

How I Treat HER2+ Breast Cancer

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Disclosures

- Research Support (institutional)
 - Genentech, Astra Zeneca, Seattle Genetics, Pfizer, Daiichi Sankyo, Duality Bio, D3 Bio, Nuvation Bio, BioNTech, ALX Oncology, BriaCell
- Scientific Consulting/Advisory/Speaker
 - Daiichi Sankyo, Eli Lilly, Genentech, Gilead, Seattle Genetics, Pfizer, Gilead, BMS, Nuvation Bio, D3 Bio, AstraZeneca, BioNTech, Boehringer Ingelheim, Ataraxis, Jazz Pharmaceuticals
- Speakers Bureau
 - None

Outline

HER2+ MBC

- Pivotal First Line Trials
- Updated Approach to Selection and Sequencing of Systemic Therapies
- New Directions

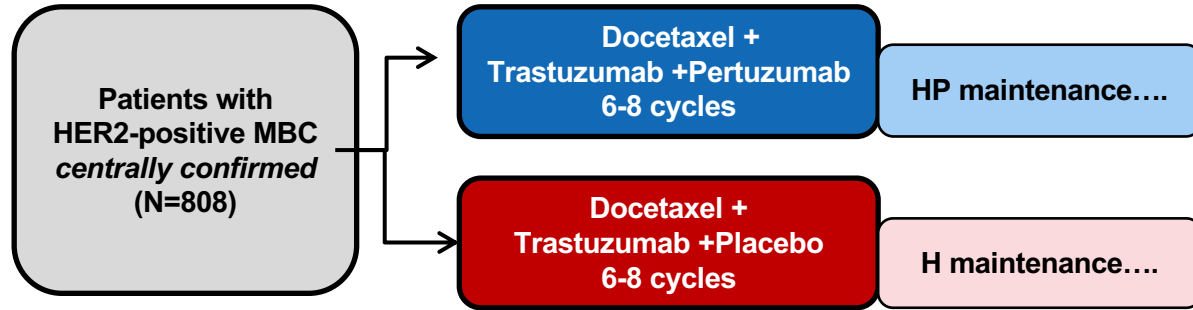
HER2+ EBC

- De-Escalation Strategies
- Preop vs Postop T-DXD
- Treatment Personalization

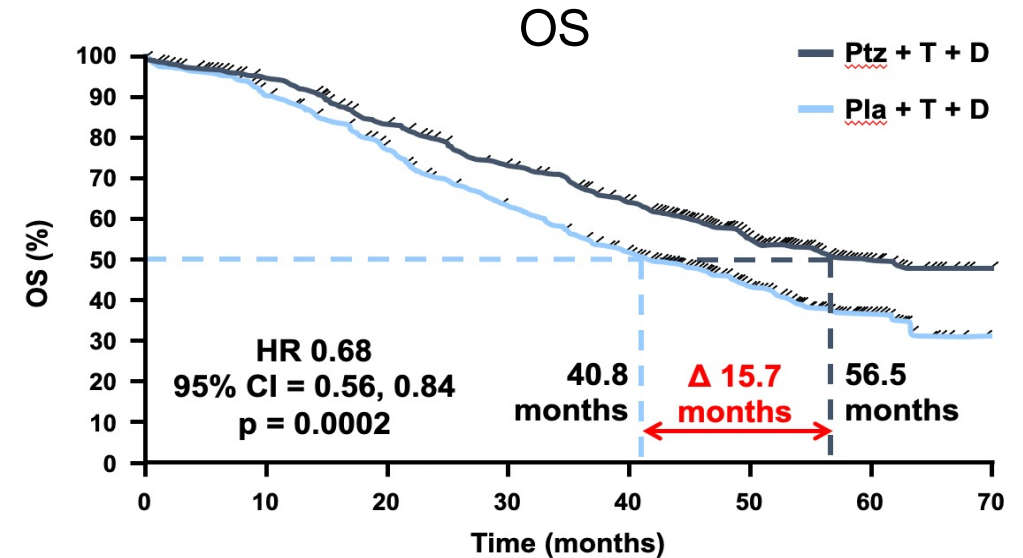
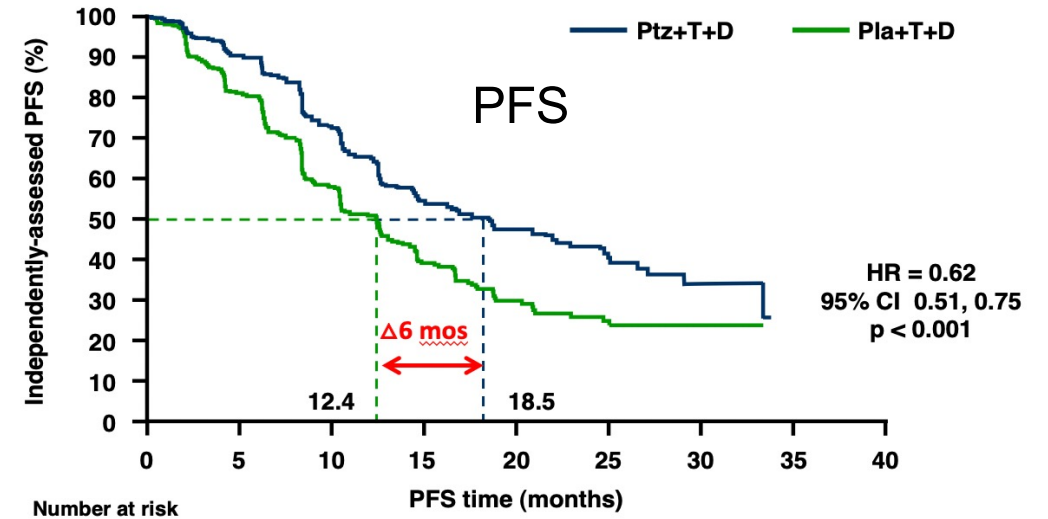
1st Line Setting

CLEOPATRA Trial : Dual HER2 Blockade

Adding Pertuzumab to Trastuzumab + Docetaxel Improves PFS & OS



- Established dual HER2 blockade and the induction–maintenance strategy
- All taxane works
- Adding ET in HR+ BC improves outcomes



DESTINY-Breast09 study design

A randomized, multicenter, open-label,* Phase 3 study (NCT04784715)

Eligibility criteria

- Centrally confirmed 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)

R
1:1:1

n=387

T-DXd[‡] + placebo

n=383

T-DXd[‡] + pertuzumab[§]

n=387

THP

Taxane (paclitaxel or docetaxel)[¶] +
trastuzumab^{||} + pertuzumab[§]

Endpoints

Primary

- PFS (BICR)

Key secondary

- OS

Secondary

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

- If T-DXd was discontinued due to AEs (except Grade >2 ILD), patients could switch to trastuzumab^{**}
- Concurrent use of ET (AI or tamoxifen) was allowed for those with HR+ disease after six cycles of T-DXd or discontinuation of taxane in THP arm

*Open label for THP arm. Double blinded for pertuzumab in experimental arms; [‡]HER2-targeted therapy or chemotherapy; [‡]5.4 mg/kg Q3W; [§]840 mg loading dose, then 420 mg Q3W; [¶]paclitaxel 80 mg/m² QW or 175 mg/m² Q3W, or docetaxel 75 mg/m² Q3W for a minimum of six cycles or until intolerable toxicity; ^{||}8 mg/kg loading dose, then 6 mg/kg Q3W; ^{**}without loading dose

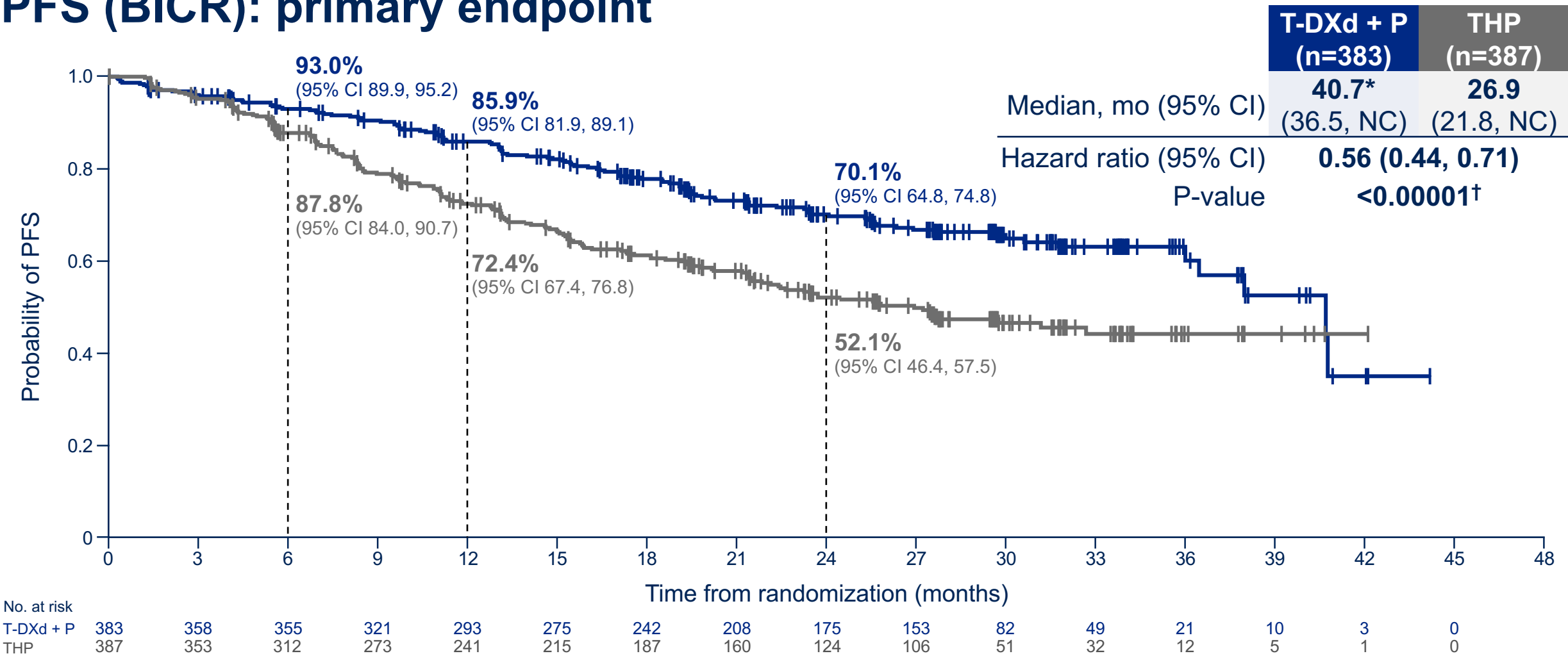
AE, adverse event; AI, aromatase inhibitor; a/mBC, advanced/metastatic breast cancer; BICR, blinded independent central review; DFI, disease-free interval; DOR, duration of response; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HER2+, HER2-positive; HR+/-, hormone receptor-positive/-negative; ILD, interstitial lung disease; INV, investigator; mets, metastases; mo, months; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival; *PIK3CA*m, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha mutation; Q3W, every 3 weeks; QW, once every week; R, randomization; T-DXd, trastuzumab deruxtecan
NCT04784715. Updated. May 6, 2025. Available from: <https://clinicaltrials.gov/study/NCT04784715> (Accessed May 29, 2025)

DB-09: Patient demographics and key baseline characteristics

	T-DXd + P (n=383)	THP (n=387)
Age, median (range), years	54 (27–85)	54 (20–81)
Female, n (%)	383 (100)	387 (100)
Geographical region, n (%)		
Asia	188 (49.1)	191 (49.4)
Western Europe and North America	87 (22.7)	78 (20.2)
Rest of World	108 (28.2)	118 (30.5)
ECOG performance status, n (%)		
0 (normal activity)	256 (66.8)	246 (63.6)
1 (restricted activity)	127 (33.2)	141 (36.4)
HER2 score by central test, n (%)		
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)
HR status, n (%)		
Positive*	207 (54.0)	209 (54.0)
Negative	176 (46.0)	178 (46.0)
De-novo disease at diagnosis, n (%)	200 (52.2)	200 (51.7)
PIK3CA mutations detected, n (%)	116 (30.3)	121 (31.3)
Brain metastases, n (%)†	25 (6.5)	22 (5.7)
Visceral metastases, n (%)	281 (73.4)	268 (69.3)

*Defined as estrogen receptor–positive and/or progesterone receptor–positive (≥1%); †participants were eligible if they had brain metastases that were clinically inactive or treated/asymptomatic
ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; NR, not recorded; P, pertuzumab; T-DXd, trastuzumab deruxtecan;
THP, taxane + trastuzumab + pertuzumab

PFS (BICR): primary endpoint



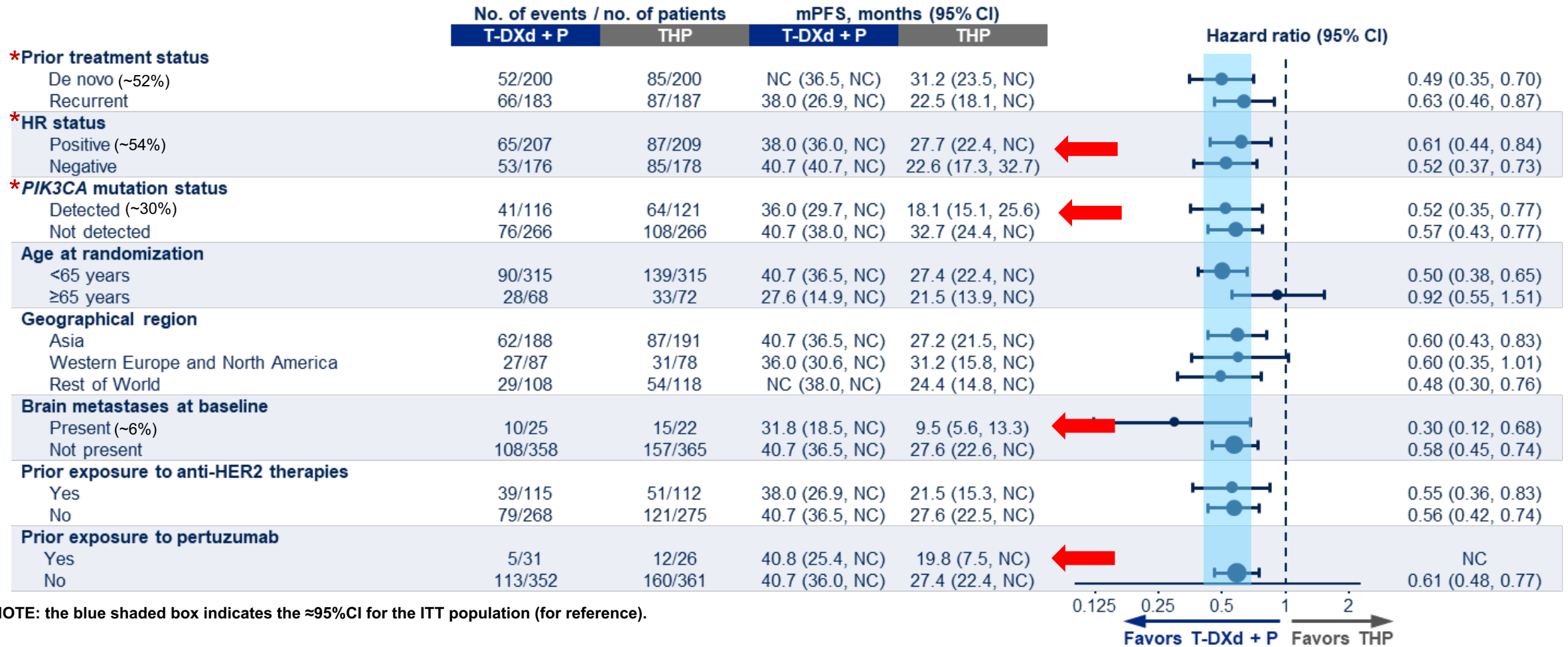
Statistically significant and clinically meaningful PFS benefit with T-DXd + P (median Δ 13.8 mo)

At med 29mo f/u, OS data show a trend favoring T-DXd + P; ~22% xs-over to T-DXd on control arm

*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

Tolaney , ASCO 2025

PFS (BICR): Subgroup Analyses

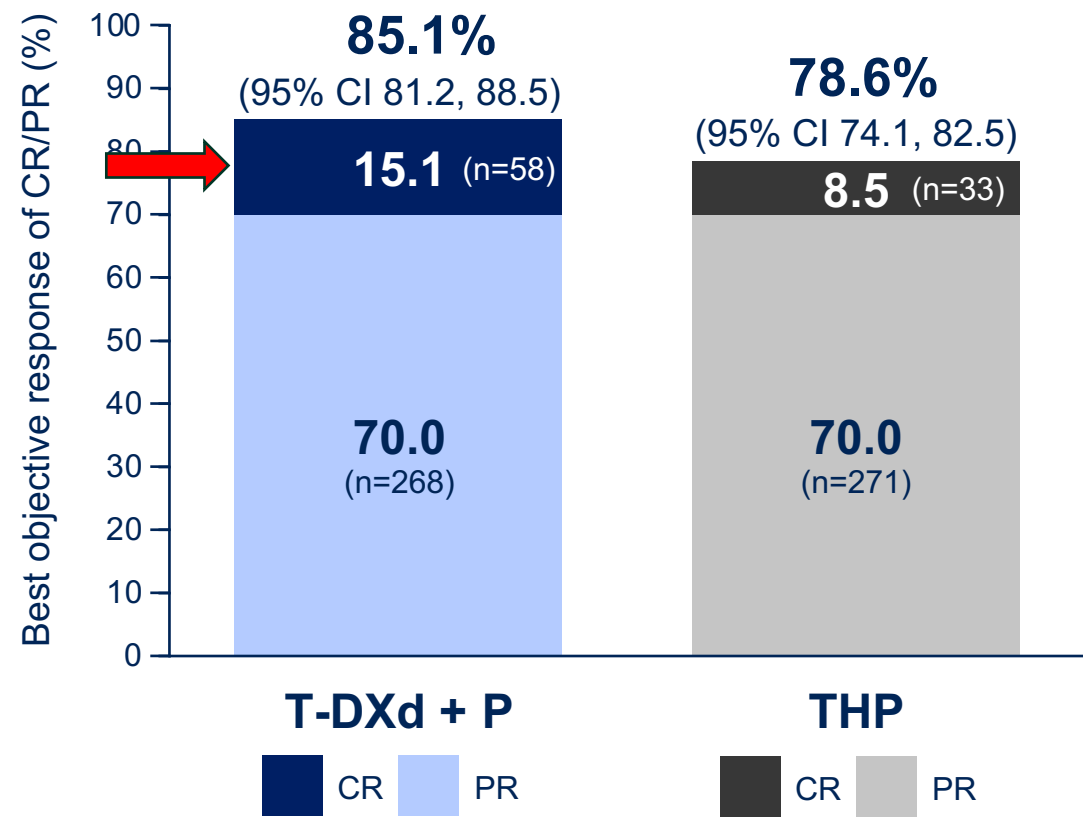


PFS benefit with T-DXd + P vs THP was consistently observed across prespecified subgroups

