OS11-2

DESTINY-Lung01/02

T-DXd in HER2-mutant (HER2m) metastatic NSCLC with and without brain metastases: pooled analyses from DESTINY-Lung01/02

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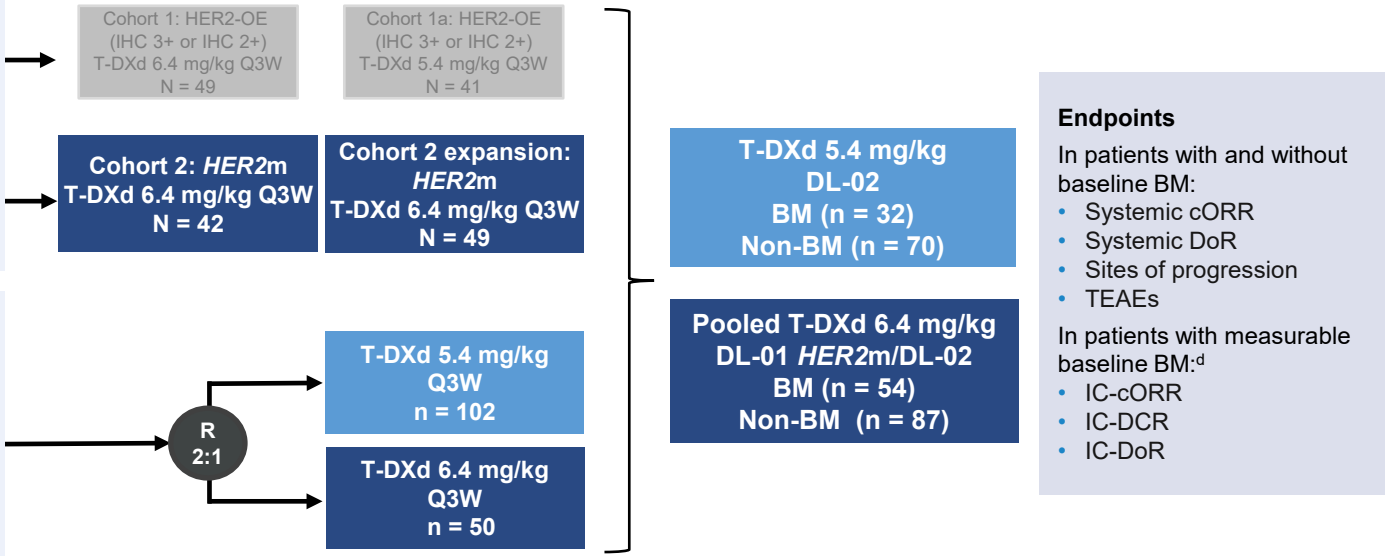
Exploratory Pooled Brain Metastases Analyses: DESTINY-Lung01[1,2] and DESTINY-Lung02[3]

DESTINY-Lung01[a]

- Unresectable/metastatic nonsquamous NSCLC
- Relapsed from or is refractory to standard treatment
- Measurable disease by RECIST v1.1
- ECOG PS of 0 or 1
- Locally reported *HER2*m (Cohort 2)
- Asymptomatic BM allowed[c]

DESTINY-Lung02[b]

- Metastatic *HER2*m NSCLC
- ≥1 prior anticancer therapy (2L+), including platinum-based chemotherapy
- Measurable disease per RECIST v1.1
- ECOG PS of 0 or 1
- Locally reported *HER2*m
- Asymptomatic BM allowed[c]



Endpoints

In patients with and without baseline BM:

- Systemic cORR
- Systemic DoR
- Sites of progression
- TEAEs

In patients with measurable baseline BM:[d]

