DESTINY-Breast11: neoadjuvant trastuzumab deruxtecan alone or followed by paclitaxel + trastuzumab + pertuzumab vs ddAC-THP for high-risk HER2+ early breast cancer

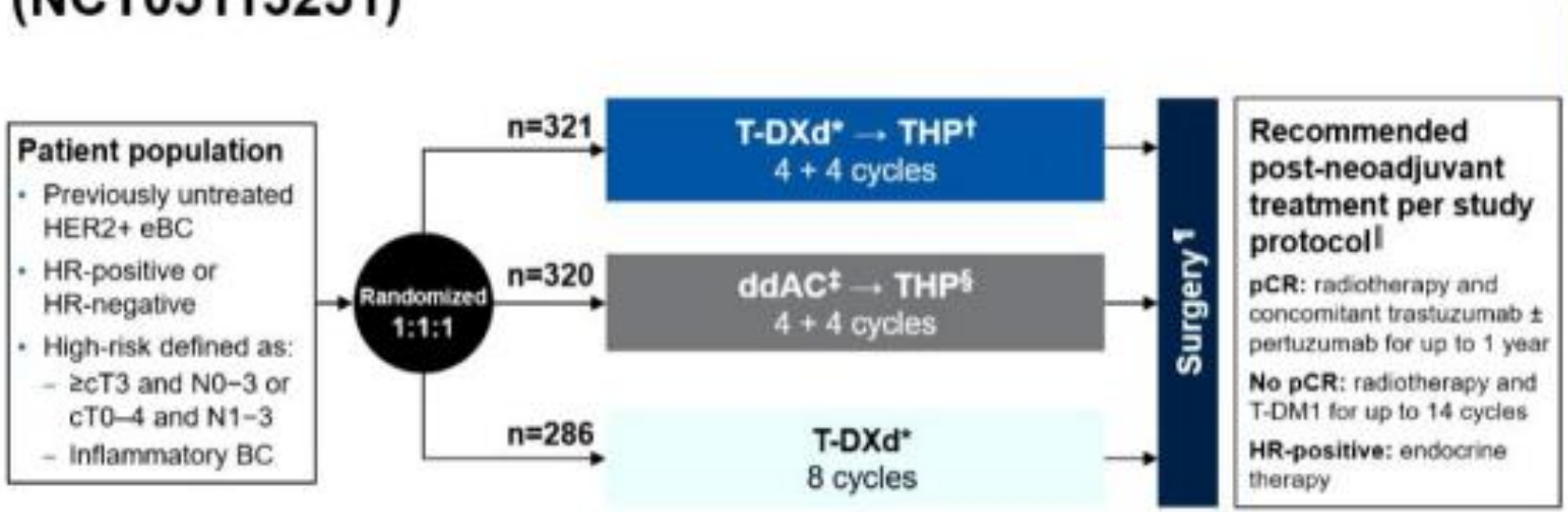
Background

- With no new therapies in over a decade,[1] there remains an unmet need for more effective and less toxic neoadjuvant regimens for HER2+ early-stage breast cancer (eBC)
- Pathologic complete response (pCR) is a prognostic factor for event-free survival (EFS) and overall survival in patients with HER2+ eBC[2–4] and provides essential information to support clinical decision-making
  - With existing SOC regimens, 39–64% of patients[1,5–9] have pCR; rates are lower in patients with hormone receptor (HR)–positive disease and those who are high risk (large tumor size, extensive nodal involvement)[5,6]
  - Patients with pCR are eligible for less burdensome subsequent treatments (reduction in extent of surgery and less toxic post-neoadjuvant therapy)[10–12]
- SOC regimens (eg ddAC-THP, TCbHP) have acute (hematological and gastrointestinal) AEs[13,14] and long-term sequelae, including cardiotoxicity,[10,15] secondary leukemia,[10] and neuropathy[5]
- T-DXd has demonstrated improved survival outcomes vs previous SOC in the metastatic setting[16,17]

DESTINY-Breast11 aimed to bring T-DXd to the neoadjuvant setting to determine whether this would improve efficacy and safety for patients with high-risk, HER2+ eBC

DESTINY-Breast11 study design

A randomized, global, multicenter, open-label, Phase 3 study (NCT05113251)



Stratification factors

- HR status: ER and/or PR-positive or negative
- HER2 status: (IHC 3+ or ISH+ in the absence of IHC 3+ status)

The T-DXd alone arm closed on March 13 2024, following Independent Data Monitoring Committee recommendation

The reasons were multifactorial, including a lower pCR rate, low likelihood that T-DXd alone would be superior to ddAC-THP, and the timing of surgery