- Concurrent ET use was 13.5% (T-DXd + P) vs 38.3% (THP) among patients with HR+ disease

DB-09: ORR and DOR (BICR)

Confirmed ORR*

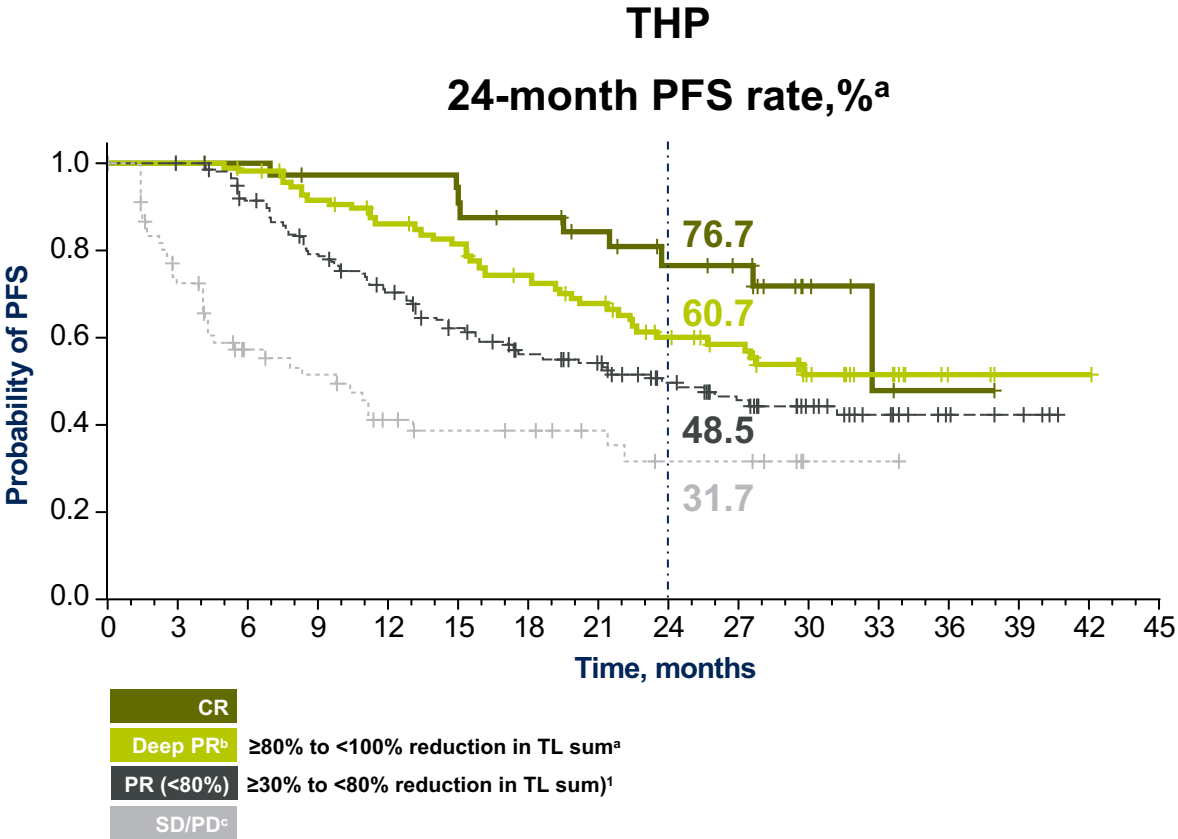
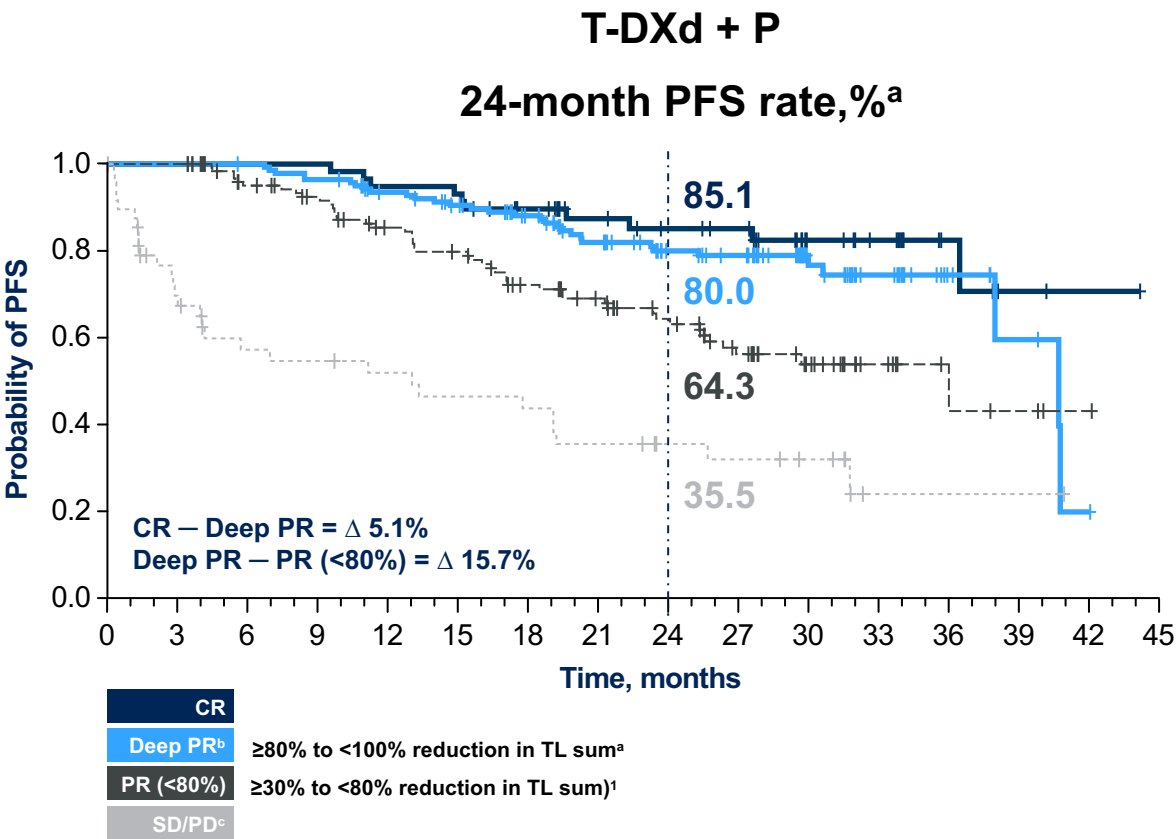


	T-DXd + P (n=383)	THP (n=387)
Median DOR, mo (95% CI)	39.2 (35.1, NC)	26.4 (22.3, NC)
Remaining in response at 24 mo (%)	73.3	54.9
Stable disease, n (%)	38 (9.9)	56 (14.5)

Response rates were greater with T-DXd + P vs THP and were durable

*Based on RECIST v1.1; response required confirmation after 4 weeks
BICR, blinded independent central review; CI, confidence interval; CR, complete response; DOR, duration of response; mo, months; NC, not calculable; ORR, objective response rate; P, pertuzumab; PR, partial response;
RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

Progression-Free Survival by Tumor Response (exploratory)



In the T-DXd arm, achieving CR and deep PR was associated with similar durable PFS outcomes.
In the THP arm, achieving deep PR was not associated with similar outcomes to achieving CR

~53% achieved CR or deep PR in the T-DXd + P arm; ~ 37% achieve CR+ Deep PR on THP

^a95% CIs for T-DXd + P 24-mo PFS rates: CR: 72.2, 92.3; deep PR: 71.7, 86.1; PR (<80%): 54.3, 72.8; SD/PD: 21.1, 50.2. 95% CIs for THP 24-mo PFS rates: CR: 56.9, 88.2; deep PR: 50.3, 69.6; PR (<80%): 39.8, 56.6; SD/PD: 18.6, 45.5. ^bPR with $\geq 80\%$ to <100% reduction in TL sum and CR or non-CR/non-PD in non-TLs, or CR in TL and non-CR/non-PD in non-TLs. ^cOf the 377 total patients included in the T-DXd + P arm of the DESTINY-Breast09 responder analysis, 38 patients had SD and 13 patients had PD; of the 372 patients included in the THP arm of the DESTINY-Breast09 responder analysis, 56 patients had SD and 12 patients had PD.
CR, complete response; P, pertuzumab; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; T-DXd, fam-trastuzumab deruxtecan-nxki; THP, taxane, trastuzumab, and pertuzumab; TL, target lesion.
Park YH, et al. Presented at: American Society of Clinical Oncology; May 31, 2026; Chicago, IL.

Response Characteristics (exploratory)

T-DXd + P					THP ^a				
	CR (n=58)	Deep PR ^b (n=141)	PR (<80%) (n=127)	SD/PD ^c (n=51)		CR (n=33)	Deep PR ^b (n=110)	PR (<80%) (n=161)	SD/PD ^c (n=68)
Time to best response (median, mo) [95% CI]	8.4 [5.6-11.1]	9.6 [6.8-11.0]	1.5 [1.4-2.0]	NA	Time to best response (median, mo) [95% CI]	5.6 [2.8-9.8]	8.2 [6.8-9.6]	1.5 [1.4-1.5]	NA
Duration of best response (median, mo) [95% CI]	NC [35.1-NC]	39.2 [35.3-NC]	34.8 [22.8-NC]	NA	Duration of best response (median, mo) [95% CI]	31.3 [31.3-NC]	NC [22.3-NC]	20.1 [13.1-30.1]	NA
Patients remaining in best response, % [95% CI]					Patients remaining in best response, % [95% CI]				
12 mo	94.8 [84.8-98.3]	91.3 [85.1-95.0]	78.9 [70.1-85.3]	NA	12 mo	93.7 [77.2-98.4]	83.8 [75.2-89.6]	61.9 [53.6-69.2]	NA
24 mo	85.0 [72.1-92.3]	78.9 [70.4-85.2]	60.4 [50.0-69.3]	NA	24 mo	76.4 [56.5-88.1]	60.4 [49.9-69.4]	46.5 [37.7-54.9]	NA
Total treatment duration, median, mo, [range] ^d	28.0 [4.8-44.5]	25.4 [3.4-42.7]	20.6 [2.8-41.8]	4.4 [0.3-37.2]	Total treatment duration, median, mo, [range] ^e	28.1 [7.6-38.2]	20.2 [2.7-40.8]	17.9 [2.9-41.7]	5.9 [1.4-35.2]
PFS at 24 mo, % [95% CI]	85.1 [72.2-92.3]	80.0 [71.7-86.1]	64.3 [54.3-72.8]	35.5 [21.1-50.2]	PFS at 24 mo, % [95% CI]	76.7 [56.9-88.2]	60.7 [50.3-69.6]	48.5 [39.8-56.6]	31.7 [18.6-45.5]

Patients who achieved CR and deep PR had the longest treatment duration, with responses deepening over time in the T-DXd + P arm.
80% of patients (ITT) achieved a maximal tumor reduction by 24 months in the T-DXd + P arm

^aMedian duration of follow-up (range, mo): CR: 29.5 (20.8-38.9); deep PR: 30.5 (11.3-43.2); PR (<80%): 29.2 (5.5-44.7); SD/PD: 20.1 (2.4-40.9). ^bPR with ≥80% to <100% reduction in TL sum and CR or non-CR/non-PD in non-TLs, or CR in TL and non-CR/non-PD in non-TLs. ^cOf the 377 total patients included in the T-DXd + P arm of the DESTINY-Breast09 responder analysis, 38 patients had SD and 13 patients had PD; of the 372 patients included in the THP arm of the DESTINY-Breast09 responder analysis, 56 patients had SD and 12 patients had PD. ^dPer protocol, a small proportion of patients in each group transitioned to trastuzumab (CR, 8 [13.8%]; deep PR, 11 [7.8%]; PR<80%, 10 [6.9%]; SD/PD, 5 [10.0%]). ^eIncludes both the induction and maintenance phases.

DB-09: Adverse events of special interest

Adjudicated drug-related ILD/pneumonitis*

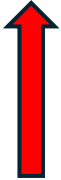
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd + P (n=381)	17 (4.5)	27 (7.1)	0	0	2 (0.5)	46 (12.1)
THP (n=382)	2 (0.5)	2 (0.5)	0	0	0	4 (1.0)

Left ventricular dysfunction†

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd + P (n=381)	4 (1.0)	30 (7.9)	7 (1.8)	1 (0.3)	0	42 (11.0)
THP (n=382)	1 (0.3)	19 (5.0)	7 (1.8)	0	0	27 (7.1)

Safety analysis set
*Adjudicated drug-related ILD/pneumonitis (grouped term) includes: chronic obstructive pulmonary disease, interstitial lung disease, organizing pneumonia, pneumonia, and pneumonitis, †left ventricular dysfunction (grouped term) includes: potential heart failure, cardiac failure, cardiac failure chronic, ejection fraction decreased, left ventricular dysfunction, and right ventricular failure
ILD, interstitial lung disease; P, pertuzumab; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

T-DXd + P is a new first-line standard of care for patients with HER2+ MBC

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- Significantly moves first line therapy forward by approximately 14mo of PFS
 - Trend for OS
 - More effective across all subgroups of patients including HR+ and HR-
 - Higher ORR and higher CR rate 15% vs 8.5%
 - **Substantially higher proportion of patients achieving deep and durable responses (~53%)**
 - More effective for patients with Brain mets
 - More effective in cases of Pi3k mutations
- 
- Comes with more toxicity (alopecia and GI, but less neuropathy)
 - Need for ILD monitoring in all patients with risk of high grade events <1%
 - Role of Pertuzumab still uncertain

THP with Escalated Maintenance Therapy

PATINA Phase 3 Trial in HR+ HER2+ MBC: 1st Line maintenance HP+ET+ Palbociclib vs HP+ ET

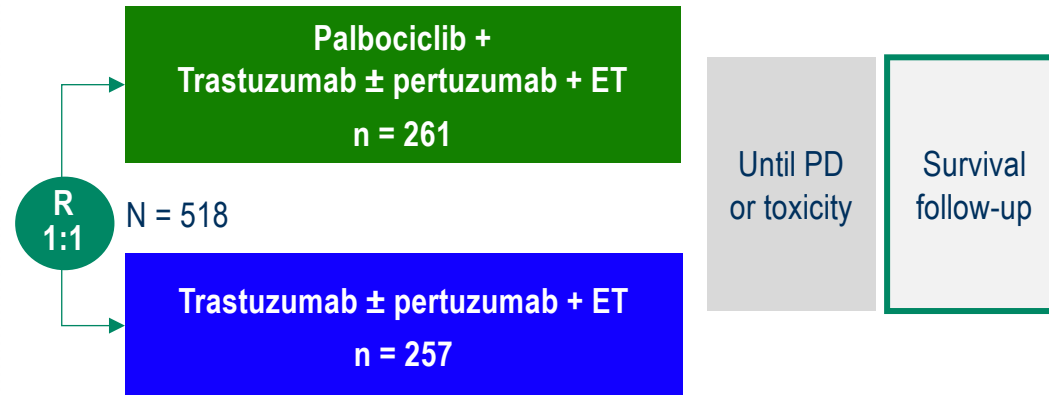
Objective: To evaluate the addition of palbociclib to anti-HER2 and ET for patients with HR+/HER2+ breast cancer

REGISTRATION

- Histologically (local testing) HR+/HER2+ mBC
- No prior treatment in the advanced setting beyond induction treatment
- 6–8 cycles of treatment, including trastuzumab ± pertuzumab and taxane/vinorelbine

KEY ELIGIBILITY CRITERIA

- Completion of induction chemotherapy and no evidence of disease progression (ie, CR, PR, or SD)
- Patients with a history or presence of asymptomatic CNS metastases were eligible



Primary Outcome

- Investigator-assessed PFS

Secondary Outcomes

- OS
- 3- and 5-year survival probabilities
- ORR / DOR / CBR
- Safety
- PRO
- Incidence of CNS metastases

Stratification Factors

- Pertuzumab use (yes vs no)
 - The non-pertuzumab option is limited to up to 20% of the population
- Prior anti-HER2 therapy in the (neo)adjuvant setting (yes vs no, including de novo)^{II}
- Response to induction therapy (CR or PR vs SD) by investigator assessment^{II}
- Type of ET (fulvestrant vs aromatase inhibitor)

H- trastuzumab; P- pertuzumab; ET – endocrine therapy: options included an aromatase inhibitor or fulvestrant.

