T-DXd in HER2+ advanced/metastatic breast cancer patients with/without brain metastases: results from DESTINY-Breast12

脳転移を伴う又は伴わない治療歴のあるHER2陽性の進行/転移性乳癌患者を対象とする
トラスツズマブ デルクステカンの試験結果 (DESTINY-Breast12)

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On behalf of the DESTINY-Breast12 investigators

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Conflict of Interest disclosure slide for representative speakers or investigators

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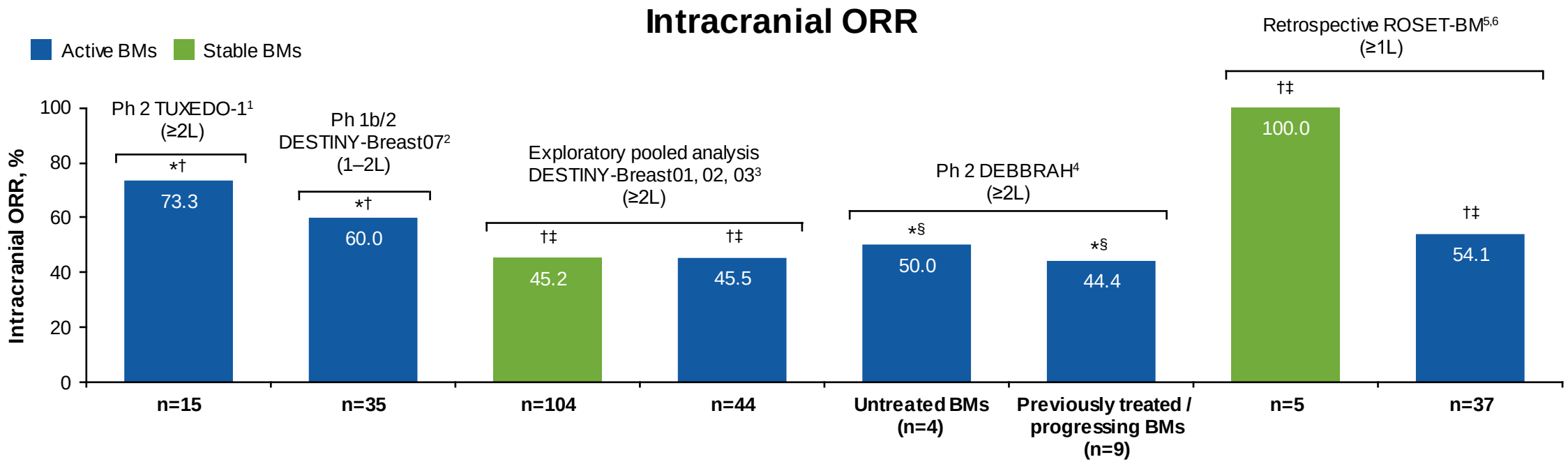
Current evidence base for T-DXd benefit in patients with HER2+ mBC and BMs

Promising preliminary evidence of T-DXd intracranial activity in HER2+ mBC has been observed in small prospective patient cohorts, retrospective studies, and exploratory analyses:[1–6]



Active BMs include patients with untreated and previously treated / progressing BMs, unless otherwise stated
*Per RANO-BM; †per independent central review; ‡per RECIST 1.1; §per investigator
1L, first line; 2L, second line; BM, brain metastasis; HER2+, human epidermal growth factor receptor 2–positive; mBC, metastatic breast cancer; ORR, objective response rate; Ph, Phase; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; T-DXd, trastuzumab deruxtecan

1. Bartsch R, et al. *Nat Med*. 2022;28:1840–1847; 2. Anders C, et al. Poster presented at ESMO Breast Cancer 2024 (Abstract FPN 185P); 3. Hurvitz SA, et al. Oral presentation at ESMO 2023 (Abstract 377O); 4. Pérez-García JM, et al. *Neuro Oncol*. 2023;25:157–166; 5. Niikura N, et al. *NPJ Breast Cancer*. 2023;9:82; 6. Niikura N, et al. *NPJ Breast Cancer*. 2023;9:82 (Supplementary Appendix)

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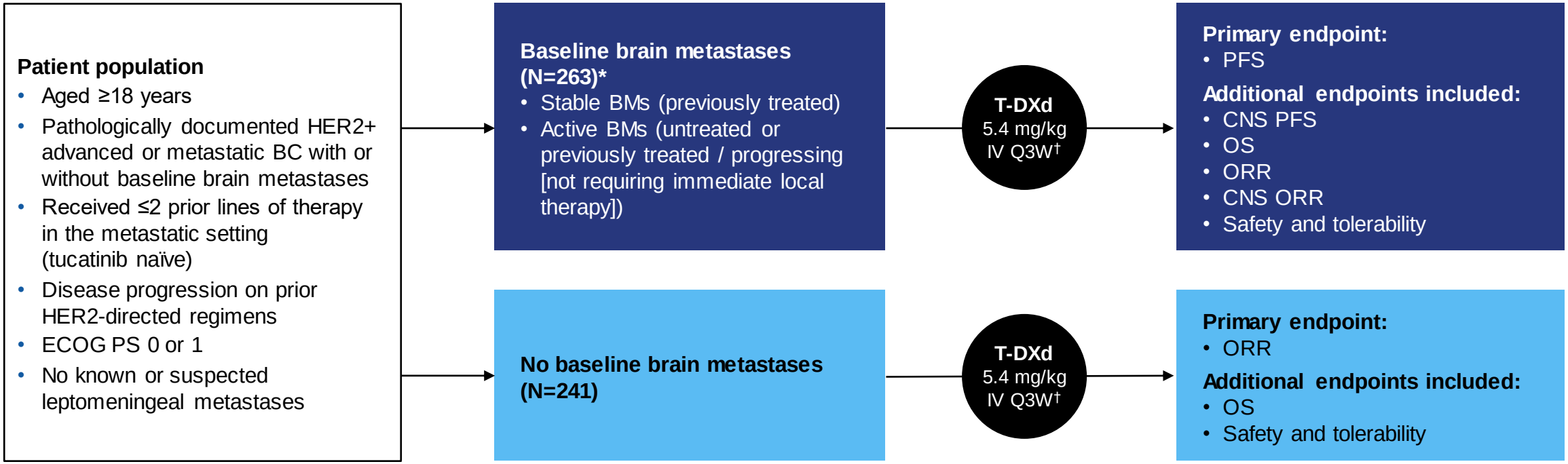
DESTINY-Breast12 study design

