



Multidisciplinary Approaches to Cancer Symposium

Optimal Approaches to Sequencing Therapy for Early and Advanced Stage HER2 Positive Breast Cancer

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Disclosures

- Consultant for BrBioNTech, Bristol Myers Squibb, Helsinn, & Nap
- Grant/Research Support to UCSF from AstraZeneca, Ambryx, Daiichi Sankyo, Eli Lilly, F.Hoffman-LaRoche/Genentech, Gilead Sciences, Merck & Co., Novartis, Pfizer, & Stemline Therapeutics
- Grant/Research from ALX Oncology, Bicyclic Therapeutics, F.Hoffman-La Roche/Genentech, Mabwell, Merck & Co., Pfizer, PhoenixMD, Relay Therapeutics, & Stemline Therapeutics

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

The off-label/investigational use of T-DXd and Tucatinib will be addressed.



Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *Access to effective therapies and toxicity varies based on cultural diversity; communication can overcome these barriers.*
- *In this case there is overlap with cultural diversity - access to therapy varies based on distance from treating site, costs of care, co-morbidities (primarily cardiac and pulmonary in this setting).*



Maximizing Personalization of Therapy for Early HER2+ Breast Cancer

Neoadjuvant therapy enables a risk-adapted approach

Preferred for almost all patients with HER2+ breast cancer

Multiple benefits

- Less therapy for excellent responders

- Escalated therapy for poor responders

Knowledge is power

Understanding response allows modification of treatment to:

- Minimize toxicity and cost

- Maximize disease free and overall survival

ASCO guidelines 2021 (Korde et al, JCO 2021)

Neoadjuvant therapy should be offered to patients with high-risk HER2+ in whom the finding of residual disease would guide recommendations related to adjuvant therapy

- Only group where neoadjuvant therapy not *routinely* recommended is T1a, b and N0

pCR (defined as absence of disease in breast and node) should be used to measure response to guide clinical decision making



Personalizing Therapy for Early Stage HER2+ Breast Cancer

Escalate for those with increased risk

Add additional targeted agents:

Pertuzumab in the neoadjuvant setting for $\geq$ stage II disease

Adjuvant benefit in N+ only

T-DM1 for residual disease post neoadjuvant therapy

Replace therapy with more effective agents: Destiny Breast Trials

De-escalate for those with lower risk

Substitute with less toxic chemotherapy or with targeted agents

Decrease amount of chemotherapy

Less exposure/different agents

Decrease duration of therapy



Pathologic Complete Response

No difference with the addition of carboplatin

neoCARHP Rx Arm N=774	pCR Overall	pCR in ER-positive	pCR in ER-negative
TCHPx6	66%	59%	78%
THPx6	64%	56%	78%

- Compares favorably with prior neoadjuvant TCHP trials
 - Tryphaena (TCHP x 6, pCR 66.2%) , TRAIN-2 (TCHP x 9 with weekly paclitaxel, pCR 68%, 55% ER+, 84% ER-), Kristine (TCHP x 6, pCR 55.7% overall, 44% in ER+ vs 73% in ER-)
 - All taxanes given every 3 weeks, 36% node negative, mix of taxanes
- Safety:
 - Increased grade 3/4 adverse events in TCHP arm: neutropenia (16.4% vs 6.8%), febrile neutropenia (2.6% vs. 1.3%), thrombocytopenia (4.2% vs. 0.3%), anemia (6.6% vs. 2.1%)
 - Higher all grade nausea, vomiting, increased creatinine with TCHP
 - Unclear data on neuropathy with 6 cycles of THP; only 19% received paclitaxel



CompassHER2 pCR Trial (EZ1181): THP for Stage II/III HER2+ BC: Secondary Results

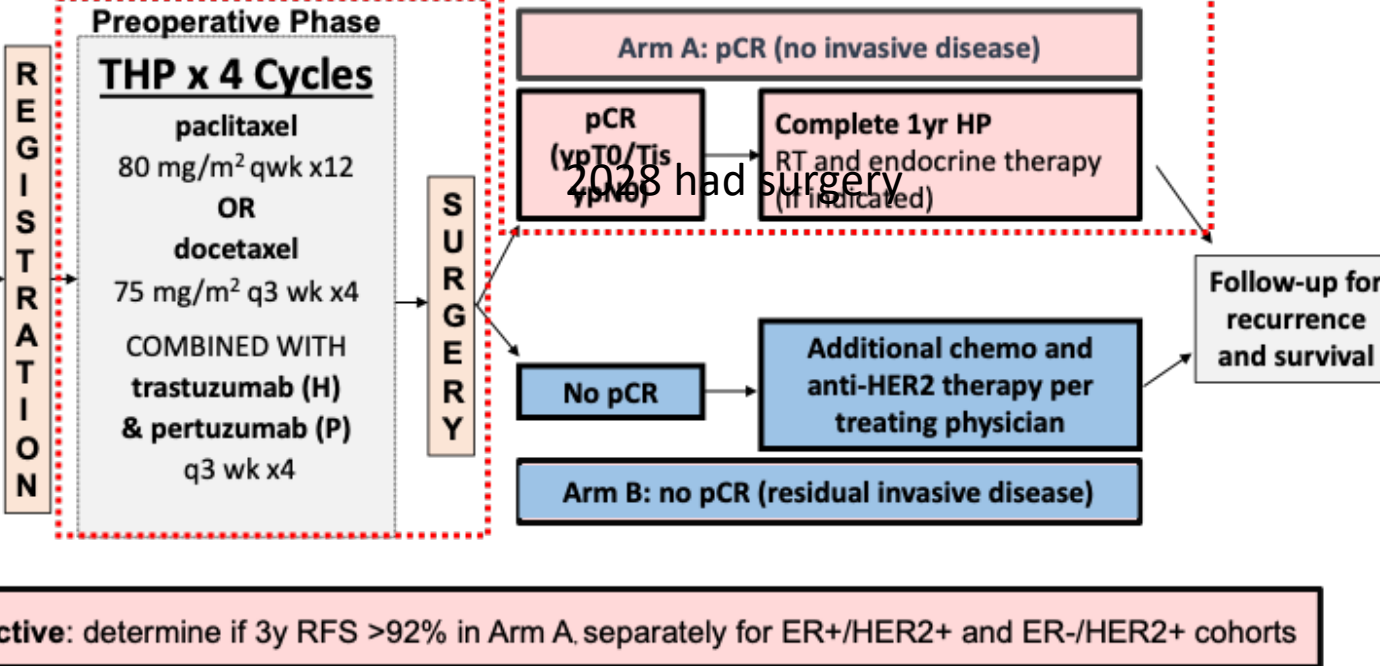
Activation Feb 2020
Accrued thru Oct 2023

Target accrual: n=2,156
Accrual completed n=2,175

Eligibility: *
Stage II or IIIA HER2+ BC

- cN0 eligible if T >2 cm*
- cN1-2 eligible, any T1-3
- T4, N3 NOT eligible

*ER+ cT 2-3 cm, cN0 capped at 20% of study population
ER+ defined as ≥1% ER+



Median age: 55 years

White race: 75%

ECOG PS 0: 88%

Clinical stage IIA: 58%

Clinical stage T2: 75%

Clinical stage N+: 46%

Taxane received: paclitaxel 63%

Grade 3: 56%

ER-: 36%

ER+: ~2/3 >70% expression

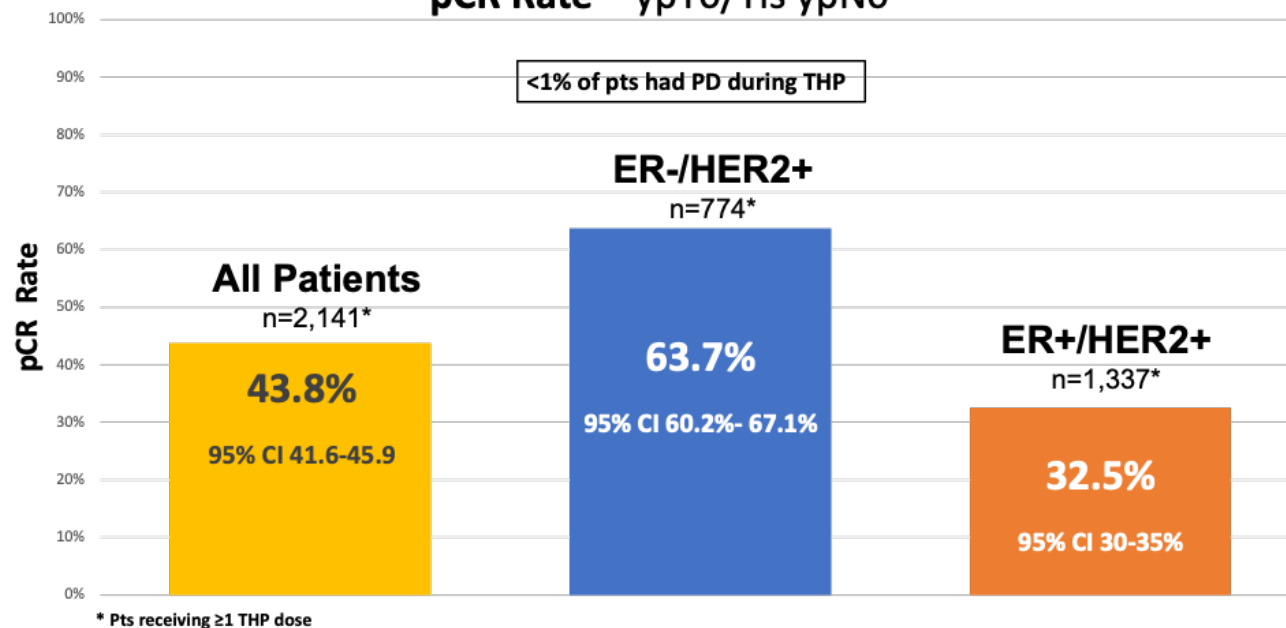
HER2 IHC 3+: 79%

ER+ compared to ER- tumors

Fewer grade 3

More HER2 IHC 2+/ISH+

pCR Rate* ypT0/Tis ypN0



• HER2Dx pCR likelihood score

- 27 genes: immune activation, luminal differentiation, tumor cell proliferation, HER2 amplicon
 - 569 out of 2141 patients had testing available
 - High HER2DX pCR score associated with a ~40% higher absolute pCR rate compared to a low score

In multivariate analysis, 3 CP factors and 3 molecular markers were associated with pCR

