A DESTINY-Breast09 analysis of trastuzumab deruxtecan (T-DXd) + pertuzumab (P) vs taxane + trastuzumab + pertuzumab (THP) for patients with HER2+ advanced/metastatic breast cancer (a/mBC) and baseline (BL) brain metastases (BMs)

Cristina Saura,[1] Sibylle Loibl,[2] ZeFei Jiang,[3] Romualdo Barroso-Sousa,[4] Yeon Hee Park,[5] Mothaffar F Rimawi,[6] Andreas Schneeweiss,[7] Masakazu Toi,[8] Keun Seok Lee,[9] Yongkui Lu,[10] Mehmet AN Sendur,[11] Toshimi Takono,[12] Quchung Ouyang,[13] Annie Darilay,[14] Jagdish Shetty,[14] Angela Zeng,[14] Sara M Tolaney[15]

[1]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [2]Johann Wolfgang Goethe-Universität and German Breast Group, Frankfurt am Main, Germany; [3]Department of Breast Oncology, Fifth Medical Center of PLA General Hospital, Beijing, China; [4]Hospital Brasilía, Rede Américas, Brasilía, DF, Brazil; [5]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [6]Baylor College of Medicine, Houston, TX, USA; [7]National Center for Tumor Diseases, University Hospital and German Cancer Research Center, Heidelberg, Germany; [8]Tokyo Metropolitan Cancer and Infectious Disease Center, Komagome Hospital, Tokyo, Japan; [9]National Cancer Center Korea, Goyang-si, Republic of Korea; [10]The Affiliated Cancer Hospital, Guangxi Medical University, Nanning, China; [11]Ankara Yıldırım Beyazıt University, Ankara, Turkey; [12]Department of Breast Medical Oncology, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan; [13]Hunan Cancer Hospital, Xiangya School of Medicine, Central South University, Changsha, China; [14]Late-Stage Development, Oncology R&D, AstraZeneca, Gaithersburg, MD, USA; [15]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

October 26, 2026
Presentation LBA49

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

Declaration of interests

Cristina Saura, MD, PhD

I have the following relevant financial relationships to disclose:

Institutional support

- Amgen, AstraZeneca, Bayer Pharma, BeiGene, Boehringer Ingelheim, Bristol-Myers Squibb, Byondis B.V., Cooperative breast cancer group SOLTI, Cytomx Therapeutics, Daiichi Sankyo, Debiopharm International S.A., Eli Lilly, F. Hoffmann–La Roche Ltd, GlaxoSmithKline, Immunomedics, Innoup Farma, Janssen-Cilag S.A., Macrogenics, Menarini, Merck, Merus, Mirati, Novartis, Pfizer, Pharma Mar, Puma, Roche, Sanofi, Seattle Genetics, Servier, Spanish Association Against Cancer Scientific Foundation and Cancer Research UK, and Taiho Pharma USA Inc.

Advisory/speaker/committee roles

- AstraZeneca, Aventik Medical S.L.U., Boehringer Ingelheim, Bristol Myers Squibb, Byondis B.V., Daiichi Sankyo, Eisai, Exact Sciences, Exeter Pharma, F. Hoffmann–La Roche Ltd, Genentech, Gilead, GlaxoSmithKline, Innoup, Eli Lilly, Macrogenics, Menarini, Merck, Merus, Millennium, Novartis, PeerVoice PSL Group, Pfizer, Pharmalex Spain SLU, Philips, Pierre Fabre, PintPharma, Puma, Reveal Genomics S.L., Roche, Sanofi, SeaGen, Synthon Biopharmaceuticals, and Zymeworks.