Phase 3b/4, multicenter, single-arm, two-cohort, open-label study of T-DXd in previously treated HER2+ mBC with and without brain metastases (BMs); the largest prospective study of T-DXd in patients with stable or active BMs



Data reported for the full analysis set (all patients enrolled in the study who received at least one treatment dose) and safety analysis set (identical to full analysis set). No hypothesis testing or comparison of cohorts. Response and progression assessed by ICR per RECIST 1.1 in both cohorts. Patients were enrolled from Australia, Canada, Europe, Japan, and United States

***Concomitant use of ≤3 mg of dexamethasone daily or equivalent allowed for symptom control of BMs (baseline BMs cohort only)**; †until RECIST 1.1-defined disease progression outside the CNS

BC, breast cancer; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HER2+, HER2-positive; ICR, independent central review; IV, intravenous; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; T-DXd, trastuzumab deruxtecan

NCT04739761. Updated. July 19, 2024. Available from: https://www.clinicaltrials.gov/study/NCT04739761 (Accessed September 9, 2024)

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Patient disposition

Baseline BMs (N=263)

Stable BMs (n=157)*

Discontinued T-DXd (55.1%)

- PD (30.8%)
- AE (11.8%)
- Patient decision (3.4%)
- Death (2.7%)
- Consent withdrawal (2.7%)
- Subjective disease progression (2.3%)
- COVID-19 pandemic (1.1%)
- Investigator decision (0.4%)
- Patient lost to follow up (0.4%)
- Other (0.8%)

Median follow-up duration: **15.4 months (range, 0.1–30.0)**
Patients on T-DXd at DCO: **118 (44.9%)**

Active BMs (n=106)

Untreated (n=39)†

Previously treated / progressing (n=67)‡

No baseline BMs (N=241)

Discontinued T-DXd (60.6%)

- PD (35.7%)
- AE (7.5%)
- Patient decision (6.2%)
- Investigator decision (2.9%)
- Subjective disease progression (2.9%)
- Death (1.2%)
- Consent withdrawal (1.2%)
- Patient lost to follow up (0.8%)
- Severe non-compliance to protocol (0.4%)
- COVID-19 pandemic (0.4%)
- Other (1.7%)

Median follow-up duration: **16.1 months (range, 0.8–28.4)**
Patients on T-DXd at DCO: **95 (39.4%)**

Final DCO: Feb 8, 2024. Patients may have more than one reason for discontinuation
*Stable BMs: radiographically stable for ≥4 weeks since completion of treatment; †untreated BMs with lesions ≤2.0 cm; ‡previously treated BMs that had progressed since local CNS therapy, with no clinical indication for immediate retreatment with local therapy
AE, adverse event; BM, brain metastasis; CNS, central nervous system; DCO, data cutoff; PD, progressive disease; T-DXd, trastuzumab deruxtecan

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Demographics and baseline characteristics

	Baseline BMs (N=263)	No baseline BMs (N=241)
Age, median (range), years	52 (28–86)	54 (24–87)
Female, n (%)	263 (100.0)	241 (100.0)
ECOG PS at baseline, n (%)		
0	163 (62.0)	194 (80.5)
1	100 (38.0)	47 (19.5)
HER2 status, n (%)		
2+	2 (0.8)	5 (2.1)
3+	187 (71.1)	141 (58.5)
Positive*	74 (28.1)	95 (39.4)
HR status, n (%)		
Positive†	165 (62.7)	150 (62.2)
Liver metastases, n (%)	58 (22.1)	66 (27.4)
Lung metastases, n (%)	67 (25.5)	67 (27.8)
Measurable disease, n (%)	198 (75.3)	215 (89.2)

	Baseline BMs (N=263)	No baseline BMs (N=241)
Prior regimens of anticancer therapies for metastatic disease		
Number of regimens, median (range)	1.0 (0–4)	1.0 (0–4)
Number of regimens, n (%)		
0	20 (7.6)	18 (7.5)
1	132 (50.2)	124 (51.5)
2	109 (41.4)	96 (39.8)
≥3	2 (0.8)	3 (1.2)
Prior HER2 inhibitor agents, n (%)	262 (99.6)	240 (99.6)
Trastuzumab	258 (98.1)	233 (96.7)
Pertuzumab	228 (86.7)	207 (85.9)
T-DM1	106 (40.3)	94 (39.0)
Tucatinib‡	2 (0.8)	0
Other TKIs§	15 (5.7)	15 (6.2)
T-DXd	1 (0.4)	0
Specific agent not reported	1 (0.4)	0
Prior therapies for BMs, n (%)		
Intracranial radiotherapy¶	158 (60.1)	–
Whole brain radiation therapy	40 (15.2)	–
Stereotactic radiosurgery	15 (5.7)	–
Time from last intracranial radiotherapy to treatment initiation, median (range), days	164 (9–2115)	–

*Specific HER2 status unknown; †HR status positive if either or both of ER/PR status had a positive result; ‡the two patients with prior tucatinib use were recorded as protocol deviations; §lapatinib and neratinib; ¶the type of intracranial radiotherapy was not always recorded by investigators, and only whole brain radiation therapy and stereotactic radiosurgery were reported
BM, brain metastasis; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; PR, progesterone receptor; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor

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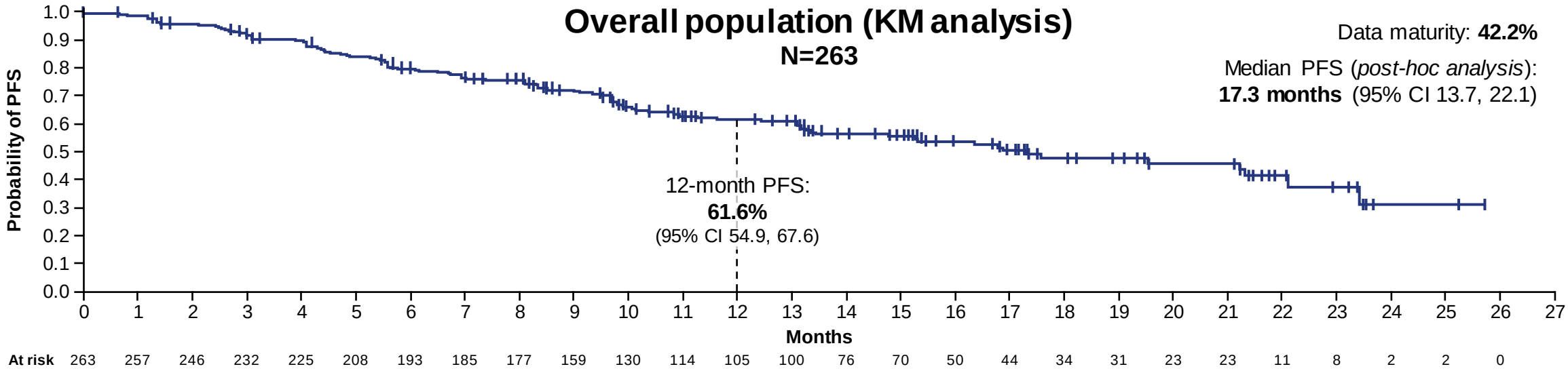
Baseline BMs: PFS (primary endpoint)



	Overall population (N=263)	Stable BMs (n=157)	Active BMs (n=106)	Active BM subgroups: Untreated (n=39) *Post-hoc analysis*	Active BM subgroups: Previously treated / progressing (n=67) *Post-hoc analysis*
Overall no. events	**111**	64	47	20	27
12-month PFS, % (95% CI)	**61.6 (54.9, 67.6)**	62.9 (54.0, 70.5)	59.6 (49.0, 68.7)	47.0 (29.6, 62.7)	66.7 (53.4, 76.9)

T-DXd showed consistent 12-month PFS in patients with stable and active BMs

PFS assessed by ICR per RECIST 1.1
BM, brain metastasis; CI, confidence interval; ICR, independent central review; KM, Kaplan-Meier; no., number of; PFS, progression-free survival; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; T-DXd, trastuzumab deruxtecan

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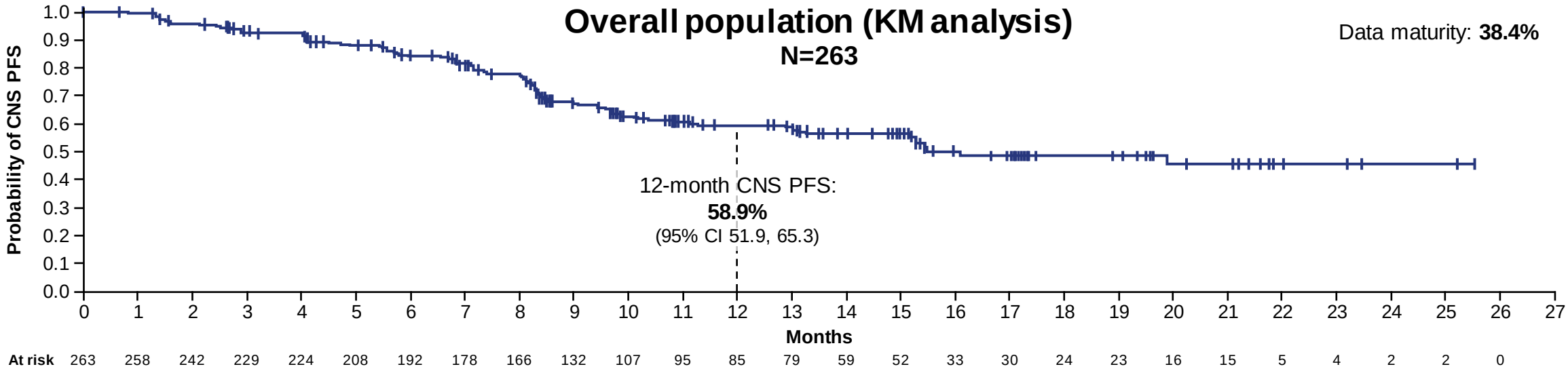
Baseline BMs: CNS PFS



	Overall population (N=263)	Stable BMs (n=157)	Active BMs (n=106)
Overall no. events	**101**	61	40
12-month CNS PFS, % (95% CI)	**58.9 (51.9, 65.3)**	57.8 (48.2, 66.1)	60.1 (49.2, 69.4)

T-DXd showed consistent 12-month CNS PFS in patients with stable and active BMs

Patients who had systemic progression, but no CNS progression, were censored at the time of the progression assessment; the analysis did not account for systemic progression as a competing event. CNS PFS assessed by ICR per RECIST 1.1

BM, brain metastasis; CI, confidence interval; CNS, central nervous system; ICR, independent central review; KM, Kaplan-Meier; no., number of; PFS, progression-free survival; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; T-DXd, trastuzumab deruxtecan