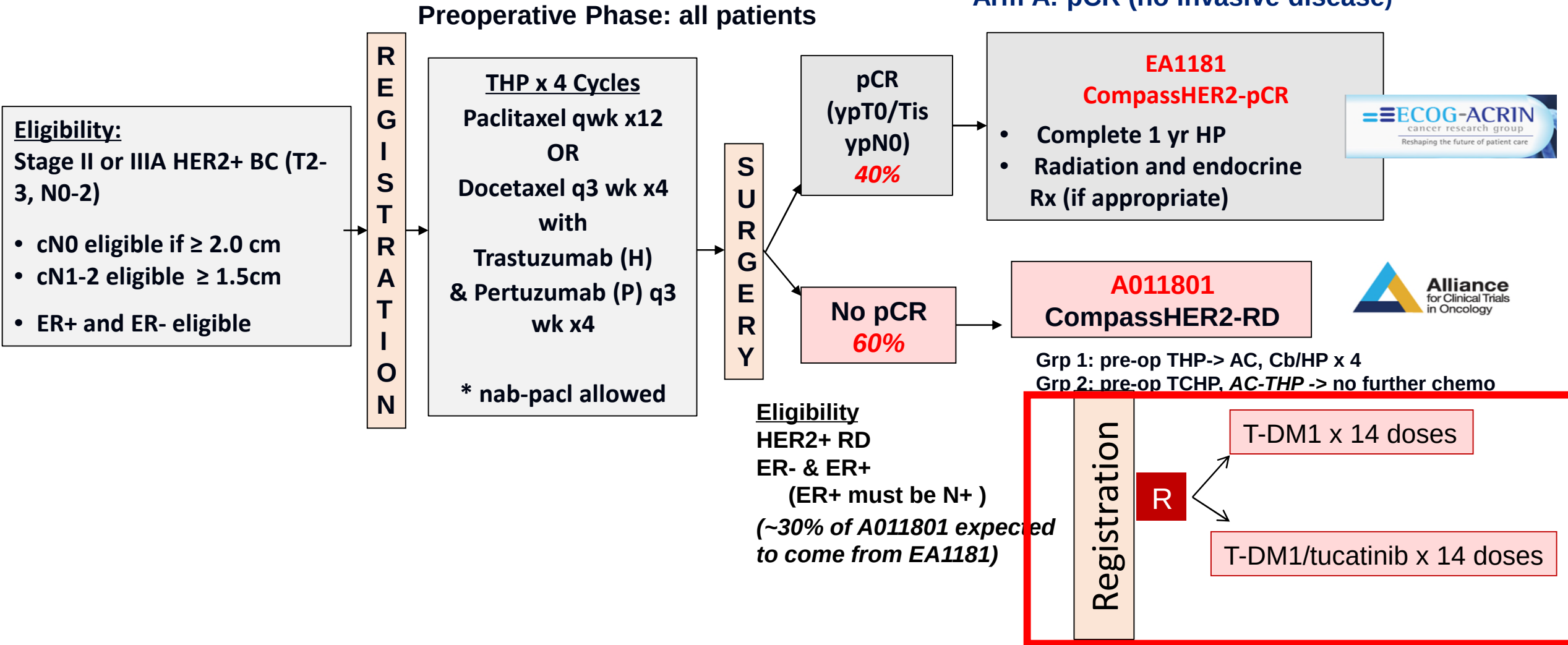
Clinical Factor/Biomarker		OR for pCR (95% CI)	# patients
ERBB2 mRNA level	ERBB2/10 units	1.33 (1.16-1.51)	569
Intrinsic subtype	non-HER2E	1.0	216
	HER2E	2.69 (1.63-4.42)	353
IgG			
	IgG/10 units	1.09 (1.02-1.16)	569
ER	ER+ >70%	1.0	244
	ER 11-70%	2.71 (1.39-5.27)	64
	ER 1-10%	2.89 (1.14-7.33)	31
	ER-	4.21 (2.57-6.91)	230
HER2 IHC			
	2+/ISH+	1.0	85
	3+	2.74 (1.14-6.59)	461
Taxane			
	docetaxel	1.0	188
	paclitaxel	1.76 (1.12-2.75)	368

	ER- (n=230)		ER+ (n=339)	
HER2Dx score	n (%) of pts	pCR rate	n (%) of pts	pCR rate
High	147 (64%)	70%	36 (11%)	58%
Low	13 (6%)	31%	214 (63%)	18%
p value		p <0.01		p <0.01

COMPASSHER2 TRIALS



Arm A: pCR (no invasive disease)



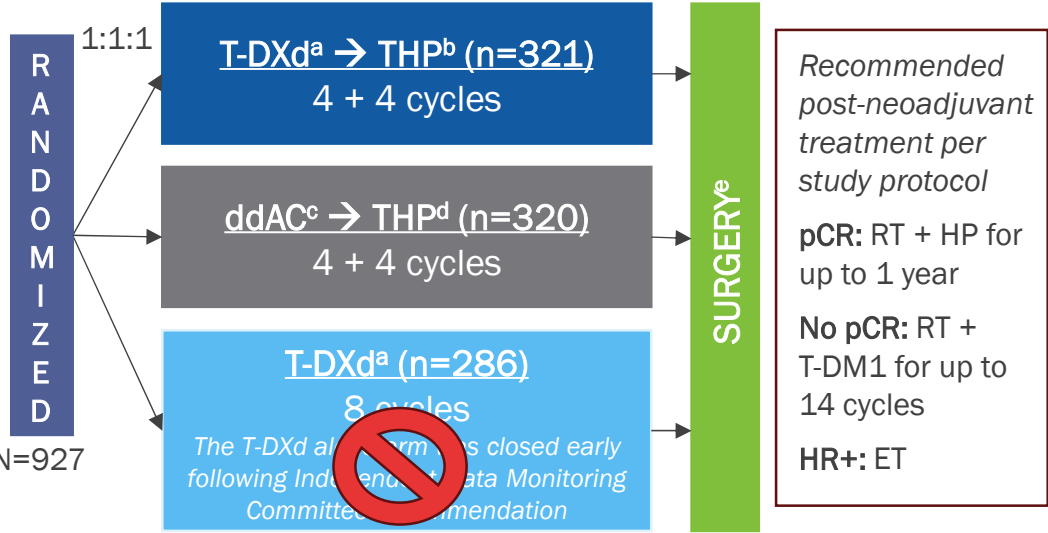
Summary

- Can we omit carboplatin from standard neoadjuvant THP for HER2+ ESBC?
 - Yes, with caveats
 - Need more data in stage III disease
 - Would recommend weekly paclitaxel or q3 week docetaxel
 - Await EFS, DFS, OS data and biomarker data
- Compass: pCR for stage II/III HER2+ BC) was 44% (64% ER- and 33% ER+)
 - Factors associated with higher pCR rate:
 - ER+ $\leq$ 70%; HER2 IHC 3+: weekly paclitaxel; higher HER2Dx pCR score
- Primary aim of 3y RFS in Compass among patients with pCR is maturing
 - Rescue strategy with tucatinib added to T-DM1: toxicities
- CP factors & molecular tools may be able to select the best candidates for less intensive chemotherapy in operable HER2+ BC

DESTINY-Breast11 Phase 3 Trial of Neoadjuvant T-DXd Alone or Followed by THP vs SOC for High-Risk HER2+ EBC: Study Design and Patients

Key Eligibility Criteria

- Previously untreated HR+ or HR- HER2+ EBC
- High risk defined as:
 - ≥cT3 and N0-3 or cT0-4 and N1-3
 - Inflammatory breast cancer



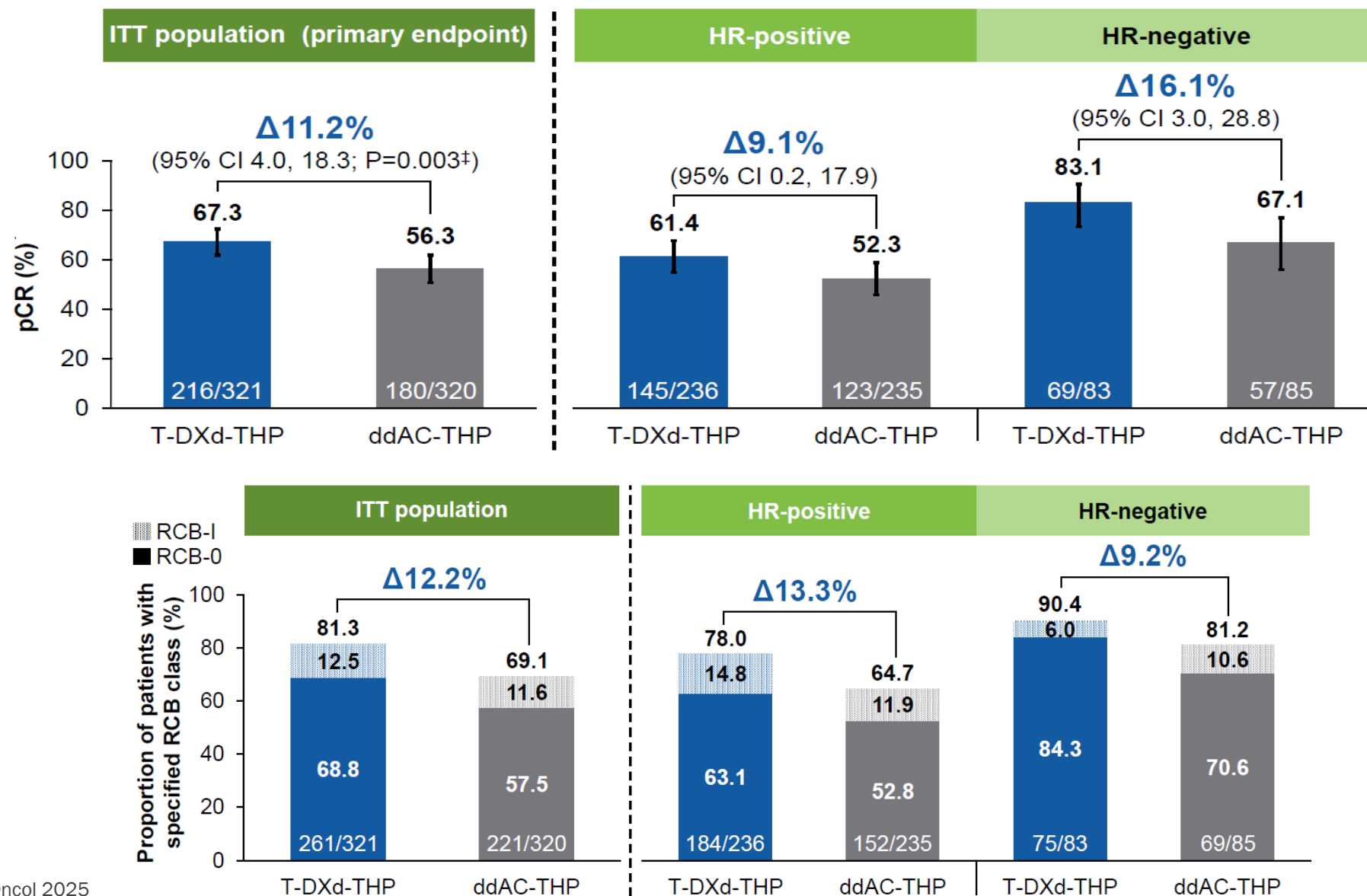
Primary endpoint: pCR (ypT0/is ypN0) by BCR
Secondary endpoints: pCR (ypT0 ypN0) by BCR, EFS, safety, PK and immunogenicity, IDFS, OS, HRQoL