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

Background

- Brain metastases (BMs) are a significant cause of morbidity and mortality in HER2+ a/mBC, affecting 30–50% of patients over the course of metastatic disease[1,2]
  - Although BMs are managed with local interventions (e.g. surgery, radiotherapy), the use of effective systemic treatments with intracranial activity is critical for the long-term control of BMs[1,2]
- Substantial intracranial activity was observed in patients treated with T-DXd, a HER2-directed antibody-drug conjugate, across different lines of therapy in **DESTINY-Breast12** and pooled analyses of **DESTINY-Breast01/02/03**[3–5]
- T-DXd + P is approved by the US FDA and the EU EMA in 1L HER2+ a/mBC, based on the interim results from **DESTINY-Breast09** (NCT04784715)[6–8]
  - Median PFS with T-DXd + P versus THP: 40.7 versus 26.9 months, respectively (HR, 0.56; p<0.00001), with consistent benefit observed across pre-planned subgroups including patients with BMs at BL[8]

Here, we present the results of an exploratory CNS efficacy analysis from DESTINY-Breast09

1L, first-line; (a/m)BC, (advanced/metastatic) breast cancer; BL, baseline; CNS, central nervous system; EU EMA, EU European Medicines Agency; HER2, human epidermal growth factor receptor 2; HER2+, HER2-positive; HR, hazard ratio; P, pertuzumab; PFS, progression-free survival; SystHERs, Systemic Therapies for HER2-Positive Metastatic Breast Cancer Study; T-DXd, trastuzumab deruxtecan; THP, paclitaxel + trastuzumab + pertuzumab; US FDA, US Food and Drug Administration.

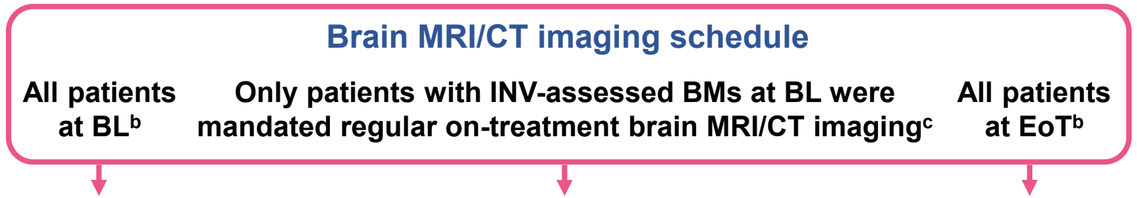
1. Garcia-Alvarez A, et al. *Cancers*. 2021;13:2927. 2. von Arx C, et al. *Front Oncol*. 2024;14:1447508. 3. Harbeck N, et al. *Nat Med*. 2024;30:3717–3727. 4. André F, et al. *Ann Oncol*. 2024;35:1169–1180. 5. Liu J, et al. *Cancer Pathog Ther*. 2026;4:72–74. 6. Enhertu® (fam-trastuzumab deruxtecan-nxki). US FDA 2025 Prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761139s038s042lbl.pdf. Accessed October 2, 2026. 7. "Enhertu plus pertuzumab approved in the EU as first new regimen in more than a decade for the 1st-line treatment of patients with HER2-positive metastatic breast cancer". AstraZeneca press release. https://www.astrazeneca.com/media-centre/press-releases/2026/enhertu-approved-in-eu-for-1l-her2-positive-mbc.html. Accessed October 2, 2026. 8. Tolaney SM, et al. *N Engl J Med*. 2026;394:551–562.

Cristina Saura

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

DESTINY-Breast09 study design

Randomized, multicenter, Phase III trial (NCT04784715)[1]



Patient population

Key eligibility criteria:

- HER2+ a/mBC
- **Asymptomatic/inactive BMs allowed**
- DFI >6 mo from last chemotherapy or HER2-targeted therapy in neoadjuvant/adjuvant setting

Prior lines of therapy:

- One prior line of ET for mBC permitted
- **No other prior systemic treatment for a/mBC[a]**

Stratification factors

- De novo vs recurrent disease
- HR+ or HR−
- *PIK3CA*m (detected vs non-detected)

R[d] 1:1:1

- n=387 → **T-DXd[e] + placebo** (Blinded until final PFS analysis)
- n=383 → **T-DXd[e] + P[f]**
- n=387 → **THP** (Taxane (paclitaxel or docetaxel)[g] + trastuzumab[h] + P[f])

ITT

Primary endpoint

- PFS (BICR per RECIST 1.1)

Key secondary endpoint

- OS

Other secondary endpoints

- PFS (INV)
- ORR (BICR/INV)
- DOR (BICR/INV)
- PFS2 (INV)
- Safety/tolerability

Exploratory efficacy analysis

- **All brain MRI/CT scans were assessed retrospectively for BMs at BL by BICR after EoT**
- **Systemic and CNS responses were assessed by BICR[i]**