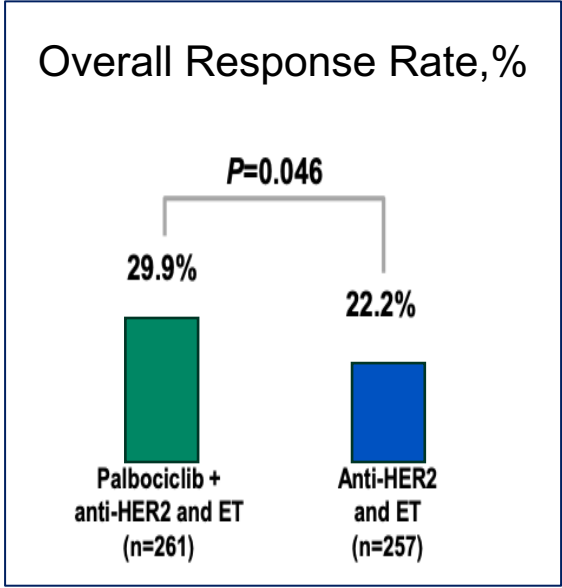
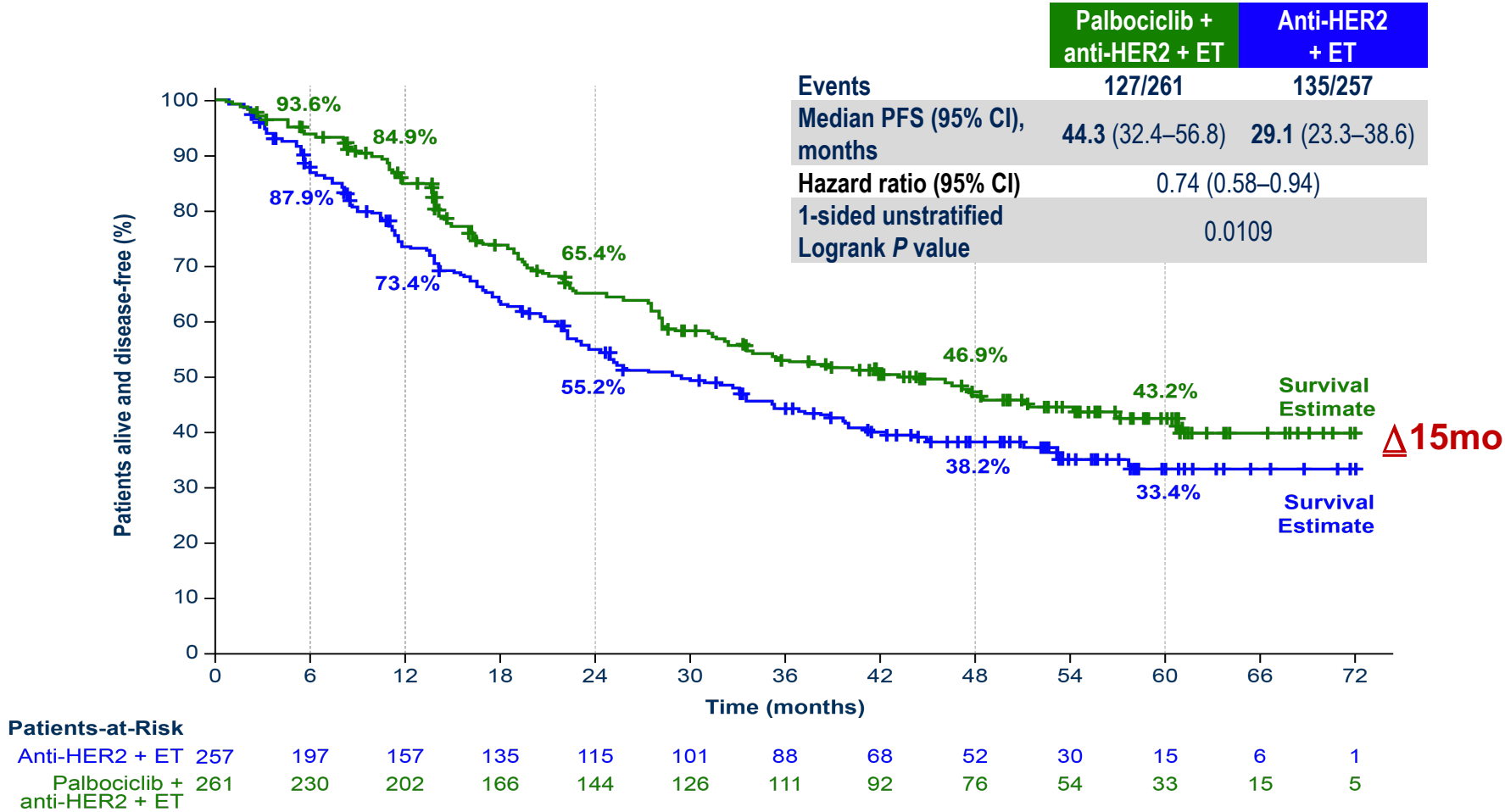
References: 1. <https://clinicaltrials.gov/study/NCT02947685>. Accessed September 11, 2025. 2. Metzger O, et al. SABCS 2024. Presentation GS2-12.

Key Baseline Characteristics

	Palbociclib + anti-HER2 + ET (n = 261)	Anti-HER2 + ET (n = 257)	Total (N = 518)
Age (in years)			
Median (IQR)	53.5 (43.6, 60.4)	53.0 (45.1, 62.8)	53.4 (44.2, 61.4)
Range	28.7, 81.7	29.9, 84.3	28.7, 84.3
Geographic region, n (%)			
North America	83 (31.8)	83 (32.3)	166 (32.0)
Western Europe; ANZ	178 (68.2)	174 (67.7)	352 (68.0)
Baseline site of metastases, n (%) ^{a,b}			
CNS	11 (4.2)	9 (3.5)	20 (3.9)
Non-visceral	57 (21.8)	60 (23.5)	117 (22.7)
Visceral	193 (73.9)	186 (72.9)	379 (73.4)
De novo disease, n (%) ^c			
Best response to induction therapy by investigator assessment, n (%) ^c	182 (69.7)	181 (71.3)	363 (70.5)
CR or PR			
SD	79 (30.3)	73 (28.7)	152 (29.5)

Endocrine Therapy, ET= 90% AI therapy; 10% fulvestrant; Median number of induction Cycles= 6

PATINA Primary Endpoint: Investigator-Assessed PFS



Interim OS = no difference; longer follow-up required

Primary Results From PATINA Phase 3 Trial of Palbociclib + Anti-HER2 Therapy + ET in HR+/HER2+ MBC: Safety and Summary

Grade ≥2 AEs in ≥10% of Patients, n (%)	Palbo + Anti-HER2 + ET (n=261)			Anti-HER2 + ET (n=248)		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Neutropenia	52 (19.9)	165 (63.2)	12 (4.6)	10 (4.0)	11 (4.4)	0
WBC decreased	30 (11.5)	30 (11.5)	1 (0.4)	2 (0.8)	0	0
Fatigue	60 (22.9)	14 (5.4)	0	32 (12.9)	0	0
Stomatitis	45 (17.2)	11 (4.2)	0	3 (1.2)	0	0
Diarrhea	69 (26.4)	29 (11.1)	0	26 (10.5)	4 (1.6)	0
URTI	30 (11.5)	1 (0.4)	0	16 (6.5)	0	0
UTI	26 (10.0)	2 (0.8)	0	19 (7.7)	1 (0.4)	0
Arthralgia	23 (8.8)	4 (1.5)	0	44 (17.7)	3 (1.2)	0
EF decreased	22 (8.4)	1 (0.4)	0	21 (8.5)	8 (3.2)	0
Cardiac failure	0	0	0	1 (0.4)	1 (0.4)	0

- The incidence of grade ≥4 AEs was similar across study arms (12.3% vs 8.9% for palbociclib-containing arm vs control, $P=0.21$)
- Discontinuations due to AEs in the palbociclib-containing arm: 14 patients (7.5%)
- No treatment-related deaths were reported in either arm of the study

Palbociclib added to HP+ET is a new option for HR+ HER2+ MBC in the post-THP 1st line maintenance setting

HER2CLIMB-05 Design: Tucatinib + HP vs HP as 1L Maintenance after Induction Tx in HER2+ MBC

HER2CLIMB-05 is a randomized, double-blind, placebo-controlled, international, phase 3 trial (NCT05132582)

Key Eligibility Criteria

- Centrally confirmed HER2+ MBC
- No evidence of progression after THP (4 to 8 cycles)
- ECOG PS of 0 or 1
- No or asymptomatic BM confirmed by contrast-enhanced MRI at screening

R
1:1

Randomization was stratified by:

- Diagnosis: *de novo* or recurrent
- HR status: positive or negative
- Presence or history of BM: yes or no

1L Maintenance Therapy

**TUC 300 mg PO BID
+ HP***
Once every 21 days
± ET
(n = 326)

**PBO PO BID
+ HP***
Once every 21 days
± ET
(n = 328)

Study treatment continues until unacceptable toxicity, disease progression, consent withdrawal, or study closure. No crossover from PBO to TUC was allowed.

Endpoints

Primary

- Investigator-assessed PFS per RECIST v1.1

Secondary

- OS (key secondary)
- PFS per BICR
- CNS-PFS**
- Safety
- HRQoL
- Pharmacokinetics

*H (6 mg/kg IV or 600 mg SC) and P (420 mg IV) or fixed-dose combination (SC) of H (600 mg), P (600 mg), and hyaluronidase (20,000 units).

HERC-05: Patient Characteristics

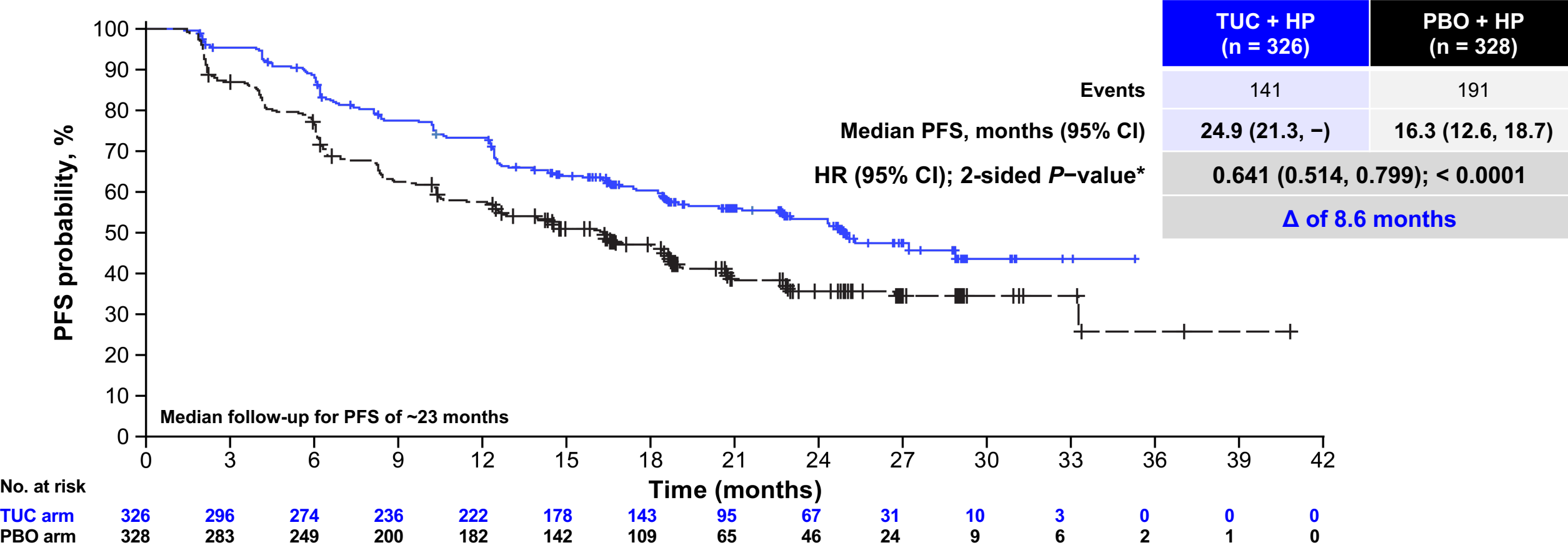
Characteristics	TUC + HP (n = 326)	PBO + HP (n = 328)
Age , years, median (range)	54.0 (24–82)	54.0 (29–83)
Race , n (%)		
White	147 (45.1)	147 (44.8)
Asian	119 (36.5)	111 (33.8)
Black/African American	10 (3.1)	9 (2.7)
Multiple or other	10 (3.1)	15 (4.6)
Not reportable/unknown	40 (12.3)	46 (14.0)
ECOG PS , n (%)		
0	215 (66.0)	204 (62.2)
1	110 (33.7)	123 (37.5)
HR status , n (%)		
Positive	168 (51.5)	176 (53.7)
Received ET	74 (44.0)	81 (46.0)
Negative	158 (48.5)	152 (46.3)
Presence or history of BM , n (%)	41 (12.6)	40 (12.2)
Visceral disease , n (%)	194 (59.5)	172 (52.4)

Characteristics	TUC + HP (n = 326)	PBO + HP (n = 328)
Disease status , n (%)		
<i>De novo</i>	227 (69.6)	226 (68.9)
Recurrent	99 (30.4)	102 (31.1)
Any prior (neo)adjuvant systemic therapy , n (%)		
Prior trastuzumab*	60 (69.0)	67 (73.6)
Prior pertuzumab*	16 (18.4)	15 (16.5)
Induction HP cycles , median (range)	6 (4–10)	6 (4–11)
Induction T cycles , median (range)	6 (4–9)	6 (3–8)
Best response to induction THP , n (%)		
CR	30 (9.2)	32 (9.8)
PR	204 (62.6)	208 (63.4)
SD	77 (23.6)	75 (22.9)
Non-CR/Non-PD	15 (4.6)	13 (4.0)

*Among patients who received prior systemic therapies in the (neo)adjuvant settings.

BM = brain metastases; CR = complete response; ECOG PS = Eastern Cooperative Oncology Group performance status; ET = endocrine therapy; H = trastuzumab; HR = hormone receptor; P = pertuzumab; PBO = placebo; PD = progressive disease; PR = partial response; SD = stable disease; T = taxane; TUC = tucatinib.

HER2C-05: Primary Endpoint: Investigator-Assessed PFS

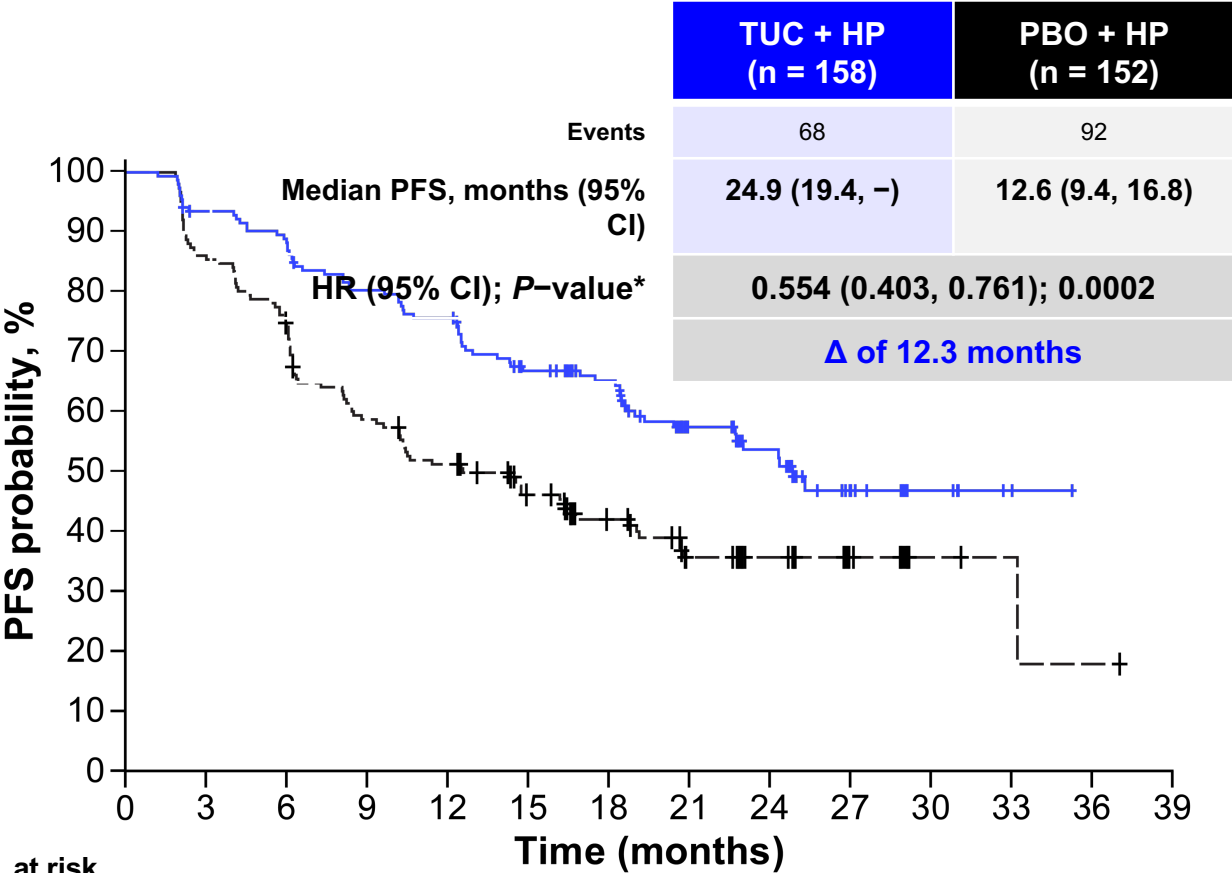


Addition of TUC to 1L maintenance therapy extended median PFS to over 2 years in patients with HER2+ MBC, an **8.6-month** improvement over HP, the standard-of-care.