Patient Characteristics, n (%)		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)
Geographic region	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)
HR+		236 (73.5)	235 (73.4)	205 (71.7)
Clinical tumor stage	cT0-2	176 (54.8)	188 (58.8)	157 (54.9)
	cT3-4	145 (45.2)	132 (41.3)	129 (45.1)
Nodal status	N0	26 (8.1)	35 (10.9)	20 (7.0)
	N+	287 (89.4)	281 (87.8)	254 (88.8)

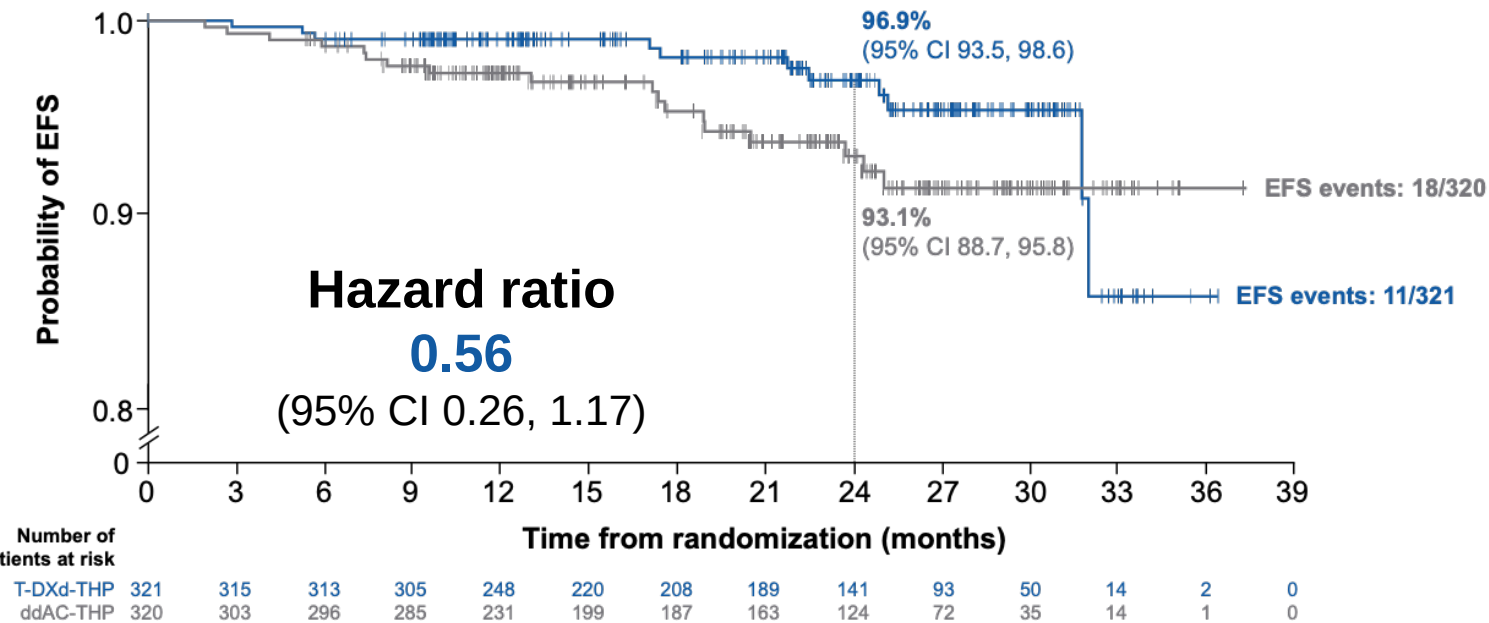
On March 13, 2024, the T-DXd alone arm closed following Independent Data Monitoring Committee recommendation.^a Patients who were still receiving T-DXd alone could remain on therapy or immediately switch to local SOC.

^a 5.4 mg/kg q3w. ^b Paclitaxel (80 mg/m² qw) + trastuzumab (6 mg/kg q3w) + pertuzumab (840 mg loading dose followed by 420 mg q3w).
^c Doxorubicin (60 mg/m² q2w) + cyclophosphamide (600 mg/m² q2w). ^d Paclitaxel (80 mg/m² qw) + trastuzumab (8 mg/kg loading dose followed by 6 mg/kg q3w) + pertuzumab (840 mg loading dose followed by 420 mg q3w). ^e Recommended window for surgery was 3-6 weeks following administration of the last dose of neoadjuvant study treatment.
Harbeck N, et al. Ann Oncol 2025.

DESTINY-Breast11: pCR and RCB with T-DXd-THP vs AC-THP



EFS and Post Surgery Treatment

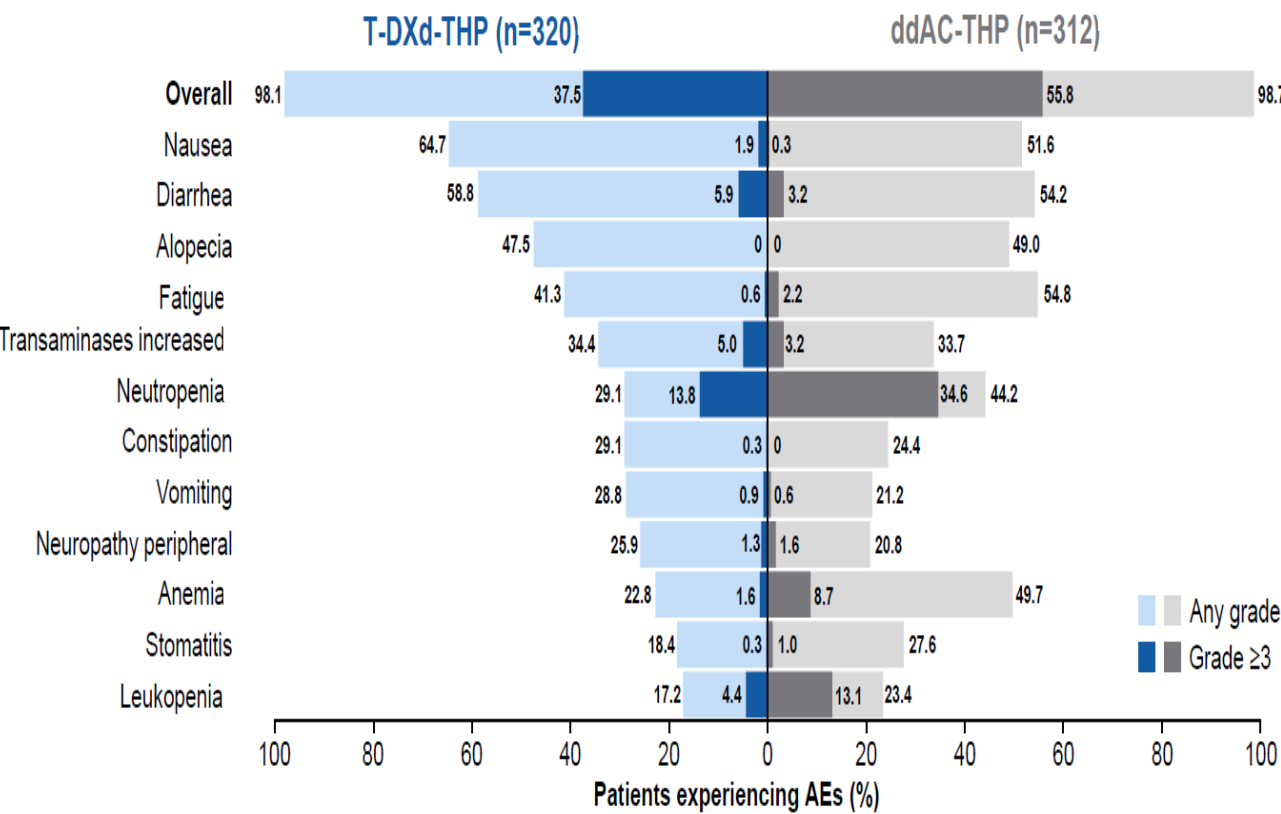


- Post neoadjuvant treatment for patients without pCR
 - T-DM1
 - T-DXd/THP: 52.6%
 - ddAC/THP: 56.9%
 - Trastuzumab regimen
 - T-DXd/THP: 38.9%
 - ddAC/THP: 26.2%

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

At data cutoff (March 12, 2025),
EFS event maturity was 4.5%; at final cutoff, maturity is predicted to be ~10%*

DESTINY-Breast11 Phase 3 Trial of Neoadjuvant T-DXd Alone or Followed by THP vs SOC for High-Risk HER2+ EBC: Safety



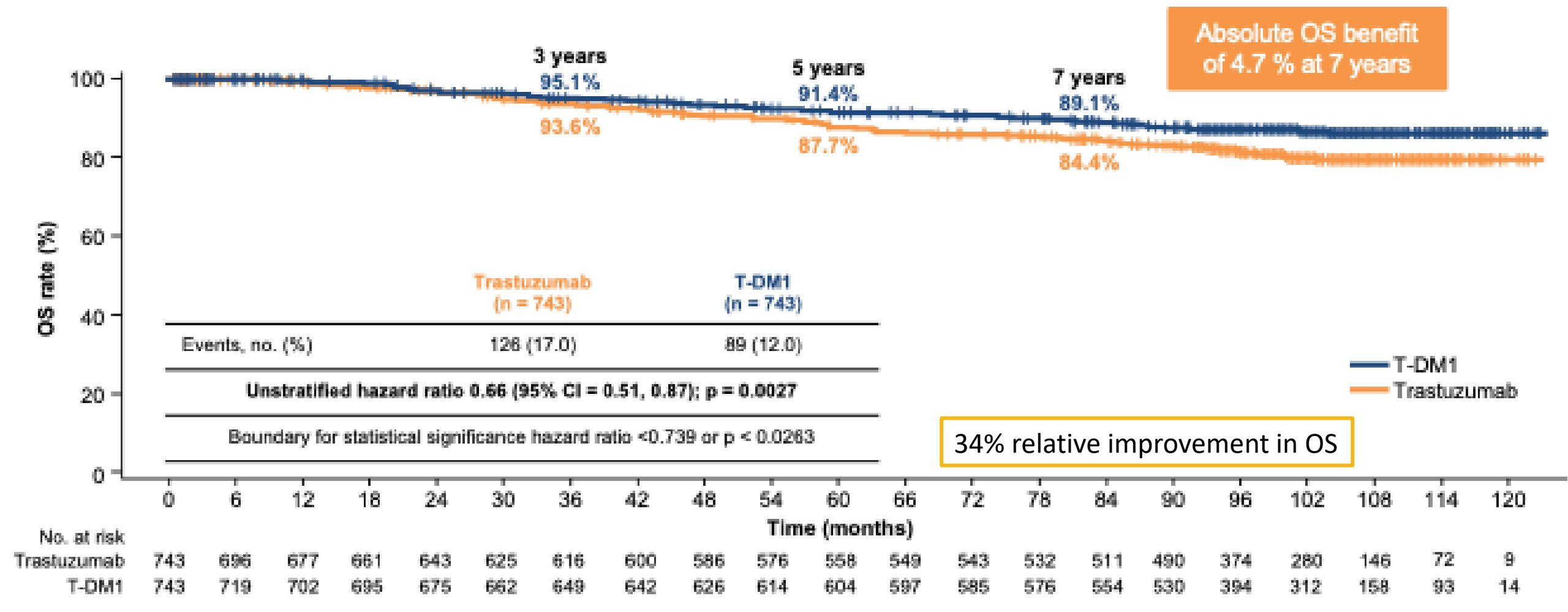
Safety Overview, n (%)	T-DXd-THP (n=320)	ddAC-THP (n=312)
Any AE	314 (98.1)	308 (98.7)
Grade ≥3	120 (37.5)	174 (55.8)
Any SAE	34 (10.6)	63 (20.2)
AE leading to any dose reduction	58 (18.1)	60 (19.2)
AE leading to any drug interruption	121 (37.8)	170 (54.5)
AE leading to any treatment discontinuation	45 (14.1)	31 (9.9)
Any AE with outcome of death ^a	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 ^b	11 (3.4)	8 (2.6)