Data cutoff: March 12, 2025

Primary endpoint

- pCR (ypT0/is ypN0) by blinded central review

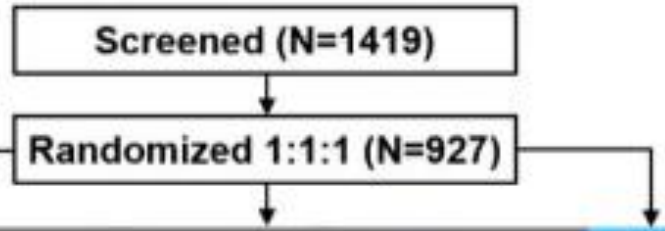
Secondary endpoints

- pCR (ypT0 ypN0) by blinded central review
- EFS
- Safety
- Pharmacokinetics and immunogenicity
- Invasive disease-free survival
- Overall survival
- Health-related quality of life

Additional outcome measures

- Residual cancer burden (RCB)

Patient disposition



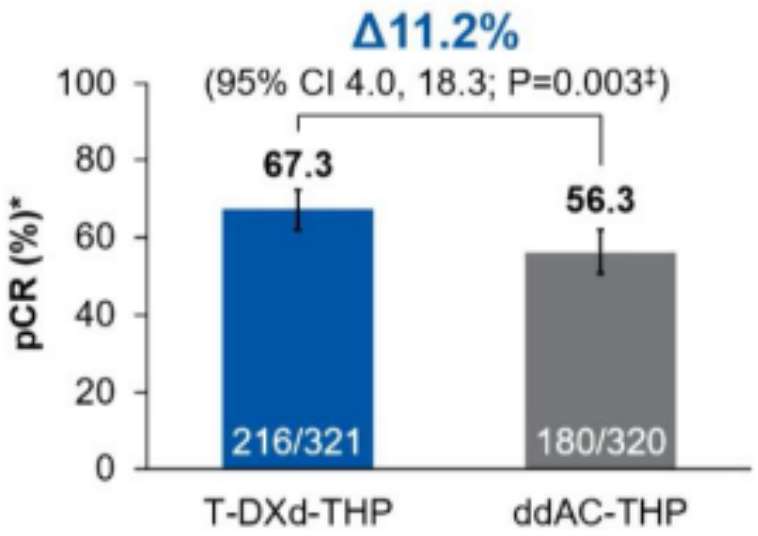
n (%)	T-DXd-THP (n=321)				ddAC-THP (n=320)				T-DXd (n=286)
Treated	320 (99.7)				312 (97.5)				283 (99.0)
Discontinued study treatment*									
Any	54 (16.9)				43 (13.8)				52 (18.4)
Individual drug	**T-DXd**	**T**	**H**	**P**	**AC**	**T**	**H**	**P**	
	9 (2.8)	45 (14.4)	7 (2.2)	7 (2.2)	9 (2.9)	36 (12.0)	9 (3.0)	11 (3.7)	
Reason for discontinuation*									
AE	4 (1.3)	41 (13.1)	7 (2.2)	7 (2.2)	3 (1.0)	27 (9.0)	4 (1.3)	5 (1.7)	22 (7.8)
Disease progression	0	0	0	0	1 (0.3)	2 (0.7)	2 (0.7)	2 (0.7)	4 (1.4)
Patient decision	3 (0.9)	2 (0.6)	0	0	4 (1.3)	6 (2.0)	2 (0.7)	3 (1.0)	4 (1.4)
Other	2 (0.6)	1 (0.3)	0	0	1 (0.3)	0	0	0	21 (7.4)
Death	0	1 (0.3)	0	0	0	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.4)
Underwent surgery on trial†	312 (97.2)				300 (93.8)				274 (95.8)

Patient demographics and key baseline characteristics

		T-DXd-THP (n=321)	ddAC-THP (n=320)	T-DXd (n=286)
Median (range) age, years		50 (25–82)	50 (23–79)	50 (23–79)
Female, n (%)		321 (100)	320 (100)	286 (100)
Geographical region, n (%)	Asia	152 (47.4)	152 (47.5)	124 (43.4)
	Western Europe	69 (21.5)	77 (24.1)	66 (23.1)
	North America	43 (13.4)	41 (12.8)	52 (18.2)
	Rest of world*	57 (17.8)	50 (15.6)	44 (15.4)
Race, n (%)†	Asian	160 (49.8)	157 (49.1)	127 (44.4)
	White	140 (43.6)	137 (42.8)	139 (48.6)
	Black or African American	5 (1.6)	7 (2.2)	7 (2.4)
	Other	12 (3.7)	10 (3.1)	8 (2.8)
Eastern Cooperative Oncology Group performance status score, n (%)	0	278 (86.6)	280 (87.5)	252 (88.1)
	1	43 (13.4)	40 (12.5)	34 (11.9)
HER2 status, n (%)‡	IHC 3+	280 (87.2)	283 (88.4)	254 (88.8)
	Other	40 (12.5)	36 (11.3)	32 (11.2)
HR status, n (%)§	Positive¶	236 (73.5)	235 (73.4)	205 (71.7)
Clinical tumor stage, n (%)	cT0–2	176 (54.8)	188 (58.8)	157 (54.9)
	cT3–4	145 (45.2)	132 (41.3)	129 (45.1)
Nodal status, n (%)‖	N0	26 (8.1)	35 (10.9)	20 (7.0)
	N+	287 (89.4)	281 (87.8)	254 (88.8)