- IC-cORR
- IC-DCR
- IC-DoR

BM, brain metastases, cORR, confirmed objective response rate; CR, complete response; CT, computed tomography; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; *HER2*, human epidermal growth factor receptor 2; *HER2*m, human epidermal growth factor receptor 2-mutant; IC-cORR, intracranial confirmed overall response rate; IC-DCR, intracranial disease control rate; IC-DoR, intracranial duration of response; IHC, immunohistochemistry; MRI, magnetic resonance imaging; NE, not evaluable; NSCLC, non–small cell lung cancer; OE, overexpressing; PD, progressive disease; PR, partial response; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; SD, stable disease; T-DXd, trastuzumab deruxtecan; TEAEs, treatment-emergent adverse events; WBRT, whole-brain radiotherapy.
[a]Data cutoff: December 3, 2021. [b]Data cutoff: December 23, 2022. [c]Patients with asymptomatic BM present at baseline were eligible if they did not need ongoing corticosteroid or anticonvulsant treatments, had recovered from acute radiotherapy toxicity, and more than 2 weeks had passed since WBRT. [d]BM were considered measurable if they were ≥10 mm in 1 dimension on CT or MRI. 14/32 patients with baseline BM in DL-01 and 30/54 in DL-02 had BM that were measurable. IC responses were evaluated in measurable baseline BM per RECIST v1.1 based on CT or MRI scans every 6 weeks from Cycle 1 Day 1; no additional scans were required for those without baseline BM unless clinically indicated.

1. Li BT et al. *N Engl J Med*. 2022;386:241-51. 2. Li BT et al. Poster presented European Society for Medical Oncology Annual Meeting; September 9-13, 2022, Paris, France. 3. Goto K et al. *J Clin Oncol* 2023 1:4852-63.

Baseline Characteristics

	T-DXd 5.4 mg/kg DL-02		Pooled T-DXd 6.4 mg/kg DL-01 *HER2*m/DL-02	
	BM n = 32	Non-BM n = 70	BM n = 54	Non-BM n = 87
Median age, years (range)	57.5 (37.0-83.0)	59.5 (30.0-79.0)	62.5 (29.0-88.0)	59.0 (27.0-83.0)
Sex, n (%)				
Female	19 (59.4)	46 (65.7)	32 (59.3)	62 (71.3)
Male	13 (40.6)	24 (34.3)	22 (40.7)	25 (28.7)
Region, n (%)				
Europe	19 (59.4)	14 (20.0)	20 (37.0)	30 (34.5)
Asia	12 (37.5)	51 (72.9)	17 (31.5)	36 (41.4)
North America	1 (3.1)	3 (4.3)	17 (31.5)	20 (23.0)
Rest of world	0	2 (2.9)	0	1 (1.1)
Median time from initial NSCLC diagnosis to randomization, months (range)	22.4 (3.2-63.0)	17.9 (3.3-149.6)	17.9 (1.7-125.9)	16.2 (3.3-151.9)
ECOG PS, n (%)				
0 | 1	6 (18.8) | 26 (81.3)	23 (32.9) | 47 (67.1)	13 (24.1) | 41 (75.9)	29 (33.3) | 58 (66.7)
History of BM, n (%)				
Yes | No	29 (90.6) | 3 (9.4)	15 (21.4) | 55 (78.6)	45 (83.3) | 9 (16.7)	15 (17.2) | 72 (82.8)
Prior regimens in the metastatic setting, n (%)				
≤2 | >2	23 (71.9) | 9 (28.1)	46 (65.7) | 24 (34.3)	33 (61.1) | 21 (38.9)	60 (69.0) | 27 (31.0)
IC progression on prior therapy	**13 (40.6)**	**1 (1.4)**	**20 (37.0)**	**8 (9.2)**
Prior treatment of BM, n (%)				
RT alone	15 (46.9)	8 (11.4)	23 (42.6)	6 (6.9)
Surgery alone	0	0	0	0
RT and surgery	2 (6.3)	4 (5.7)	1 (1.9)	0
None	15 (46.9)	58 (82.9)	30 (55.6)	81 (93.1)
Median time since prior RT to the brain, months (range)	8.5 (1.0-38.5)	6.8 (0.1-80.1)	1.6 (0.5-17.2)	13.6 (3.0-21.0)

- 31.4% and 38.3% of patients treated with T-DXd 5.4 mg/kg (DL-02) and T-DXd 6.4 mg/kg (pooled DL-01 and DL-02), respectively, had asymptomatic BM at baseline
- A higher proportion of patients with baseline BM compared to those without in both the T-DXd 5.4 mg/kg group (81.3% vs 67.1%) and 6.4 mg/kg group (75.9% vs 66.7%) had an ECOG PS of 1