Monitoring:

- **High-res CT chest scans:** Q6W during treatment; if ILD/pneumonitis was suspected on T-DXd, treatment was interrupted and a full investigation completed
- **Echo or MUGA:** during screening (<28 days prior to randomization), during treatment (<3 days before Cycle 5), and at end of treatment to assess LVEF

Improving Post-Neoadjuvant Therapy for HER2+ ESBC

KATHERINE OS Final Analysis; Median Follow-up 8.4 Years (101 months)

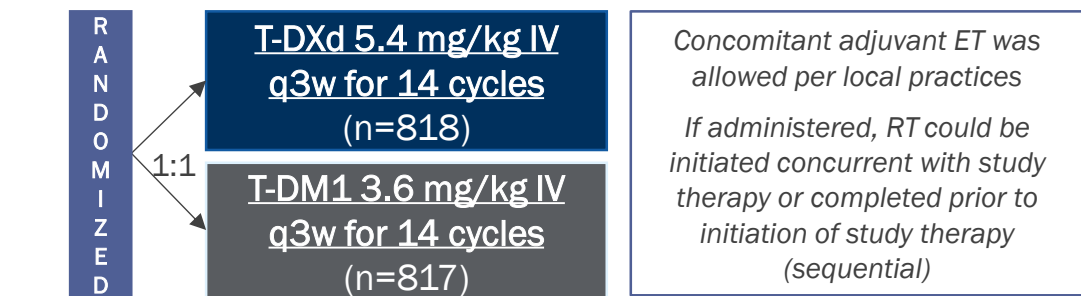


* p-value for IDFS is now exploratory given the statistical significance was established at the primary analysis.
CI, confidence interval; IDFS, invasive disease-free survival; T-DM1, ado-trastuzumab emtansine.

Interim Analysis of DESTINY-Breast05 Phase 3 Trial of T-DXd vs T-DM1 in High-Risk HER2+ EBC: Study Design and Patients

Key Eligibility Criteria

- Centrally confirmed HER2+ (IHC 3+ or ISH+) EBC with residual invasive disease in breast and/or axillary lymph nodes after NAT with HER2-directed therapy^a
- High-risk defined as presentation prior to NAT with:
 - Inoperable EBC (cT4, N0-3, M0 or cT1-3, N2-3, M0) OR
 - Operable EBC (cT1-3, N0-1, M0) with axillary node-positive disease (ypN1-3) after NAT



ILD monitoring program for patients treated with RT

- All patients had baseline non-contrast, low dose (LD) chest CT during screening
- All RT patients (concurrent and sequential) had LD chest CT 6 weeks after start of study therapy, then Q12W while on therapy, and at 40-day follow-up
- Sequential RT patients had additional LD chest CT after completion of RT prior to therapy

Primary endpoint: IDFS

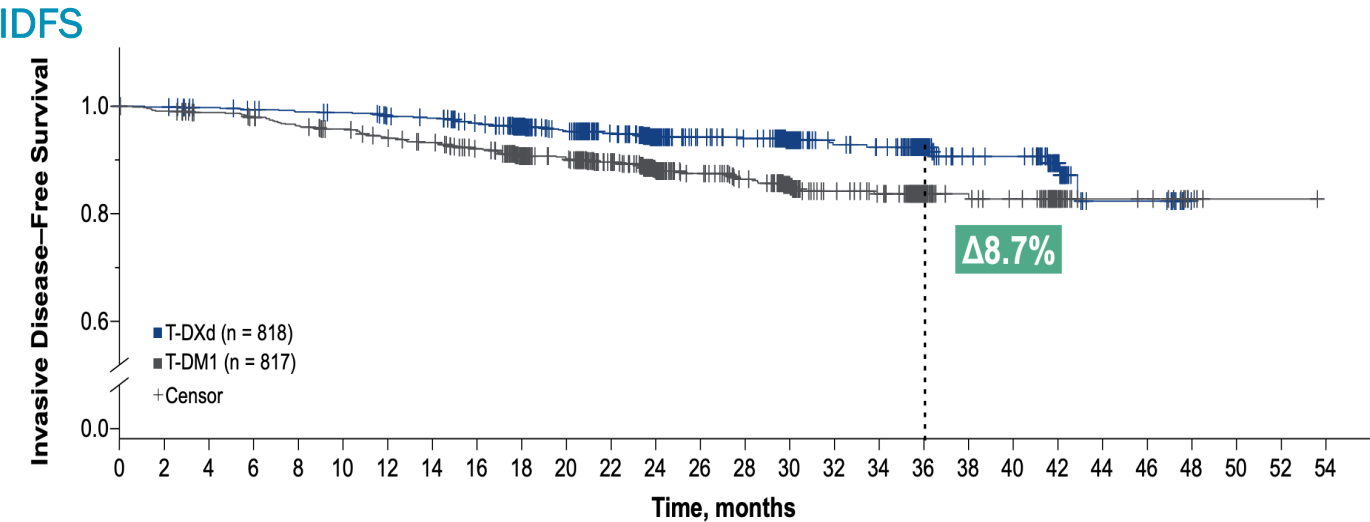
Key secondary endpoint: DFS

Secondary endpoints: OS, BMFI, DRFI, safety

Patient Characteristics, n (%)		T-DXd (n=818)	T-DM1 (n=817)
Median age (range), years		50.3 (24-78)	50.6 (21-83)
HER2 expression	IHC 3+	676 (82.6)	670 (82.0)
	IHC 2+ and ISH+	129 (15.8)	133 (16.3)
	IHC 2+ and ISH-	2 (0.2)	0
	IHC 1+ and ISH+	11 (1.3)	14 (1.7)
HR+		581 (71.0)	583 (71.4)
Inoperable disease at presentation		431 (52.7)	424 (51.9)
Positive nodal status after NAT		660 (80.7)	658 (80.5)
Neoadjuvant HER2-targeted therapy	H	176 (21.5)	171 (20.9)
	HP	637 (77.9)	641 (78.5)
	Other	5 (0.6)	5 (0.6)
Radiotherapy treatment	Concurrent	438 (53.5)	480 (58.8)
	Sequential	326 (39.9)	279 (34.1)
	No radiotherapy	54 (6.6)	58 (7.1)

^a NAT is defined as ≥16 weeks' NAT with ≥9 weeks trastuzumab ± pertuzumab and ≥9 weeks taxane-based Chemo. b Geyer CE, et al. ESMO 2025. Abstract LBA1; Loibl et al, NEJM 2025

DESTINY-Breast05: IDFS with T-DXd vs T-DM1 in High-Risk HER2+ EBC

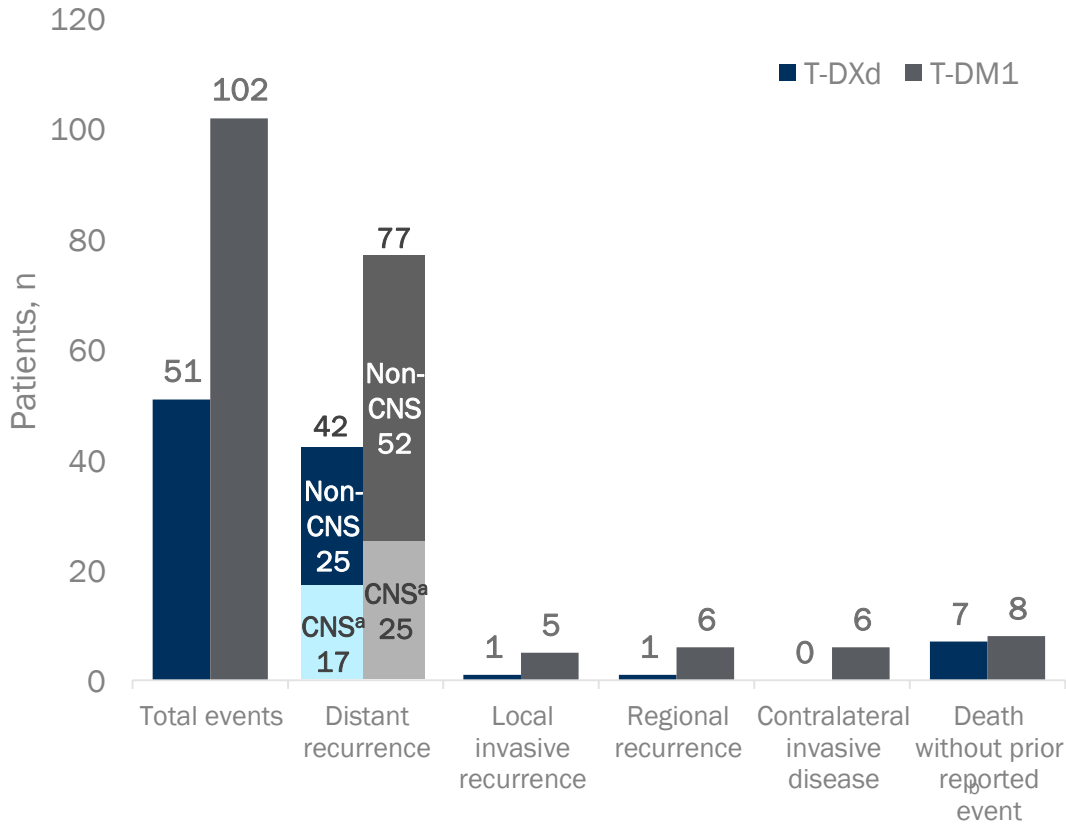


Number at Risk:

T-DXd	818	788	781	776	771	768	758	753	731	684	634	544	440	380	370	275	218	212	129	92	90	46	14	14	0	0	0	0
T-DM1	817	781	769	760	745	734	719	708	687	632	599	527	417	355	337	233	186	177	120	84	79	38	14	13	4	1	1	0