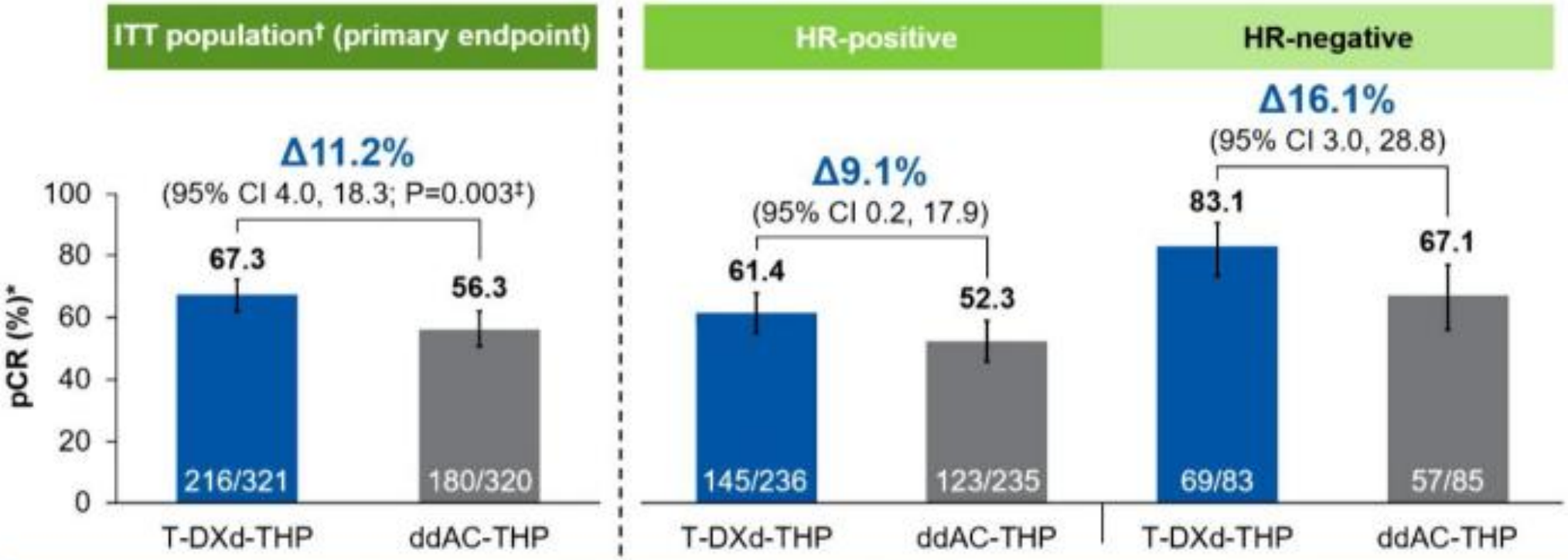
pCR (ypT0/is ypN0): primary endpoint

ITT population† (primary endpoint)



Neoadjuvant T-DXd-THP demonstrated a statistically significant and clinically meaningful improvement in pCR vs ddAC-THP

