Destiny BREAST 09- ASCO 2025

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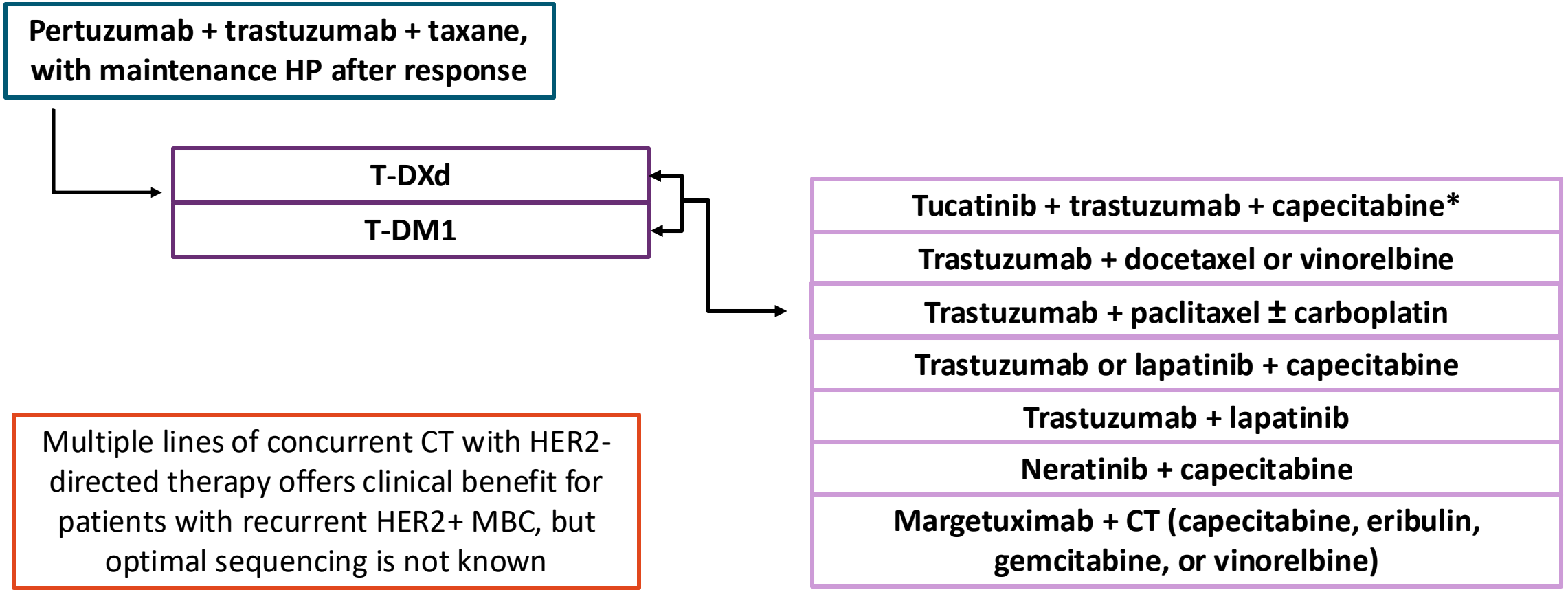
Proposed Strategy for Managing Patients With HER2+ MBC



Multiple lines of concurrent CT with HER2-directed therapy offers clinical benefit for patients with recurrent HER2+ MBC, but optimal sequencing is not known

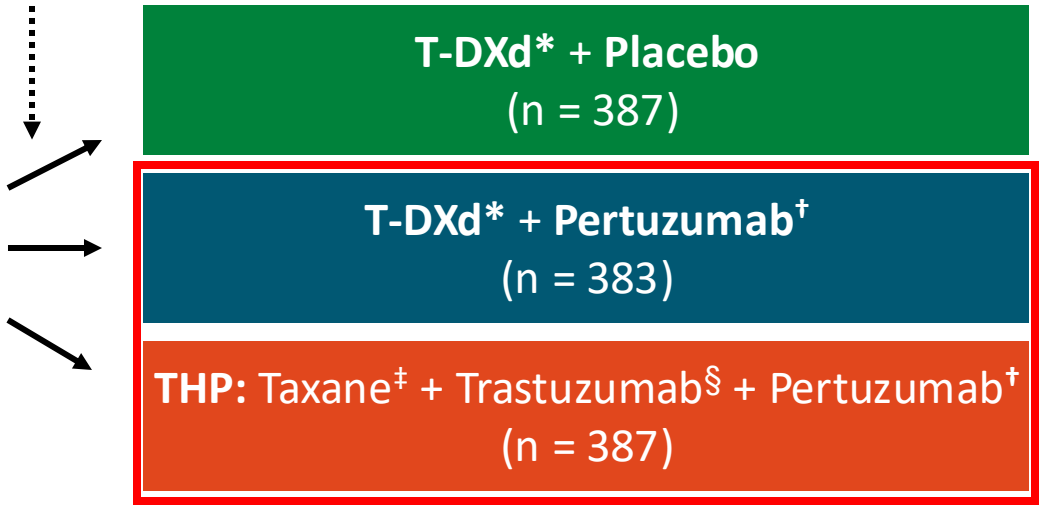
*Consider for patients with systemic and CNS progression in third line and beyond (may also be given as second line).