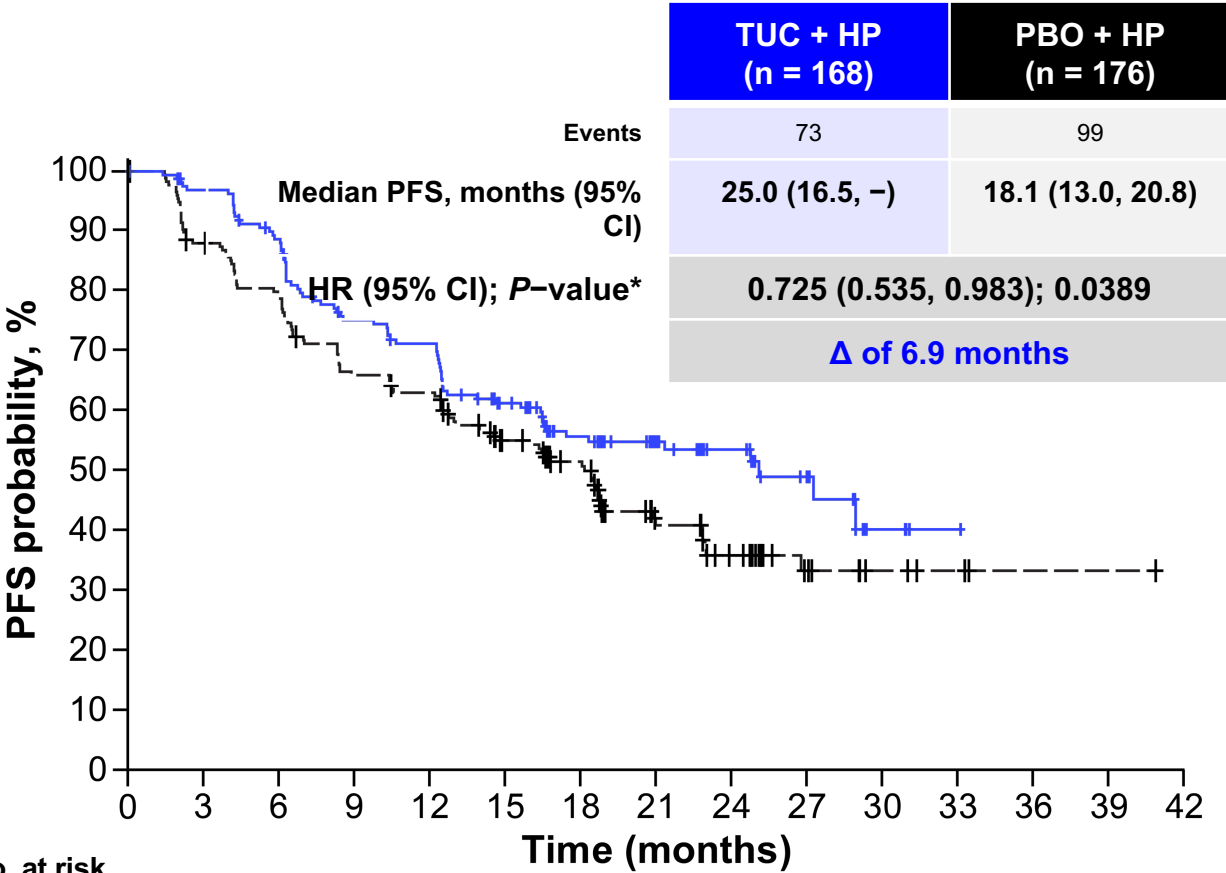
There was a numerical trend for OS improvement in the TUC arm

HER2C-05 PFS by Hormone Receptor Status

Hormone receptor-negative



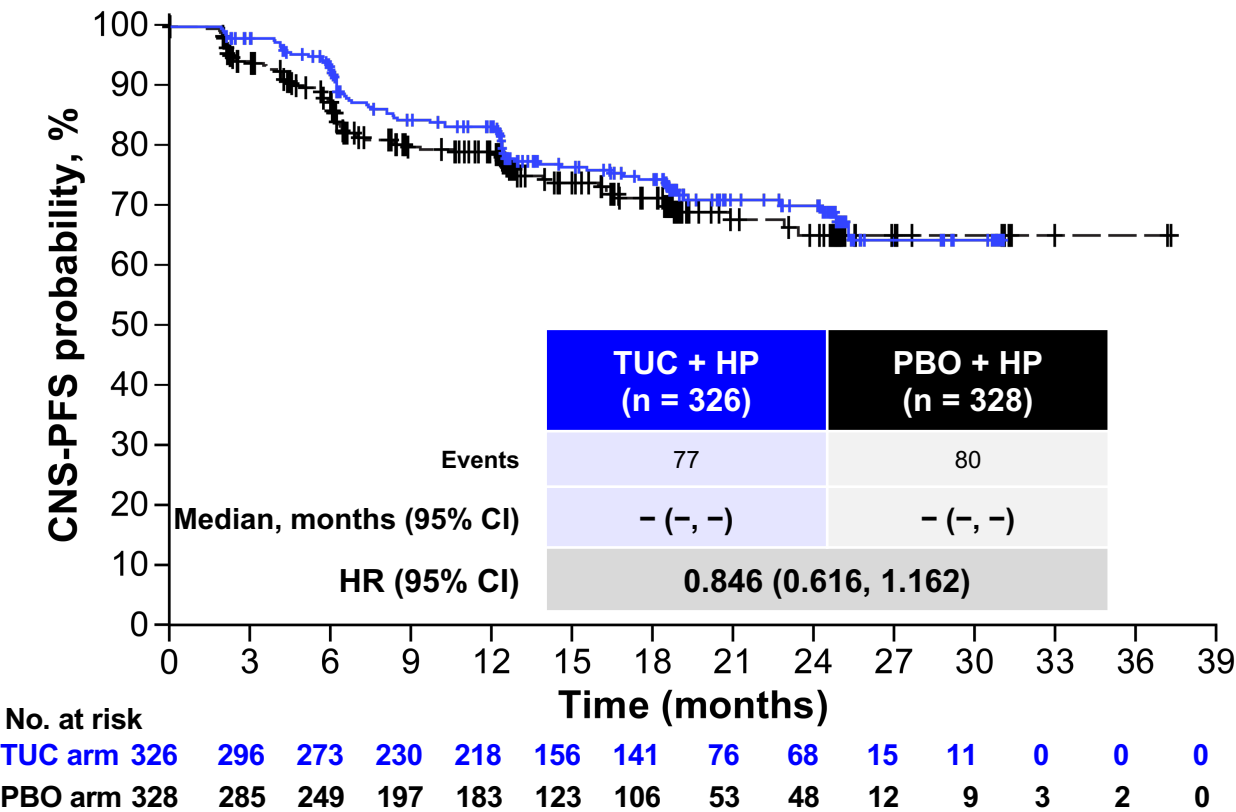
Hormone receptor-positive



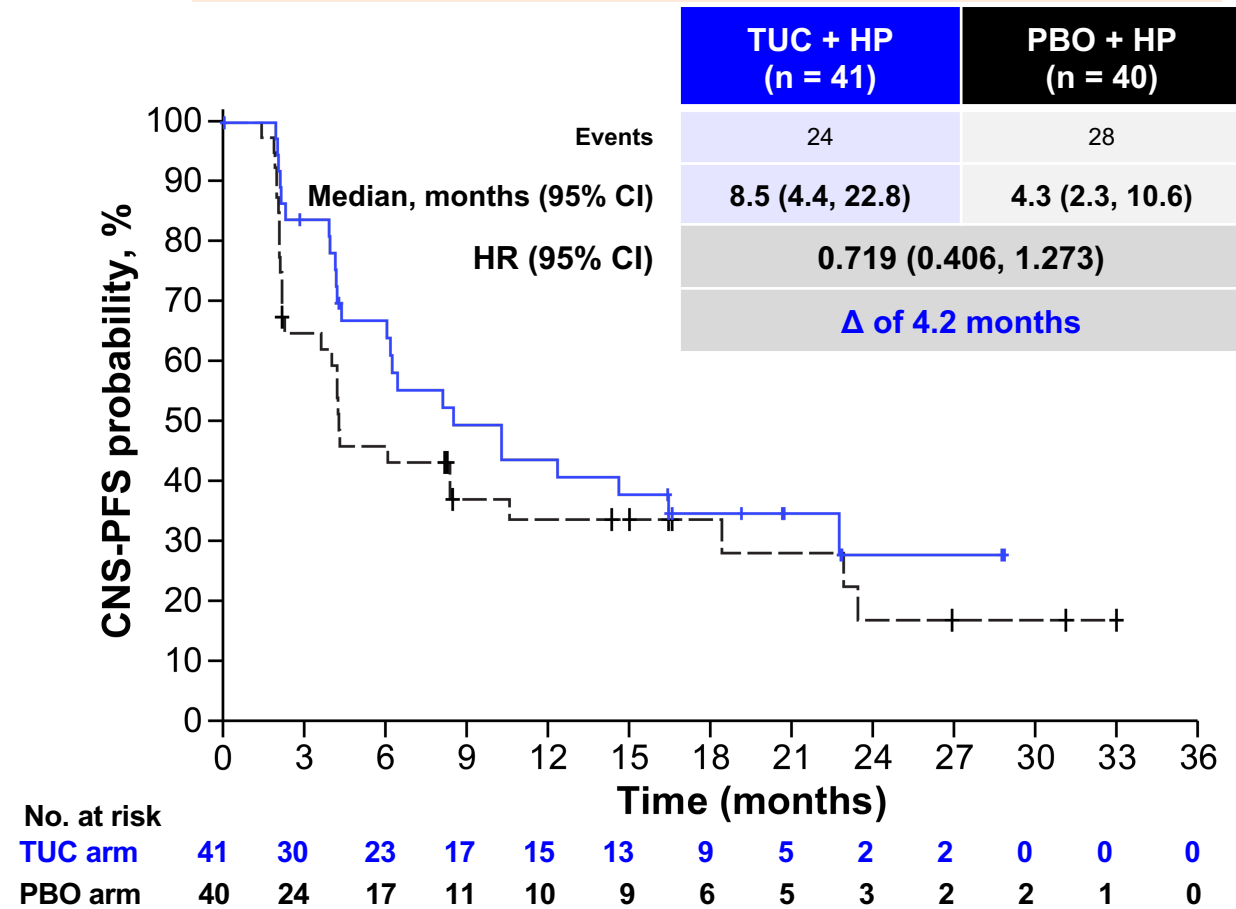
*Two-sided nominal *P*-value based on stratified log-rank test.
CI = confidence interval; H = trastuzumab; HR = hazard ratio; P = pertuzumab; PBO = placebo; PFS = progression-free survival; TUC = tucatinib.

HER2C-05 Secondary Endpoint: CNS-PFS

ITT population

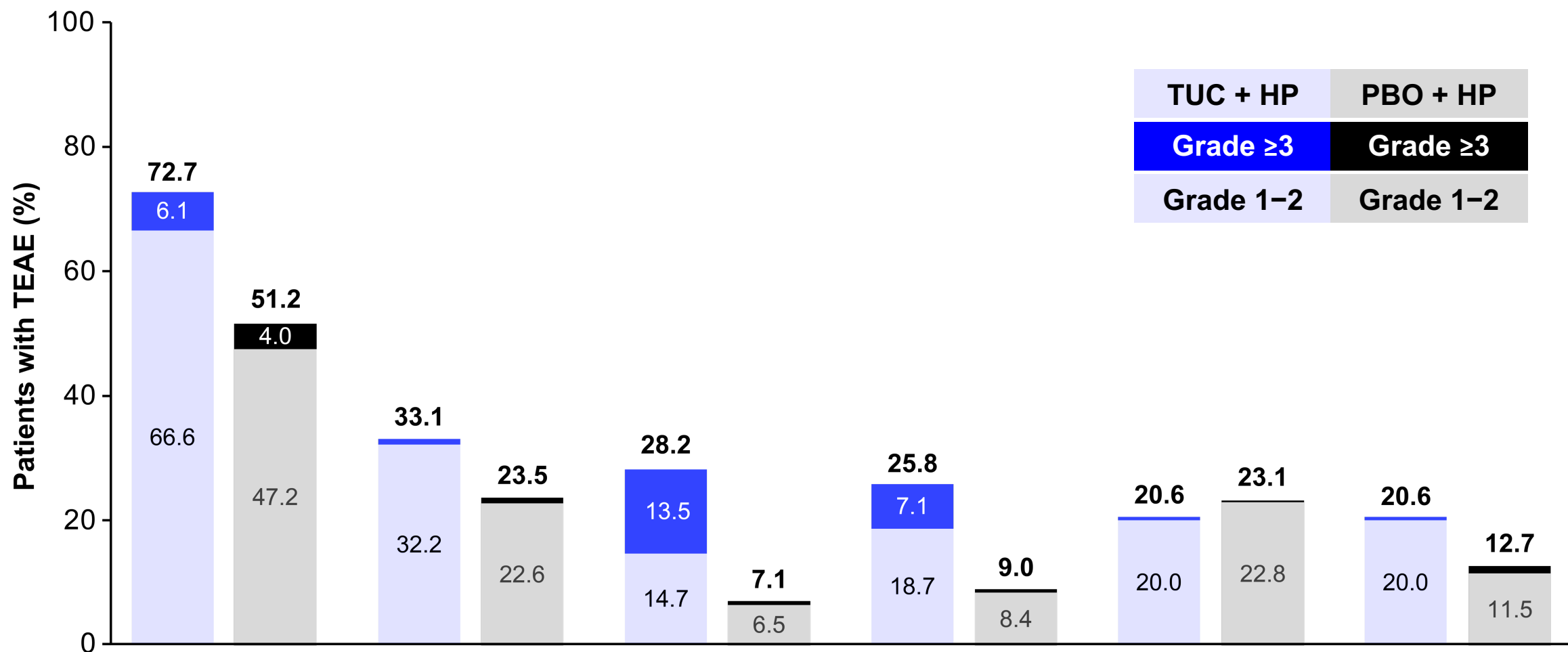


Exploratory analysis: Patients with baseline BM



Contrast brain MRI required at screening and end of treatment; pts with a history of BM received MRIs every 9 weeks. For patients without BM at baseline, MRI was repeated every 27 weeks (~6 months).

HER2C-05: TEAEs Experienced in $\geq 20\%$ of Patients



Tucatinib added to HP (+/-ET) is another 1L maintenance option post-THP for patients with HER2+ MBC

Reported Data in PATINA, DESTINY-Breast09, and HER2CLIMB-05 Trials

		DESTINY-Breast09		PATINA (THP)		HER2CLIMB-05 (THP)	
Patient population		HER2+ advanced or mBC		HR+, HER2+ mBC, 1L Maintenance w/o progression following 6-8 cy THP ind.		HER2+ mBC, 1L Maintenance w/o progression following 4-8 cy THP ind.	
Trial design		Primary endpoint: PFS by BICR		Primary endpoint: PFS (INV)		Primary endpoint: PFS (INV)	
		T-DXd + P (n=383)	THP (n=387)	Palbociclib + anti-HER2 + ET (n=261)	Anti-HER therapy + ET (n=257)	TUC + HP (n=326)	PBO + HP (n=328)
Efficacy	mPFS, mo	40.7 (by BICR)	26.9 (by BICR)	44.3 (by INV)	29.1 (by INV)	28.9 (by BICR)	16.0 (by BICR)
	Hazard Ratio	0.56		0.74		0.64	
	OS, no	NC	NC	NC	77	NC	NC
	ORR, n (%)	85.1 ^b	78.6	29.9	22.2	22.6	15.2
Endocrine Therapy Use	(%)	14%	38%	100%	100%	44%	46%
Brain Mets	(%)	6.5%	5.7%	4.2%	3.5%	12.6%	12.2%

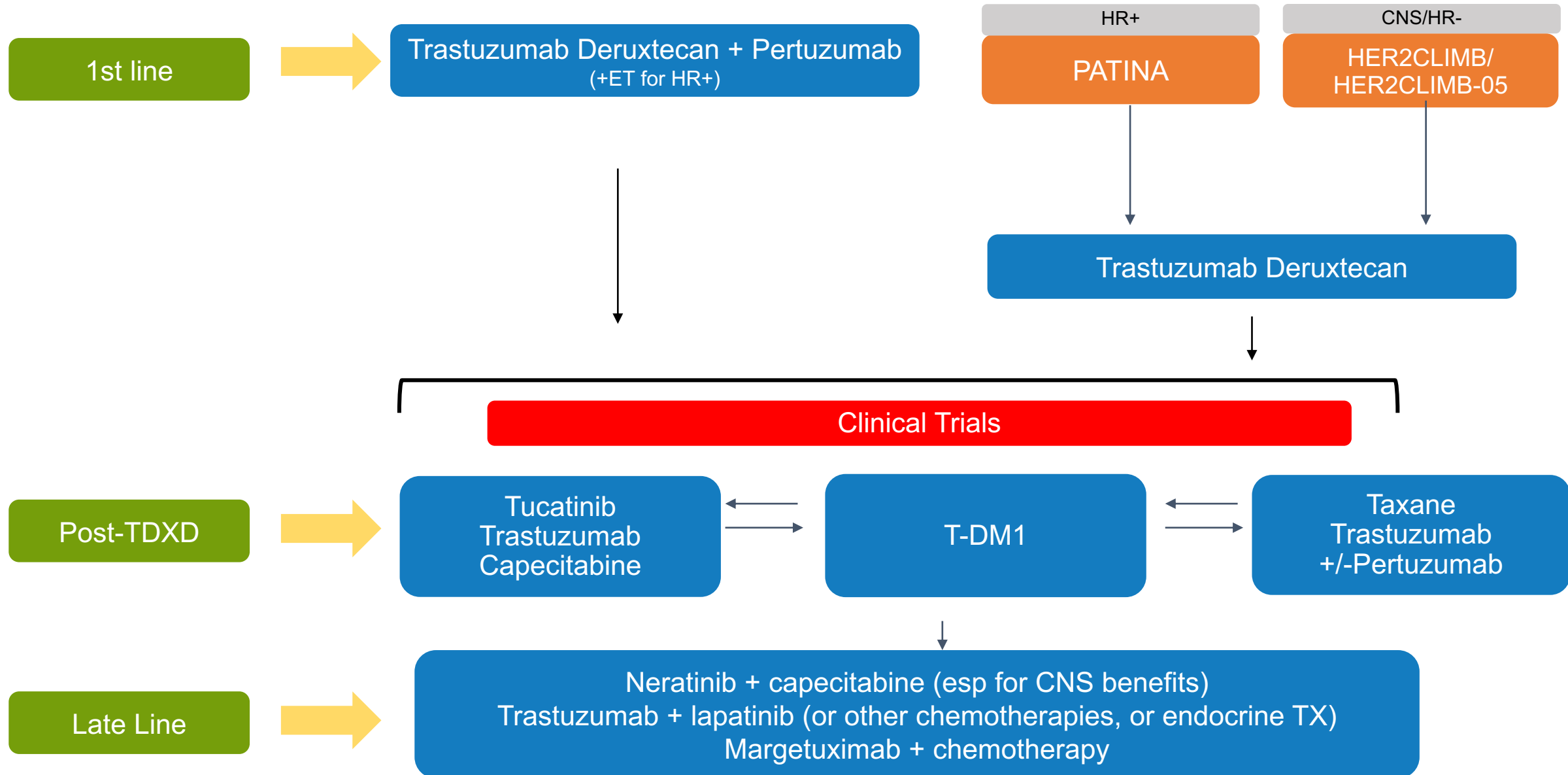
Comparisons across trials should not be made. Information should be interpreted with the due context that these trials have different populations, designs and methodologies