[a]HER2-targeted therapy or chemotherapy. [b]Patients without INV-assessed BMs at BL received brain MRI/CT scans at EoT but no regular follow-up brain MRI/CT scans, unless clinically indicated. [c]Concurrently with regular tumor imaging per RECIST 1.1, patients with INV-assessed BMs at BL received additional brain MRI/CT scans: Q6W ±1 week from R up to Week 48, and Q9W ±1 week from Week 48 until PD per RECIST 1.1. Radiographic progression (PD by RECIST 1.1) required collection of a subsequent scan 4 to 6 weeks after the prior assessment of PD, or any additional scans as clinically indicated. [d]Open label for THP arm. Double-blinded for pertuzumab in experimental arms. [e]5.4 mg/kg Q3W. [f]840 mg loading dose, then 420 mg Q3W. [g]Paclitaxel 80 mg/m^2 QW or 175 mg/m^2 Q3W, or docetaxel 75 mg/m^2 Q3W for a minimum of 6 cycles or until intolerable toxicity. [h]8 mg/kg loading dose, then 6 mg/kg Q3W. [i]Modified RECIST 1.1 criteria[2] were adopted for assessment of CNS responses in patients who had radiotherapy prior to enrolling into the trial.

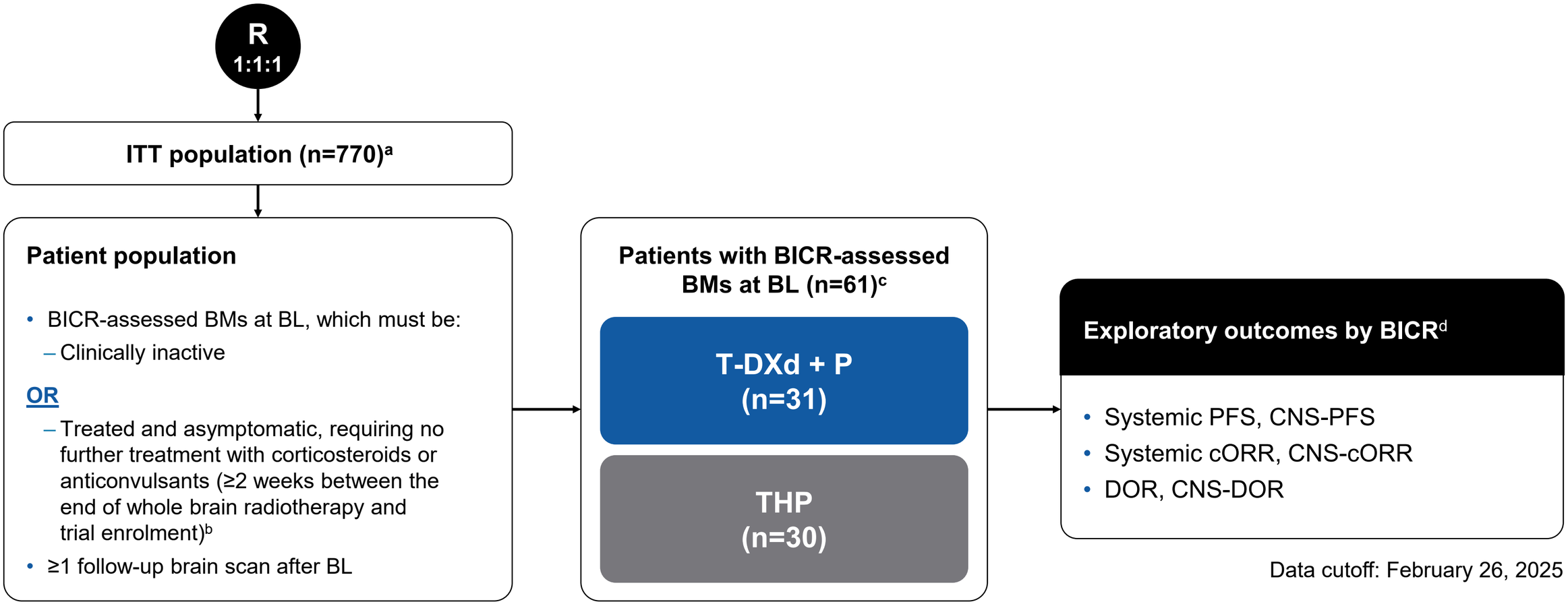
BICR, blinded independent central review; CT, computed tomography; DFI, disease-free interval; DOR, duration of response; EoT, end of treatment; ET, endocrine therapy; INV, investigator; ITT, intention-to-treat; mo, months; MRI, magnetic resonance imaging; OS, overall survival; ORR, objective response rate; PD, progressive disease; PFS2, second progression-free survival; *PIK3CA*m, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha mutation; Q3W, every 3 weeks; Q6W, every 6 weeks; Q9W, every 9 weeks; QW, once every week; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors.

