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Integrating Recent Advances into the Management of HER2-Positive Breast Cancer

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Disclosures

Advisory Committees	Tempus
Consulting Agreements	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Novartis, Pfizer Inc, Stemline Therapeutics Inc
Contracted Research	AstraZeneca Pharmaceuticals LP, Genentech, a member of the Roche Group, Greenwich LifeSciences Inc, Pfizer Inc, Stemline Therapeutics Inc

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Agenda

Module 1: Localized HER2-Positive Breast Cancer (BC)

Module 2: Clinician Survey Results

Module 3: First-Line Treatment of HER2-Positive Metastatic BC (mBC)

Module 4: Clinician Survey Results

Module 5: Maintenance Therapy for HER2-Positive mBC

Module 6: Clinician Survey Results

Module 7: Novel Investigational Strategies for HER2-Positive BC

Module 8: Clinician Survey Results

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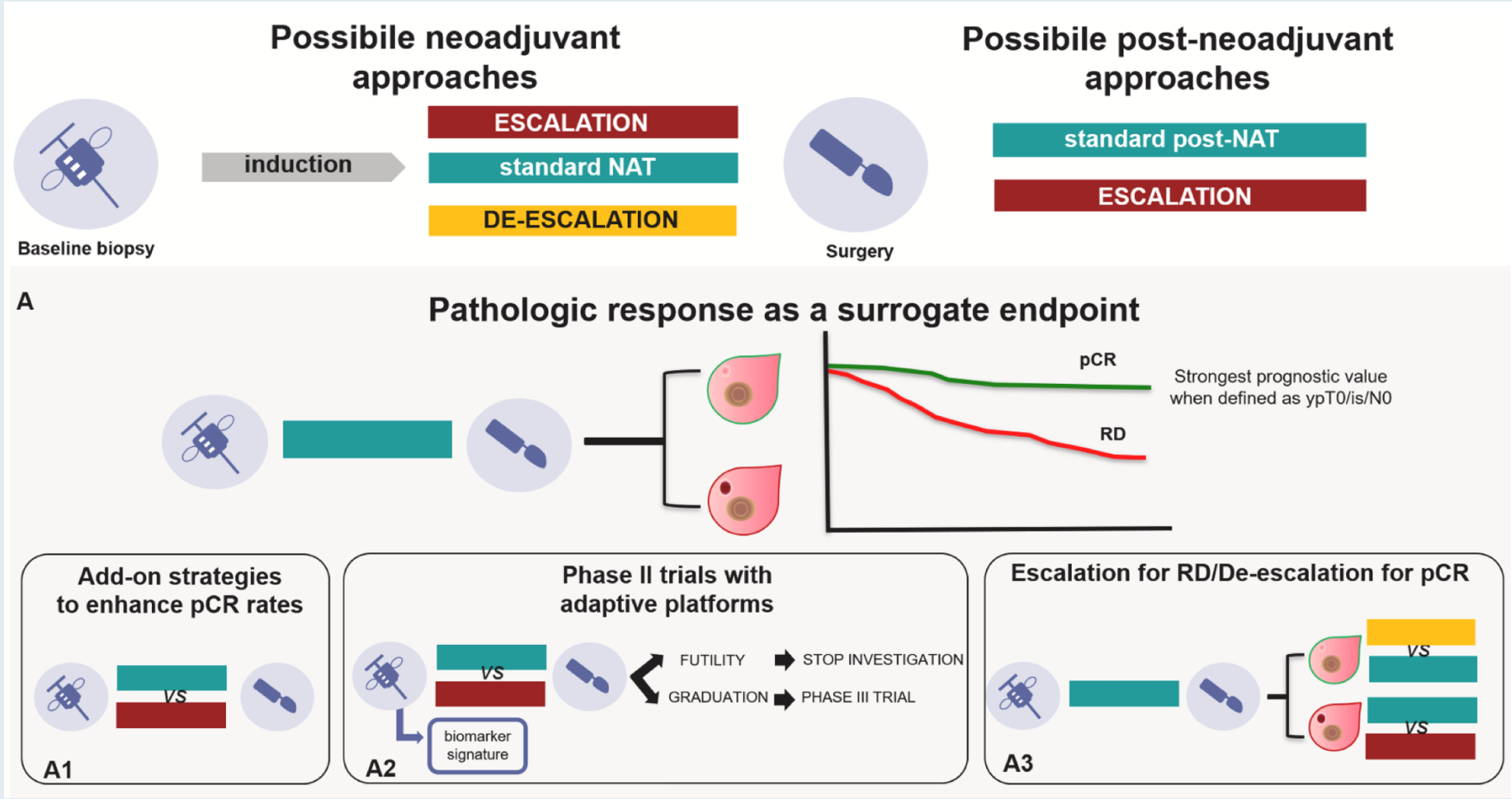
Module 6: Clinician Survey Results