Choosing Among New 1st Line Options for HER2+ MBC

Clinical Scenario:	Regimen to Consider:	Rationale:
High disease burden	DB09	Highest and deepest responses
HER2 IHC 2+/ISH+	DB09	ADC bystander advantage
PIK3CA+	DB09	Exploratory subgroup signal
Brain metastases	DB09/HER2Climb-05	CNS Activity
HR+/indolent	PATINA	Prolonged PFS
Frail patient/co-morbidities	PATINA/HER2C05	Balance efficacy and tolerability

Individualizing Treatment Based on Disease Biology/Characteristics and Patient Priorities

My Preferred Approach to Therapy for HER2+ MBC



Future Directions

Ongoing Phase 3 Trials in HP Maintenance Setting in HER2+ MBC

INAVO122

Eligibility criteria

- 1st line HER2-positive disease
- PIK3CA-mutation

Induction:
**PHESGO +
taxane-based ChT**

R
1:1
N=230

Inavolisib + PHESGO
+/- ET if HR+

Placebo + PHESGO
+/- ET if HR+

Primary endpoint

- PFS assessed by investigator

Secondary endpoints

- OS, ORR, DoR, CBR, PFS2, HRQoL, safety

NCT 05894239

heredERA

Patients with
ER+, HER2+ LA/mBC,
previously untreated in
the mBC setting

N = 812

Induction

**PH FDC SC
+ taxane
4–6 cycles**

R
1:1

N = 730

Maintenance

**Giredestrant 30 mg po qd
+ PH FDC SC q3w**

PH FDC SC q3w^a

**Until disease
progression or
unacceptable
toxicity or
withdrawal**

NCT05296798

DEMETHER:

Phase II Trial of **T-DXd induction** followed by subcutaneous HP maintenance for patients with 1L HER2+ MBC

Eligibility criteria

- Unresectable locally recurrent mBC
- HER2-overexpressing tumor status
- Known ER and PgR status
- No prior ChT and/or HER2-targeted therapy for advanced disease (one prior line of endocrine therapy is allowed for mBC)
- May have received adjuvant or neoadjuvant chemotherapy and/or HER2-targeted therapy before study treatment initiation

N=165

**T-DXd induction
(6-cycles)**

**HP (PHESGO)
maintenance**

- No pertuzumab
- No cdk4/6i or Tucatinib maintenance
- Is 6 cycles of T-DXD optimal?

Primary endpoint

- 1-year PFS rate
- 3-year OS rate

Secondary endpoints

- PFS
- OS
- ORR
- CBR
- TTR
- DoR
- QoL
- Safety and tolerability

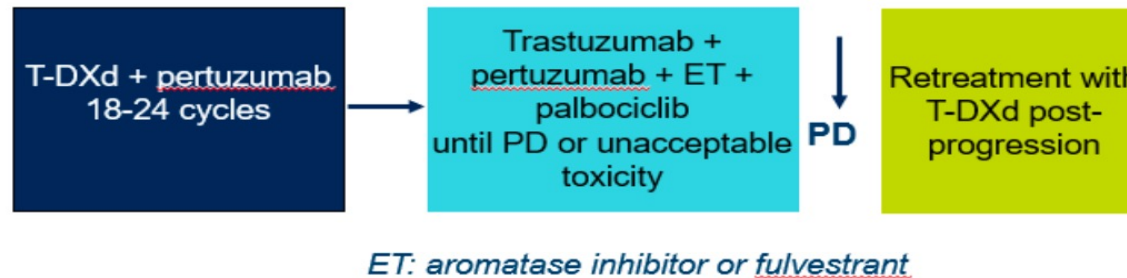
NCT06172127

DESTINY-Breast Guide Trial:

T-DXd+ Pertuzumab Followed by Palbociclib, Endocrine Therapy and HP in First-line HER2+/HR+ MBC and Retreatment with T-DXd

Participants (n=200)

- Participants ≥18 years of age
- HER2+ (IHC 3+ or IHC 2+/ISH+)^a/HR+, *de novo* or recurrent mBC^b
- No prior chemotherapy or HER2-targeted therapy for advanced or mBC^b
- ECOG PS 0 or 1
- DFI >6 months^c
- Brain metastasis are allowed if asymptomatic and do not require intervention



Primary Endpoint

- PFS^d rate at 24 months (FA)

Secondary Endpoints

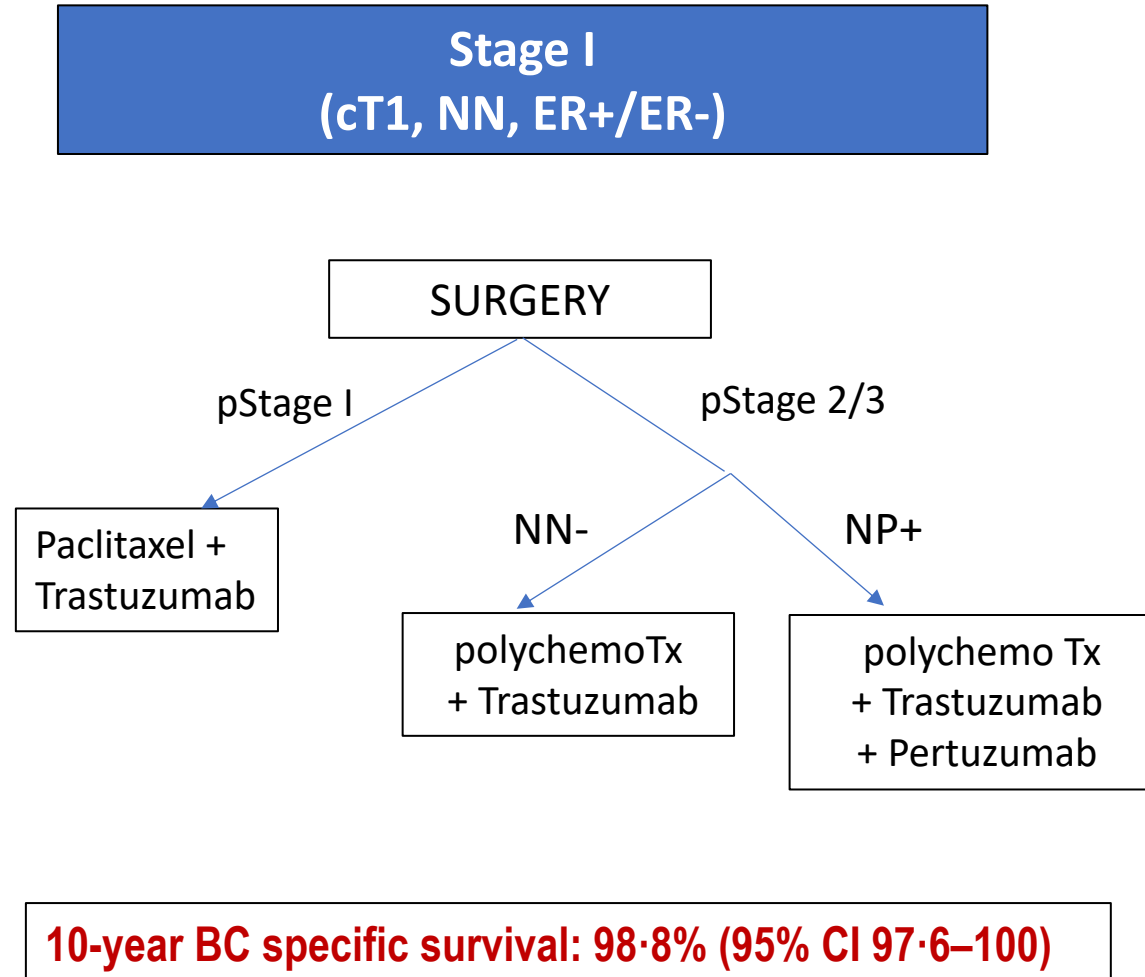
- PFS^d rate at 12 months (IA)
- ORR^d during Upfront Treatment
- ORR^d to Retreatment
- Safety and tolerability
- QoL
- PFS^d rate from start of Maintenance Treatment
- OS rate at 24 months

Exploratory Endpoints

- PFS2
- To assess the impact of objective response level achieved prior to transition to Maintenance Treatment on PFS
- ctDNA analyses
- ORR^d during trastuzumab + trastuzumab + ET + palbociclib
- PFS from start of Maintenance Treatment
- Treatment side-effects per the scale

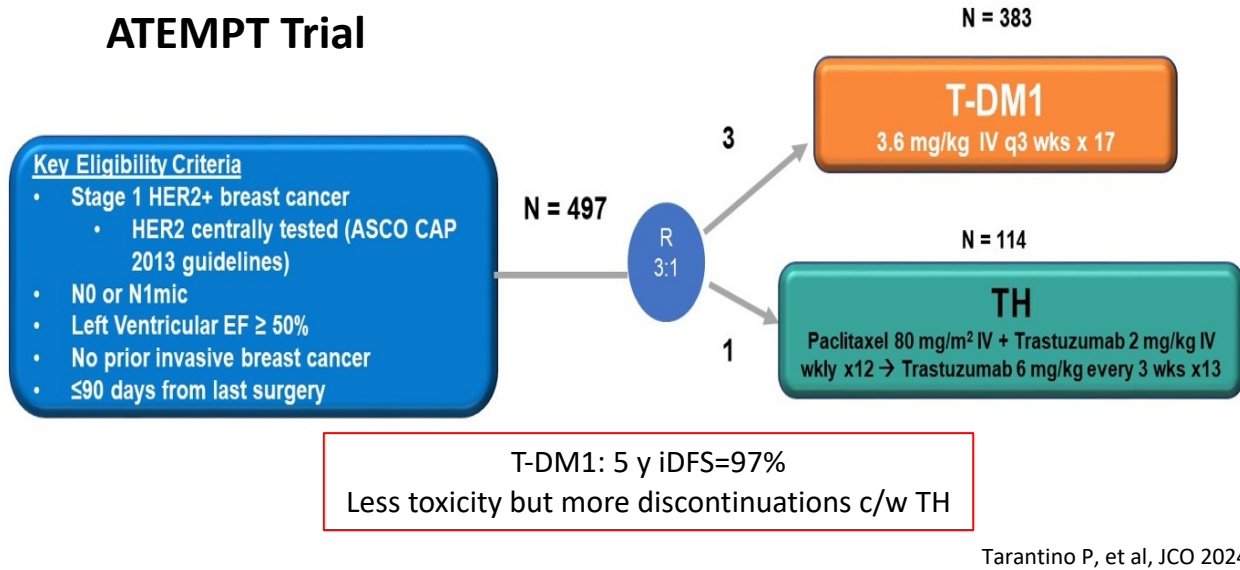
Early Stage HER2+ Breast Cancer

HER2+ Early Breast Cancer: Stage I

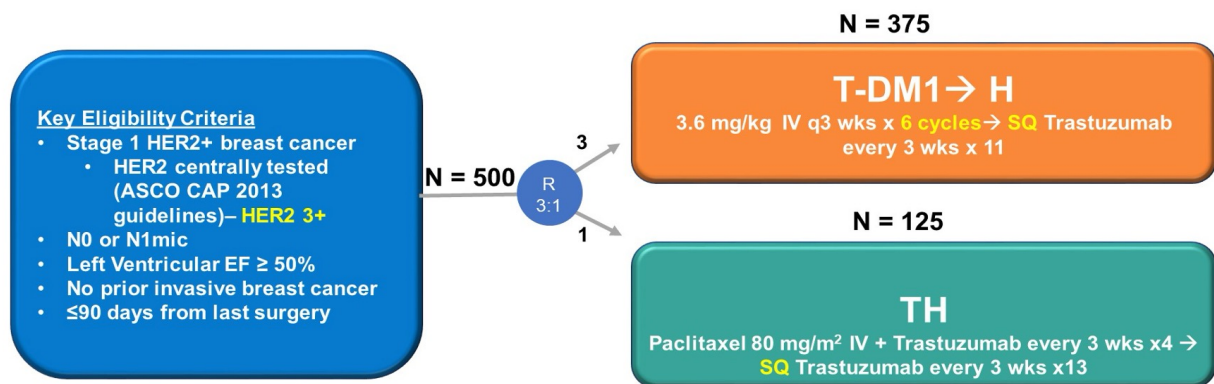


De-escalation Trials for HER2+ Stage I BC

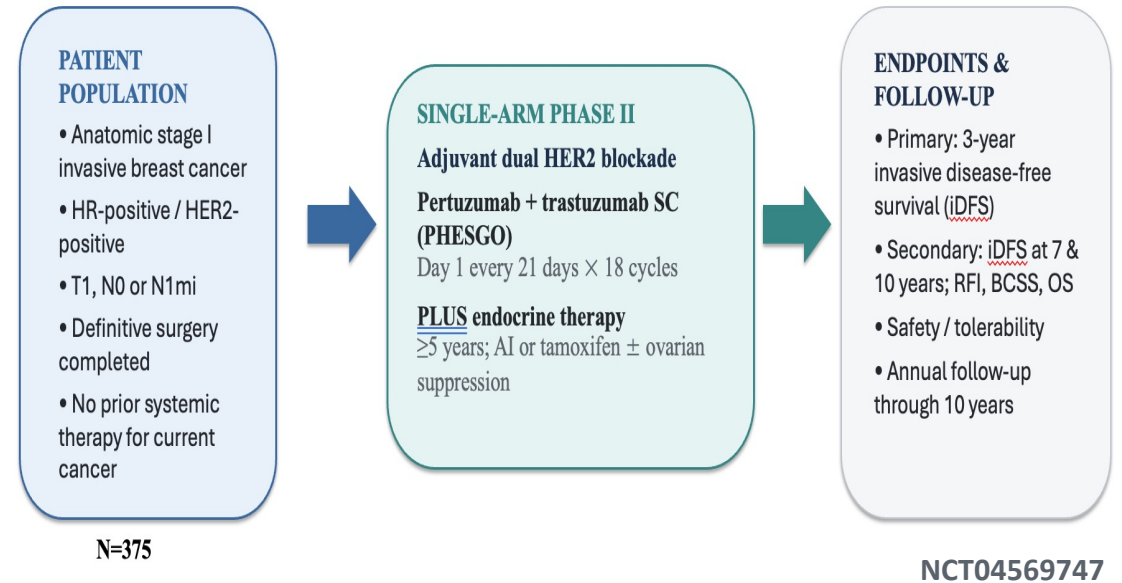
ATEMPT Trial



ATEMPT 2.0 Trial

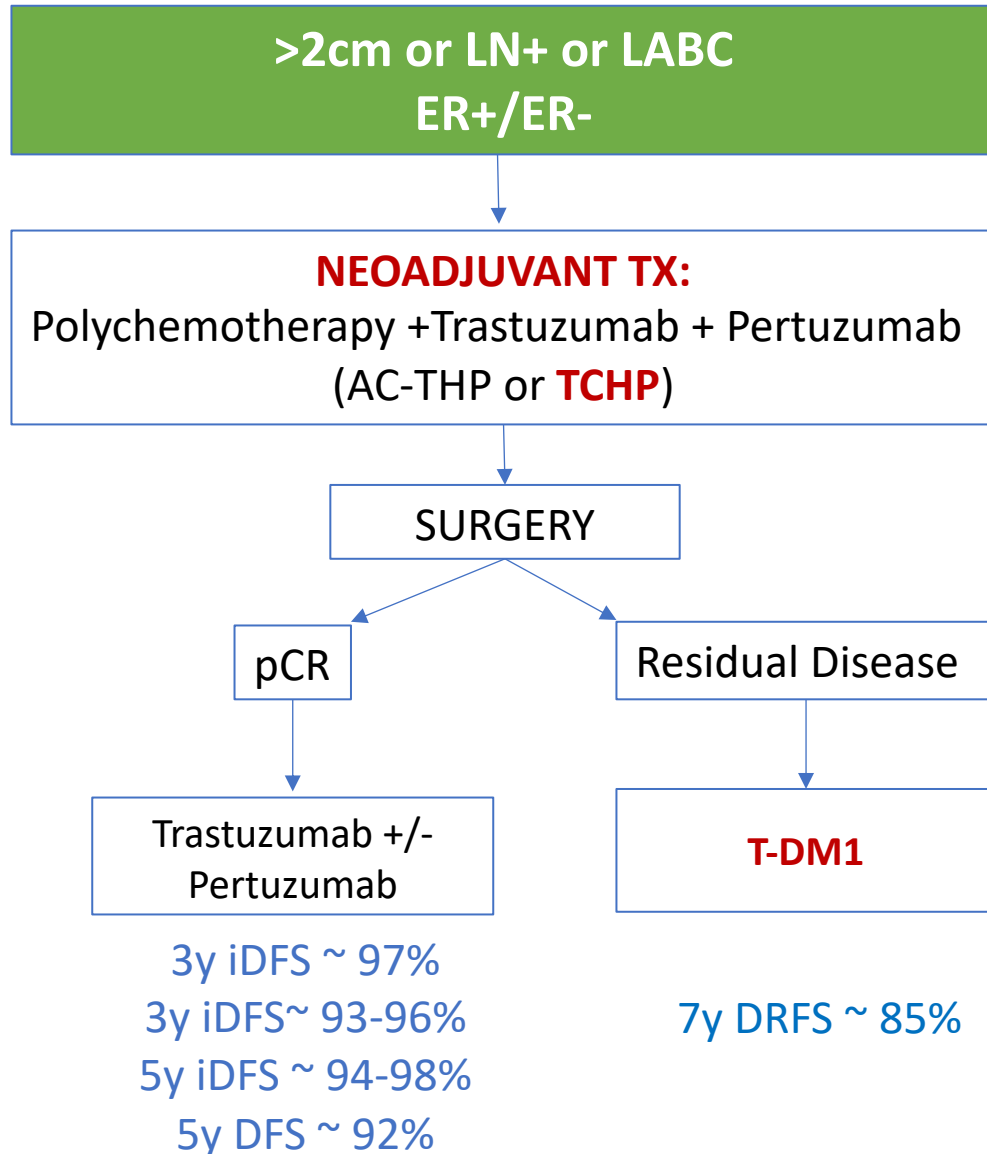


ADEPT Trial: ET+ HP for HR+ HER2+BC Elimination of Chemotherapy De-escalation Trial



ET: endocrine therapy; HP: trastuzumab and pertuzumab

Personalizing Therapy for Early Stage 2/3 HER2+ BC



Neoadjuvant

Pathological CR

De-escalating chemotherapy:

Eliminate polychemotherapy?