Outcome Measure	T-DXd (n=818)	T-DM1 (n=817)
Patients with events, n (%)	51 (6.2)	102 (12.5)
3-year IDFS, % (95% CI)	92.4 (89.7-94.4)	83.7 (80.2-86.7)
HR (95% CI)	0.47 (0.34-0.66)	
P value	<0.0001	

Categories of First IDFS Events

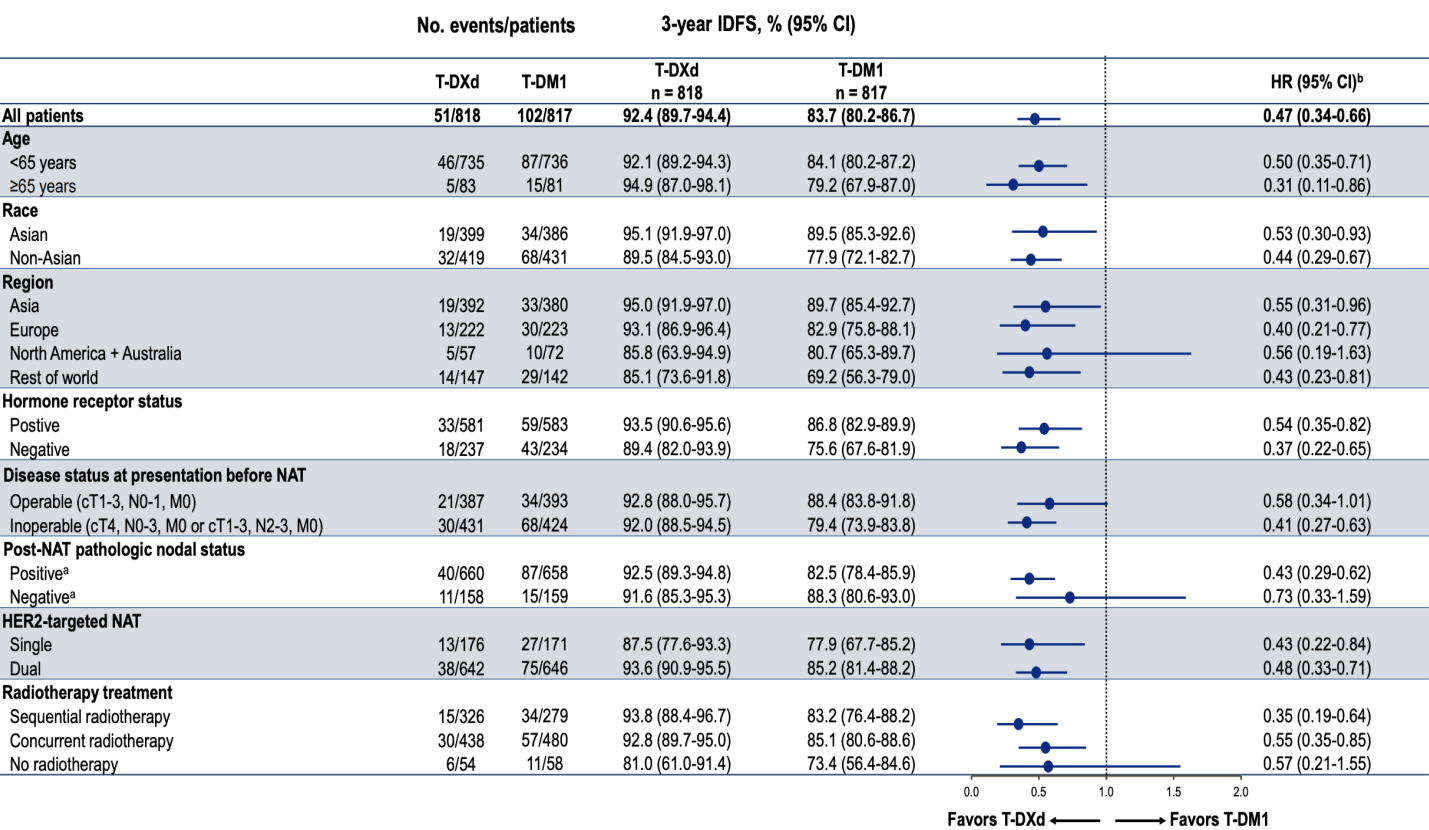


^a CNS as sole site for distant recurrence or one of multiple distant recurrent sites. ^b Causes of death in the T-DXd arm were 2 drug-related ILD, unrelated respiratory tract infection, acute respiratory failure (outside AE reporting period), acute respiratory distress syndrome (outside AE reporting period), and 2 disease progression, and in the T-DM1 arm were drug-related sepsis, unrelated ovarian cancer, unrelated aneurysm, unrelated pneumothorax, unrelated leiomyosarcoma, self-inflicted gun wound, and 2 disease progression.

Geyer CE, et al. ESMO 2025. Abstract LBA1; Loibl et al, NEJM 2025

DESTINY-Breast05: Additional Efficacy Analyses

IDFS Subgroup Analysis



Central HER2 status						
IHC 3+	46/676	86/670	91.8 (88.7–94.1)	83.2 (79.2–86.5)		0.49 (0.34–0.70)
ISH-positive	5/140	16/147	96.2 (91.0–98.4)	86.5 (78.1–91.8)		0.35 (0.13–0.97)

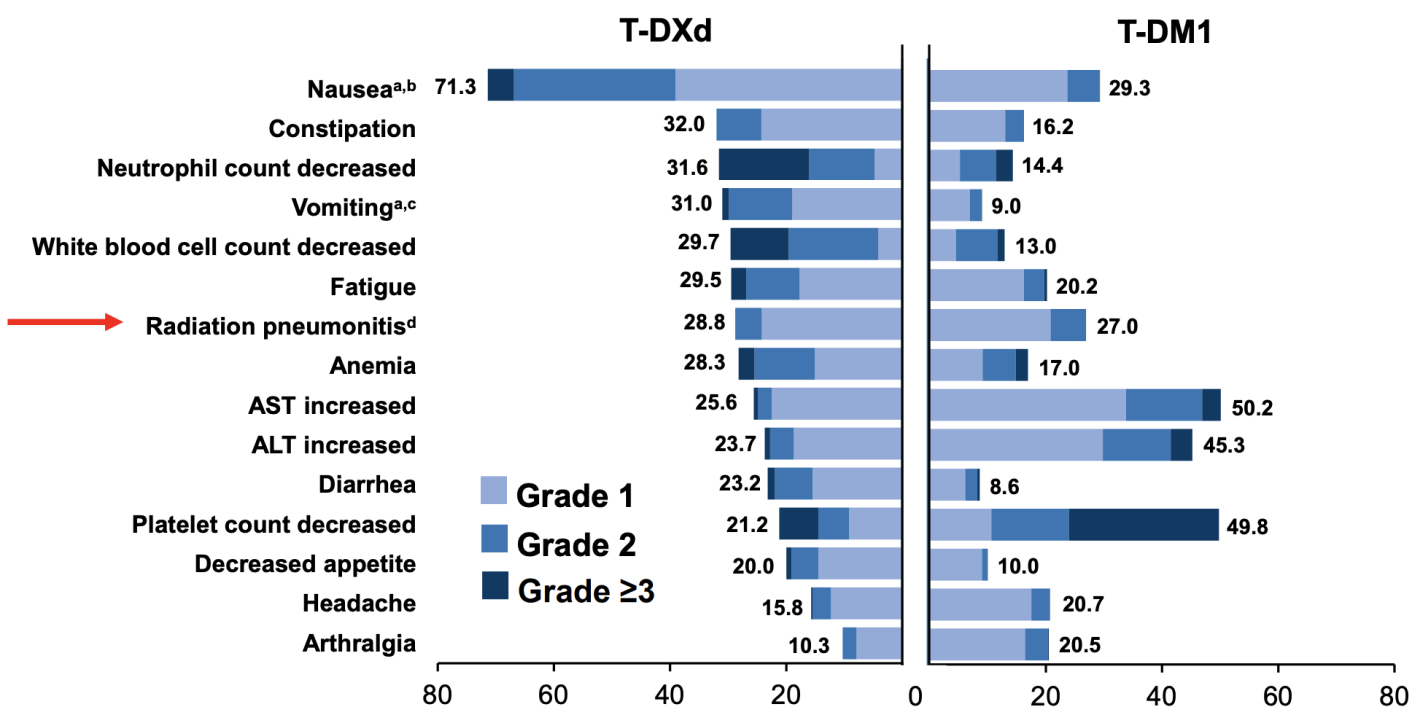
^a Positive pathologic nodal status defined as ypN1-3, and negative pathologic nodal status defined as ypN0. ^b From unstratified Cox proportional hazards model.
Geyer CE, et al. ESMO 2025. Abstract LBA1; Loibl et al, NEJM 2025

Outcome Measure		T-DXd (n=818)	T-DM1 (n=817)
DRFI ^b	Events, n (%)	42 (5.1)	81 (9.9)
	3-year DRFI, % (95% CI)	93.9 (91.4-95.7)	86.1 (82.5-89.1)
	HR (95% CI)	0.49 (0.34-0.71)	
BMFI	Patients with recurrence in CNS, n (%)	17 (2.1)	26 (3.2)
	3-year BMFI rate, % (95% CI)	97.6 (96.2-98.5)	95.8 (93.6-97.2)
	HR (95% CI)	0.64 (0.35-1.17)	
OS	2.9% maturity		
	Patient deaths, n (%)	18 (2.2)	29 (3.5)
	3-year survival, % (95% CI)	97.4 (95.8-98.4)	95.7 (93.5-97.2)
	HR (95% CI)	0.61 (0.34-1.10)	

Absolute improvement in DFS: 8.8%

Interim Analysis of DESTINY-Breast05 : Safety

TEAEs in ≥20% of Patients



Safety Overview		T-DXd (n=806) ^a	T-DM1 (n=801) ^a
Overall TEAEs	Any grade	802 (99.5)	788 (98.4)
	Grade ≥3	408 (50.6)	416 (51.9)
	Serious	140 (17.4)	109 (13.6)
	Associated with drug d/c	144 (17.9)	103 (12.9)
	Associated with deaths	3 (0.4)	5 (0.6)
Adjudicated Drug-related ILD ^b	Any grade	77 (9.6)	13 (1.6)
	Grade 1	16 (2.0)	8 (1.0)
	Grade 2	52 (6.5)	5 (0.6)
	Grade 3	7 (0.9)	0
	Grade ≥4	2 (0.2) ^c	0
LV Dysfunction	Any grade	23 (2.9)	14 (1.7)
	Grade 1	1 (0.1)	0
	Grade 2	20 (2.5)	11 (1.4)
	Grade 3	2 (0.2)	3 (0.4)
	Grade ≥4	0	0

^a Prophylactic antiemetics were recommended but not mandatory. ^b In the T-DXd and T-DM1 arms: 39.1% and 23.7% grade 1, 27.8% and 5.5% grade 2, and 4.5% and 0.1% grade 3 events, respectively. ^c In the T-DXd and T-DM1 arms: 19.0% and 6.9% grade 1, 10.9% and 2.0% grade 2, and 1.1% and 0.1% grade 3 events, respectively. ^d In the T-DXd and T-DM1 arms: 24.2% and 20.8% grade 1 and 4.6% and 6.1% grade 2 events, respectively. Geyer CE, et al. ESMO 2025. Abstract LBA1; Loibl et al, NEJM 2025

ILD Risks in Early-Stage Disease

Destiny Breast05: 14 cycles of adjuvant T-DXd

- Drug-related ILD: 9.6%
 - Grade 5: 0.2% (n=2)
 - Associated with drug discontinuation: 10.8%

Destiny Breast11: 4 cycles of neoadjuvant T-DXd then THP

- Drug-related ILD: 4.4% vs 5.1% for control
 - Grade 5: 0.3% (n=1), identical to ddAC/THP
 - No difference in delay to surgery (~3%)
 - More treatment interruption with DDAC/THP

What did we learn?