Module 7: Novel Investigational Strategies for HER2-Positive BC

Module 8: Clinician Survey Results

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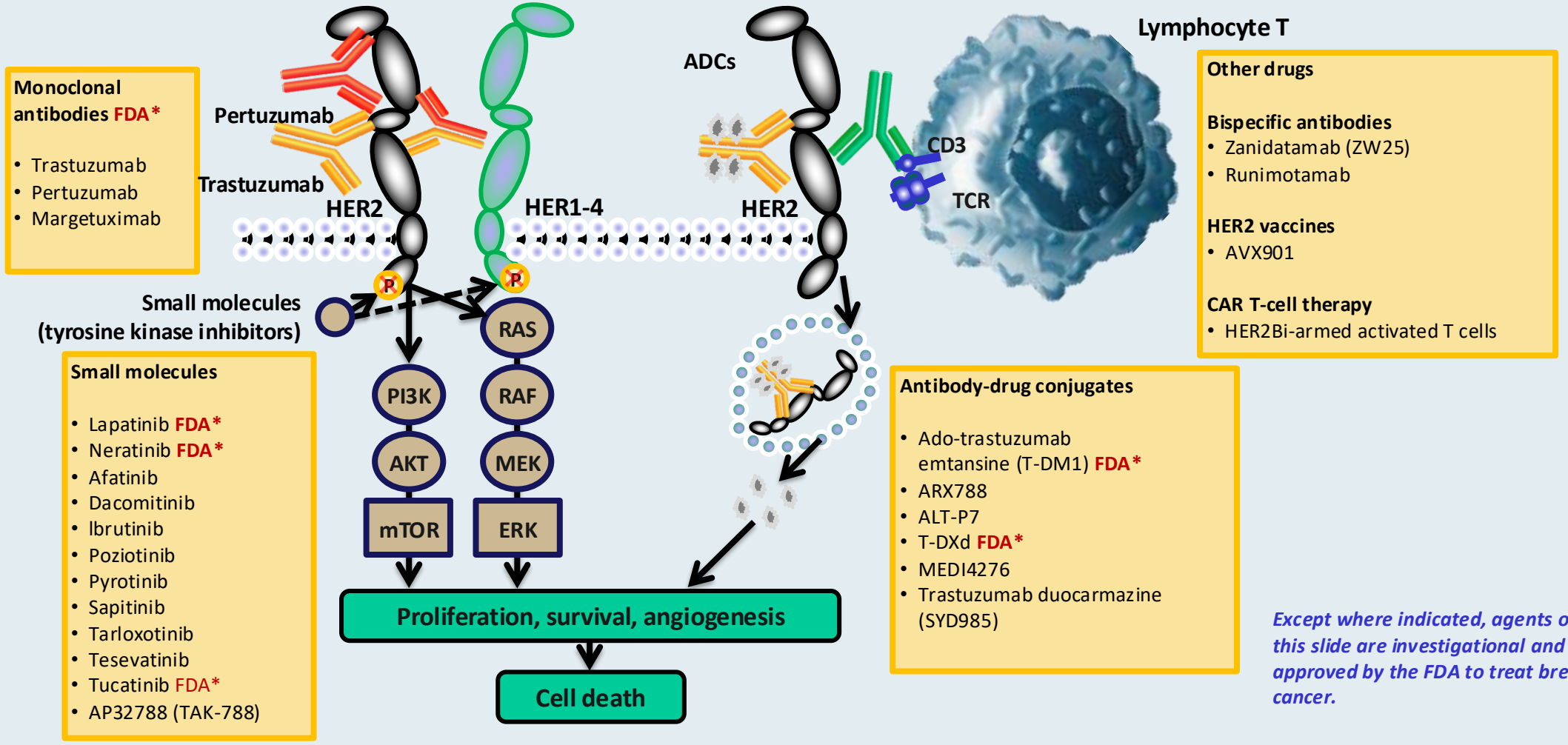
Escalating/De-escalating Treatment Strategies for HER2-Positive Localized Breast Cancer