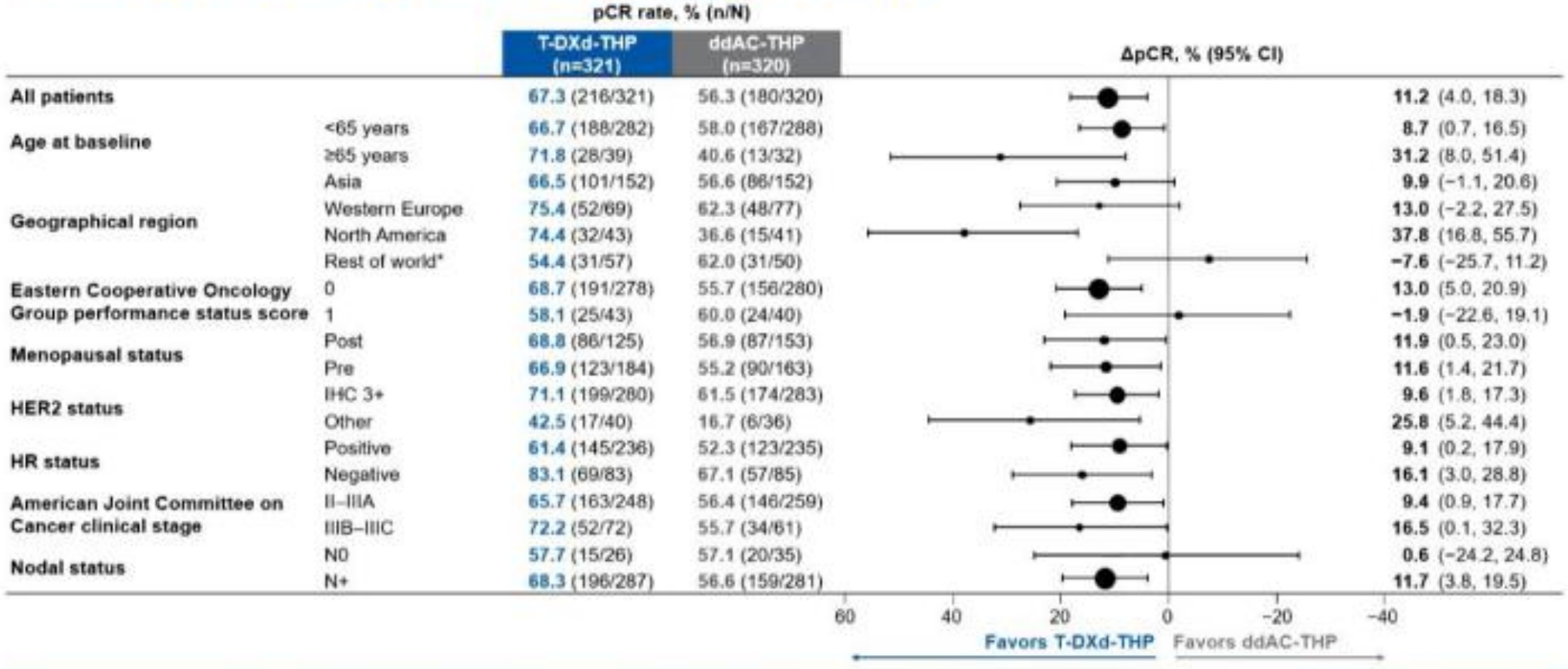
pCR (ypT0/is ypN0): primary endpoint



Neoadjuvant T-DXd-THP demonstrated a statistically significant and clinically meaningful improvement in pCR vs ddAC-THP

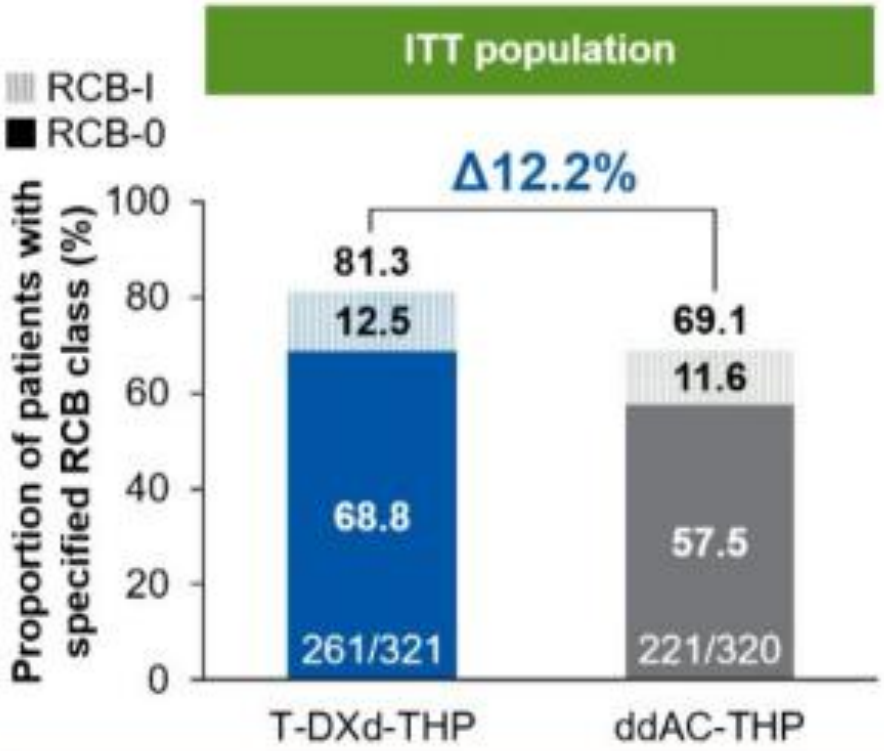
Improvement was observed in both the HR-positive and HR-negative subgroups