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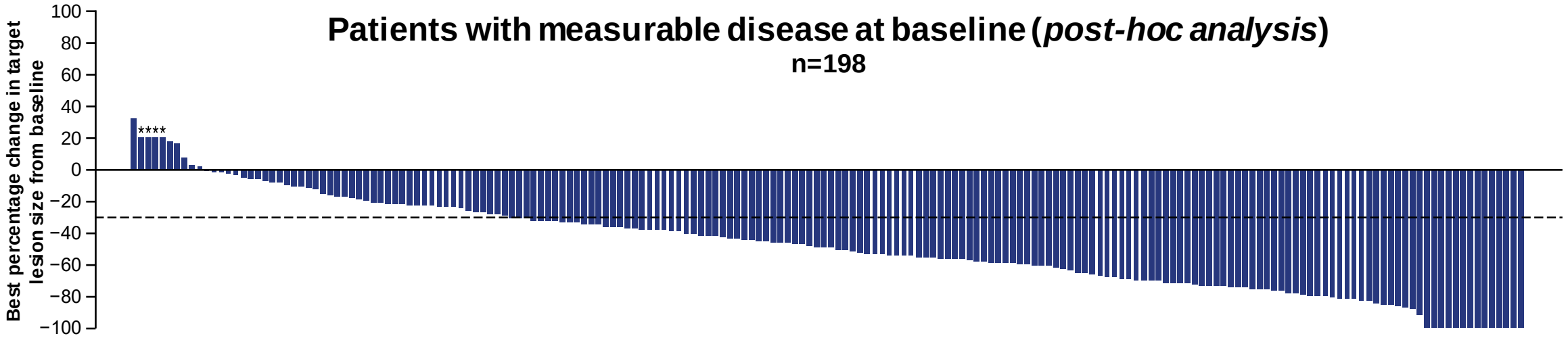
Baseline BMs: ORR



	Full analysis set†			Measurable disease at baseline (*post-hoc analysis*)		
	Overall population (N=263)	Stable BMs (n=157)	Active BMs (n=106)	All patients (n=198)	Stable BMs (n=109)	Active BMs (n=89)
Confirmed ORR, % (95% CI)	**51.7 (45.7, 57.8)**	49.7 (41.9, 57.5)	54.7 (45.2, 64.2)	**64.1 (57.5, 70.8)**	67.0 (58.1, 75.8)	60.7 (50.5, 70.8)
CR, n (%)	11 (4.2)	–	–	2 (1.0)	–	–
PR, n (%)	125 (47.5)	–	–	125 (63.1)	–	–

T-DXd showed substantial responses in the overall BMs population, including patients with stable and active BMs

Median duration of response in the overall population was not calculated. Dashed line indicates a 30% decrease in target tumor size (PR). Response obtained by assessing target lesions, non-target lesions, and new lesions (extracranial and CNS)

*Imputed values: a value of +20% was imputed if best percentage change could not be calculated because of missing data if: a patient had a new lesion or progression of non-target lesions or target lesions, or had withdrawn because of PD and had no evaluable target lesion data before or at PD; †includes 65 patients with no measurable disease at baseline

BM, brain metastasis; CI, confidence interval; CNS, central nervous system; CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; T-DXd, trastuzumab deruxtecan

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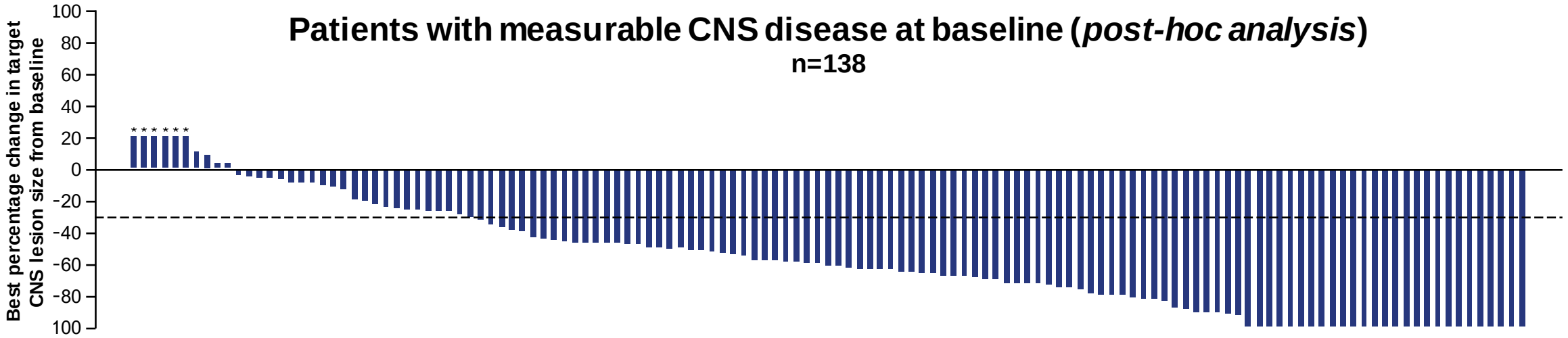
Baseline BMs: CNS ORR



Measurable CNS disease at baseline	All patients (n=138)	Stable BMs (n=77)	Active BMs (n=61)	Active BM subgroups: Untreated (n=23) *Post-hoc analysis*	Active BM subgroups: Previously treated / progressing (n=38) *Post-hoc analysis*
Confirmed CNS ORR, % (95% CI)	**71.7 (64.2, 79.3)**	79.2 (70.2, 88.3)	62.3 (50.1, 74.5)	82.6 (67.1, 98.1)	50.0 (34.1, 65.9)

T-DXd showed substantial CNS responses in the overall BMs population, including patients with stable and active BMs

Dashed line indicates a 30% decrease in target tumor size (PR)
*Imputed values: a value of +20% was imputed if best percentage change could not be calculated because of missing data if: a patient had a new lesion or progression of non-target lesions or target lesions, or had withdrawn because of PD and had no evaluable target lesion data before or at PD
BM, brain metastasis; CI, confidence interval; CNS, central nervous system; ORR, objective response rate; PD, progressive disease; PR, partial response; T-DXd, trastuzumab deruxtecan