DESTINY-Breast09: 1L Trastuzumab Deruxtecan ± Pertuzumab vs THP for Advanced HER2+ Breast Cancer

- Multicenter, randomized, open-label phase III trial (data cutoff: February 26, 2025)

Stratified by previous treatment status (de novo vs recurrent); HR status (positive vs negative); PIK3CA mutation status (present vs absent)

Patients with HER2+ a/mBC; DFI >6 mo from last CT or HER2-targeted therapy in (neo)adjuvant setting; no prior systemic therapy for mBC (1 prior line of ET for mBC permitted); asymptomatic or inactive brain mets allowed; ECOG PS 0/1 (N = 1157)



- If T-DXd is discontinued due to AEs (except grade >2 ILD) → option to switch to trastuzumab
- Concurrent use of ET (AI or tamoxifen) allowed for HR+ disease after 6 cycles of T-DXd or taxane discontinuation in THP arm

*T-DXd 5.4 mg/kg Q3W. †Pertuzumab 840 mg loading dose → 420 mg Q3W. ‡Paclitaxel 80 mg/m^2 QW or 175 mg/m^2 Q3W, or docetaxel 75 mg/m^2 Q3W for minimum of 6 cycles or until intolerable toxicity. §Trastuzumab 8 mg/kg loading dose → 6 mg/kg Q3W.

- **Primary endpoint:** PFS (BICR)
- **Key secondary endpoints:** PFS and PFS2 (investigator), ORR, DoR, OS, and safety

DESTINY-Breast09: Baseline Characteristics

Characteristic	T-DXd + P (n = 383)	THP (n = 387)
Median age, yr (range)	54 (27-85)	54 (20-81)
Female, n (%)	383 (100)	387 (100)
Geographic region, n (%)		
▪ Asia	188 (49.1)	191 (49.4)
▪ W Europe/N America	87 (22.7)	78 (20.2)
▪ Rest of world	108 (28.2)	118 (30.5)
ECOG PS, n (%)		
▪ 0	256 (66.8)	246 (63.6)
▪ 1	127 (33.2)	141 (36.4)
Site of metastases, n (%)		
▪ Brain*	25 (6.5)	22 (5.7)
▪ Visceral	281 (73.4)	268 (69.3)
De novo disease, n (%)	200 (52.2)	200 (51.7)

Characteristic, n (%)	T-DXd + P (n = 383)	THP (n = 387)
HR status		
▪ Positive (ER/PgR ≥1%)	207 (54.0)	209 (54.0)
▪ Negative	176 (46.0)	178 (46.0)
HER2 score by central test		
▪ IHC 3+	318 (83.0)	315 (81.4)
▪ IHC <3/ISH+	62 (16.2)	71 (18.3)
▪ IHC NR/ISH+	3 (0.8)	1 (0.3)
PIK3CA mutation-positive	116 (30.3)	121 (31.3)

*Participants eligible if they had clinically inactive or treated/asymptomatic CNS metastases.