pCR (ypT0/is ypN0) by subgroups



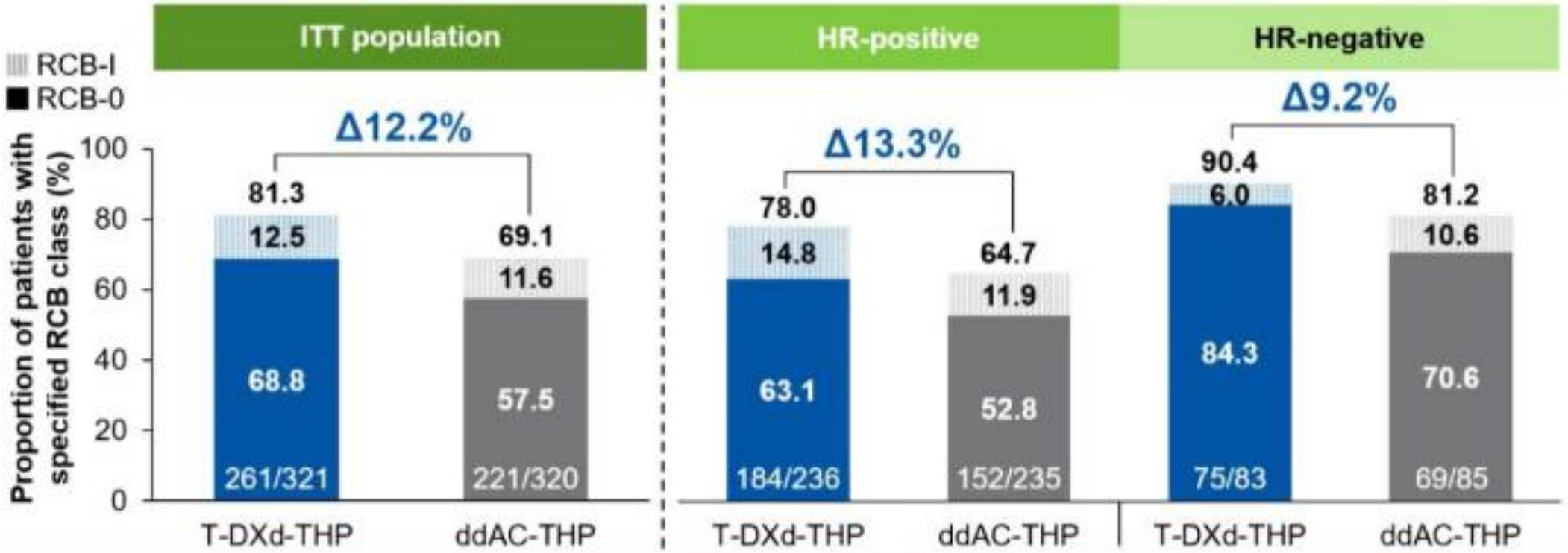
Improvement in pCR for T-DXd-THP vs ddAC-THP was observed across most pre-specified subgroups

RCB outcomes



After surgery, 81.3% of patients receiving T-DXd-THP had no or minimal residual invasive cancer (RCB-0+I) detected in the resected breast or lymph node tissue vs 69.1% of those receiving ddAC-THP