NAT = neoadjuvant therapy; pCR = pathologic complete response; RD = residual disease

Miglietta F et al. *Cancer Treat Rev* 2021;98:102222.

HER2-Targeted Therapies: Approved and Investigational



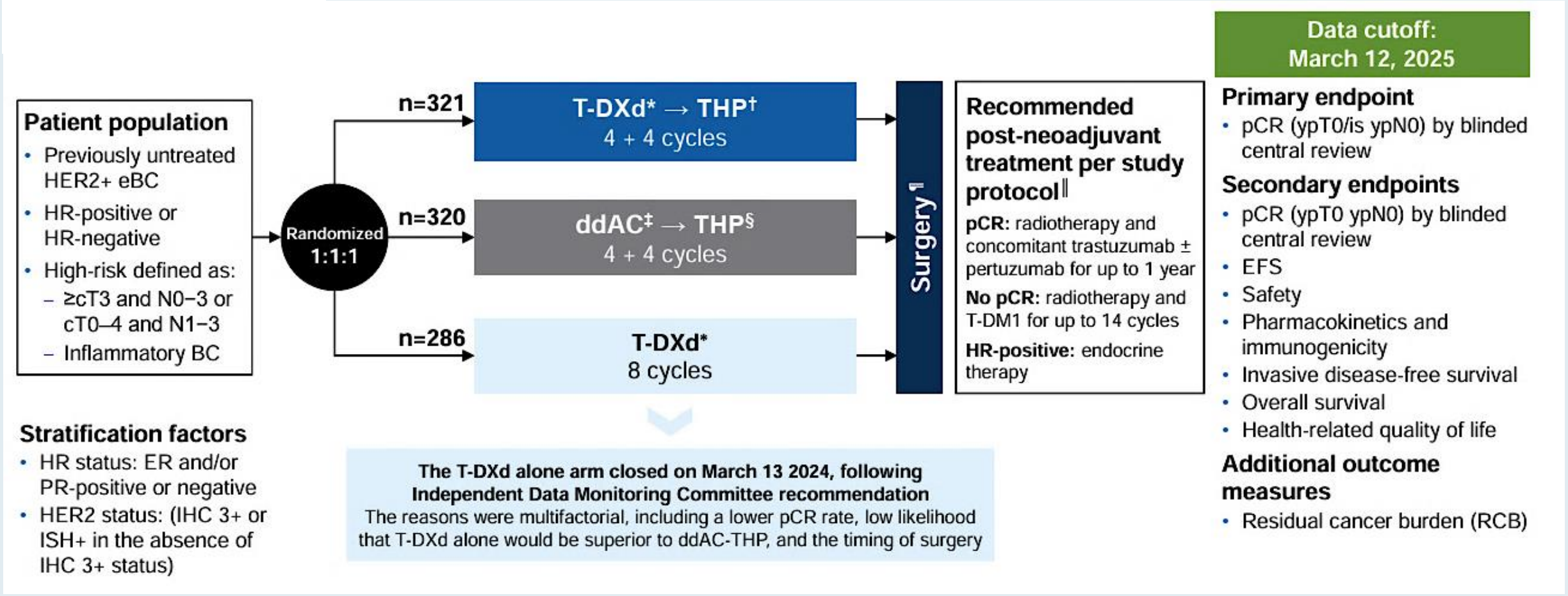
Except where indicated, agents on this slide are investigational and not approved by the FDA to treat breast cancer.

