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Dato-DXd vs docetaxel in patients with advanced nonsquamous non-small cell lung cancer with brain metastases: results from TROPION-Lung01

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Objective

- Analyze the safety and systemic efficacy of Dato-DXd in patients with advanced NSQ NSCLC from the TROPION-Lung01 trial (NCT04656652) by baseline brain metastases (mets) status

Conclusions

- In patients receiving Dato-DXd, trends towards improved systemic efficacy were observed vs docetaxel in patients with and without baseline brain mets
- Dato-DXd had a manageable safety profile regardless of baseline brain mets status
- Trials examining the intracranial activity of Dato-DXd are ongoing in patients with breast cancer (TUXEDO-2; NCT05866432 and DATO-BASE; NCT06176261)[1]
- Further investigation into the intracranial activity of Dato-DXd in patients with brain mets is warranted

Plain language summary

Why did we perform this research?

Brain metastases (mets) are relatively common in patients with non-small cell lung cancer (NSCLC) that has spread to other parts of the body. Patients with brain mets may not live as long as those without. Datopotamab deruxtecan (Dato-DXd) is an antibody–drug conjugate (ADC), which consists of an antibody (datopotamab) which binds to TROP2 to deliver an anticancer drug (deruxtecan) to tumor cells. In a separate trial called TROPION-Lung05 (NCT04484142), Dato-DXd showed intracranial anticancer activity in patients with NSCLC and brain mets, who had previously received other treatments for NSCLC.

How did we perform this research?

Patients with NSCLC that has spread to other parts of the body and cannot be completely removed with surgery, who had previously received other treatments for NSCLC were included in TROPION-Lung01. This analysis focused on the group of patients who had a type of NSCLC called nonsquamous (NSQ) NSCLC. The safety and activity of Dato-DXd compared with docetaxel was analyzed in patients with or without brain mets at baseline.

What were the findings of this research?

Patients with NSQ NSCLC who received Dato-DXd tended to survive longer after the start of treatment without their tumors getting worse (progression free survival), and to live longer (overall survival), compared with those who received docetaxel, regardless of whether they had brain mets at baseline. The safety of Dato-DXd was manageable in patients with NSQ NSCLC with and without baseline brain mets.

What are the implications of this research?

The findings suggest that Dato-DXd can benefit patients with advanced NSQ NSCLC with or without brain mets.

Where can I access more information?

For more information about the TROPION-Lung01 study, please visit https://clinicaltrials.gov/study/NCT04656652.

Poster

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Poster presented at ESMO 2024; September 13–17, 2024; Barcelona, Spain
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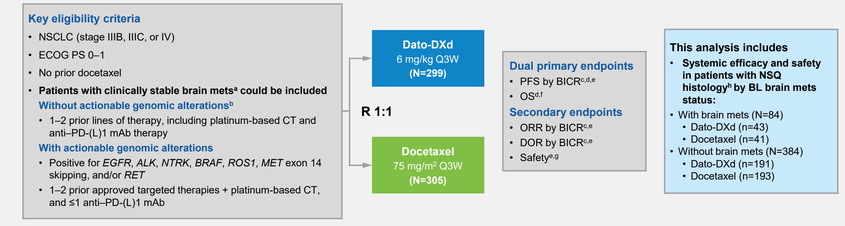
Background

- **Dato-DXd** is a **TROP2-directed ADC**, composed of an anti-TROP2 mAb covalently linked to a highly potent, membrane permeable, topoisomerase I inhibitor payload, via a plasma-stable, tumor-selective, tetrapeptide-based cleavable linker[2,3]
- In patients with advanced NSCLC, there is a high prevalence of brain mets, particularly in those with certain actionable genomic alterations, indicative of poor prognosis[4]
- In TROPION-Lung05 (NCT04484142), Dato-DXd showed intracranial antitumor activity in patients with heavily pretreated advanced NSCLC with baseline brain mets[5]
- Two other DXd ADCs, trastuzumab deruxtecan and patritumab deruxtecan, have also shown intracranial antitumor activity in NSCLC[6,7]
- In the phase 3 TROPION-Lung01 trial, Dato-DXd demonstrated a statistically significant improvement in PFS and a numerical improvement in OS vs docetaxel in patients with previously treated advanced NSCLC; efficacy was driven by patients with NSQ histology[8]
  - In the NSQ population, median PFS was 5.5 months and 3.6 months and median OS was 14.6 months and 12.3 months for those who received Dato-DXd and docetaxel, respectively[8]
- Here we report a post hoc analysis of the safety and systemic efficacy of Dato-DXd in patients with NSQ NSCLC from TROPION-Lung01, by brain mets status at study entry