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DESTINY-Breast09: Previous Therapy for Breast Cancer

Prior Therapy Received, n (%)	T-DXd + P (n = 383)	THP (n = 387)
(Neo)adjuvant setting		
▪ Any	166 (43.3)	169 (43.7)
▪ Chemotherapy	159 (41.5)	152 (39.3)
▪ Endocrine therapy	74 (19.3)	85 (22.0)
▪ Targeted therapy	112 (29.2)	108 (27.9)
– Trastuzumab	110 (28.7)	108 (27.9)
– Pertuzumab	31 (8.1)	24 (6.2)
– T-DM1	3 (0.8)	4 (1.0)
– Pyrotinib	1 (0.3)	1 (0.3)
– CDK4/6 inhibitor	0	1 (0.3)
1L a/mBC setting		
▪ Endocrine therapy	5 (1.3)	5 (1.3)

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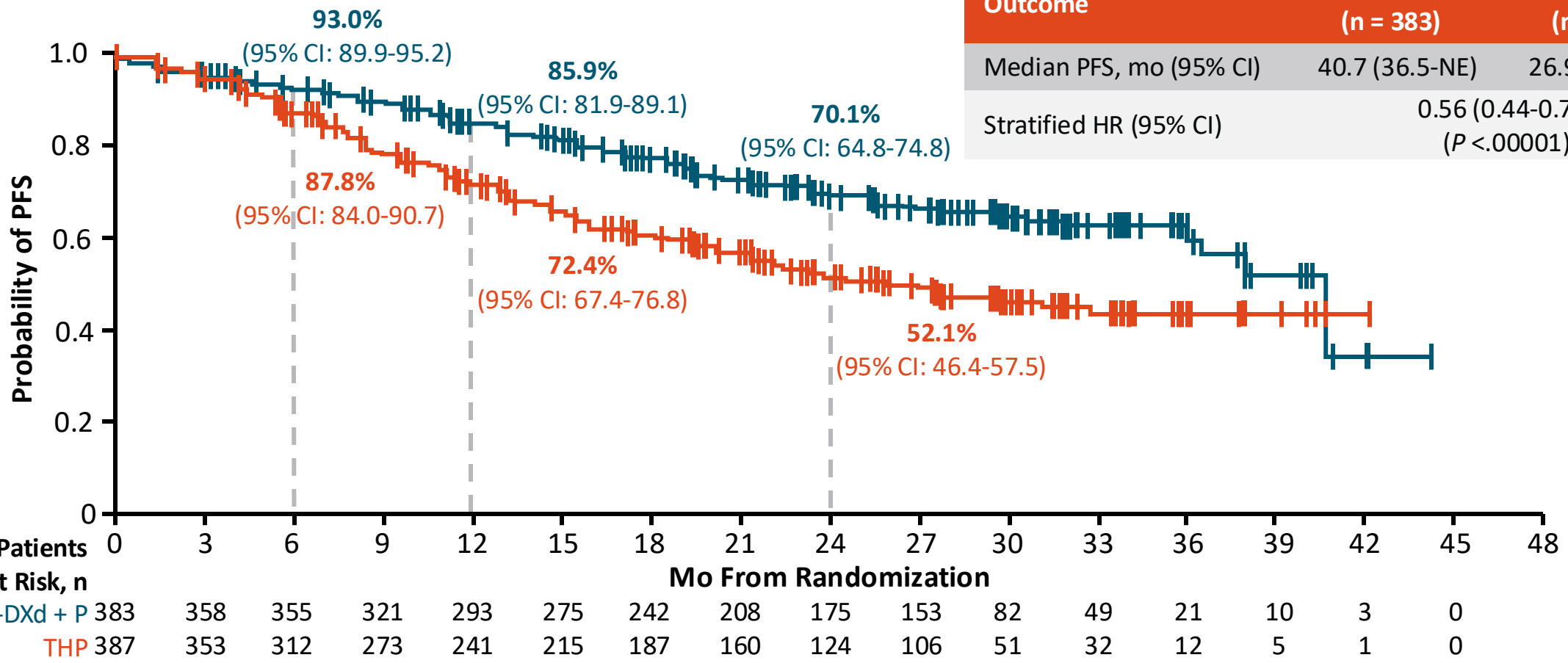
DESTINY-Breast09: PFS (BICR)

Outcome	T-DXd + P (n = 383)	THP (n = 387)
Median PFS, mo (95% CI)	40.7 (36.5-NE)	26.9 (21.8-NE)
Stratified HR (95% CI)	0.56 (0.44-0.71) (*P* <.00001)	



- PFS benefit was consistently in favor of T-DXd + P vs THP across prespecified subgroups, including all stratification factors
  - PFS benefit seen regardless of previous treatment status, HR status, *PIK3CA* mutation status, age, geographic region, brain metastases at baseline, and prior exposure to HER2-directed therapies or pertuzumab