ADCs = antibody-drug conjugates; TCR = T-cell receptor; CAR = chimeric antigen receptor; HER2Bi = anti-HER2 bispecific antibody; PI3K = phosphoinositide-3 kinase; AKT = a serine/threonine kinase; mTOR = mammalian target of rapamycin

Meric-Bernstam F et al. *Clin Cancer Res* 2019;25:2033-41. Content courtesy of Reshma Mahtani, DO.

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Phase III DESTINY-Breast11 Study Design

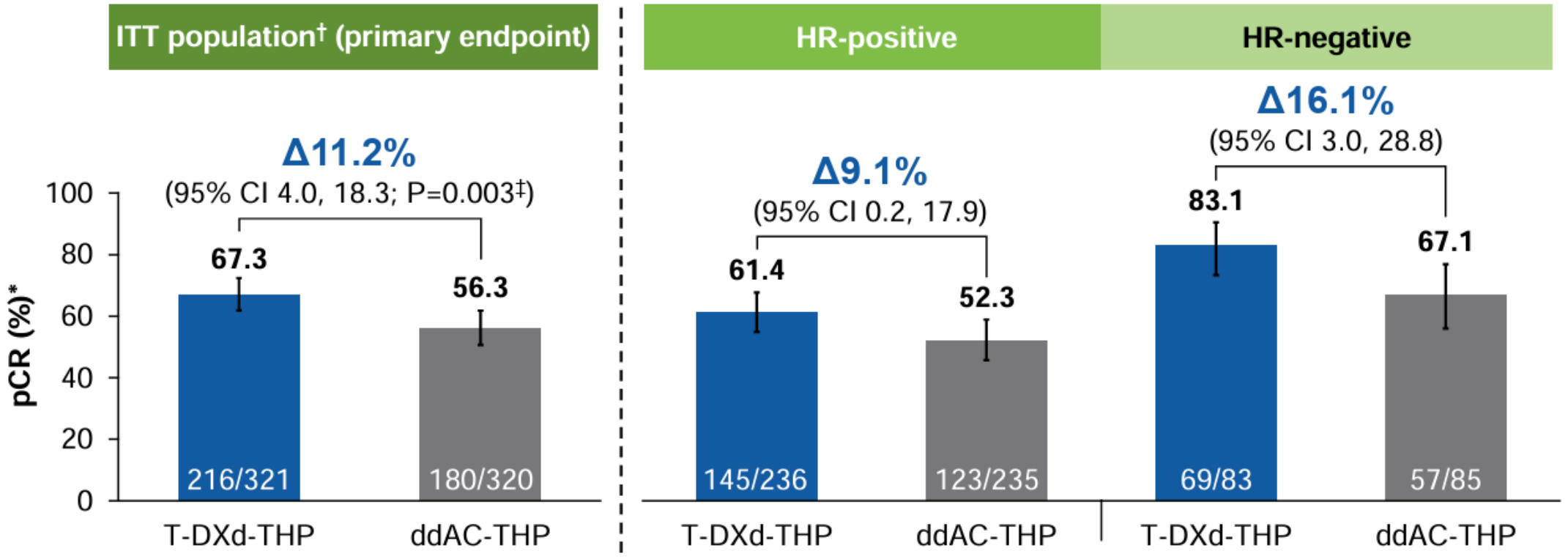


eBC = early breast cancer; T-DXd = trastuzumab deruxtecan; ddAC = dose-dense doxorubicin and cyclophosphamide; THP = paclitaxel/trastuzumab/pertuzumab; EFS = event-free survival

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Harbeck N et al. ESMO 2025;Abstract 291O; Harbeck N et al. *Ann Oncol* 2026;37:166-79.