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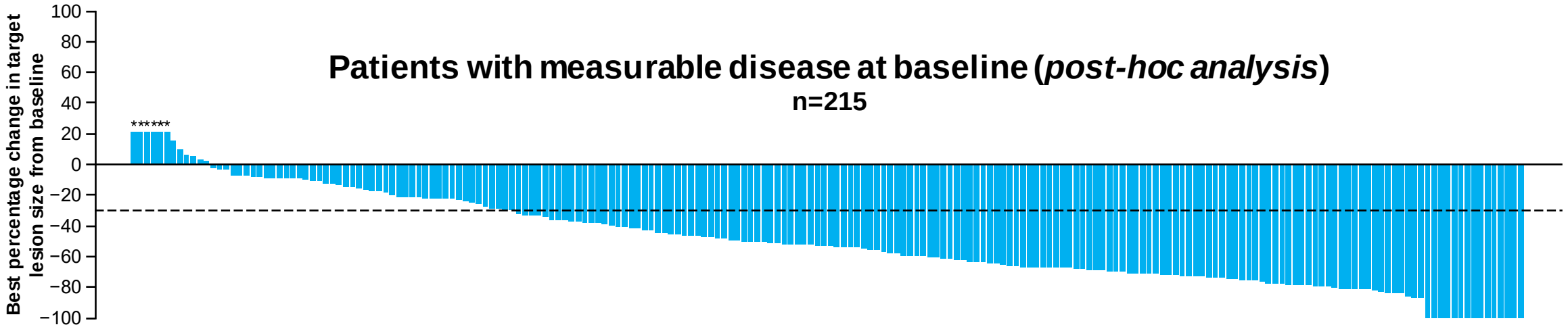
No baseline BMs: ORR (primary endpoint)

ORR is in line with previous Phase 3 T-DXd trials in this setting[1,2]



	Full analysis set Overall population (N=241)†	Measurable disease at baseline (n=215) *Post-hoc analysis*
Confirmed ORR, % (95% CI)	**62.7 (56.5, 68.8)**	**68.4 (62.2, 74.6)**
CR, n (%)	23 (9.5)	20 (9.3)
PR, n (%)	128 (53.1)‡	127 (59.1)

Median duration of response in the overall population was not calculated. Dashed line indicates a 30% decrease in target tumor size (PR)
*Imputed values: a value of +20% was imputed if best percentage change could not be calculated because of missing data if: a patient had a new lesion or progression of non-target lesions or target lesions, or had withdrawn because of PD and had no evaluable target lesion data before or at PD; †includes 26 patients with no measurable disease at baseline; ‡one patient with no measurable disease at baseline was assigned PR by ICR
BM, brain metastasis; CI, confidence interval; CR, complete response; ICR, independent central review; ORR, objective response rate; PD, progressive disease; PR, partial response; T-DXd, trastuzumab deruxtecan
1. André F, et al. *Lancet.* 2023;401:1773–1785; 2. Cortés J, et al. *N Engl J Med.* 2022;386:1143–1154

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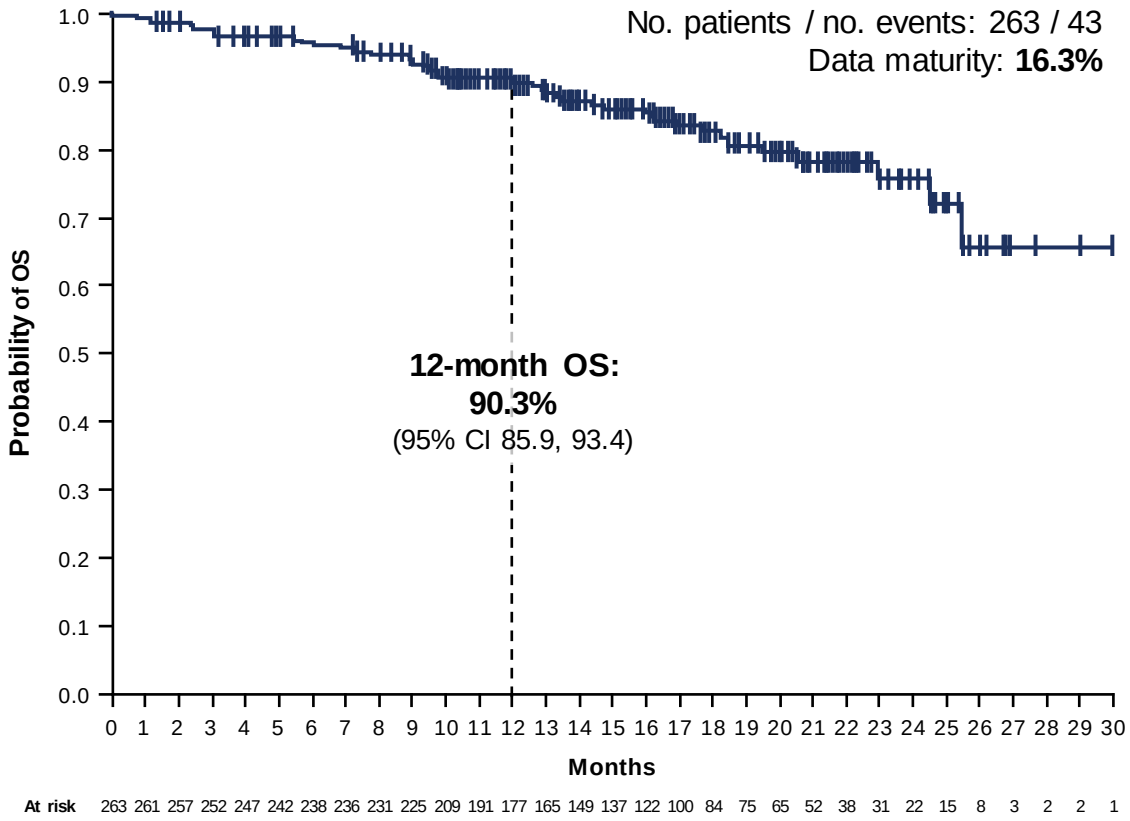
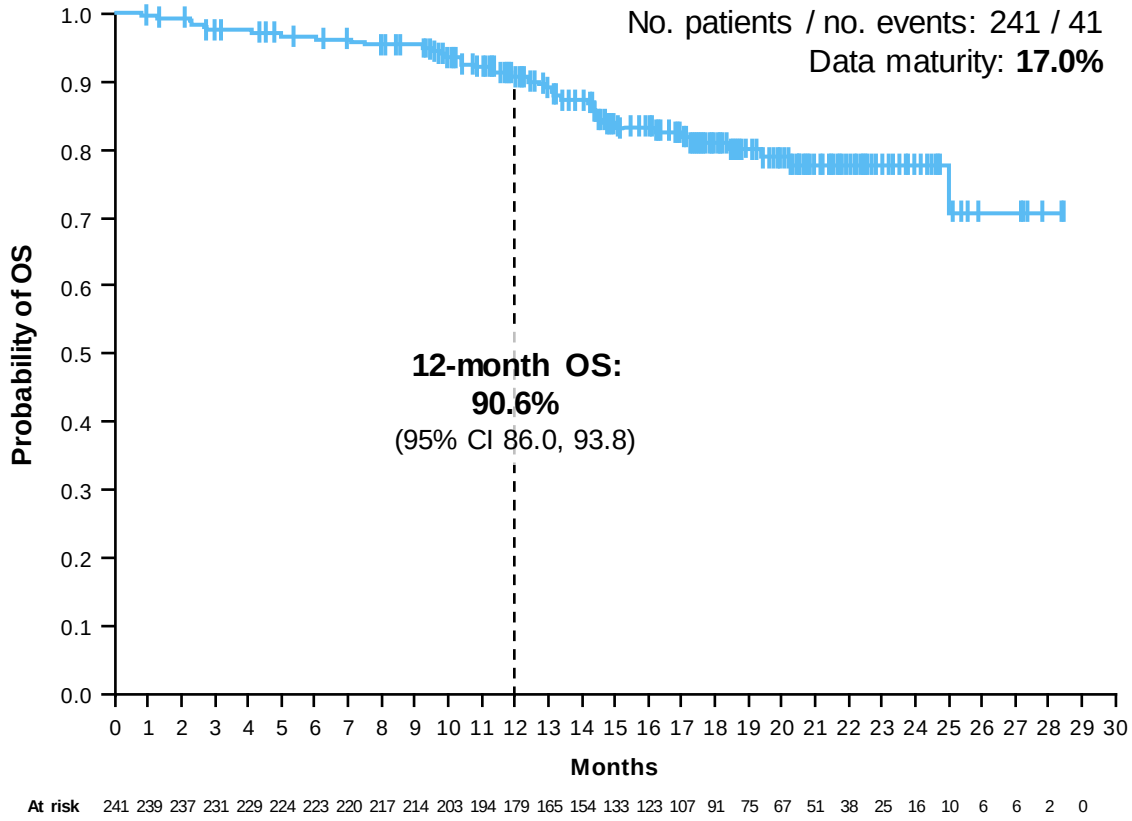
OS in patients with and without baseline BMs