1. Tolaney SM, et al. *N Engl J Med.* 2026;394:551–562. 2. Eisenhauer EA, et al. *Eur J Cancer.* 2009;45:228–247.

Cristina Saura

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

Exploratory efficacy analysis



[a]T-DXd + P and THP arms only; the T-DXd + placebo arm will remain blinded until the final PFS analysis. [b]Patients with treated, no longer symptomatic BMs could be included in the study if patients had recovered from the acute toxic effect of radiotherapy. [c]A total of 47 patients (T-DXd + P, n=25; THP, n=22) had INV-assessed BMs at BL before retrospective BICR assessment at EoT. Retrospective BICR assessment confirmed a total of 61 patients with BMs at BL: 32 patients had BMs at BL as assessed both by BICR and INV (16 in each arm), while 29 patients had BMs at BL as assessed by BICR but not by INV (T-DXd + P, n=15; THP, n=14). Discordance levels across BICR- and INV-assessed BMs at BL (i.e., number of patients whose BMs were not identified during either BICR or INV assessments divided by the overall number of assessments) were comparable across treatment arms (T-DXd + P vs THP: 0.063 vs 0.052). [d]Endpoints not prespecified in the clinical study protocol.
CNS-cORR, confirmed objective response rate in the CNS; CNS-DOR, duration of response in the CNS; CNS-PFS, progression-free-survival in the CNS; cORR, confirmed objective response rate.

Cristina Saura

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

Baseline demographics and disease characteristics

Characteristic, n (%) unless otherwise specified	Patients with BICR-confirmed BMs at BL		ITT population	
	T-DXd + P (n=31)	THP (n=30)	T-DXd + P (n=383)	THP (n=387)
Age, median (range), years	56 (27–79)	54 (26–71)	54 (27–85)	54 (20–81)
Geographical region				
Asia	17 (54.8)	11 (36.7)	188 (49.1)	191 (49.4)
Western Europe and North America	5 (16.1)	5 (16.7)	87 (22.7)	78 (20.2)
Other geographic regions	9 (29.0)	14 (46.7)	108 (28.2)	118 (30.5)
ECOG performance status				
0 (normal activity) / 1 (restricted activity)	20 (64.5) / 11 (35.5)	18 (60.0) / 12 (40.0)	256 (66.8) / 127 (33.2)	246 (63.6) / 141 (36.4)
HER2 score by central test[a]				
IHC 3+	28 (90.3)	24 (80.0)	318 (83.0)	315 (81.4)
IHC <3 / ISH+	3 (9.7)	6 (20.0)	62 (16.2)	71 (18.3)
HR status				
Positive[b] / Negative	16 (51.6) / 15 (48.4)	14 (46.7) / 16 (53.3)	207 (54.0) / 176 (46.0)	209 (54.0) / 178 (46.0)
***De novo* disease at diagnosis**	11 (35.5)	7 (23.3)	200 (52.2)	200 (51.7)
***PIK3CAm* detected**	NA	NA	116 (30.3)	121 (31.3)
Visceral metastases	30 (96.8)	28 (93.3)	281 (73.4)	268 (69.3)
Prior radiotherapy to the brain	7 (22.6)[c]	6 (20.0)[c]	NA	NA

Baseline demographics and disease characteristics of patients with BMs at BL were generally consistent with the ITT population, although rates of *de novo* disease were higher in the T-DXd + P arm versus the THP arm in the BM subgroup