Methods

- TROPION-Lung01 is a phase 3, multicenter, randomized, open-label study evaluating Dato-DXd vs docetaxel in patients with previously treated advanced NSCLC with or without actionable genomic alterations[8]
- A brain scan was required for all patients at baseline. Patients with baseline brain mets were required to have brain scans every 6 weeks; regular brain scans were not required for patients without baseline brain mets
- In this exploratory analysis, systemic ORR, DCR, and PFS by BICR per RECIST v1.1, OS, and safety results were determined in patients with NSQ histology with and without baseline brain mets



Randomization stratified by: histology,[i] actionable genomic alteration(s),[j] anti–PD-(L)1 mAb included in most recent prior therapy, geography[k]

[a]Clinically stable defined as asymptomatic, previously treated, or untreated. [b]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. [c]Evaluated per RECIST v1.1. [d]PFS and OS by histology were prespecified subgroup analyses. [e]Data cutoff: March 29, 2023. [f]Data cutoff: March 01, 2024. [g]Safety analyses by histology were post hoc. [h]CRF derived. [i]Squamous vs NSQ. [j]Presence vs absence. [k]United States/Japan/Western Europe vs rest of world.

Results

Demographics and baseline characteristics

Characteristic	With BL brain mets: Dato-DXd (n=43)	With BL brain mets: Docetaxel (n=41)	Without BL brain mets: Dato-DXd (n=191)	Without BL brain mets: Docetaxel (n=193)
Age, median (range), years	61 (26–81)	58 (34–74)	64 (33–81)	64 (24–88)
Male, n (%)	27 (63)	28 (68)	107 (56)	122 (63)
Race, n (%)				
Asian	17 (40)	14 (34)	75 (39)	82 (42)
White	17 (40)	20 (49)	79 (41)	70 (36)
Black or African American	0	1 (2)	4 (2)	2 (1)
Other	8 (19)	5 (12)	28 (15)	34 (18)
Missing	1 (2)	1 (2)	5 (3)	5 (3)
ECOG PS,[a] n (%)				
0	15 (35)	10 (24)	60 (31)	64 (33)
1	28 (65)	31 (76)	131 (69)	129 (67)
Smoking status				
Never	9 (21)	8 (20)	48 (25)	40 (21)
Former	28 (65)	25 (61)	125 (65)	126 (65)
Current	6 (14)	8 (20)	18 (9)	25 (13)
Missing	0	0	0	2 (1)
Actionable genomic alterations, n (%)	14 (33)	16 (39)	34 (18)	34 (18)
Liver mets at study entry,[b] n (%)	13 (30)	7 (17)	42 (22)	28 (15)
Time from diagnosis to randomization, median (range), months	10.4 (3.0–66.9)	20.5 (2.0–73.1)	17.4 (3.1–175.9)	16.7 (2.3–104.0)

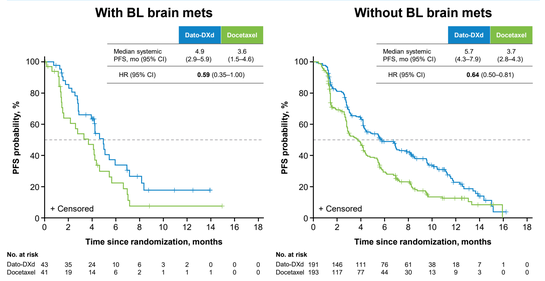
Patients with NSQ histology. Percentages may not add up to 100 due to rounding. [a]ECOG PS at screening. [b]Brain and liver mets identified by BICR.

Safety summary

TRAEs,[a] n (%)	With BL brain mets: Dato-DXd (n=43)	With BL brain mets: Docetaxel (n=37)	Without BL brain mets: Dato-DXd (n=189)	Without BL brain mets: Docetaxel (n=184)
Any grade	37 (86)	31 (84)	168 (89)	164 (89)
Grade ≥3	3 (7)	10 (27)	48 (25)	80 (43)
Associated with				
Dose reduction	5 (12)	7 (19)	44 (23)	59 (32)
Treatment interruption	4 (9)	4 (11)	34 (18)	20 (11)
Treatment discontinuation	3 (7)	5 (14)	17 (9)	22 (12)
Death	0	1 (3)	1 (1)	1 (1)
Serious TRAEs	1 (2)	3 (8)	18 (10)	22 (12)
Grade ≥3	1 (2)	3 (8)	14 (7)	20 (11)

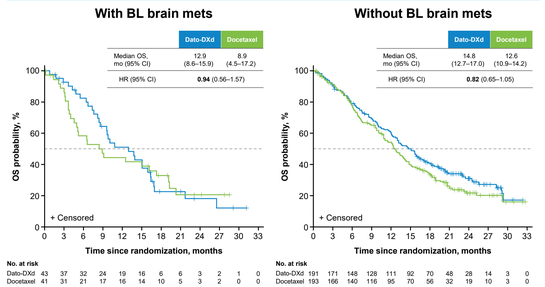
Patients with NSQ histology. Data cutoff: March 29, 2023. [a]Percentage incidences are calculated using the number of patients included in the Safety Analysis Set in the subgroup columns.