BM, brain metastases; DL, DESTINY-Lung; ECOG PS, Eastern Cooperative Oncology Group performance status; *HER2*m, human epidermal growth factor receptor 2-mutant; IC, intracranial; NSCLC, non–small cell lung cancer; T-DXd, trastuzumab deruxtecan; RT, radiotherapy

Systemic Efficacy

	T-DXd 5.4 mg/kg DL-02		Pooled T-DXd 6.4 mg/kg DL-01 HER2m/DL-02	
	BM n = 32	Non-BM n = 70	BM n = 54	Non-BM n = 87
Systemic cORR, n (%)[a]	15 (46.9)	35 (50.0)	27 (50.0)	51 (58.6)
95% CI[b]	29.1-65.3	37.8-62.2	36.1-63.9	47.6-69.1
DCR, n (%)[a]	29 (90.6)	66 (94.3)	50 (92.6)	80 (92.0)
95% CI[b]	75.0-98.0	86.0-98.4	82.1-97.9	84.1-96.7
DoR, median, months[c]	4.6	16.8	7.2	14.1
95% CI	4.2-9.5	8.7-NE	5.3-NE	9.3-NE
Sites of progression, n (%)				
Intracranial only	3 (9.4)	0	8 (14.8)	0
Extracranial only	6 (18.8)	14 (20.0)	9 (16.7)	23 (26.4)
Both	3 (9.4)	0	0	2 (2.3)
Missing	1 (3.1)	1 (1.4)	5 (9.3)	10 (11.5)
Median PFS, months	7.1	18.0	7.1	11.9
95% CI	5.5-9.7	8.5-NE	4.5-9.6	7.2-16.1
Median OS, months	13.6	19.5	13.8	27.9
95% CI	9.4-NE	14.9-NE	11.1-19.5	17.8-NE

BM, brain metastases; cORR, confirmed objective response rate; DCR, disease control rate; DL, DESTINY-Lung; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; *HER2*m, human epidermal growth factor receptor 2-mutant; NE, not evaluable; NSCLC, non–small cell lung cancer; OS, overall survival; PFS, progression-free survival; TEAE, treatment-emergent adverse event; T-DXd, trastuzumab deruxtecan; RT, radiotherapy. [a]Denominator for percentages is the number of patients in the full analysis set with brain metastases tumor assessment. [b]Based on Clopper-Pearson method for single proportion. [c]Calculated as time from first confirmed response until progression.

Overall Safety

	T-DXd 5.4 mg/kg DL-02		Pooled T-DXd 6.4 mg/kg DL-01 *HER2*m/DL-02	
	BM n = 31	Non-BM n = 70	BM n = 54	Non-BM n = 87
Median treatment duration, range (months)	**5.75 (0.7-14.0)**	**8.28 (0.7-20.8)**	**5.55 (0.7-22.6)**	**8.54 (0.7-33.8)**
Any-grade TEAE, n (%)	**31 (100.0)**	**70 (100.0)**	**54 (100.0)**	**87 (100.0)**
Drug related	28 (90.3)	69 (98.6)	54 (100.0)	84 (96.6)
Grade ≥3 TEAE, n (%)	**20 (64.5)**	**33 (47.1)**	**41 (75.9)**	**55 (63.2)**
Drug related	12 (38.7)	27 (38.6)	32 (59.3)	39 (44.8)
Serious TEAEs, n (%)	**15 (48.4)**	**22 (31.4)**	**25 (46.3)**	**34 (39.1)**
Drug related	6 (19.4)	8 (11.4)	16 (29.6)	14 (16.1)
TEAEs associated with drug discontinuation, n (%)	**5 (16.1)**	**10 (14.3)**	**16 (29.6)**	**32 (36.8)**
Drug related	5 (16.1)	9 (12.9)	12 (22.2)	22 (25.3)
TEAEs associated with drug interruption, n (%)	**13 (41.9)**	**32 (45.7)**	**27 (50.0)**	**50 (57.5)**
Drug related	7 (22.6)	20 (28.6)	17 (31.5)	38 (43.7)
TEAEs associated with dose reduction, n (%)	**3 (9.7)**	**15 (21.4)**	**22 (40.7)**	**28 (32.2)**
Drug related	3 (9.7)	14 (20.0)	21 (38.9)	28 (32.2)
TEAEs associated with an outcome of death, n (%)	**2 (6.5)**	**4 (5.7)**	**6 (11.1)**	**9 (10.3)**
Drug related	1 (3.2)	0	1 (1.9)	1 (1.1)