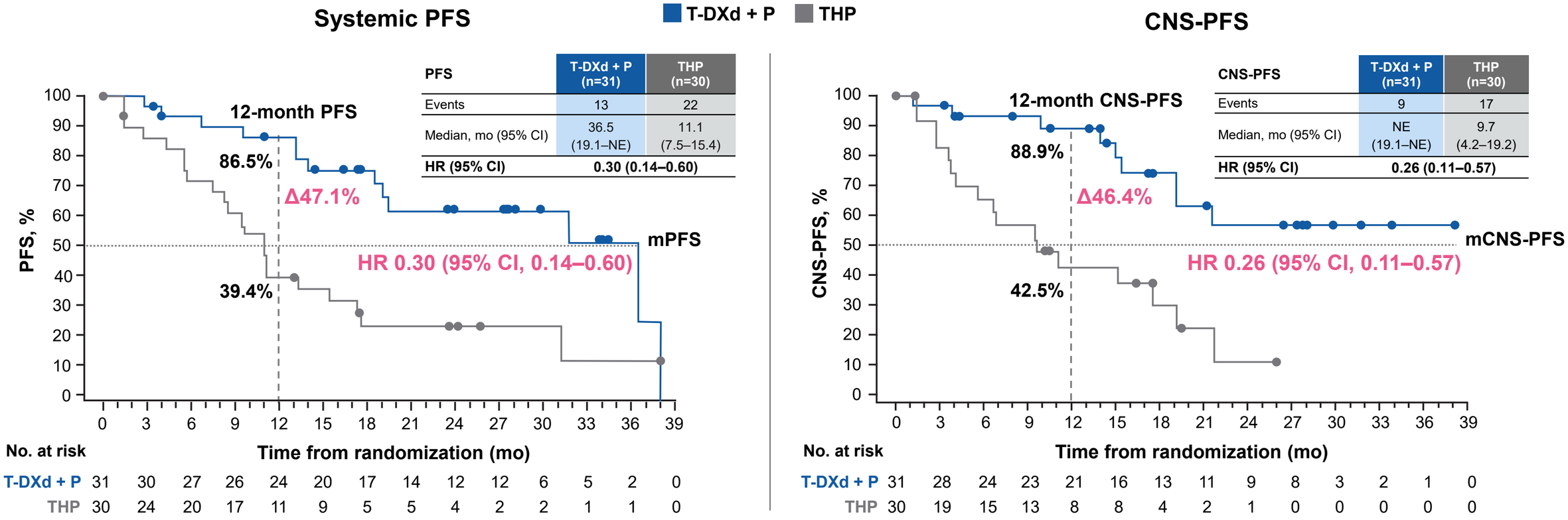
Data cutoff: February 26, 2025 (median [range] follow-up: 23.6 mo [2.8–41.4]). [a]IHC NR / ISH+ status: subgroup with BMs at BL, NA (both treatment arms); ITT population, 3 (0.8%) and 1 (0.3%) patients in the T-DXd + P and THP treatment arms, respectively. [b]Defined as ER-positive and/or PR-positive. [c]Median (range) time from last radiotherapy to study treatment start date was 26.0 (20–43) days and 29.0 (15–90) days in the T-DXd + P and THP arms, respectively.
ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; IHC, immunohistochemistry; ISH+, *in situ* hybridization positive; NA, not available; NR, not recorded; PR, progesterone receptor.

Cristina Saura

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

Systemic PFS and CNS-PFS in patients with BMs at BL

BMs at BL assessed by BICR



PFS	T-DXd + P (n=31)	THP (n=30)
Events	13	22
Median, mo (95% CI)	36.5 (19.1–NE)	11.1 (7.5–15.4)
HR (95% CI)	0.30 (0.14–0.60)	

CNS-PFS	T-DXd + P (n=31)	THP (n=30)
Events	9	17
Median, mo (95% CI)	NE (19.1–NE)	9.7 (4.2–19.2)
HR (95% CI)	0.26 (0.11–0.57)	