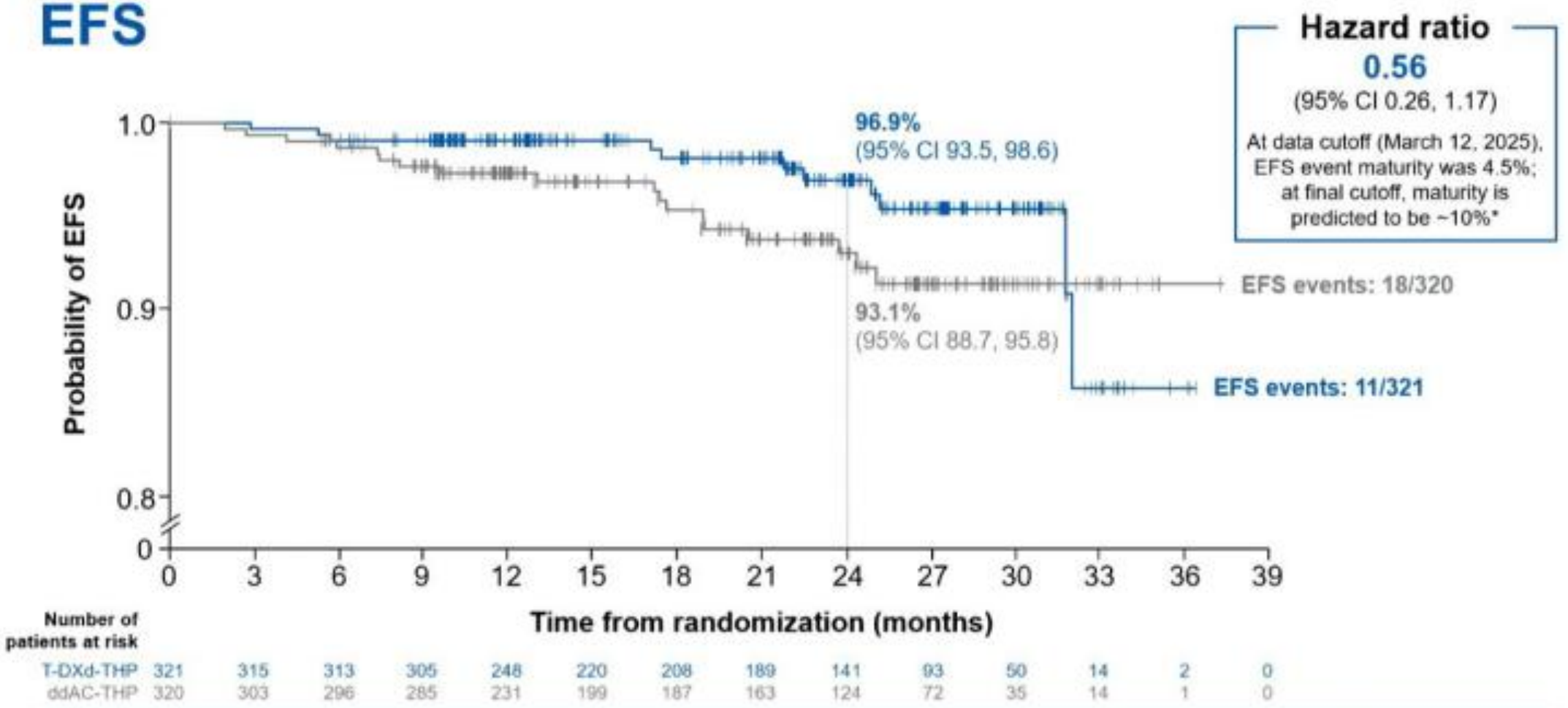
RCB outcomes



After surgery, 81.3% of patients receiving T-DXd-THP had no or minimal residual invasive cancer (RCB-0+I) detected in the resected breast or lymph node tissue vs 69.1% of those receiving ddAC-THP

Almost 80% of patients with HR-positive disease had RCB-0+I with T-DXd-THP

EFS



An early positive trend in EFS was observed, favoring T-DXd-THP vs ddAC-THP

Post-neoadjuvant treatments

n (%)	Patients with pCR*		Patients without pCR*	
	T-DXd-THP (n=226)	ddAC-THP (n=190)	T-DXd-THP (n=95)	ddAC-THP (n=130)
Any adjuvant treatment†	224 (99.1)	187 (98.4)	85 (89.5)	107 (82.3)
Any cytotoxic chemotherapy-containing regimen	13 (5.8)	11 (5.8)	10 (10.5)	12 (9.2)
Any T-DM1-containing regimen	4 (1.8)	4 (2.1)	50 (52.6)	74 (56.9)
Any trastuzumab-containing regimen	213 (94.2)	174 (91.6)	37 (38.9)	34 (26.2)

Post-neoadjuvant treatments were generally well balanced between T-DXd-THP and ddAC-THP arms
In both arms, more than half of patients without pCR received post-neoadjuvant T-DM1

Overall safety summary

n (%)	T-DXd-THP (n=320)*	ddAC-THP (n=312)*
Any AE	314 (98.1)	308 (98.7)
Grade ≥3	120 (37.5)	174 (55.8)
Any serious AE	34 (10.6)	63 (20.2)
AE leading to any dose reduction	58 (18.1)	60 (19.2)
AE leading to any drug interruption	121 (37.8)	170 (54.5)
AE leading to any treatment discontinuation	45 (14.1)	31 (9.9)
Any AE with outcome of death†	2 (0.6)	2 (0.6)
AE of special interest		
Drug-related adjudicated ILD/pneumonitis	14 (4.4)	16 (5.1)
Grade ≥3	2 (0.6)	6 (1.9)
Grade 5	1 (0.3)	1 (0.3)
Left ventricular dysfunction	4 (1.3)	19 (6.1)
Grade ≥3	1 (0.3)	6 (1.9)
Grade 5	0	0
AE leading to surgical delay‡	11 (3.4)	8 (2.6)

The overall safety profile of T-DXd-THP was favorable vs ddAC-THP, with reduced rates of Grade ≥3 AEs, serious AEs, treatment interruptions, and left ventricular dysfunction

