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DESTINY-Breast11: Neoadjuvant trastuzumab deruxtecan alone (T-DXd) or followed by paclitaxel + trastuzumab + pertuzumab (T-DXd-THP) vs SOC for high-risk HER2+ early breast cancer (eBC)

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Background

Current neoadjuvant HER2+ eBC SOC is H + P concurrently or in sequence with polychemotherapy. We report neoadjuvant T-DXd or T-DXd-THP vs dose-dense doxorubicin + cyclophosphamide (ddAC)-THP in a phase 3, multicenter, open-label, randomized study. In March 2024, the Independent Data Monitoring Committee advised enrollment closure to T-DXd alone; data in this arm will be reported at presentation.

Methods

Adults with untreated high-risk (≥T3, node positive [N1–3], or inflammatory) HER2+ eBC were randomized to T-DXd (5.4 mg/kg Q3W [8 cycles]), T-DXd-THP (T-DXd [4 cycles] followed by T QW + H Q3W + P Q3W [4 cycles]), or ddAC-THP (A + C Q2W [4 cycles] followed by THP [4 cycles]). Primary endpoint was pathologic complete response (pCR; ypT0/Tis ypN0). Secondary endpoints included event-free survival (EFS) and safety.

Results

As of March 12 2025, 321 (T-DXd-THP) and 320 (ddAC-THP) patients (pts) were randomized. pCR rates were 67.3% (T-DXd-THP) and 56.3% (ddAC-THP; ΔpCR rate 11.2% [95% CI 4.0, 18.3; P=0.003]) with improvement observed in HR+ (61.4% [145/236] T-DXd-THP vs 52.3% [123/235] ddAC-THP) and HR– (83.1% [69/83] T-DXd-THP vs 67.1% [57/85] ddAC-THP) groups. At data cutoff, T-DXd-THP vs ddAC-THP demonstrated an early favorable EFS trend (Table). Grade ≥3 AE rates were 37.5% (T-DXd-THP) vs 55.8% (ddAC-THP). AESIs were drug-related adjudicated interstitial lung disease (ILD) / pneumonitis (4.4% T-DXd-THP vs 5.1% ddAC-THP) and left ventricular dysfunction (1.9% T-DXd-THP vs 9.0% ddAC-THP). No AE prevented surgery in any arm.Table: 291O

	T-DXd-THP	ddAC-THP
Full analysis set, n	321	320
pCR rate, %*	67.3	56.3
ΔpCR vs ddAC-THP, % (95% CI; P value)†	11.2 (4.0, 18.3; 0.003)	–
EFS hazard ratio (95% CI)‡	0.56 (0.26, 1.17)	–
Safety analysis set, n	320	312
Any SAE, n (%)	34 (10.6)	63 (20.2)

	T-DXd-THP	ddAC-THP	
Any AE leading to, n (%)	Dose reduction	58 (18.1)	60 (19.2)
Dose interruption	121 (37.8)	170 (54.5)	
Drug discontinuation	45 (14.1)	31 (9.9)	
Death	2 (0.6)	2 (0.6)	
Drug-related adjudicated ILD / pneumonitis, n (%)	14 (4.4)	16 (5.1)	
Grade	≥3	2 (0.6)	6 (1.9)
5	1 (0.3)	1 (0.3)	
Left ventricular dysfunction, n (%)	6 (1.9)	28 (9.0)	
Grade ≥3	1 (0.3)	7 (2.2)	

*By blinded central review †Stratified Miettinen & Nurminen method; P value crossed the 0.03 prespecified boundary ‡4.5% maturity

Conclusions

Neoadjuvant T-DXd-THP demonstrated a clinically meaningful and statistically significant pCR improvement, an early favorable EFS trend, and improved safety profile vs ddAC-THP. These results support neoadjuvant T-DXd-THP as a potential new anthracycline-free regimen with improved efficacy and less toxicity vs ddAC-THP for pts with high-risk HER2+ eBC.

Clinical trial identification

NCT05113251.

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Legal entity responsible for the study

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