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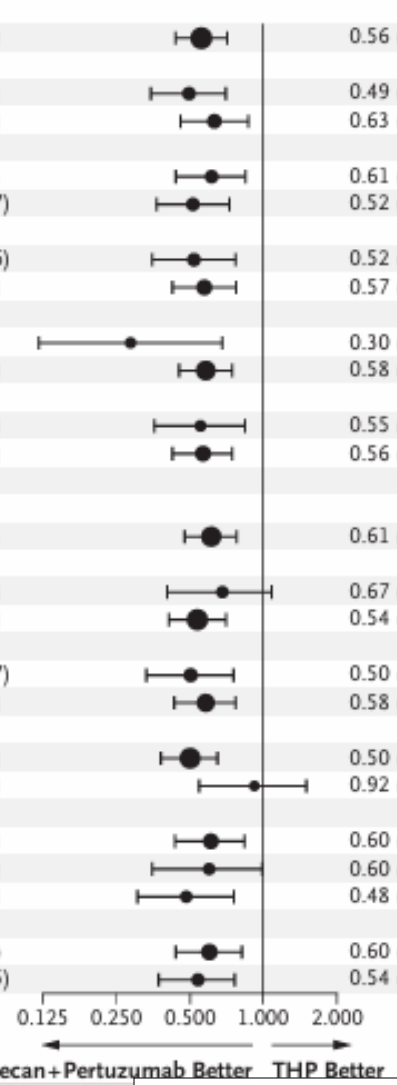
B Subgroup Analysis of Progression-free Survival

Subgroup	Trastuzumab Deruxtecan+ Pertuzumab	THP	Median Progression-free Survival (95% CI)		Hazard Ratio for Disease Progression or Death (95% CI)
			Trastuzumab deruxtecan+ pertuzumab	THP	
	no. of events/no. of patients		*mo*		
All patients	118/383	172/387	40.7 (36.5–NC)	26.9 (21.8–NC)	0.56 (0.44–0.71)
Disease status					
Newly diagnosed	52/200	85/200	NC (36.5–NC)	31.2 (23.5–NC)	0.49 (0.35–0.70)
Recurrent	66/183	87/187	38.0 (26.9–NC)	22.5 (18.1–NC)	0.63 (0.46–0.87)
Hormone-receptor status					
Positive	65/207	87/209	38.0 (36.0–NC)	27.7 (22.4–NC)	0.61 (0.44–0.84)
Negative	53/176	85/178	40.7 (40.7–NC)	22.6 (17.3–32.7)	0.52 (0.37–0.73)
PIK3CA mutation status					
Detected	41/116	64/121	36.0 (29.7–NC)	18.1 (15.1–25.6)	0.52 (0.35–0.77)
Not detected	76/266	108/266	40.7 (38.0–NC)	32.7 (24.4–NC)	0.57 (0.43–0.77)
Brain metastasis at baseline					
Present	10/25	15/22	31.8 (18.5–NC)	9.5 (5.6–13.3)	0.30 (0.12–0.68)
Not present	108/358	157/365	40.7 (36.5–NC)	27.6 (22.6–NC)	0.58 (0.45–0.74)
Previous exposure to anti-HER2 therapies					
Yes	39/115	51/112	38.0 (26.9–NC)	21.5 (15.3–NC)	0.55 (0.36–0.83)
No	79/268	121/275	40.7 (36.5–NC)	27.6 (22.5–NC)	0.56 (0.42–0.74)
Previous exposure to pertuzumab					
Yes	5/31	12/26	40.8 (25.4–NC)	19.8 (7.5–NC)	NC
No	113/352	160/361	40.7 (36.0–NC)	27.4 (22.4–NC)	0.61 (0.48–0.77)
Previous exposure to endocrine therapy					
Yes	28/80	40/88	38.0 (25.4–NC)	23.7 (19.4–NC)	0.67 (0.41–1.09)
No	90/303	132/299	40.7 (36.5–NC)	27.4 (21.4–NC)	0.54 (0.41–0.70)
Previous exposure to anthracycline					
Yes	40/110	57/111	38.0 (25.7–NC)	19.4 (13.0–27.7)	0.50 (0.33–0.76)
No	78/273	115/276	40.7 (36.5–NC)	31.2 (23.3–NC)	0.58 (0.43–0.77)
Age at randomization					
<65 yr	90/315	139/315	40.7 (36.5–NC)	27.4 (22.4–NC)	0.50 (0.38–0.65)
≥65 yr	28/68	33/72	27.6 (14.9–NC)	21.5 (13.9–NC)	0.92 (0.55–1.51)
Geographic region					
Asia	62/188	87/191	40.7 (36.5–NC)	27.2 (21.5–NC)	0.60 (0.43–0.83)
Western Europe and North America	27/87	31/78	36.0 (30.6–NC)	31.2 (15.8–NC)	0.60 (0.35–1.01)
Rest of the world	29/108	54/118	NC (38.0–NC)	24.4 (14.8–NC)	0.48 (0.30–0.76)
Baseline ECOG performance-status score					
0	71/256	94/246	40.7 (36.5–NC)	NC (27.2–NC)	0.60 (0.44–0.81)
1	47/127	78/141	NC (26.3–NC)	19.2 (13.2–23.5)	0.54 (0.37–0.77)