ILD incidence was low and similar in both arms

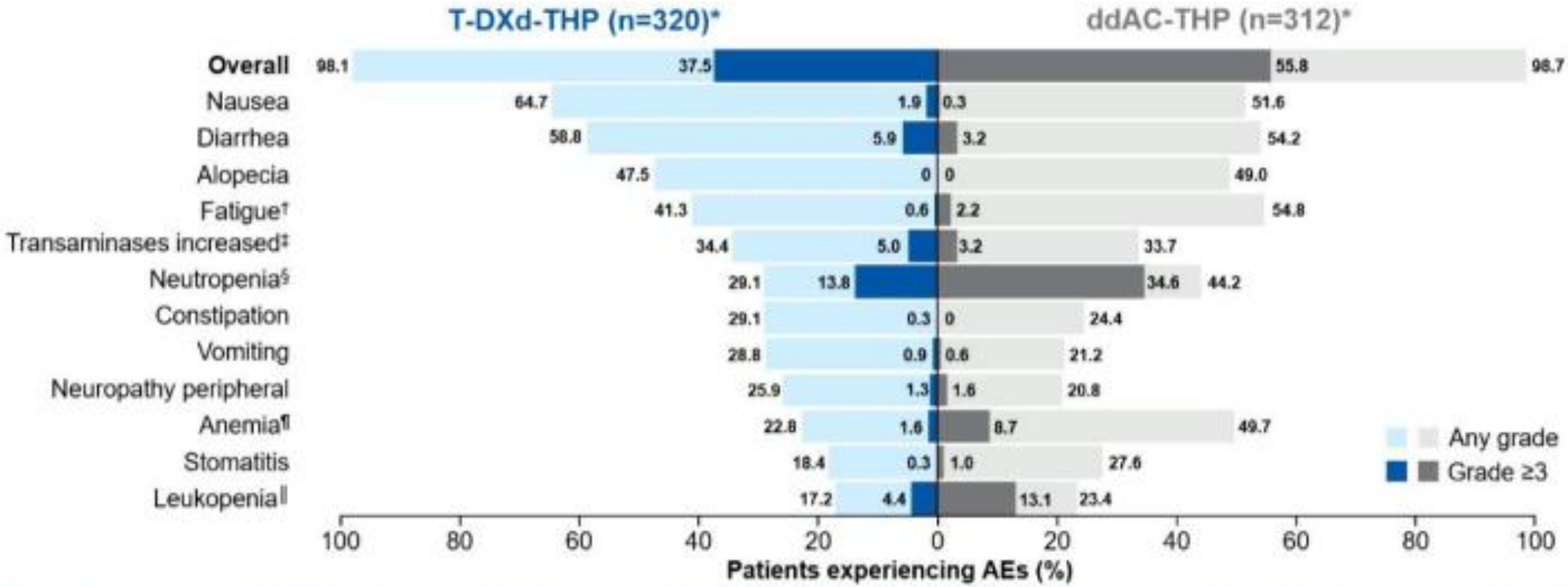
Overall safety summary

n (%)	T-DXd-THP (n=320)*	ddAC-THP (n=312)*
Any AE	314 (98.1)	308 (98.7)
Grade ≥3	120 (37.5)	174 (55.8)
Any serious AE	34 (10.6)	63 (20.2)
AE leading to any dose reduction	58 (18.1)	60 (19.2)
AE leading to any drug interruption	121 (37.8)	170 (54.5)
AE leading to any treatment discontinuation	45 (14.1)	31 (9.9)
Any AE with outcome of death†	2 (0.6)	2 (0.6)
AE of special interest		
Drug-related adjudicated ILD/pneumonitis	14 (4.4)	16 (5.1)
Grade ≥3	2 (0.6)	6 (1.9)
Grade 5	1 (0.3)	1 (0.3)
Left ventricular dysfunction	4 (1.3)	19 (6.1)
Grade ≥3	1 (0.3)	6 (1.9)
Grade 5	0	0
AE leading to surgical delay‡	11 (3.4)	8 (2.6)

The overall safety profile of T-DXd-THP was favorable vs ddAC-THP, with reduced rates of Grade ≥3 AEs, serious AEs, treatment interruptions, and left ventricular dysfunction

ILD incidence was low and similar in both arms

TEAEs in at least 20% of patients in either arm



T-DXd-THP had fewer any-grade and Grade ≥3 hematological and fatigue events than ddAC-THP
Aside from nausea, gastrointestinal toxicity was comparable between arms