DESTINY-Breast11: Pathologic Complete Response (pCR) — ypT0/is ypN0

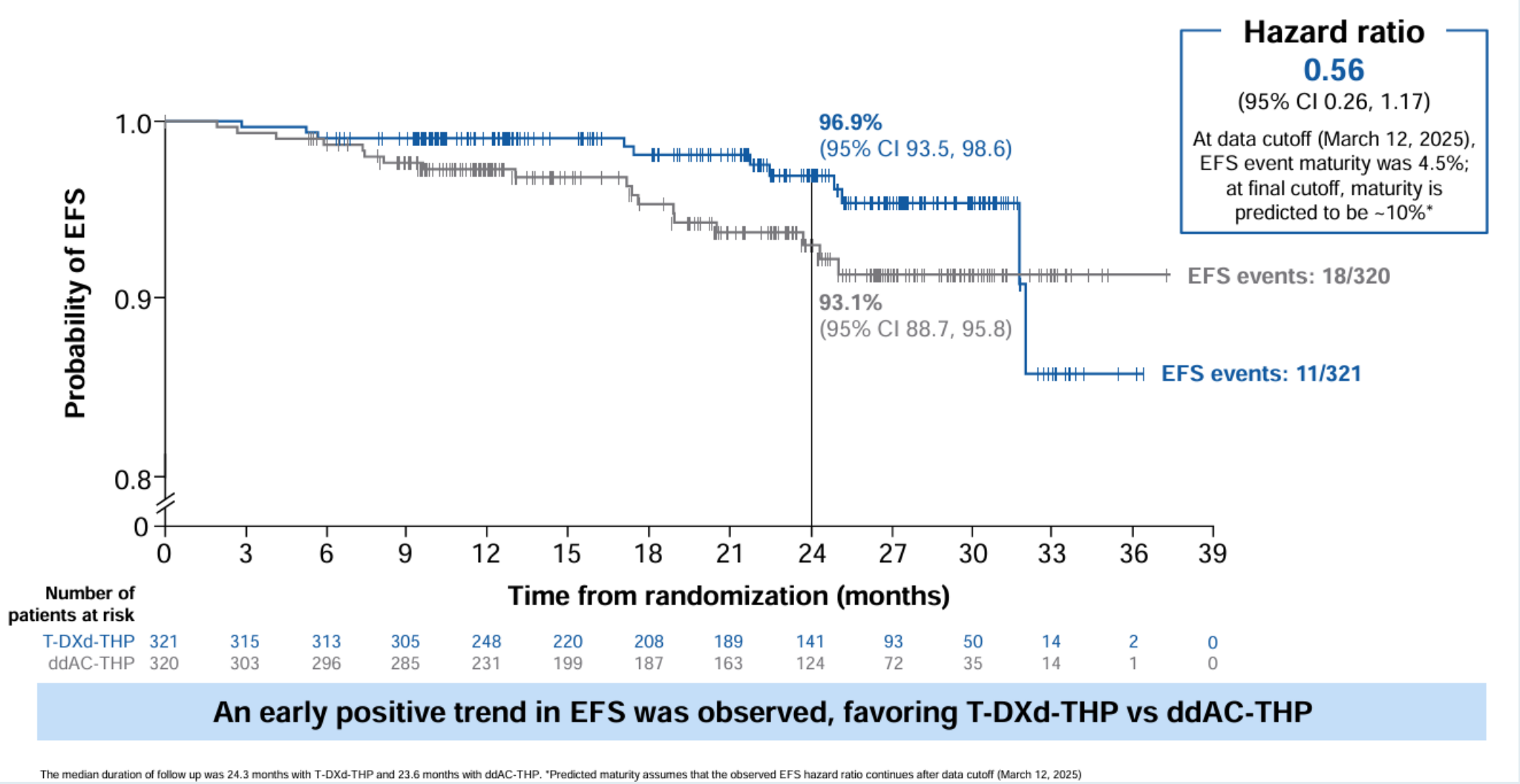


Neoadjuvant T-DXd-THP demonstrated a statistically significant and clinically meaningful improvement in pCR vs ddAC-THP