Baseline BMs (KM analysis)



No baseline BMs (KM analysis)



T-DXd showed consistent 12-month OS in patients with and without BMs

Median follow-up duration was 15.4 months in patients with BMs and 16.1 months in patients without BMs
BM, brain metastasis; CI, confidence interval; KM, Kaplan-Meier; no., number of; OS, overall survival; T-DXd, trastuzumab deruxtecan

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Overall safety summary

	Baseline BMs (N=263)	No baseline BMs (N=241)
Median treatment duration, months (range)	11.5 (0.1–26.9)	12.0 (0.7–28.4)
Any AE, n (%)	259 (98.5)	237 (98.3)
Possibly related to treatment*	242 (92.0)	230 (95.4)
Grade ≥3 AE, n (%)	134 (51.0)	118 (49.0)
Possibly related to treatment*	100 (38.0)	98 (40.7)
Serious AEs, n (%)	62 (23.6)	46 (19.1)
Possibly related to treatment*	25 (9.5)	25 (10.4)
AEs leading to discontinuation, n (%)	40 (15.2)	23 (9.5)
AEs leading to dose interruptions, n (%)	146 (55.5)	124 (51.5)
AEs leading to dose reductions, n (%)	60 (22.8)	65 (27.0)
AEs leading to death, n (%)	8 (3.0)	6 (2.5)
Possibly related to treatment*	6 (2.3)†	5 (2.1)‡

*As assessed by the investigator; †ILD/pneumonitis (n=6); ‡IILD/pneumonitis (n=3), bronchopulmonary aspergillosis not associated with ILD/pneumonitis (n=1), and general disorders and administration site conditions (n=1)
AE, adverse event; BM, brain metastasis; ILD, interstitial lung disease