Any role for chemotherapy-free regimens?

Adjuvant

Residual Disease

Escalation using Novel Agents:

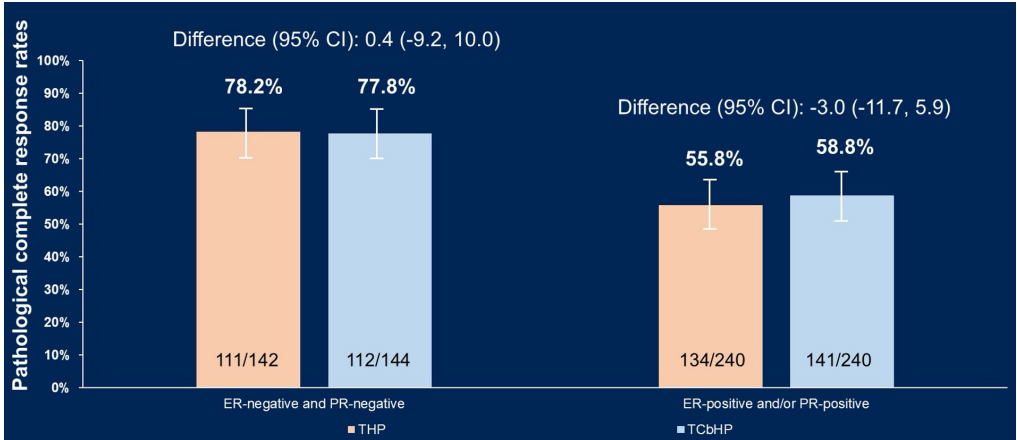
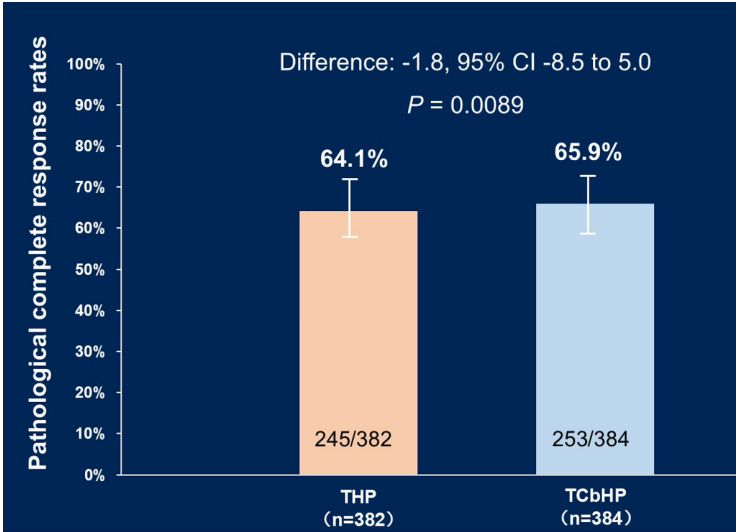
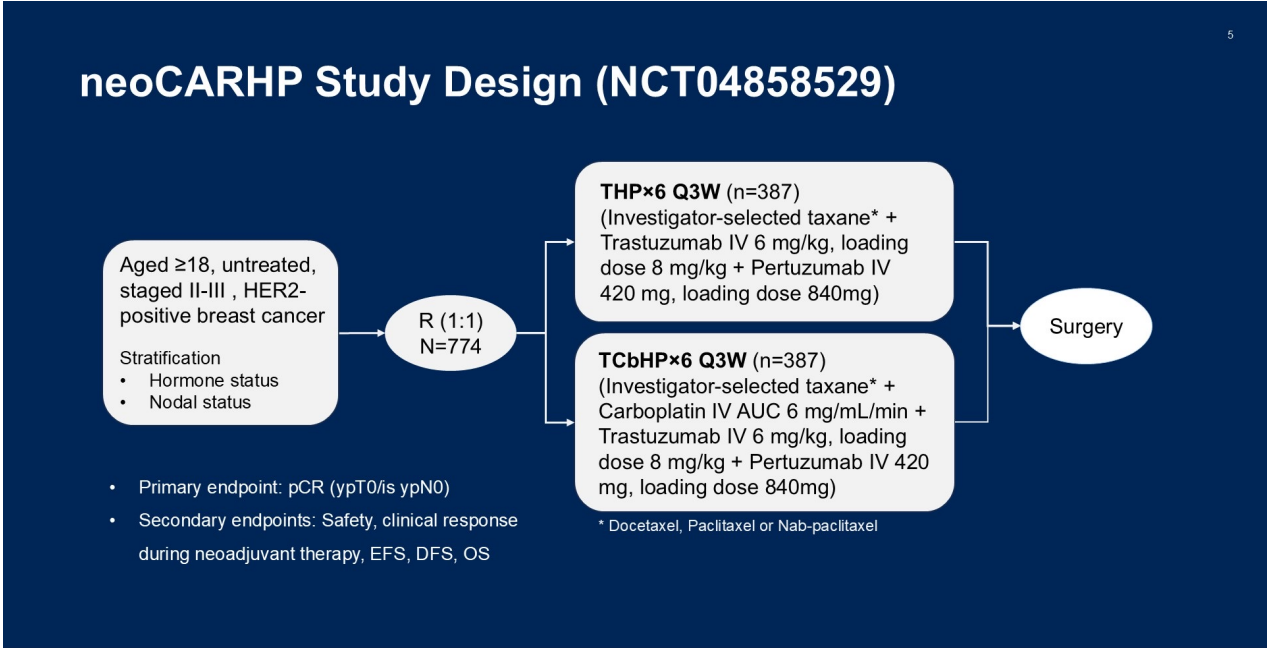
Trastuzumab Deruxtecan

Tucatinib

Immune therapies

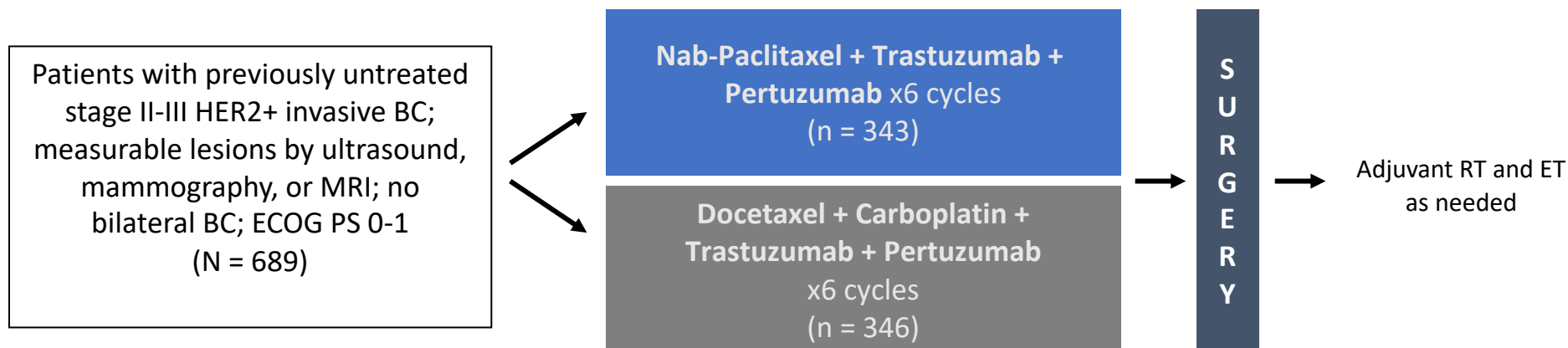
neoCARHP: Randomized PH 3 Trial of Neoadjuvant TCHP vs THP for HER2+ EBC

de-escalation by removing carboplatin

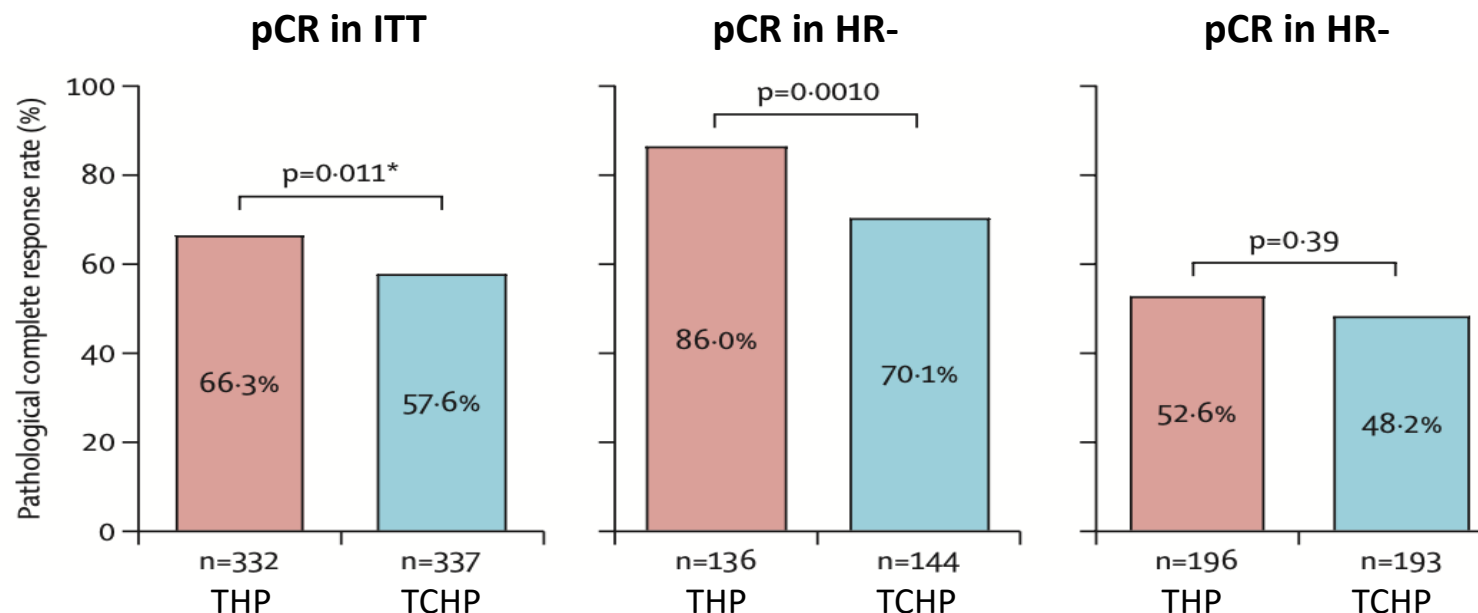


HELEN-006: Neoadjuvant THP vs TCHP in HER2+ EBC

Randomized, phase III study of de-escalation of Carboplatin

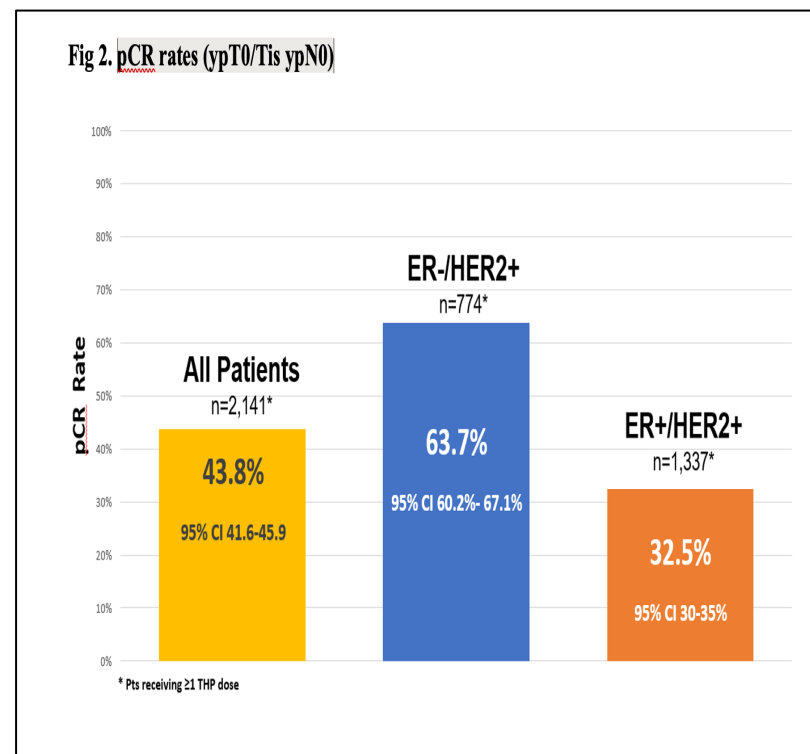
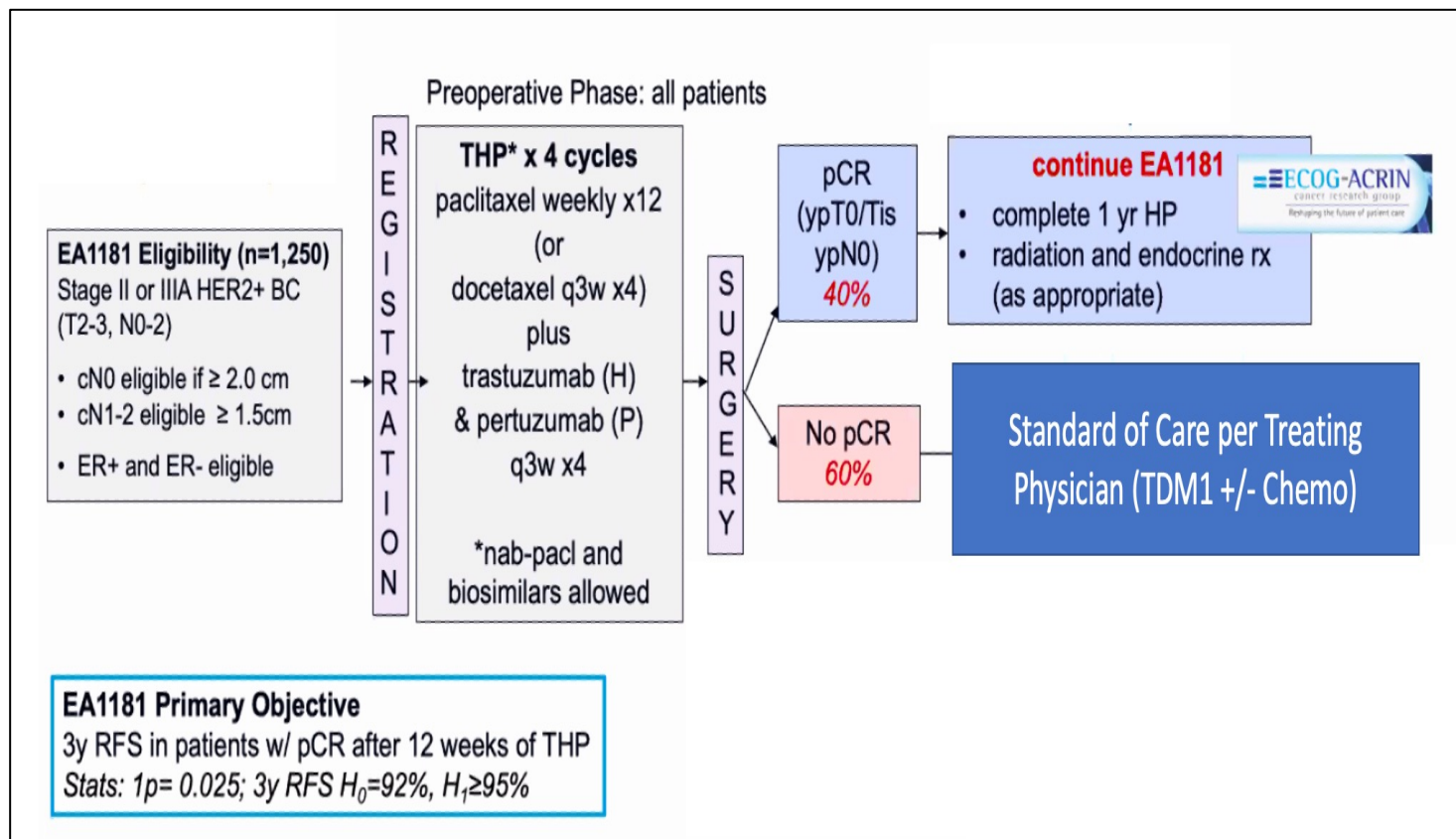


Primary endpoint:
pCR (ypT0/is ypN0)



CompassHER2 Neoadjuvant Trial:

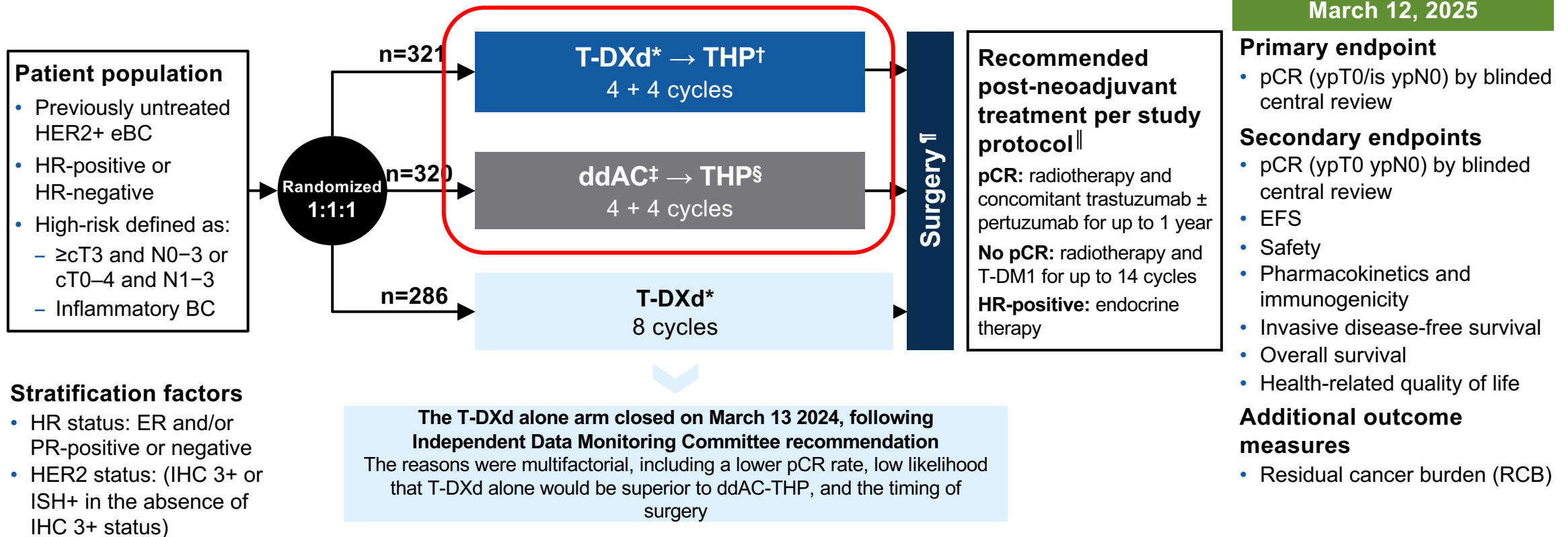
de-escalation to single agent paclitaxel and fewer cycles



Awaiting RFS results.....

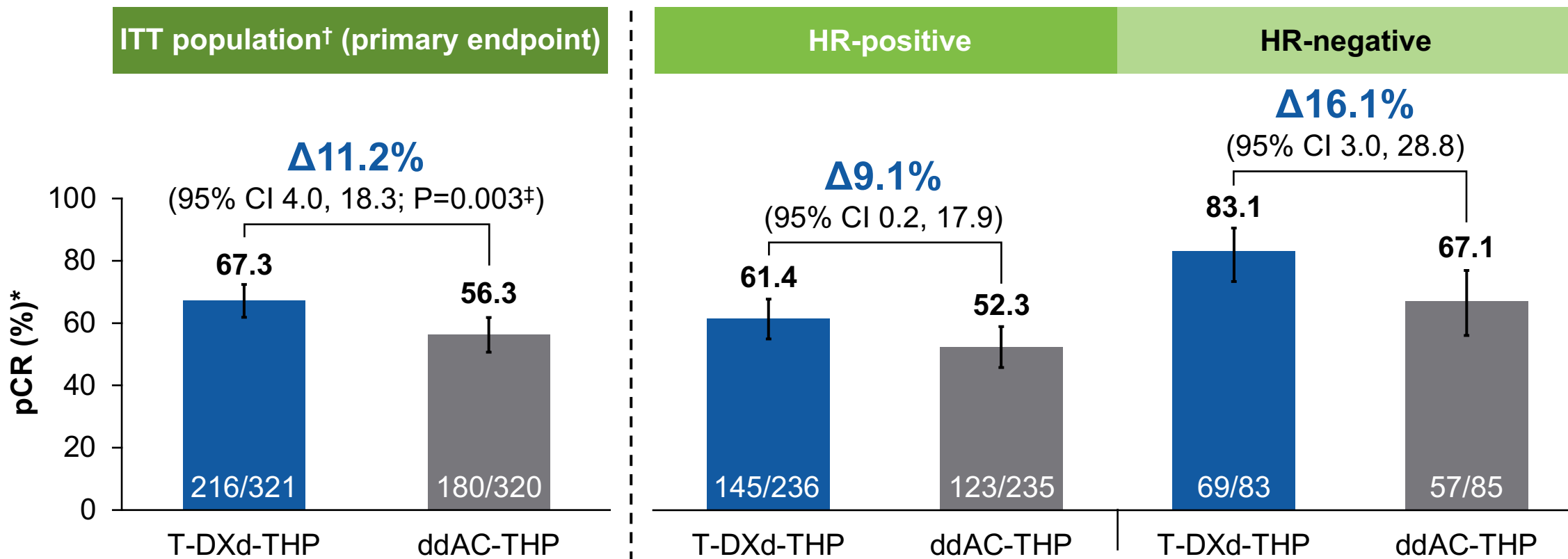
DESTINY-Breast11 study design

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



High-resolution computed tomography chest scans were performed every 6 weeks during treatment; if ILD/pneumonitis was suspected while receiving T-DXd, treatment was interrupted and a full investigation completed. Echocardiograms or multigated acquisition scans were performed during screening (<28 days prior to randomization), during treatment (<3 days before Cycle 5), and at end of treatment to assess left ventricular ejection fraction. *5.4 mg/kg Q3W; †paclitaxel (80 mg/m² QW) + trastuzumab (6 mg/kg Q3W) + pertuzumab (840 mg loading dose followed by 420 mg Q3W); ‡doxorubicin (60 mg/m² Q2W) + cyclophosphamide (600 mg/m² Q2W); §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); ¶the recommended window for surgery was 3–6 weeks following administration of the last dose of neoadjuvant study treatment; †administered as part of the patient's SOC at the investigator's discretion. cT, clinical tumor stage; ER, estrogen receptor; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH+, in situ hybridization-positive; N, nodal stage; PR, progesterone receptor; QXW, every X weeks; T-DM1, trastuzumab emtansine; ypT0/is ypN0, absence of invasive cancer in the breast and axillary nodes; ypT0 ypN0, absence of invasive and in-situ cancer in the breast and axillary nodes

pCR (ypT0/is ypN0): primary endpoint

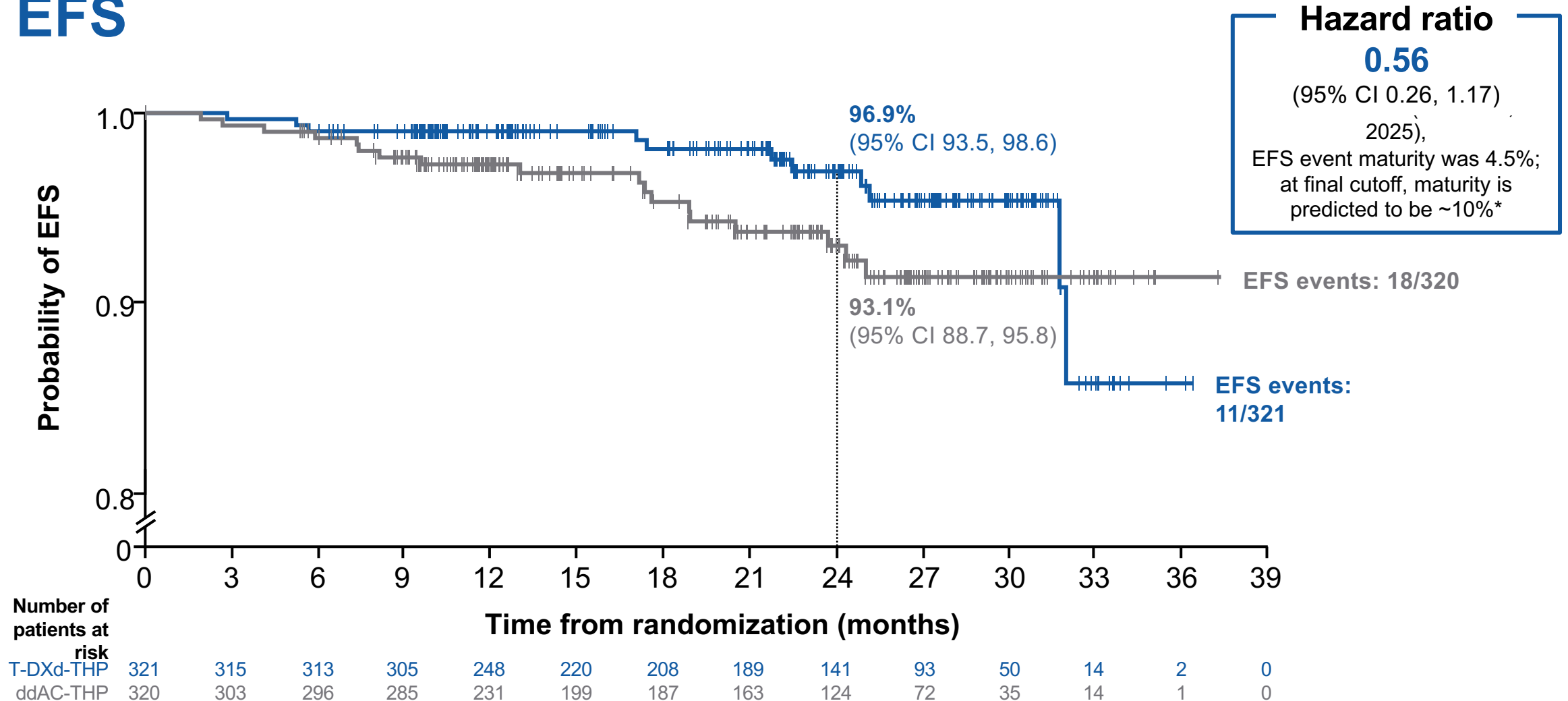


Neoadjuvant T-DXd-THP demonstrated a statistically significant and clinically meaningful improvement in pCR vs ddAC-THP

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

For the ITT population, treatment effects were estimated by the difference in pCR with 95% CIs and P-values based on the stratified Miettinen and Nurminen's method, with strata weighting by sample size (ie Mantel-Haenszel weights). Patients with no valid records regarding pCR status for any reason were considered to be non-responders (including but not limited to withdrawal from the study, progression of disease or death before surgery, lack of surgical specimen, or defined as not evaluable by the central pathologist). Subgroup analyses were unstratified. *By blinded central review; †pCR responders were defined as patients who only received randomized study treatment (at least one dose) and had pCR; ‡two-sided P-value crossed the 0.03 prespecified boundary. ITT, intent-to-treat

EFS



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

The median duration of follow up was 24.3 months with T-DXd-THP and 23.6 months with ddAC-THP. *Predicted maturity assumes that the observed EFS hazard ratio continues after data cutoff (March 12, 2025)

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)

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

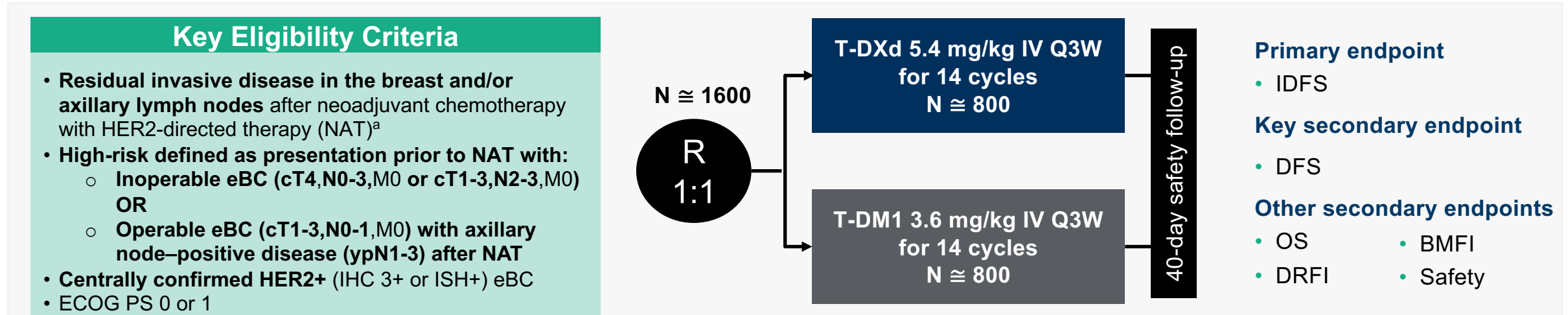
ILD incidence was low and similar in both arms

High-resolution computed tomography chest scans were performed every 6 weeks during treatment; if ILD/pneumonitis was suspected while receiving T-DXd, treatment was interrupted and a full investigation completed. Echocardiograms or multigated acquisition scans were performed during screening (<28 days prior to randomization), during treatment (<3 days before Cycle 5), and at end of treatment to assess left ventricular ejection fraction. Median total treatment duration of whole regimen was 24.1 months (T-DXd-THP), and 21.0 months (ddAC-THP). *Safety analyses included all patients who received at least one dose of any study treatment; †T-DXd-THP arm: death of unknown cause (n=1), drug-related pneumonitis adjudicated by the Independent ILD Adjudication Committee (n=1); ddAC-THP arm: investigator-determined drug-related bacterial encephalitis (n=1), drug-related pneumonitis adjudicated by the ILD Adjudication Committee (n=1); ‡defined as surgery not occurring within 3–6 weeks after the last cycle of neoadjuvant treatment

T-DXd +THP represents a new SOC option for high risk HER2+ EBC

DESTINY B-05 (RP3): Adjuvant T-DXd in High Risk HER2+ BC with RD

Escalation with ADC therapy for high-risk residual disease

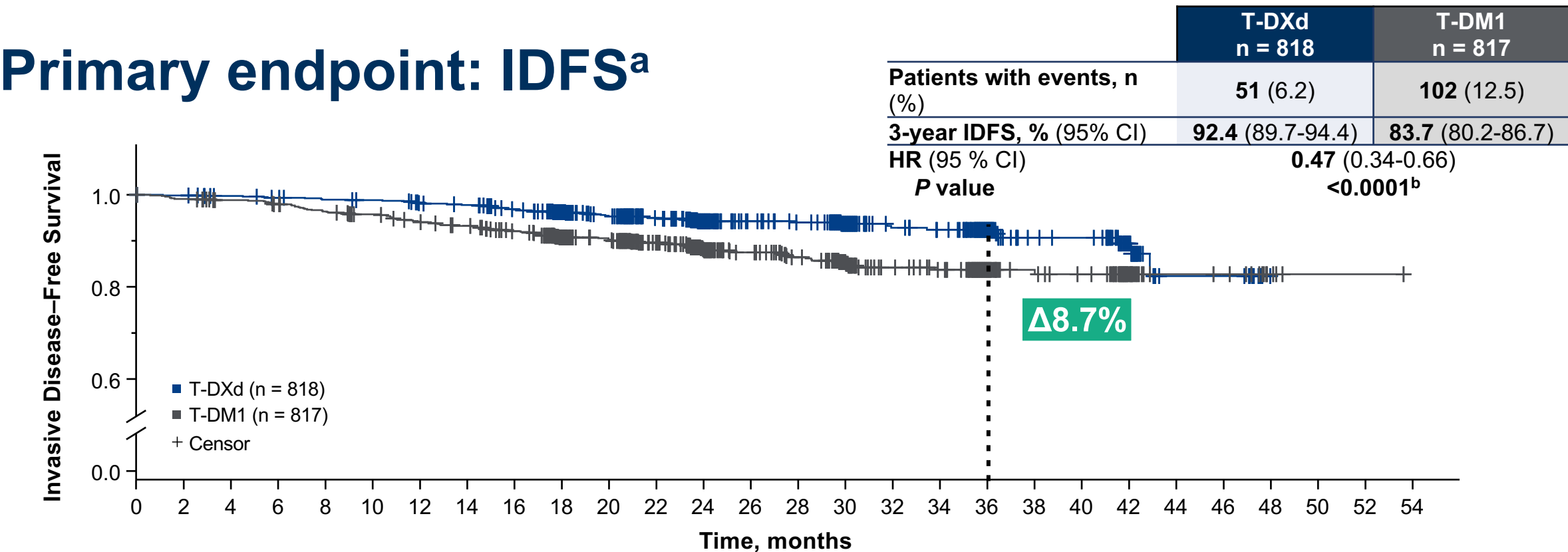


- Concomitant endocrine therapy was permitted
- Adjuvant XRT permitted (sequential or concurrent)
- Rigorous ILD monitoring with CT Chest scans

BMFI, brain metastasis-free interval; CT, computed tomography; eBC, early breast cancer; DCO, data cutoff; DFS, disease-free survival; DRFI, distant recurrence-free interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; IDFS, invasive disease-free survival; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, in situ hybridization; IV, intravenous; NAT, neoadjuvant therapy; OS, overall survival; Q3W, every 3 weeks; R, randomization; RT, radiotherapy; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

^aNAT is defined as ≥16 weeks' NAT with ≥9 weeks trastuzumab ± pertuzumab and ≥9 weeks taxane-based chemotherapy.