Systemic PFS by brain mets status at baseline



Patients with NSQ histology. Data cutoff: March 29, 2023.

OS by brain mets status at baseline



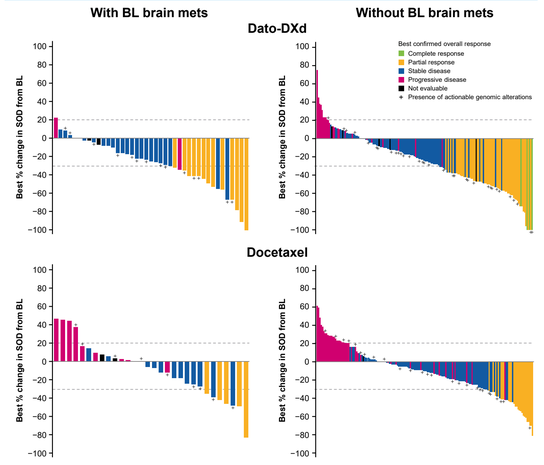
Patients with NSQ histology. Data cutoff: March 01, 2024.

Patterns of relapse by brain mets status at baseline

Patients, n (%)	With BL brain mets: Dato-DXd (n=43)	With BL brain mets: Docetaxel (n=41)	Without BL brain mets: Dato-DXd (n=191)	Without BL brain mets: Docetaxel (n=193)
New lesions	13 (30)	10 (24)	44 (23)	60 (31)
Brain	1 (2)	4 (10)	4 (2)	10 (5)
Non-brain	10 (23)	5 (12)	38 (20)	47 (24)
Brain and non-brain[a]	2 (5)	1 (2)	2 (1)	3 (2)

Patients with NSQ histology. [a]Includes patients with multiple lesions including brain lesions.

Best change in sum of diameters from baseline



Patients with NSQ histology. Data cutoff: March 29, 2023.

Systemic efficacy by brain mets status at baseline

Confirmed response[a]	With BL brain mets: Dato-DXd (n=43)	With BL brain mets: Docetaxel (n=41)	Without BL brain mets: Dato-DXd (n=191)	Without BL brain mets: Docetaxel (n=193)
ORR,[b] n (%) [95% CI][c]	13 (30) [17–46]	5 (12) [4–26]	60 (31) [25–39]	25 (13) [9–19]
CR	0	0	4 (2)	0
PR	13 (30)	5 (12)	56 (29)	25 (13)
SD	23 (53)	14 (34)	90 (47)	96 (50)
Non-CR/Non-PD	0	0	2 (1)	3 (2)
PD	4 (9)	9 (22)	27 (14)	44 (23)
NE	3 (7)	13 (32)	12 (6)	25 (13)
DOR,[d] median [95% CI],[e] months	NE [2.8–NE]	5.6 [2.1–NE]	7.7 [5.6–11.1]	5.6 [4.3–10.4]
≥6 months, n (%)	4 (31)	1 (20)	27 (45)	6 (24)
≥9 months, n (%)	1 (8)	0	16 (27)	2 (8)
DCR,[f] n (%) [95% CI][c]	36 (84) [69–93]	19 (46) [31–63]	152 (80) [73–85]	124 (64) [57–71]

Patients with NSQ histology. Data cutoff: March 29, 2023. [a]Confirmed responses require at least two determinations of responses ≥4 weeks apart before progression. [b]CR + PR. [c]The 2-sided 95% CIs are based on the Clopper-Pearson exact binomial method. [d]Based on the KM method. [e]The 2-sided 95% CIs are computed using the Brookmeyer-Crowley method. [f]CR + PR + SD + non-CR/non-PD.

Abbreviations

ADC, antibody–drug conjugate; BICR, blinded independent central review; BL, baseline; 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; KM, Kaplan-Meier; mAb, monoclonal antibody; mets, metastases; n, number; 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; Q3W, every 3 weeks; R, randomized; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; SOD, sum of diameters; TRAE, treatment-related adverse event; TROP2, trophoblast cell surface antigen 2; vs, versus.

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Disclosures

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