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DESTINY-Breast09: Secondary Efficacy Endpoints

Response	T-DXd + P (n = 383)	THP (n = 387)
Confirmed ORR, % ▪ CR ▪ PR	85.1 15.1 70.0	78.6 8.5 70.0
SD, %	9.9	14.5
Median DoR, mo (95% CI)	39.2 (35.1-NE)	26.4 (22.3-NE)
Ongoing response at 24 mo, %	73.3	54.9

Survival	T-DXd + P (n = 383)	THP (n = 387)
mPFS (by INV), mo (95% CI)	40.7 (36.5-NE)	20.7 (17.3-23.5)
Hazard ratio (95% CI)	0.49 (0.39-0.61); *P* <.00001	
mPFS2 (by INV), mo (95% CI)	NC	36.5 (36.1-NE)
Hazard ratio (95% CI)	0.60 (0.45-0.79); *P* = .00038	
mOS,* mo	NC	NC
Hazard ratio (95% CI)	0.84 (0.59-1.19)	

*Data only 16% mature.

- 10.1% of patients in the THP arm proceeded to receive 2L therapy with T-DXd after treatment discontinuation

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DESTINY-Breast09: Safety

Event	T-DXd + P (n = 381)	THP (n = 382)
Total exposure, patient-yr	659.7	564.0
Any TEAE, n (%)	380 (99.7)	378 (99.0)
Possible TEAE (by INV), n (%)	373 (97.9)	369 (96.6)
▪ Grade ≥3	209 (54.9)	200 (52.4)
Serious TEAE, n (%)	103 (27.0)	96 (25.1)
TEAE management/outcomes, n (%)		
▪ Treatment discontinuation	79 (20.7)	108 (28.3)
▪ Dose interruption	262 (68.8)	187 (49.0)
▪ Dose reduction	175 (45.9)	76 (19.9)
▪ Death	13 (3.4)	3 (0.8)
– Possible TRAE (by INV)*	5 (1.3)	1 (0.3)

*Cause of deaths in T-DXd + P arm: pneumonitis, sepsis, septic shock, febrile neutropenia, and dyspnea (n = 1 each); cause of death in THP arm: anemia (n = 1).

- Median overall tx duration
  - T-DXd + P: 21.7 mo (range: 0.3-44.5)
    - T-DXd: 20.0 mo
  - THP: 16.9 mo (range: 0.7-41.7)
- Median taxane duration
  - Docetaxel: 5.5 mo (range: 0.7-37.4)
  - Paclitaxel: 4.4 mo (range: 0.2-30.7)
- Median number of taxane cycles
  - Docetaxel: 8 (range: 1-51)
  - Paclitaxel: 6 (range: 1-42)

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DESTINY-Breast09: Most Frequent TEAEs and AESIs

TEAEs in ≥20% of Patients, %	T-DXd + P (n = 381)		THP (n = 382)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Nausea	71.1	5.0	28.8	0.3
Diarrhea	55.9	6.8	54.2	5.2
Neutropenia	48.8	23.9	44.5	33.2
Fatigue	48.3	7.9	34.6	2.1
Alopecia	46.2	0	50.0	0.5
Vomiting	42.0	2.4	13.4	0.5
Increased transaminases	36.0	4.5	18.8	2.1
Anemia	35.4	8.4	39.0	3.7
Leukopenia	29.4	4.5	30.6	17.5
Decreased appetite	28.6	2.4	15.4	0.8
Decreased weight	23.9	2.6	6.8	0.3
Thrombocytopenia	23.4	6.3	4.5	0.8
Constipation	22.3	0.3	6.8	0
Hypokalemia	21.5	10.2	6.3	1.6