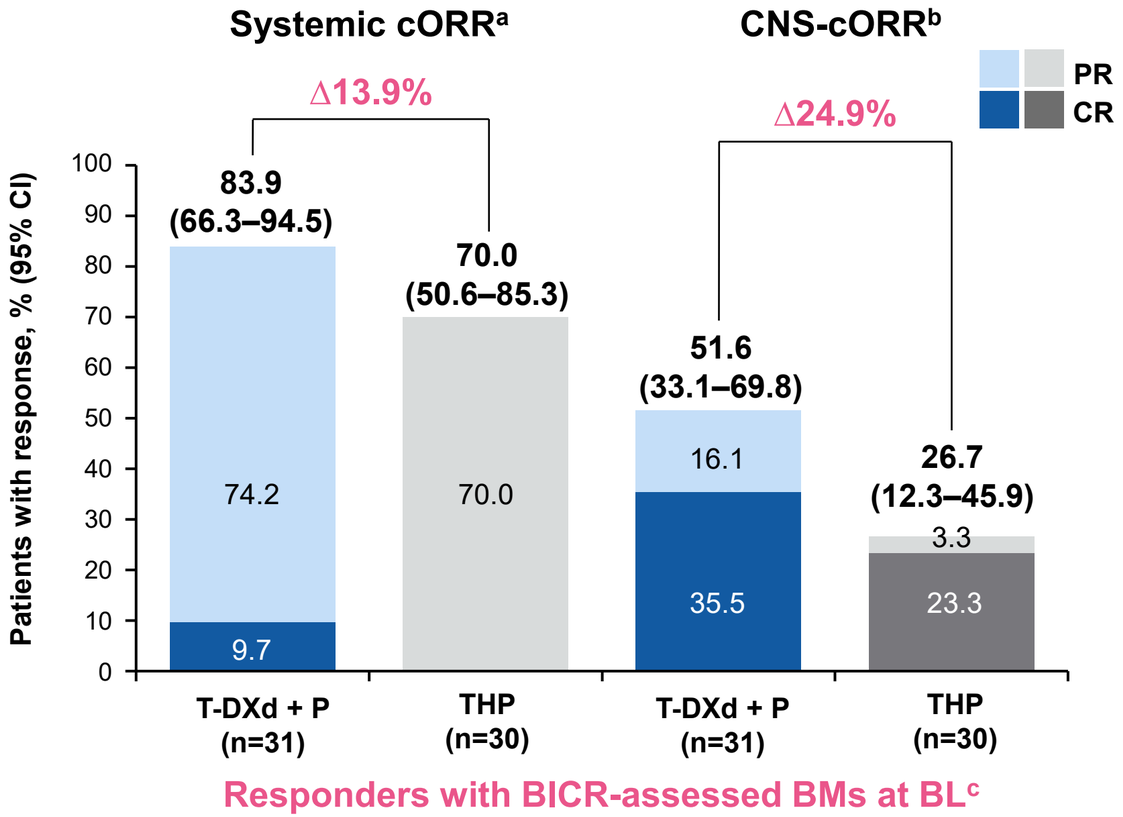
Patients with BMs at BL in the T-DXd + P arm had substantially longer systemic PFS and CNS-PFS than those in the THP arm

Responses by BICR. Data cutoff: February 26, 2025 (median [range] follow-up: 23.6 mo [2.8–41.4]). Results should be interpreted with caution due to the low number of patients in the subgroup.
Due to the low number of events recorded, PFS could not be calculated for the 32 patients with BMs at BL assessed by both BICR and INV.
CI, confidence interval; m(CNS)-PFS, median (central nervous system) progression-free survival; NE, not evaluable.

Cristina Saura

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

Systemic cORR, CNS-cORR, and DORs



Responders with BICR-assessed BMs at BL[c]

Response duration	T-DXd + P (n=31)	THP (n=30)
Patients with objective response, n (%)	26 (83.9)	21 (70.0)
Median DOR, mo (95% CI)	35.1 (17.1–NE)	10.5 (6.7–30.1)
Patients with objective CNS response, n (%)	16 (51.6)	8 (26.7)
Median CNS-DOR, mo (95% CI)	NE (14.3–NE)	18.5 (8.3–NE)