- In the 5.4 mg/kg group, 6 patients (19.4%) with BM and 21 patients (30.0%) without BM were still undergoing treatment at DCO
- In the 6.4 mg/kg group, 6 patients (11.1%) with BM and 19 patients (21.8%) without BM were still undergoing treatment at DCO
- Patients with and without baseline BM exhibited comparable safety outcomes overall; numerically higher occurrences of grade ≥3 and serious TEAEs were reported in patients with BM compared to patients without

BM, brain metastases; DCO, data cutoff; DL, DESTINY-Lung; *HER2*m, human epidermal growth factor receptor 2-mutant; NSCLC, non–small cell lung cancer; T-DXd, trastuzumab deruxtecan; TEAEs, treatment-emergent adverse events.

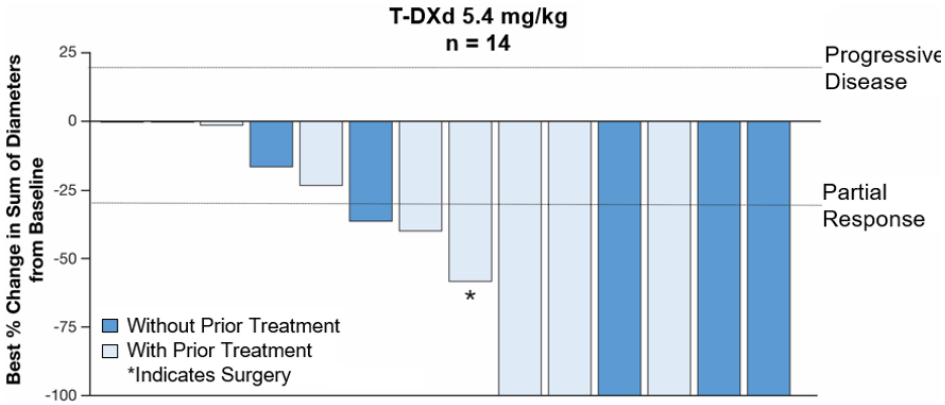
IC Objective Response Rates

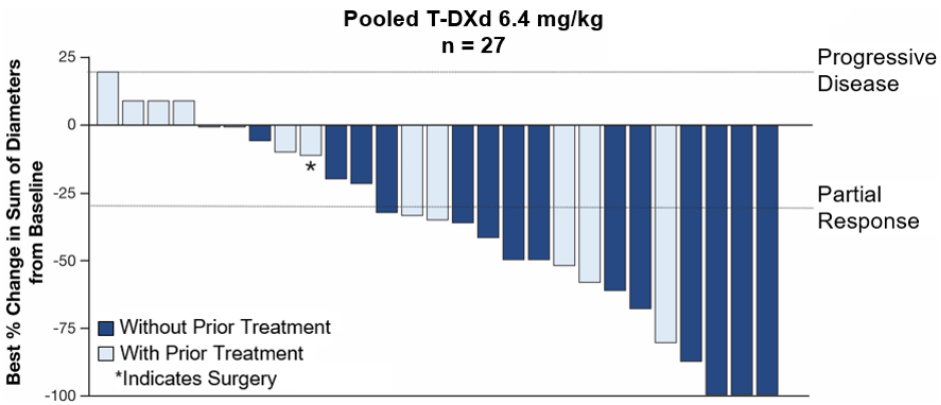
Measurable BM at Baseline

	T-DXd 5.4 mg/kg DL-02 BM n = 14	Pooled T-DXd 6.4 mg/kg DL-01 *HER2m*/DL-02 BM n = 30
IC-cORR, n (%)[a]	**7 (50.0)**	**9 (30.0)**
95% CI[b]	23.0-77.0	14.7-49.4
CR	3 (21.4)	0
PR	4 (28.6)	9 (30.0)
SD	6 (42.9)	13 (43.3)
PD	1 (7.1)	4 (13.3)
NE[c]	0	2 (6.7)
Missing	0	2 (6.7)
IC-DCR, n (%)[a]	**13 (92.9)**	**22 (73.3)**
95% CI[b]	66.1-99.8	54.1-87.7
IC-DoR, months[d]		
Median, (95% CI)[e]	9.5 (3.6-NE)	4.4 (2.9-10.2)