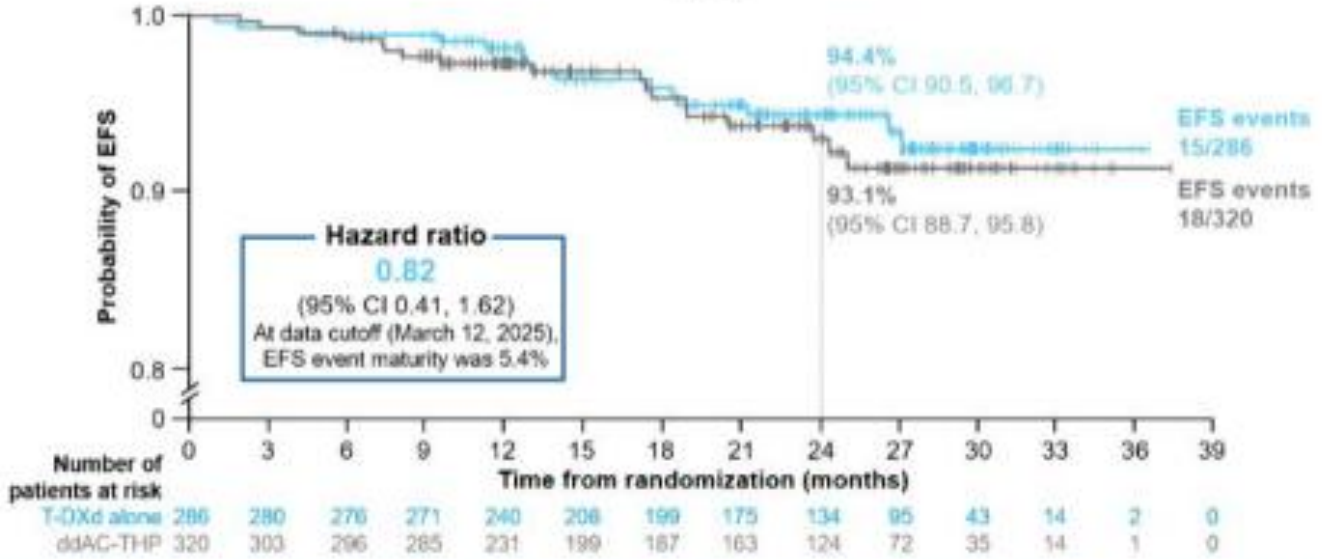
T-DXd alone arm: efficacy summary

On March 13, 2024, the T-DXd alone arm closed following Independent Data Monitoring Committee recommendation.*
Patients who were still receiving T-DXd alone could remain on therapy or immediately switch to local SOC

pCR rate

%	T-DXd (n=286)	ddAC-THP (n=320)
Primary analysis Switch to local SOC classified as non-pCR		
pCR†	43.0	56.3
Δ (95% CI)	−13.2 (−20.8, −5.4)	
Prespecified supplementary analysis Switch to local SOC not automatically classified as non-pCR		
pCR†	51.4	57.2
Δ (95% CI)	−5.8 (−13.4, 1.9)	

EFS



T-DXd alone showed inferior but robust pCR compared with the five-agent ddAC-THP
EFS data were similar for T-DXd alone and ddAC-THP

T-DXd alone arm: safety summary

n (%)	T-DXd (n=283)*	ddAC-THP (n=312)*
Any AE	276 (97.5)	308 (98.7)
Grade ≥3	64 (22.6)	174 (55.8)
Any serious AE	29 (10.2)	63 (20.2)
AE leading to any dose reduction	19 (6.7)	60 (19.2)
AE leading to any drug interruption	51 (18.0)	170 (54.5)
AE leading to any treatment discontinuation	22 (7.8)	31 (9.9)
Any AE with outcome of death†	1 (0.4)	2 (0.6)
AE of special interest		
Drug-related adjudicated ILD/pneumonitis	14 (4.9)	16 (5.1)
Grade ≥3	0	6 (1.9)
Grade 5	0	1 (0.3)
Left ventricular dysfunction	2 (0.7)	19 (6.1)
Grade ≥3	0	6 (1.9)
Grade 5	0	0
AE leading to surgical delay‡	18 (6.4)	8 (2.6)

The overall safety profile of T-DXd alone was favorable vs ddAC-THP, with reduced rates of Grade ≥3 AEs, serious AEs, treatment reductions/interruptions, and left ventricular dysfunction

ILD incidence was low and similar in both arms

Conclusions

- In DESTINY-Breast11, **T-DXd-THP showed the highest reported pCR rate in HER2+ eBC** for a registrational study in the neoadjuvant setting, despite a **high prevalence of HR-positive disease** and a **high-risk population**[1–3*]
- **T-DXd-THP showed a statistically significant and clinically meaningful improvement in pCR rate** vs ddAC-THP: Δ11.2% (95% CI 4.0, 18.3)
  - pCR benefit for T-DXd-THP vs ddAC-THP was independent of HR status and disease stage
- An **early positive trend in EFS** was observed, favoring T-DXd-THP vs ddAC-THP
  - Hazard ratio: 0.56 (95% CI 0.26, 1.17)
- The **safety profile of T-DXd-THP was favorable vs ddAC-THP**
  - Lower rates of Grade ≥3 AEs, serious AEs, and AEs leading to dose interruptions
  - Lower rates of hematological AEs, left-ventricular dysfunction, and fatigue
  - ILD rates were low and similar between arms

pCR rate

67.3%

More than two thirds of patients in the T-DXd-THP arm had a pCR

HR-positive: **61.4%**
HR-negative: **83.1%**

DESTINY-Breast11 results support T-DXd-THP as a more effective and less toxic neoadjuvant treatment compared with ddAC-THP, and it may become a preferred regimen for patients with high-risk HER2+ eBC

Acknowledgments

Thank you

- Patients and their families for their participation
- Study-site staff for their contributions
- Members of the Independent Data Monitoring Committee and the Interstitial Lung Disease Adjudication Committee
- Labcorp Central Laboratory Services for pathology support

This study was sponsored by AstraZeneca, and designed by AstraZeneca in collaboration with Daiichi Sankyo

Medical writing support was funded by AstraZeneca and provided by:

Jade Murdoch, MChD/BChD, and Frances Singer, PhD,
of Helios Medical Communications, part of Helios Global Group