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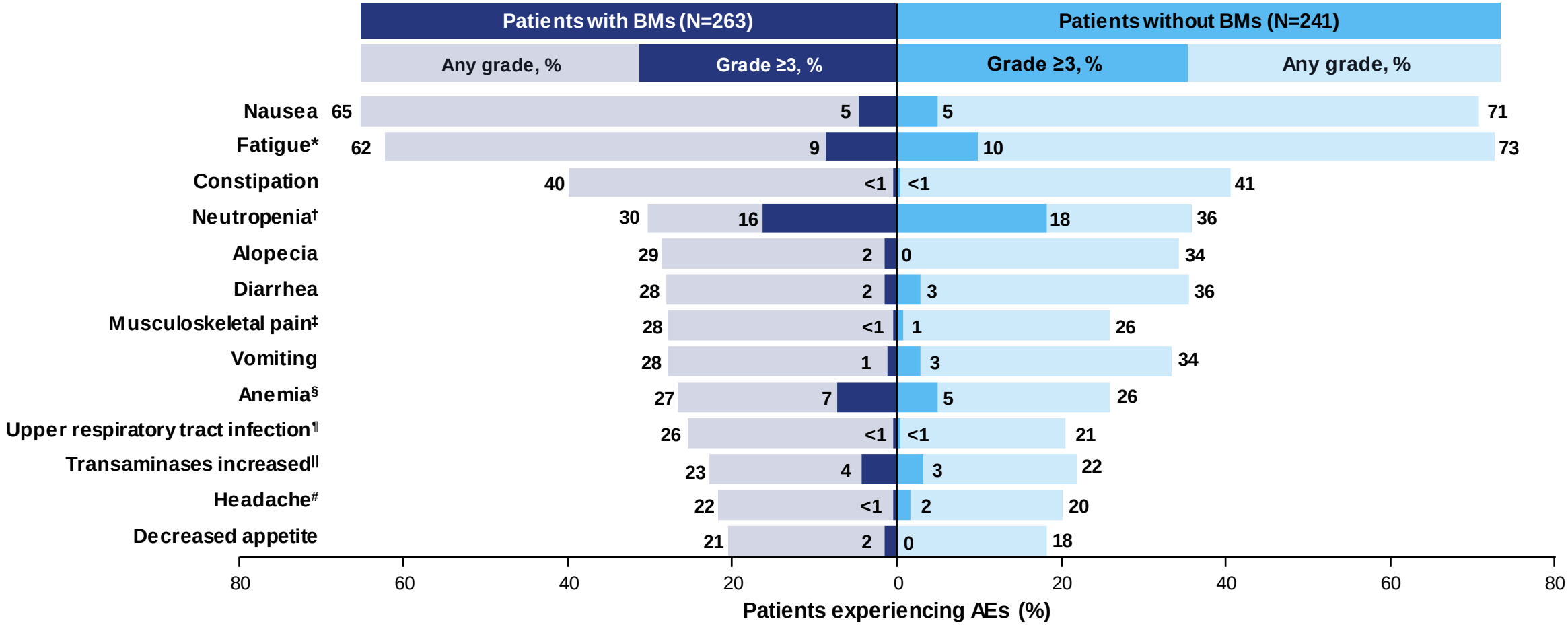
AEs in ≥20% of patients in either cohort



Grade 3 alopecia was an investigator input error

*Includes the preferred terms 'asthenia', 'fatigue', 'lethargy', and 'malaise'; †includes the preferred terms 'neutropenia' and 'neutrophil count decreased'; ‡includes the preferred terms 'back pain', 'bone pain', 'limb discomfort', 'muscle spasms', 'musculoskeletal chest pain', 'musculoskeletal pain', 'myalgia', 'neck pain', and 'pain in extremity'; §includes the preferred term 'anemia', 'hemoglobin decreased', and 'red blood cell count decreased'; ¶includes the preferred terms 'influenza', 'influenza-like illness', 'laryngitis', 'nasopharyngitis', 'pharyngitis', 'rhinitis', 'sinusitis', and 'upper respiratory tract infection'; ‖includes the preferred terms 'alanine aminotransferase increased', 'aspartate aminotransferase increased', 'gamma-glutamyltransferase increased', 'hypertransaminasemia', 'liver function test abnormal', and 'transaminases increased'; #includes the preferred terms 'headache', 'migraine', and 'sinus headache'

AE, adverse event; BM, brain metastasis

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AEs of special interest

Investigator-reported ILD/pneumonitis*

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
Patients with BMs (N=263)	26 (9.9)	8 (3.0)	1 (0.4)	1 (0.4)	6 (2.3)	42 (16.0)
Reported as co-occurring with opportunistic infection†	0	0	0	1 (0.4)	4 (1.5)	5 (1.9)‡
Patients without BMs (N=241)	22 (9.1)	6 (2.5)	0	0	3 (1.2)	31 (12.9)
Reported as co-occurring with opportunistic infection†	0	0	0	0	0	0

LVEF decrease from baseline§

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
Patients with BMs (N=263)	0	29 (11.0)	2 (0.8)	0	0	31 (11.8)
Patients without BMs (N=241)	4 (1.7)	22 (9.1)	0	0	0	26 (10.8)

Median time to first onset of ILD/pneumonitis for patients was 168.0 days (range 35–646) in patients with BMs (n=42) and 169.0 days (range 24–484) in patients without BMs (n=31)
*Grouped term; includes the preferred terms 'ILD', 'lung infiltration', 'pneumonitis', and 'pulmonary fibrosis' (patients with BMs) and 'ILD', 'lung opacity', 'pneumonitis', 'pulmonary fibrosis', and 'radiation pneumonitis' (patients without BMs). There was no adjudication in the study; †no systematic testing for infection during the study; ‡*Aspergillus*: n=1 (Grade 5 ILD/pneumonitis), PJ infection: n=1 (Grade 4 ILD/pneumonitis), PJ pneumonia: n=3 (Grade 5 ILD/pneumonitis); §includes the preferred terms 'ejection fraction decreased', 'ischemic contracture of the left ventricle', and 'left ventricular dysfunction' (patients with BMs) and 'cardiac failure chronic', 'ejection fraction decreased', and 'troponin T increased' (patients without BMs)
AE, adverse event; BM, brain metastasis; ILD, interstitial lung disease; LVEF, left ventricular ejection fraction; PJ, *Pneumocystis jirovecii*

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Conclusions

- In this prospective Phase 3b/4 study, T-DXd exhibited substantial and durable overall and intracranial clinical activity in a large patient cohort with HER2+ mBC with stable and active BMs
  - PFS at 12 months was **61.6%** overall (stable BMs: **62.9%**; active BMs: **59.6%**); estimated median PFS **17.3 months***
  - CNS ORR was **71.7%** overall (stable BMs: **79.2%**; active BMs: **62.3%**)
- T-DXd activity in patients without baseline BMs was consistent with previous reports
  - ORR was **62.7%**
- 12-month OS was maintained in patients with BMs (**90.3%**) and without BMs (**90.6%**)
- The safety profile of T-DXd was consistent with previous reports; no new safety signals were identified
  - ILD/pneumonitis remains an important identified safety risk of T-DXd