- Duration of T-DXd clearly plays a role in risk and severity of ILD
- Radiation does not appear to increase risk or severity of ILD
- Mortality persists despite optimal management
 - Rates are lower than that seen in the metastatic setting
 - Mortality may be a later risk in some cases, related to subsequent therapy

DB05: Role of adjuvant Radiation

- Timing of adjuvant RT did not impact incidence or severity of adj drug-related ILD in either arm
 - Concurrent: 9.6% (n=438), 1 gr 5
 - Sequential: 10.7% (n=319), 1 gr 5
- T-DXd arm: adjuvant RT timing had no effect on time to onset or duration of adj drug-related ILD
- Most patients with drug-related ILD had recovered or were recovering at the data cutoff
 - T-DXd arm: The proportion recovered from ILD was higher with concurrent RT vs sequential RT (69.0% vs 58.8%)

Neoadjuvant or Adjuvant?

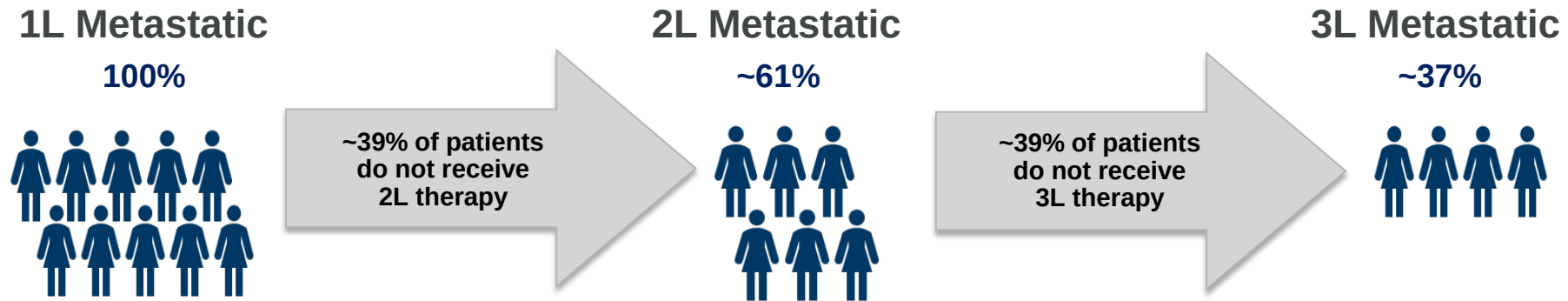
- Individualizing therapy based on response is a critical next step
 - THP is sufficient for a subset of patients, as is T-DXd x 4
- Start with THP then rescue pre-operatively with T-DXd? (NCCN 2026)?
 - Toxicities of hair loss and peripheral neuropathy can be largely avoided with cooling techniques
 - Allows continued rescue with T-DXd if responding but non-pCR
- If we start with T-DXd, and there is residual disease after THP, what is the next best step?
 - Essentially unknown – more T-DXd? T-DM1?
- At present, and with regulatory approval
 - DB11 for high risk/high disease burden
 - Start with THP (or TH for stage I), rescue with T-DXd pre-op for lower risk disease
 - If residual disease following TCHP or THP, rescue with T-DXd post-surgery
 - It is safe to give concomitant radiation with T-DXd
 - Optimal management of toxicity is critical
- Next steps
 - Imaging and ctDNA to individualize response
 - Early clearance of ctDNA correlates with pCR and EFS in multiple studies
- MRI functional tumor volume plus biopsy and ctDNA correlates highly with pCR

Individualizing therapy will help cure more patients with high risk HER2+ ESBC

Treatment Options for HER2-Positive mBC Are Expanding, Yet Not All Patients Receive Multiple Lines of Therapy^{1-6a}

Early intervention with optimal HER2-directed therapies is crucial for improving outcomes in HER2-positive mBC¹

HER2-Positive mBC Real-World Patient Attrition Rates^{1-6,a}

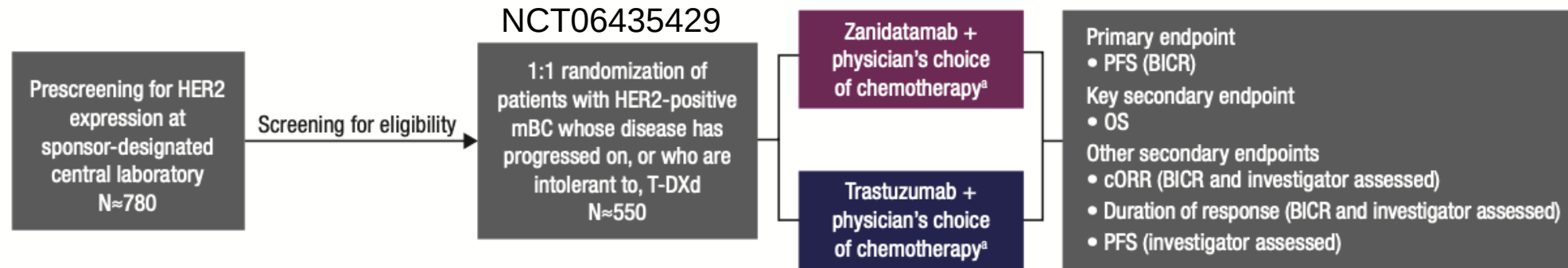


Significant patient drop-off rates from one therapy line to the next highlight the need for the most effective treatment to be used as early as possible

^aThe attrition rates portrayed are the calculated average of the attrition rates for the cited studies.

1. Hall PS et al. Presented at SABCS; Dec 5-9, 2023; San Antonio, TX. Poster PO3-16-11. 2. Hartkopf AD et al. *Geburtshilfe Frauenheilkd.* 2024;84(5):459-469. 3. Harper-Wynne C et al. Presented at 2023 ASCO Annual Meeting; June 2-6, 2023; Chicago, IL. Abstract e13039. 4. Ibragimova KIE et al. *Breast Cancer Res Treat.* 2023;198:239-251. 5. Varghese D et al. Presented at SABCS; Dec 6-10, 2022; San Antonio, TX. Poster #P1-11-19. 6. Lam C et al. Presented at SABCS; Dec 6-10, 2022; San Antonio, TX. Poster #P4-03-34.

EmpowHER-303: A Phase 3 Study to Evaluate the Efficacy and Safety of Zanidatamab vs Trastuzumab With Chemotherapy in Patients With Metastatic HER2+ Breast Cancer Whose Disease Has Progressed on T-DXd



Prescreening and HER2 testing to be done within 6 months of randomization

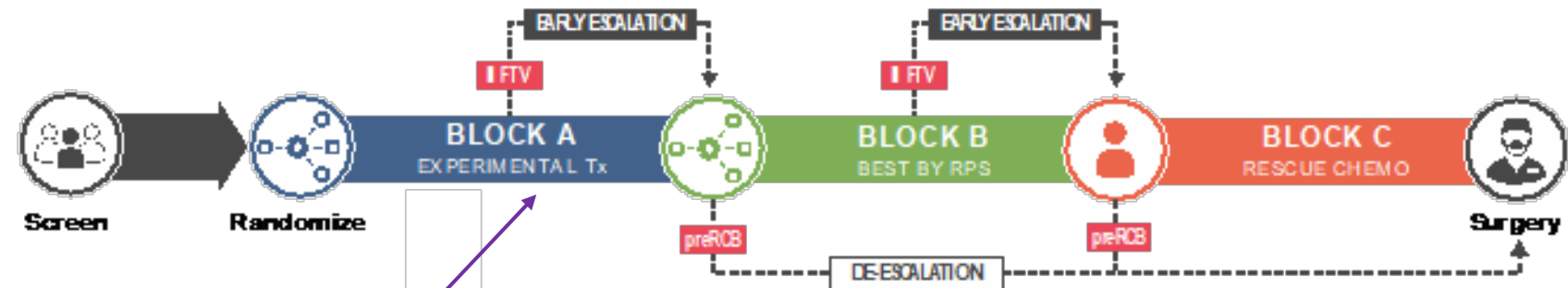
Tolaney et al, SABCS 2024 TIP

Physician's chemotherapy^a: eribulin, vinorelbine, gemcitabine, or capecitabine

I-SPY 2.2: Zanidatamab

Every 2 weeks x 6 doses in Block A
Expansion trial open now

- Randomized to block A v B 3:1
- Escalate to block B based on response at week 6
- Block B randomized to Zani or HP with chemotherapy
- Add carboplatin based on response in block B at week 3



Eligibility for Zanidatamab:
Anatomic Stage II/III
HER2 positive
All have Mammaprint/Blueprint

Treatment Assignment Stratification

HR+ HER2- Immune- DRD-	Taxol	AC
HR- HER2- Immune- DRD-	Taxol + Carbo + Pembro	AC + Pembro
HER2- Immune+	Taxol + Carbo + Pembro	AC + Pembro
HER2- Immune- DRD+	Taxol + Carbo + Pembro	AC + Pembro
HER2- Immune- DRD+	Taxol + Carbo	AC + Pembro

Destiny-Breast09: Moving T-DXd to the 1st Line Setting

Eligibility criteria

- HER2+ a/mBC
- Asymptomatic/inactive brain mets allowed
- DFI >6 mo from last chemotherapy or HER2-targeted therapy in neoadjuvant/adjuvant setting
- One prior line of ET for mBC permitted
- **No other prior systemic treatment for mBC[†]**