Primary endpoint: IDFS^a



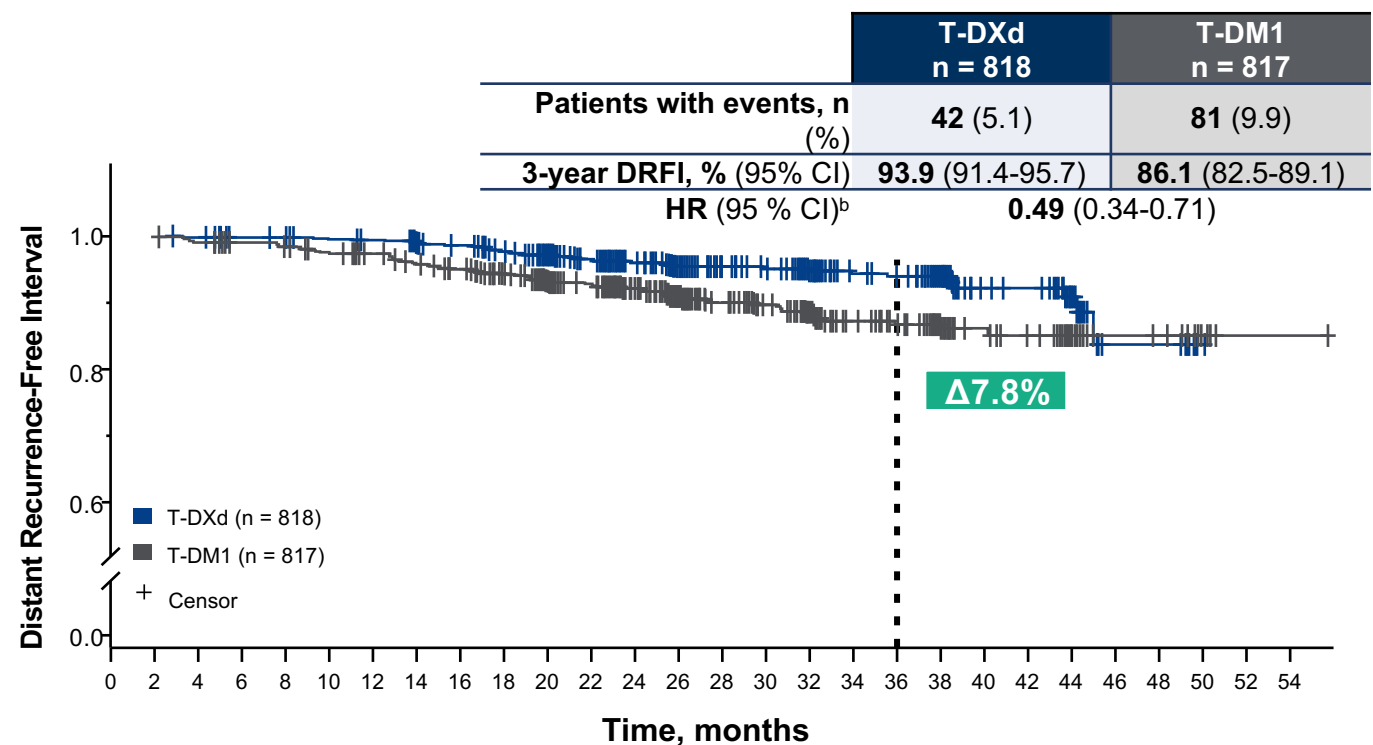
Number at Risk:

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

53% reduction in the risk of invasive disease recurrence or death for T-DXd compared with T-DM1

HR, hazard ratio; IDFS, invasive disease-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Efficacy stopping boundary, $P = 0.0183$.
^aIDFS is defined as the time from randomization until the date of first occurrence of one of the following events: recurrence of ipsilateral invasive breast tumor, recurrence of ipsilateral locoregional invasive breast cancer, contralateral invasive breast cancer, a distant disease recurrence, or death from any cause. ^bTwo-sided P value from stratified log-rank test. Hazard ratio and 95% CI from stratified Cox proportional hazards model with stratification factor of operative status at disease presentation.

Secondary endpoints: DRFI^a, BMFI, and OS



	T-DXd n = 818	T-DM1 n = 817
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) ^b	0.64 (0.35-1.17)	
OS (2.9% maturity)		
Patient deaths, n (%)	18 (2.2)	29 (3.5)
Survival at 3 years % (95% CI)	97.4 (95.8-98.4)	95.7 (93.5-97.2)
HR (95% CI) ^b	0.61 (0.34-1.10)	

BMFI, brain metastasis-free interval; DRFI, distant recurrence-free interval; HR, hazard ratio; OS, overall survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
^aDRFI is defined as the time between randomization and the date of distant breast cancer recurrence. ^bHR and 95% CI from stratified Cox proportional hazards model with stratification factor of operative status at disease presentation.

Adverse events of special interest: ILD/pneumonitis and LV dysfunction

n (%)	Adjudicated Drug-related ILD					
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
T-DXd (n = 806) ^a	77 (9.6)	16 (2.0)	52 (6.5)	7 (0.9)	0	2 (0.2)
T-DM1 (n = 801) ^a	13 (1.6)	8 (1.0)	5 (0.6)	0	0	0

Adjuvant radiotherapy timing (sequential or concurrent) showed no differences in adjudicated drug-related ILD

Similar distributions of any grade adjudicated drug-related ILD events were observed with sequential and concurrent radiotherapy in both treatment arms (T-DXd: 10.7% and 9.6.% vs T-DM1: 2.6% and 1.0%, respectively)

n (%)	LV dysfunction					
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
T-DXd (n = 806) ^a	23 (2.9)	1 (0.1)	20 (2.5)	2 (0.2)	0	0
T-DM1 (n = 801) ^a	14 (1.7)	0	11 (1.4)	3 (0.4)	0	0

CT, computed tomography; ILD, interstitial lung disease; LV, left ventricular; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

^aAll patients who received at least 1 dose of study treatment.

T-DXd represents a new SOC for the post-neoadjuvant high risk RD setting

Clinical Dilemma: Pre-Op versus Post-op T-DXd for HER2+ EBC?

Neoadjuvant T-DXd

- Shorter course (4 cycles)
- Lower ILD rates (4.9%)
- Greater RCB responses
 - Avoid ALND ($\Delta 9\%$ nodal PCR rates)
- More likely yo de-escalate adjuvant tx
- Less Neuropathy
- Non-anthracycline regimen

Downsides:

- More T-DXd given on a population level
 - Alopecia
 - Net higher ILD
- Unclear what to do in residual disease
- EFS immature

Adjuvant T-DXd

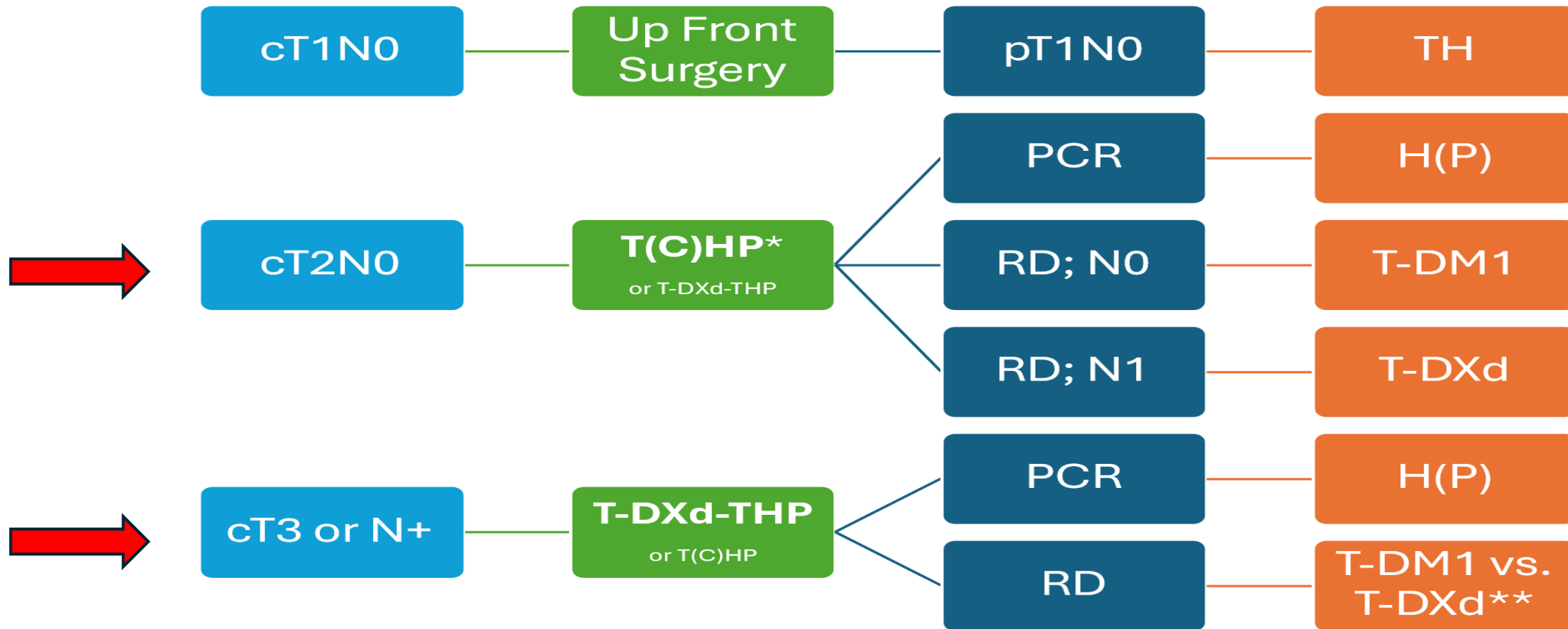
- More risk-driven approach
- EFS benefit is clear
- Clear treatment algorithm

Downsides:

- Longer course (14 cycles)
 - 17.9% discontinuation
- Higher ILD rates (9.6%)
 - Diagnostic uncertainty with RT
- Only included very high-risk patients (unresectable or ypN+)



My Updated Approach To Early Stage HER2+ BC



*TCHP x6 remains the NCCN preferred regimen; Consider carboplatin omission and/or use of weekly taxol based on equivalent PCR rates

**No prospective data exist to guide management; Consider patient specific factors and use shared decision-making

ADAPT-HER2-IV is investigating neoadjuvant T-DXd in HER2-positive eBC in lower risk patients compared to DESTINY-Breast11^{1,2}

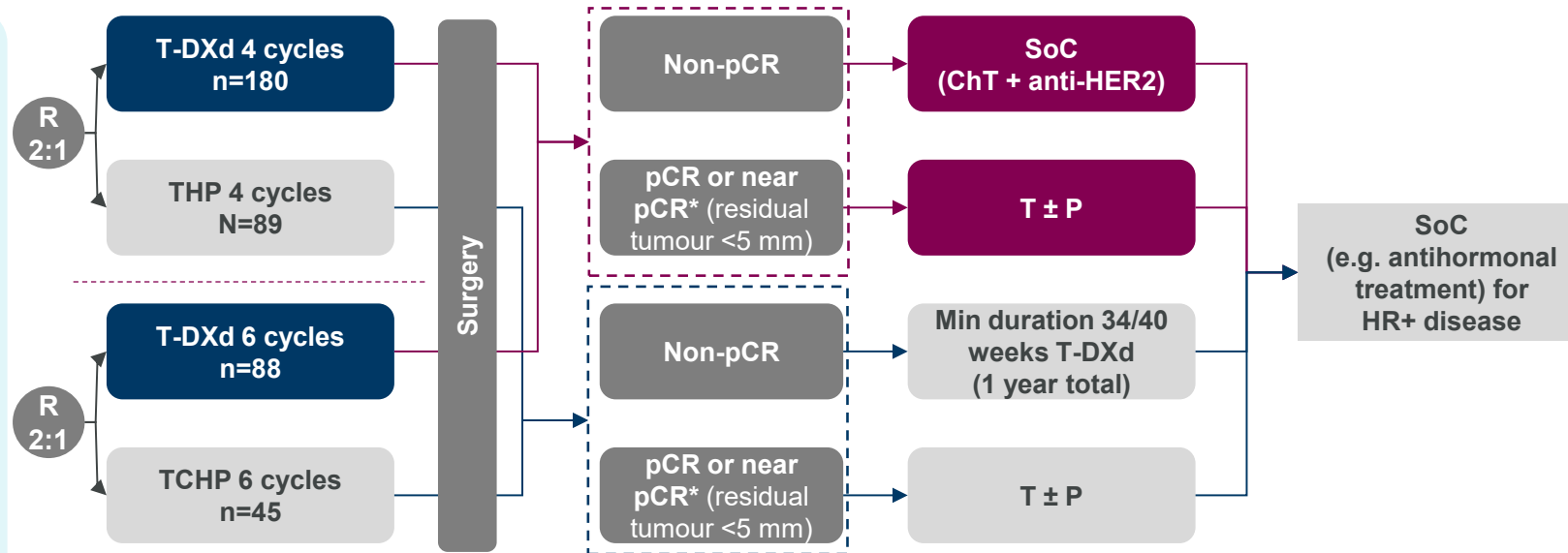
Eligibility criteria

Cohort 1

- HER2-positive and low-to-intermediate risk per investigator's decision
- Recommendation
 - cT1c–T2 (1–≤3 cm), cN0
 - cT1a/b excluded

Cohort 2

- HER2-positive and intermediate-to-high risk per investigator's decision
- Recommendation:
 - cT2 (>3–≤5 cm), cN0



Dual primary endpoints

- pCR
- DDFS[†]

Secondary endpoints

- Clinical response
- DDFS with pCR
- pCR after different treatment durations
- pCR in T-DXd vs. comparator
- IDFS[†]
- OS[†]
- LRFS[†]
- BCFS[†]
- DRFI[†]
- QoL

Study Location: Germany

*Treatment of near pCR at investigator's discretion; [†]By STEEP 2.0 criteria.

BCFS, breast cancer-free survival; c, clinical; C, carboplatin; (D/I)DFS, (distant/invasive) disease-free survival; DRFI, distant recurrence-free interval; eBC, early breast cancer; H, trastuzumab; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LRFS, local recurrence-free survival; N, lymph node; OS, overall survival; P, pertuzumab; pCR, pathological complete response; QoL, quality of life; R, randomised; SoC, standard of care; STEEP=Standardised Definitions for Efficacy Endpoints; T, taxane; Tx, tumour; T-DXd, trastuzumab deruxtecan.

1. Harbeck N, et al. Presented at American Society of Clinical Oncology Annual Meeting 2024. Abstract #TPS63; 2. NCT05704829. Available from: <https://clinicaltrials.gov/study/NCT05704829>. Accessed November 2025.

Watch for this at SABC 2026

Residual Disease Trials in HER2+ Early Breast Cancer

COMPASS RD: Phase 3 TRIAL

Eligibility A011801

HER2+ RD
ER- & ER+

(must have N+ if ER+)

(~30% of A011801 participants
expected to come from EA1181)

N=1031 pts

Registration

R

T-DM1 + placebo
x 14 doses

T-DM1+ tucatinib x 14
doses

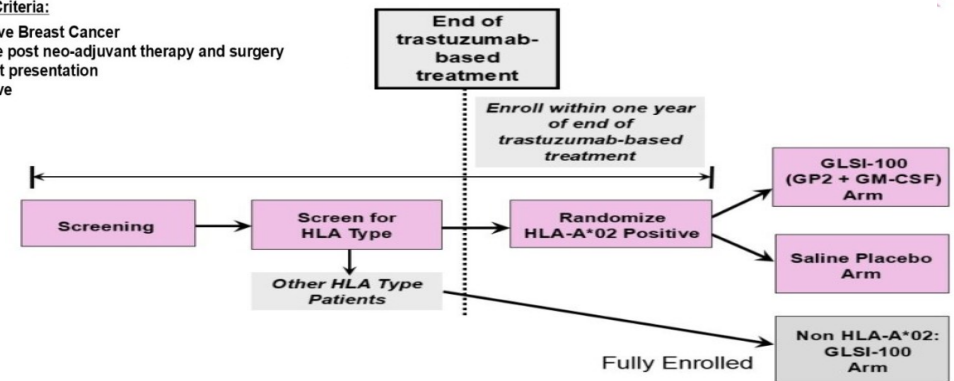
Primary Endpoint: iDFS
Secondary: Brain Met Free Survival

NCT04457596

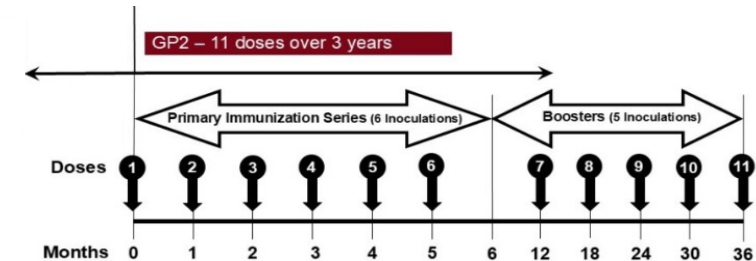
Flamingo-01, RP3 Adjuvant Trial: GLSI-100 (GP2 + GM-CSF) vaccine vs Placebo in pts with HER2+ BC with RD or high-risk PCR

Major Screening Criteria:

- HER2/neu Positive Breast Cancer
- Residual disease post neo-adjuvant therapy and surgery
- pCR if Stage III at presentation
- HLA-A*02 Positive



Vaccine Treatment



Primary end point: invasive breast cancer-free survival
Secondary end points: of iDFS, DDFS, OS, and QoL

ASTEFANIA: Phase 3 TRIAL

Eligibility

- Residual invasive disease in the breast and/or axillary lymph nodes after neoadjuvant chemotherapy
- 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
- Centrally confirmed HER2+

N ≅ 1188

R
1:1

T-DM1 + Atezolizumab

T-DM1 + placebo

Primary Endpoint:
iDFS

NCT04873362

Summary: HER2+ High Risk Early Stage Breast Cancer

- Prevailing paradigm is personalization of therapy
- TDXD is part of the new SOC in early stage HER2+ BC for high risk patients
 - neoadjuvant or adjuvant therapy
- Still exploring TKI and IO options in HER2+ EBC
- Await the next generation of Trials where we use multiplex of markers and adaptive designs to truly individualize therapy

Thank you