BM, brain metastases; CR, complete response; DCR, disease control rate; DL, DESTINY-Lung; DoR, duration of response; *HER2*m, human epidermal growth factor receptor 2-mutant; IC, intracranial; IC-cORR, intracranial confirmed objective response rate; IC-DCR, intracranial disease control rate; IC-DoR, intracranial duration of response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan. [a]Denominator for percentage is the number of patients in the full analysis set who have at least 1 target lesion at baseline, per BICR. [b]Based on Clopper-Pearson method for single proportion. [c]It was not possible to derive overall response for 1 patient due to missing data of 1 target lesion; the patient's best overall response however was calculated from available target lesion assessments and included the waterfall plot. [d]Calculated as time from first response in brain until progression in brain. [e]Based on Kaplan-Meier analysis and computed with the Brookmeyer-Crowley method.

IC Best Overall Responses





12/14 (86%) patients with measurable BM receiving T-DXd 5.4 mg/kg and 21/27 (78%) in the pooled 6.4 mg/kg group experienced a reduction in brain lesion size from baseline as their best overall response

IC Response With or Without Prior BM Treatment

Measurable BM at Baseline

	T-DXd 5.4 mg/kg DL-02 BM		Pooled T-DXd 6.4 mg/kg DL-01 *HER2*m/DL-02 BM	
	Prior treatment n = 8	No prior treatment n = 6	Prior treatment n = 14	No prior treatment n = 16
IC-cORR, n (%)[a]	**4 (50.0)**	**3 (50.0)**	**3 (21.4)**	**6 (37.5)**
95% CI[b]	15.7-84.3	11.8-88.2	4.7-50.8	15.2-64.6
CR	0	3 (50.0)	0	0
PR	4 (50.0)	0	3 (21.4)	6 (37.5)
SD	3 (37.5)	3 (50.0)	7 (50.0)	6 (37.5)
PD	1 (12.5)	0	3 (21.4)	1 (6.3)
NE	0	0	0	2 (12.5)
Missing	0	0	1 (7.1)	1 (6.3)
IC-DCR, n (%)[a]	**7 (87.5)**	**6 (100.0)**	**10 (71.4)**	**12 (75.0)**
95% CI[b]	47.3-99.7	54.1-100.0	41.9-91.6	47.6-92.7
IC-DoR, median, months[c]	**7.1**	**9.5**	**4.4**	**5.6**
95% CI[d]	3.6-NE	NE-NE	2.9-NE	2.9-NE
Time to IC progression, median, months	**2.8**	**NE**	**2.6**	**5.6**
Range	1.3-10.9	NE-NE	1.2-6.9	0.6-14.0

IC responses were similar in patients with or without prior BM treatment

BM, brain metastases; CR, complete response; DL, DESTINY-Lung; *HER2*m, human epidermal growth factor receptor 2-mutant; IC, intracranial; IC-cORR, intracranial confirmed overall response rate; IC-DCR, intracranial disease control rate; IC-DoR, intracranial duration of response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan. [a]Denominator for percentage is the number of patients in the full analysis set who have at least 1 target lesion at baseline, per BICR. [b]Based on Clopper-Pearson method for single proportion. [c]Calculated as time from first response in brain until progression in brain. [d]Based on Kaplan-Meier analysis and computed with the Brookmeyer-Crowley method.

Conclusions

- Systemic responses to T-DXd were similar in patients with and without BM at baseline
- T-DXd monotherapy demonstrated IC efficacy in exploratory analyses
  - BM size reduction in >75% of patients at each dose level (per best overall response in measurable BM)
  - IC-cORRs of 50% (5.4 mg/kg) and 30% (6.4 mg/kg), including CRs in some patients
  - Median IC-DoRs of 9.5 months (5.4 mg/kg) and 4.4 months (6.4 mg/kg)
- T-DXd IC efficacy was similar in treated and untreated BM among patients with BM at baseline
- Patients with and without BM showed similar safety outcomes overall
  - Patients with BM had higher rates of grade ≥3 and serious TEAEs than those without BM
- Limitations of this post hoc analysis include the small number of patients and the lack of a comparator arm

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