Results from DESTINY-Breast12 support the use of T-DXd for patients with HER2+ mBC, irrespective of the presence of stable or active BMs

**Post-hoc analysis*
BM, brain metastasis; CNS, central nervous system; HER2+, human epidermal growth factor receptor 2–positive; ILD, interstitial lung disease; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan

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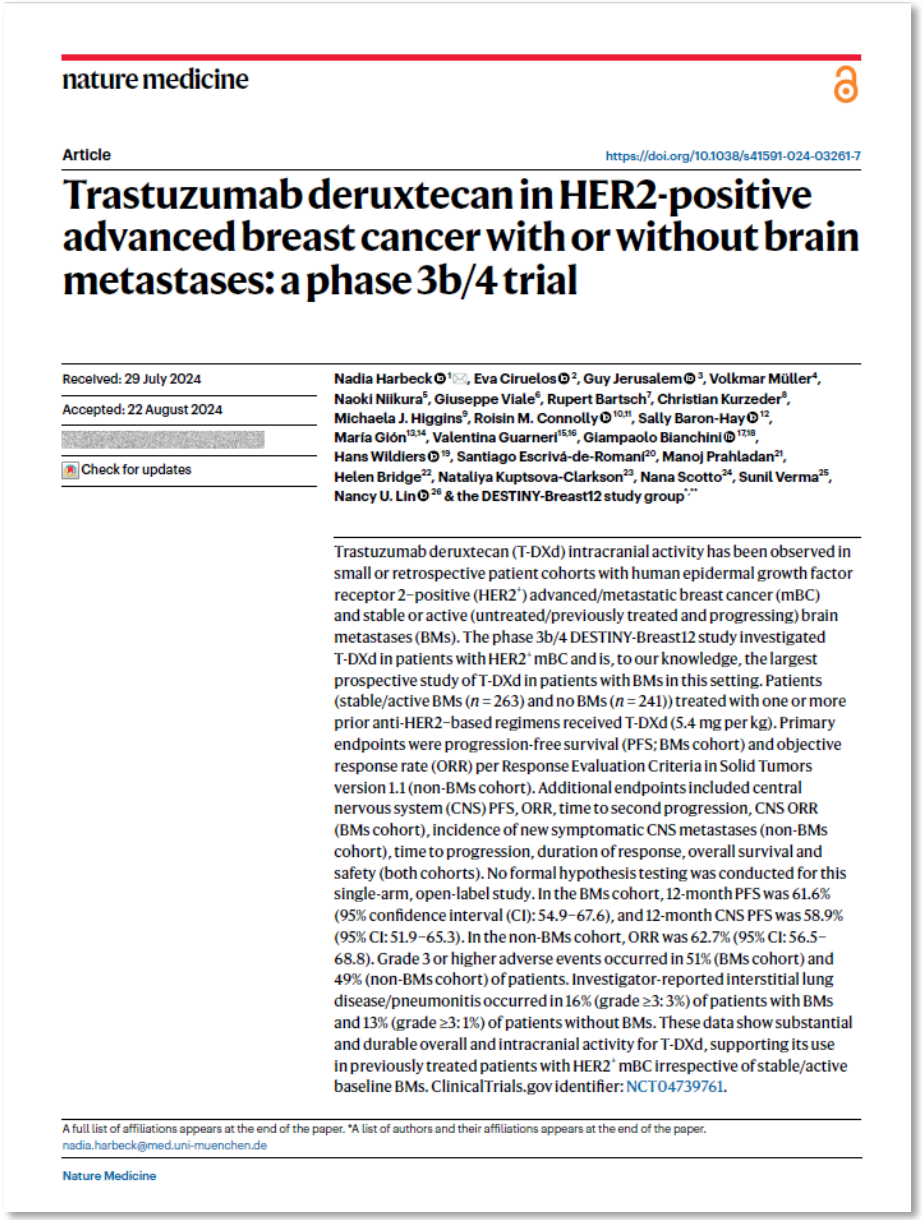

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Trastuzumab deruxtecan in HER2-positive advanced breast cancer with or without brain metastases: a phase 3b/4 trial

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Trastuzumab deruxtecan (T-DXd) intracranial activity has been observed in small or retrospective patient cohorts with human epidermal growth factor receptor 2–positive (HER2$^+$) advanced/metastatic breast cancer (mBC) and stable or active (untreated/previously treated and progressing) brain metastases (BMs). The phase 3b/4 DESTINY-Breast12 study investigated T-DXd in patients with HER2$^+$ mBC and is, to our knowledge, the largest prospective study of T-DXd in patients with BMs in this setting. Patients (stable/active BMs (n = 263) and no BMs (n = 241)) treated with one or more prior anti-HER2–based regimens received T-DXd (5.4 mg per kg). Primary endpoints were progression-free survival (PFS; BMs cohort) and objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors version 1.1 (non-BMs cohort). Additional endpoints included central nervous system (CNS) PFS, ORR, time to second progression, CNS ORR (BMs cohort), incidence of new symptomatic CNS metastases (non-BMs cohort), time to progression, duration of response, overall survival and safety (both cohorts). No formal hypothesis testing was conducted for this single-arm, open-label study. In the BMs cohort, 12-month PFS was 61.6% (95% confidence interval (CI): 54.9–67.6), and 12-month CNS PFS was 58.9% (95% CI: 51.9–65.3). In the non-BMs cohort, ORR was 62.7% (95% CI: 56.5–68.8). Grade 3 or higher adverse events occurred in 51% (BMs cohort) and 49% (non-BMs cohort) of patients. Investigator-reported interstitial lung disease/pneumonitis occurred in 16% (grade ≥3: 3%) of patients with BMs and 13% (grade ≥3: 1%) of patients without BMs. These data show substantial and durable overall and intracranial activity for T-DXd, supporting its use in previously treated patients with HER2$^+$ mBC irrespective of stable/active baseline BMs. ClinicalTrials.gov identifier: NCT04739761.

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