In patients with BICR-confirmed BMs at BL, T-DXd + P demonstrated deeper and more durable systemic responses versus THP; CNS-cORR was ~2-fold higher (51.6% vs 26.7%), and CNS-CR rates were 35.5% versus 23.3%, respectively

Responses by BICR. Data cutoff: February 26, 2025 (median [range] follow-up: 23.6 mo [2.8–41.4]). Results should be interpreted with caution due to the low number of patients in the subgroup.
[a]Confirmed systemic responses not captured in the ORR: T-DXd + P, SD (n=5, 16.1%), PD (n=0), NE, (n=0); THP, SD (n=5, 16.7%), PD (n=3, 10.0%), NE (n=1, 3.3%). [b]Confirmed CNS responses not captured in the ORR: T-DXd + P, SD (n=12, 38.7%), PD (n=3, 9.7%), NE, (n=0); THP, SD (n=13, 43.3%), PD (n=6, 20.0%), NE, (n=3, 10.0%). [c]For patients with both BICR- and INV-assessed BMs and BL, systemic cORR (95% CI) was 87.5% (61.7–98.4) with T-DXd + P versus 62.5% (35.4–84.8) with THP; CNS-cORR (95% CI) was 75.0% (47.6–92.7) with T-DXd + P versus 31.3% (11.0–58.7) with THP.
(CNS-)CR, complete response (in CNS); PR, partial response; SD, stable disease.

Cristina Saura
Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

DESTINY-Breast09

MADRID 2026 ESMO congress

Conclusions

- In this exploratory analysis of **DESTINY-Breast09**, T-DXd + P demonstrated robust systemic and intracranial disease control versus standard-of-care THP, supporting a meaningful clinical benefit in patients with BMs at BL
  - Longer systemic PFS (HR 0.30) with T-DXd + P versus THP
  - Deeper systemic and CNS responses with T-DXd + P versus THP (systemic cORR: 83.9% vs 70.0%, respectively), with CNS-cORR ~2-fold higher with T-DXd + P versus THP (CNS-cORR: 51.6% vs 26.7%)
  - More durable systemic responses with T-DXd + P versus THP (median DOR: 35.1 vs 10.5 mo)
- These findings further strengthen the body of evidence which supports the CNS activity of T-DXd in 1L HER2+ a/mBC, building on the efficacy observed in later lines of therapy from **DESTINY-Breast12** and pooled analyses of **DESTINY-Breast01/02/03**[1,2]

T-DXd + P demonstrated substantial and durable systemic and intracranial disease control versus THP, supporting its use as 1L therapy in HER2+ a/mBC

1. Harbeck N, et al. *Nat Med*. 2024;30:3717–3727. 2. André F, et al. *Ann Oncol*. 2024;35:1169–1180.

Cristina Saura

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

Acknowledgments

Thank you

- Patients and their families for their participation
- Study-site staff for their contributions

This study is sponsored by AstraZeneca and designed by AstraZeneca in collaboration with Daiichi Sankyo.

In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201).
Medical writing support was provided by Anita Toscani, PhD, from BOLDSCIENCE, Ltd, funded by AstraZeneca.

Scan the Quick Response (QR) code for a copy of this presentation

Copies of this presentation obtained through QR, AR and/or text key codes are for personal use only and may not be reproduced without written permission of the authors

Cristina Saura

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

Patients with brain metastases at baseline by INV assessment or retrospective BICR assessment

Patients with BMs at BL,[a] n	T-DXd + P	THP	Both arms
Patients with INV-assessed BMs[b]	25	22	47
Patients with BICR-assessed BMs	31	30	61
Patients with BICR- and INV-assessed BMs[b]	16	16	32
Patients with BICR-assessed BMs only	15	14	29

