and sialadenitis.

Conclusions

- In this post hoc analysis of TROPION-Lung01, intracranial response and PFS showed numerical improvement with Dato-DXd vs docetaxel
- CNS cORR with Dato-DXd was 38% among patients with measurable disease, and all evaluable patients experienced CNS disease control; no CNS responses were seen with docetaxel
- All 6 CNS responders had nonsquamous tumors (2 with *EGFR*m)
- Limitations include small numbers in some subgroups, high censoring due to missing CNS imaging, and on-treatment scans only required for patients with baseline brain metastases

Dato-DXd demonstrated intracranial activity in patients with advanced or metastatic NSCLC and brain metastases, consistent with previous studies of DXd ADCs in multiple solid tumors[1–8]

Data cutoff: August 30, 2024.
cORR, confirmed objective response rate.
1. Lisberg A et al. Presented at ASCO Annual Meeting 2024, May 31–June 4, 2024; Chicago, IL. Abstract 8593. 2. Bartsch R et al. Presented at ESMO Breast Cancer 2024, May 15–17, 2024; Berlin, Germany. Abstract 187P. 3. Planchard D et al. Presented at ESMO Congress 2023, October 20–24, 2023; Madrid, Spain. Abstract 1321MO. 4. Harbeck N et al. *Nat Med*. 2024;30(12):3717–3727. 5. Hurvitz SA et al. *ESMO Open*. 2024;9(5):102924. 6. Yu HA et al. *J Clin Oncol*. 2023;41(35):5363–5375. 7. Preusser M et al. Presented at ASCO Annual Meeting 2025, May 30–June 3, 2025; Chicago, IL. Abstract 2005. 8. Johnson ML et al. Presented at ESMO Congress 2024, September 13–17, 2024; Barcelona, Spain. Abstract 1787P.

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Thank You