Peripheral sensory neuropathy

- T-DXd + P (any: 11.3%; grade ≥3: 0)
- THP (any: 28.5%; grade ≥3: 1.0%)

AESIs with T-DXd + P vs THP

- Adjudicated ILD/pneumonitis
  - Any: 12.1% vs 1.0%
  - Grade 3/4: none on either arm
  - Grade 5: 0.5% vs 0
- LV dysfunction
  - Any: 11.0% vs 7.1%
  - Grade 3/4: 2.1% vs 1.8%
  - Grade 5: none on either arm

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DESTINY-Breast09: Investigators' Conclusions

- In the DESTINY-Breast09 trial, T-DXd + P demonstrated a clinically meaningful and statistically significant improvement in PFS vs THP
  - Median PFS (BICR): 40.7 vs 26.9 mo (HR: 0.56; 95% CI: 0.44-0.71; *P* <.00001)
  - PFS benefit with T-DXd was consistent across prespecified subgroups
- Other efficacy endpoints also favor T-DXd + P over THP
  - CR: 15.1% vs 8.5%; mDoR: 39.2 vs 26.4 mo; early OS data suggestive of a trend in favor of T-DXd + P (HR: 0.84; 95% CI: 0.59-1.19)
- The safety profile of T-DXd + P was consistent with known individual treatments
- Investigators concluded that T-DXd + P may represent a new SoC for the first-line treatment of patients with HER2+ a/mBC

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ORIGINAL ARTICLE

Trastuzumab Deruxtecan plus Pertuzumab for HER2-Positive Metastatic Breast Cancer

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ABSTRACT

BACKGROUND

Trastuzumab deruxtecan has shown efficacy in patients with previously treated human epidermal growth factor receptor 2 (HER2)–positive advanced or metastatic breast cancer. The efficacy and safety of trastuzumab deruxtecan in patients with no previous therapy for HER2-positive advanced or metastatic breast cancer are unclear.

METHODS

We conducted a phase 3 trial involving patients with HER2-positive advanced or metastatic breast cancer and no previous chemotherapy or HER2-directed therapy for metastatic disease. Patients were randomly assigned in a 1:1:1 ratio to receive trastuzumab deruxtecan plus pertuzumab; trastuzumab deruxtecan plus placebo; or a taxane, trastuzumab, and pertuzumab (THP). The primary end point was progression-free survival as assessed by blinded independent central review. Secondary end points included objective response, duration of response, and safety.

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*A list of the principal investigators in the DESTINY-Breast09 trial is provided in the Supplementary Appendix, available at NEJM.org.

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RESULTS

For this prespecified interim analysis, data for trastuzumab deruxtecan plus pertuzumab and for THP are reported; data for trastuzumab deruxtecan plus placebo remain blinded until the final analysis of progression-free survival. At the data-cutoff date (February 26, 2025), the median progression-free survival was 40.7 months with trastuzumab deruxtecan plus pertuzumab (383 patients) and 26.9 months with THP (387 patients) (hazard ratio for progression or death, 0.56; 95% confidence interval [CI], 0.44 to 0.71; P<0.00001 [P-value boundary for superiority, 0.00043]). The incidence of a confirmed response was 85.1% with trastuzumab deruxtecan plus pertuzumab and 78.6% with THP (complete responses in 15.1% and 8.5%, respectively), with a median duration of response of 39.2 months and 26.4 months. Safety was consistent with the known profiles of the individual treatments. The incidence of grade 3 or higher adverse events was 63.5% with trastuzumab deruxtecan plus pertuzumab and 62.3% with THP; the most common were neutropenia, hypokalemia, and anemia with trastuzumab deruxtecan plus pertuzumab and neutropenia, leukopenia, and diarrhea with THP. Adjudicated drug-related interstitial lung disease or pneumonitis occurred in 12.1% of patients receiving trastuzumab deruxtecan plus pertuzumab (grade 1 or 2 in 44 patients and grade 5 [death] in 2 patients) and in 1.0% of those receiving THP (all grade 1 or 2).

CONCLUSIONS

Trastuzumab deruxtecan plus pertuzumab led to a significantly lower risk of progression or death than THP when used as first-line treatment for HER2-positive advanced or metastatic breast cancer, with no new safety signals. (Funded by AstraZeneca and Daiichi Sankyo; DESTINY-Breast09 ClinicalTrials.gov number, NCT04784715.)

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