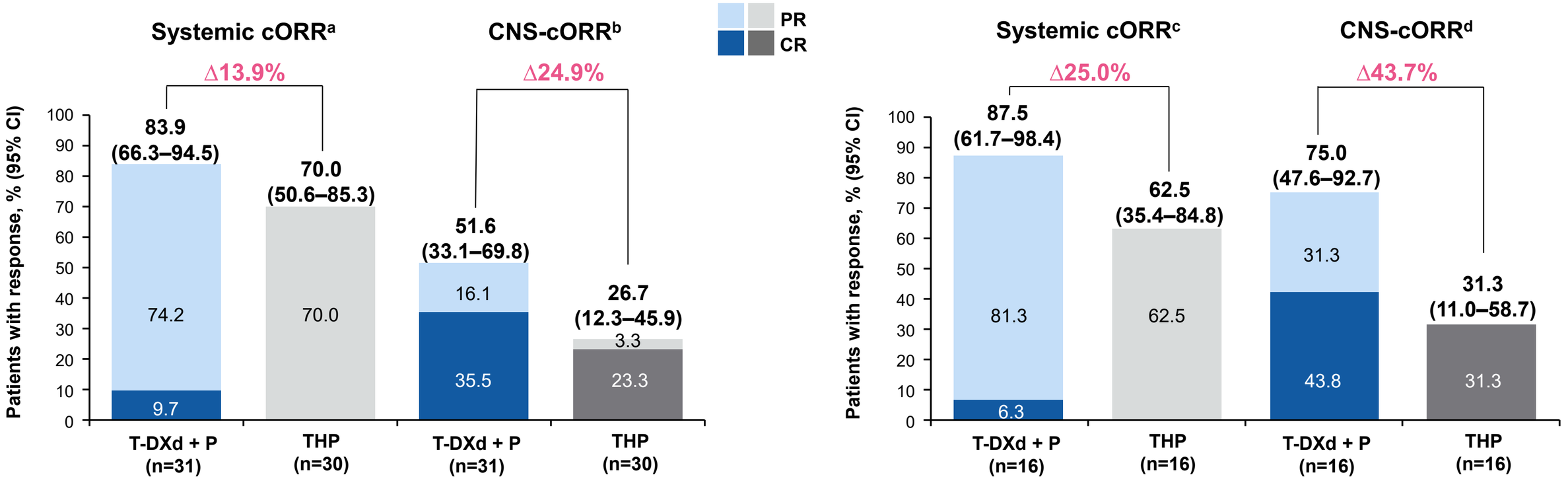
[a]INV and BICR assessment of BMs at BL may differ. Discordance levels across BICR- and INV-assessed BMs at BL (i.e., number of patients whose BMs were not identified during either BICR or INV assessments divided by the overall number of assessments) were comparable across treatment arms (T-DXd + P vs THP: 0.063 vs 0.052). [b]Only patients with INV-assessed BMs at BL were mandated regular brain MRI/CT imaging concurrently with regular tumor imaging per RECIST 1.1, as follows: Q6W ±1 week from R up to Week 48, and Q9W ±1 week from Week 48 until PD per RECIST 1.1. Radiographic progression (PD by RECIST 1.1) required collection of a subsequent scan 4 to 6 weeks after the prior assessment of PD, or any additional scans as clinically indicated.

Cristina Saura

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

Sensitivity analysis: systemic cORR and CNS-cORR

BMs at BL assessed by BICR versus assessed by BICR and INV



Responders with BICR-assessed BMs at BL[c]

Responders with BMs at BL assessed by BICR and INV[d]

Responses by BICR. Data cut-off: February 26, 2025 (median [range] follow-up: 23.6 [2.8–41.4]). Results should be interpreted with caution due to the low number of patients in the subgroups.
[a]Confirmed systemic responses: T-DXd + P, SD (n=5, 16.1%), PD (n=0), NE, (n=0); THP, SD (n=5, 16.7%), PD (n=3, 10.0%), NE, (n=1, 3.3%). [b]Confirmed CNS responses: T-DXd + P, SD (n=12, 38.7%), PD (n=3, 9.7%), NE, (n=0); THP, SD (n=13, 43.3%), PD (n=6, 20.0%), NE, (n=3, 10.0%). [c]Confirmed systemic responses: T-DXd + P, SD (n=2, 12.5%), PD (n=0), NE, (n=0); THP, SD (n=4, 25.0%), PD (n=2, 12.5%), NE, (n=0). [d]Confirmed CNS responses: T-DXd + P, SD (n=3, 18.8%), PD (n=1, 6.3%), NE (n=0); THP, SD (n=8, 50.0%), PD (n=3, 18.8%), NE (n=0).

Cristina Saura

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.