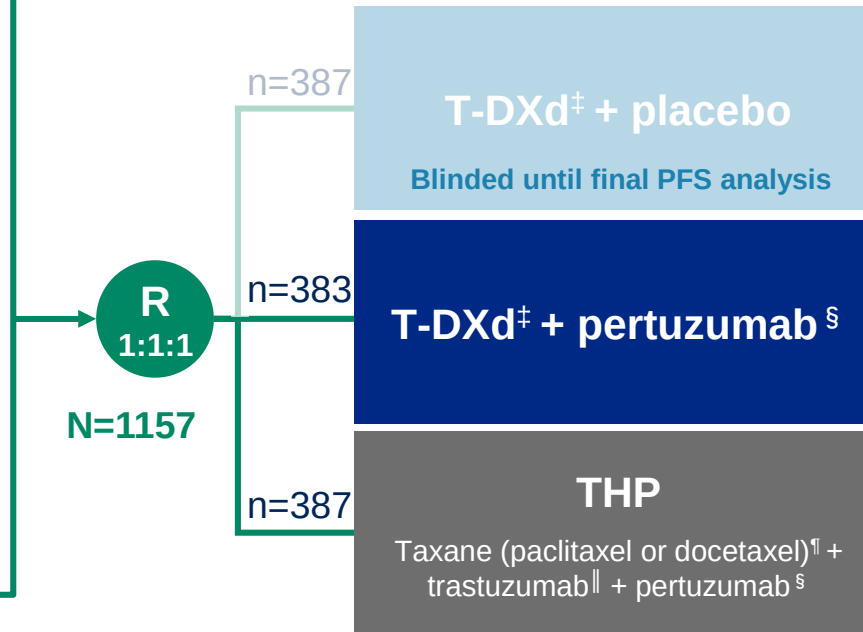
Stratification factors

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

ET allowed after TDXd x 6 or off taxane

Demographics

49% were treated in Asia
82% HER2 3+; 54% HR+; 30% *PIK3CA* mutations
52% had de novo metastatic disease, 71% visceral mets,
6% brain mets



Endpoints

Primary

- PFS (BICR)

Key secondary

- OS

Secondary

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

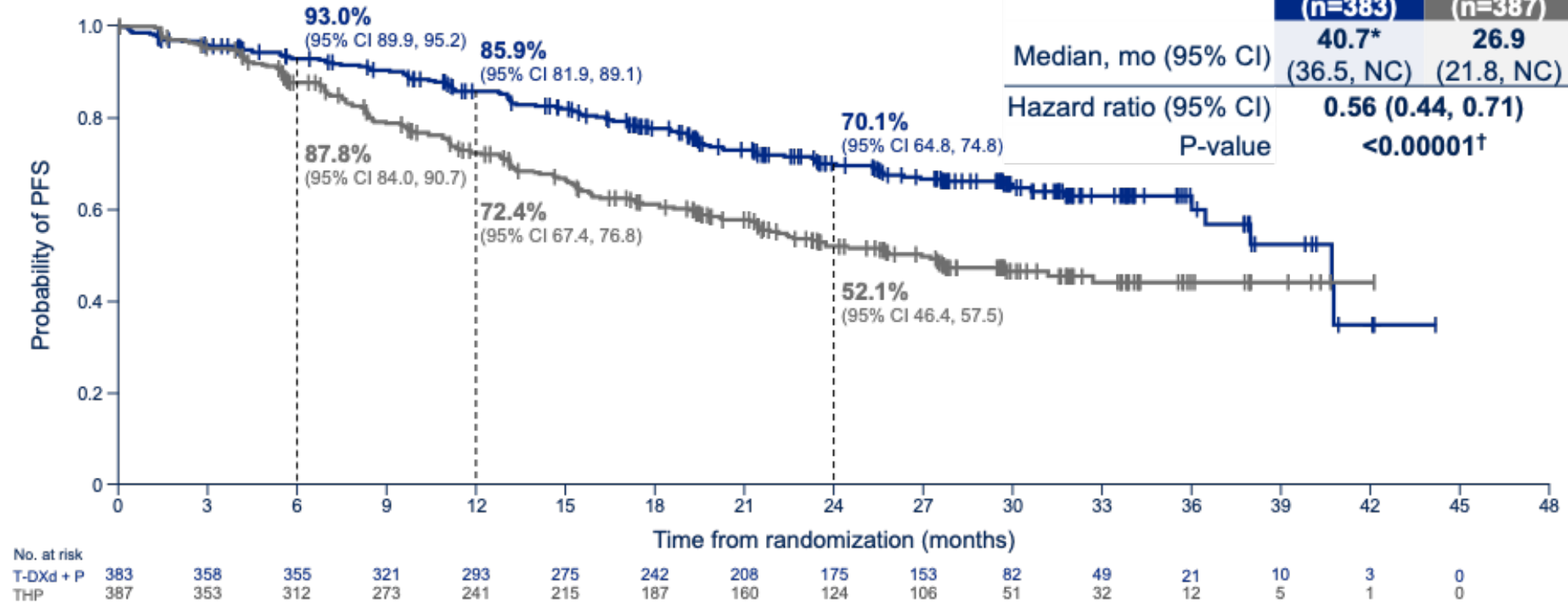
At DCO: 45.8% (n=174) T-DXd + P vs 33.4% (n=128) THP remained on any therapy

At the 1st planned interim analysis (DCO Feb 26, 2025), results were reported for the T-DXd + P and THP arms

Prior therapy

Only 7% had prior pertuzumab, 1% prior T-DM1 and 28.5% prior trastuzumab
40% prior chemotherapy, 20% prior ET

PFS (BICR): primary endpoint



Statistically significant and clinically meaningful PFS benefit with T-DXd + P (median Δ 13.8 mo)

*Median PFS estimate for T-DXd + P is likely to change at updated analysis; †stratified log-rank test. A P-value of <0.00043 was required for interim analysis superiority
BICR, blinded independent central review; CI, confidence interval; mo, months; (m)PFS, (median) progression-free survival; NC, not calculable; P, pertuzumab; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

- Consistent PFS benefit with T-DXd + P observed across stratification factors
 - Recurrent disease / prior treatment (~50% of patients in this setting)
 - HR-negative status (~50% of patients)
 - PIK3CA mutation (~30% of patients)

- Updates ESMO 2025 (Loibl et al)
 - PFS and ORR benefit seen across
 - Denovo and recurrent disease: HR 0.49 v 0.63
 - Across HR status: HR+ 0.61, HR- 0.52
 - Across mPIK3CA status: mut 0.52, wt 0.57
 - Await data on brain mets as first progression

Maintenance Therapy to Prolong Reponse: AFT-38 PATINA Phase 3 Trial of Palbociclib + Anti-HER2 Therapy + ET in HR+/HER2+ MBC

Key Eligibility Criteria

- HR+/HER2+ MBC
- 1st line induction therapy
 - 6-8 cycles Rx: tras ± pertuz and taxane/vinorelbine
- No evidence of disease progression

N=518

R
1:1

Palbo + Anti-HER2 + ET
Palbociclib (125 mg PO qd D1-D21) +
trastuzumab ± pertuzumab + ET^a

Anti-HER2 + ET
Trastuzumab ± pertuzumab + ET^a

Primary endpoint: INV-assessed PFS
Key secondary endpoint: OS

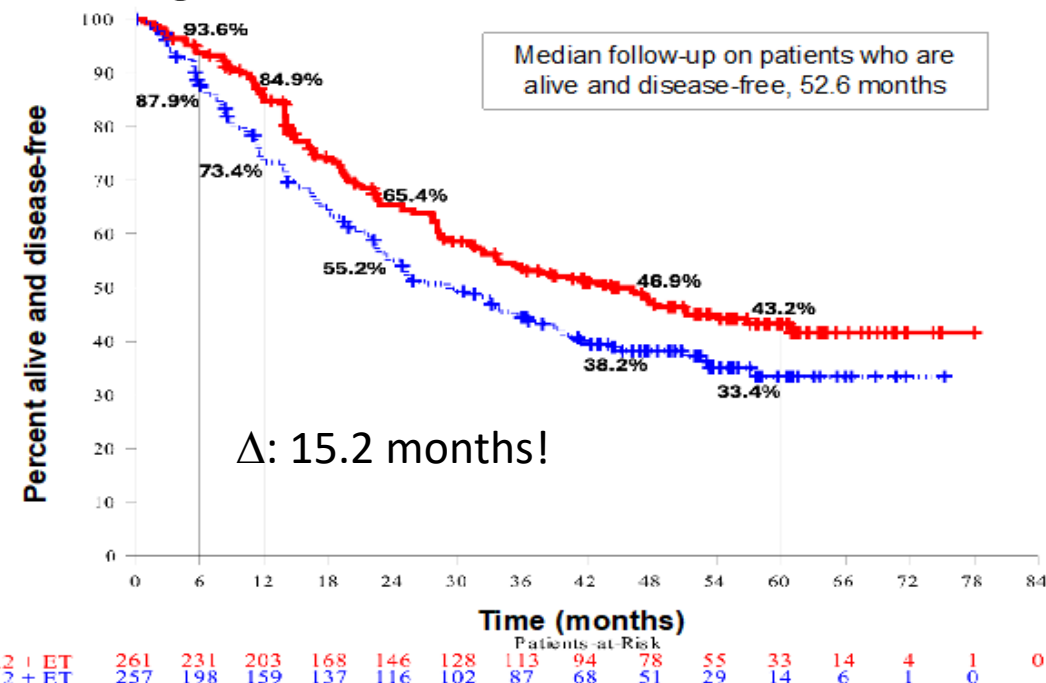
A new SOC!

Patient Characteristics, (%) N=518		Palbo + Anti-HER2 + ET (n=261)	Anti-HER2 + ET (n=257)
Median age (IQR), years		53.5 (43.6-60.4)	53.0 (45.1-62.8)
Median cycles of induction therapy (range), n		6 (4-8)	6 (4-8)
Pertuzumab use		253 (96.9)	251 (97.7)
Type of ET	AI	237 (90.8)	234 (91.1)
	Fulvestrant	24 (9.2)	23 (8.9)
Prior (neo)adjuvant anti-HER2 therapy	Yes	190 (72.8)	182 (70.8)
	No	71 (27.2)	75 (29.2)
Best response to induction therapy	CR or PR	179 (68.6)	176 (68.5)
	SD	82 (31.4)	81 (31.5)

Additional data

- Improved ORR
- OS early
- Safety: Well tolerated with low discontinuation rates
- Similar AEs, no Rx-related deaths

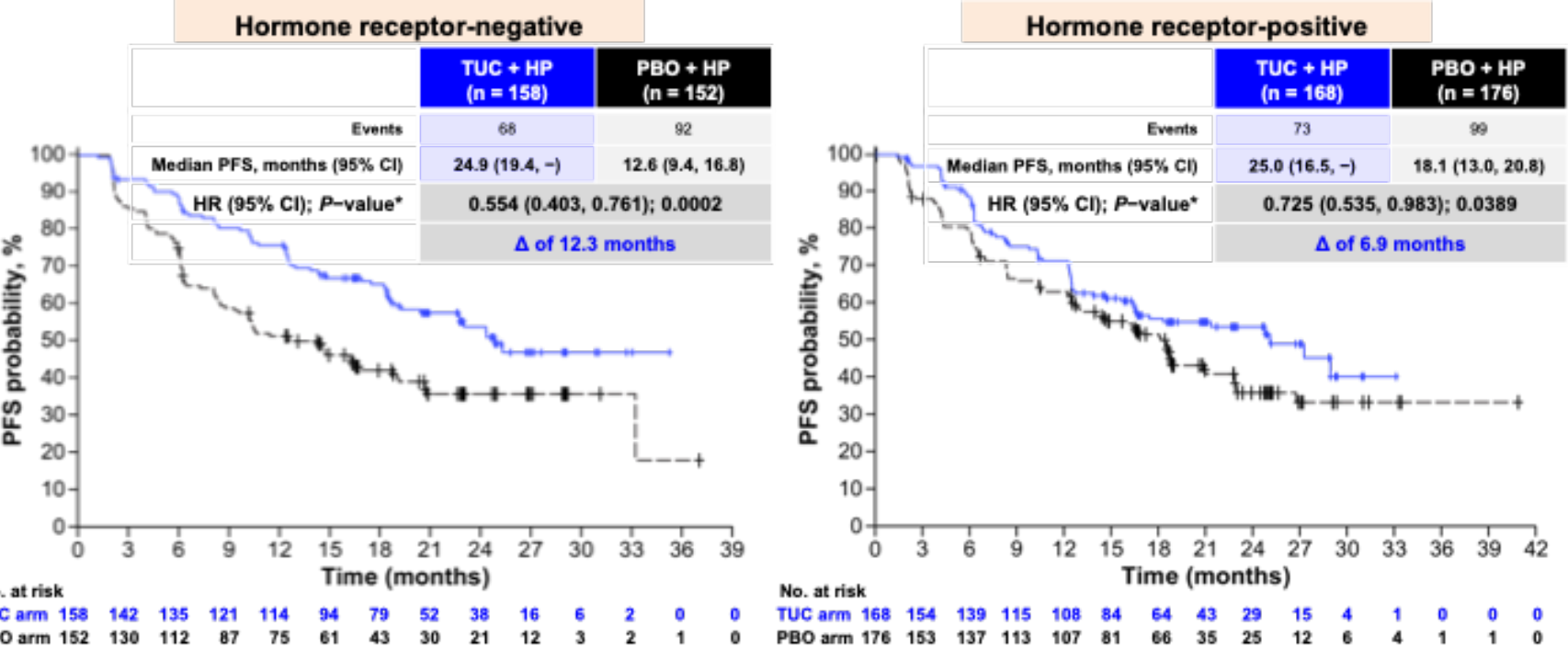
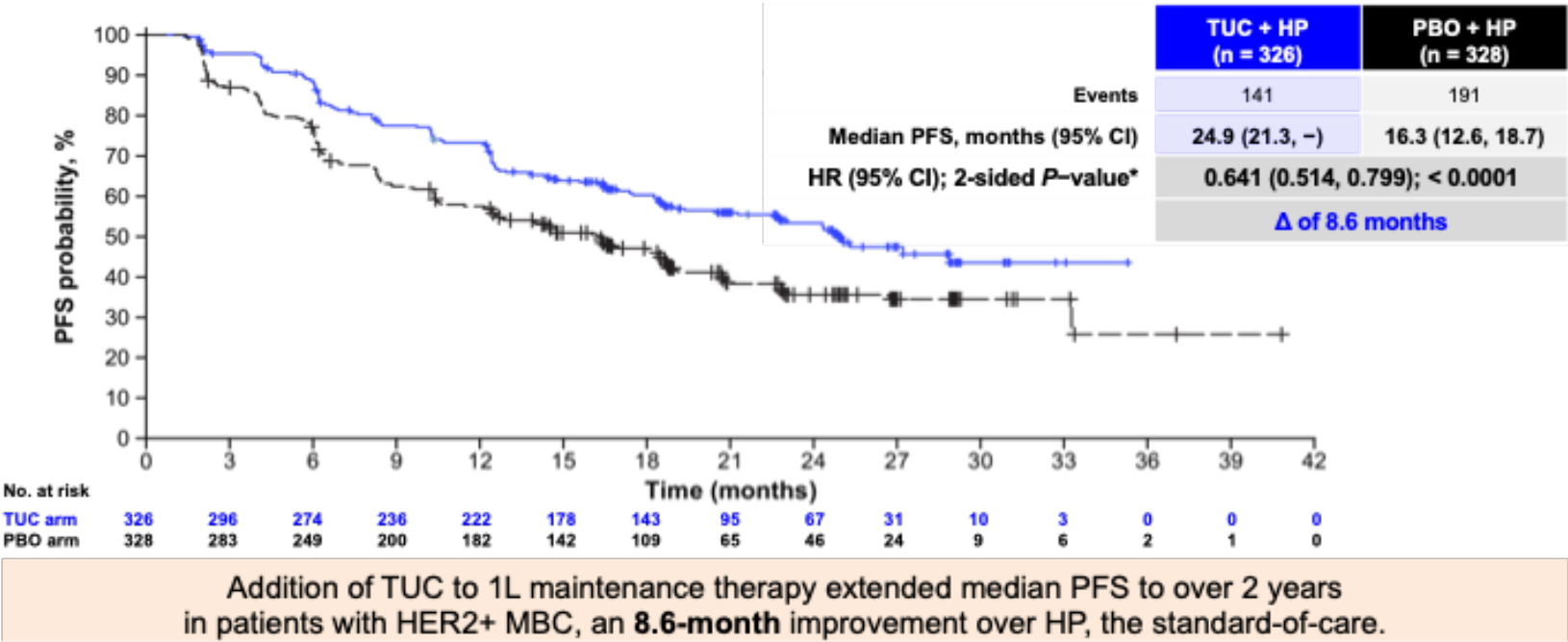
PFS (Investigator Assessed)



PFS	Palbo + Anti-HER2 + ET (n=261)	Anti-HER2 + ET (n=257)
Events	126	136
mPFS, months (95% CI)	44.3 (32.4-60.9)	29.1 (23.3-38.6)
HR (95% CI)	0.74 (0.58-0.94)	
Nominal 1-sided P-value	0.0074	

^a Trastuzumab and pertuzumab were administered per SOC. ET options include an AI or fulvestrant.
Metzger O, et al. NEJM 2026.

HER2CLIMB-05: Tucatinib as Maintenance Therapy for HER2+ MBC



Potential to reduce
brain metastases

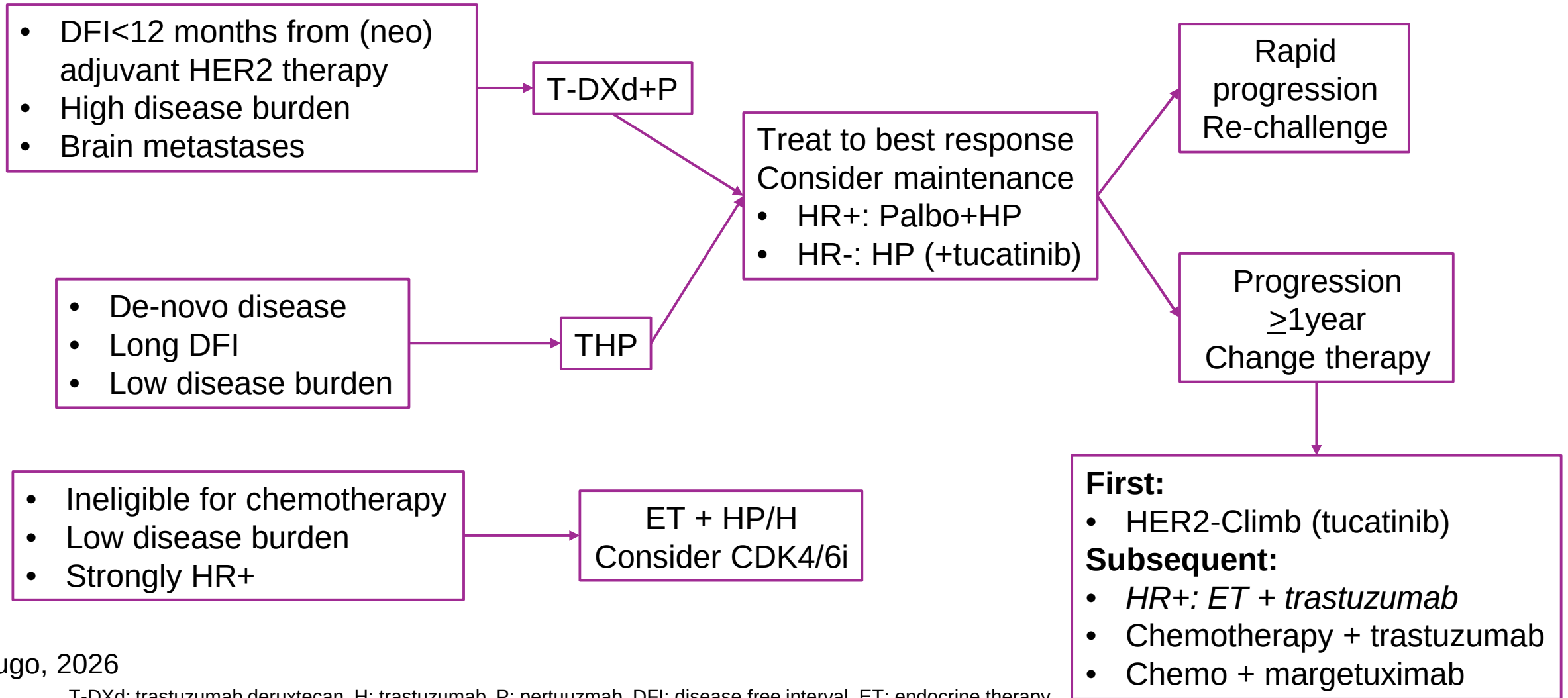
Optimal Therapy for HER2+ MBC in 2026?

- Accessibility is clearly a key issue around the world where THP remains the standard of care
 - T-DXd has regulatory approval in the US as first-line therapy based on DB09
 - When to use T-DXd in the first-line setting - Early relapse, patients presenting with brain metastases?
 - T-DXd + P is associated with more nausea, less neuropathy than THP
 - Higher mortality by 1%; 0.5% grade 5 ILD
 - Maintenance therapy is a critical question given ongoing nausea with T-DXd/risk of ILD – and now approved after THP
- Optimal treatment?
 - T-DXd or THP induction, and in those with responding or stable disease followed by:
 - ER+: ET+ trastuzumab/pertuzumab + palbociclib
 - ER-: trastuzumab/pertuzumab + tucatinib
 - Trials evaluating maintenance post T-DXd: DB-Guide, Demether

1 st Line Study	PFS, months	
TH vs THP	18.7	12.4
T-DXd/P vs THP	40.7	26.9
Palbociclib plus ET/HP vs ET/HP in responding pts	44.3	29.1
Tucatinib plus HP in responding pts	24.9	16.3

Sequencing therapy is a critical issue in interpreting trials and a key factor in improving outcome

Algorithm for Treating Metastatic HER2+ BC



Thank You!



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