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

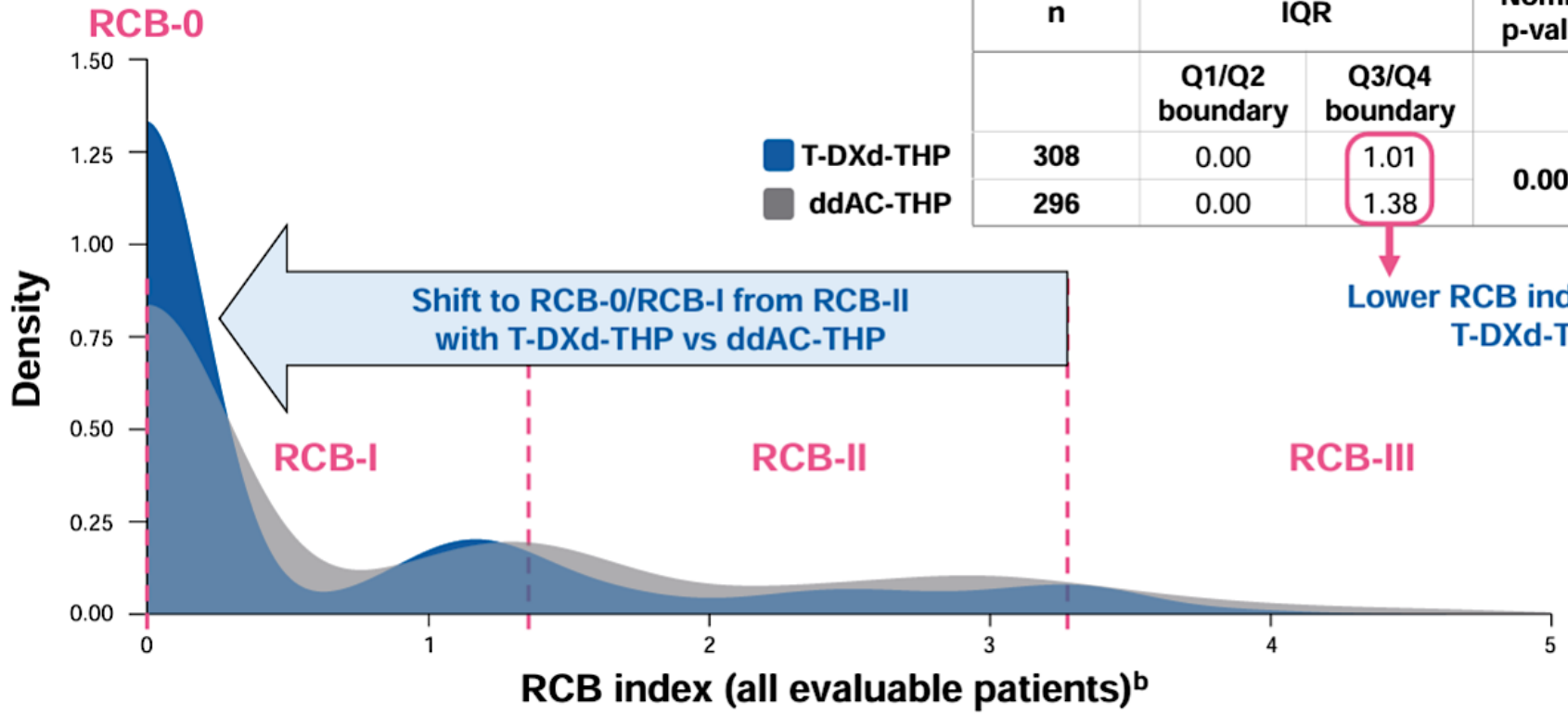
Harbeck N et al. ESMO 2025;Abstract 291O; Harbeck N et al. *Ann Oncol* 2026;37:166-79.

DESTINY-Breast11: Event-Free Survival (EFS)



Harbeck N et al. ESMO 2025;Abstract 291O; Harbeck N et al. *Ann Oncol* 2026;37:166-79.

DESTINY-Breast11: Distribution of Residual Cancer Burden (RCB)



All evaluable patients				Patients who did not achieve pCR (RCB >0)	
n	IQR		Nominal p-value[a]	n	Median
	Q1/Q2 boundary	Q3/Q4 boundary			
308	0.00	1.01	0.0059	87	1.5
296	0.00	1.38		112	1.7

Lower RCB index = less residual disease with T-DXd-THP than with ddAC-THP

Overall, and among patients who did not achieve pCR, the distribution of RCB index indicated less residual disease with T-DXd-THP than with ddAC-THP

Pusztai L et al. ESMO Breast 2026;Abstract LBA1.

DESTINY-Breast11: 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

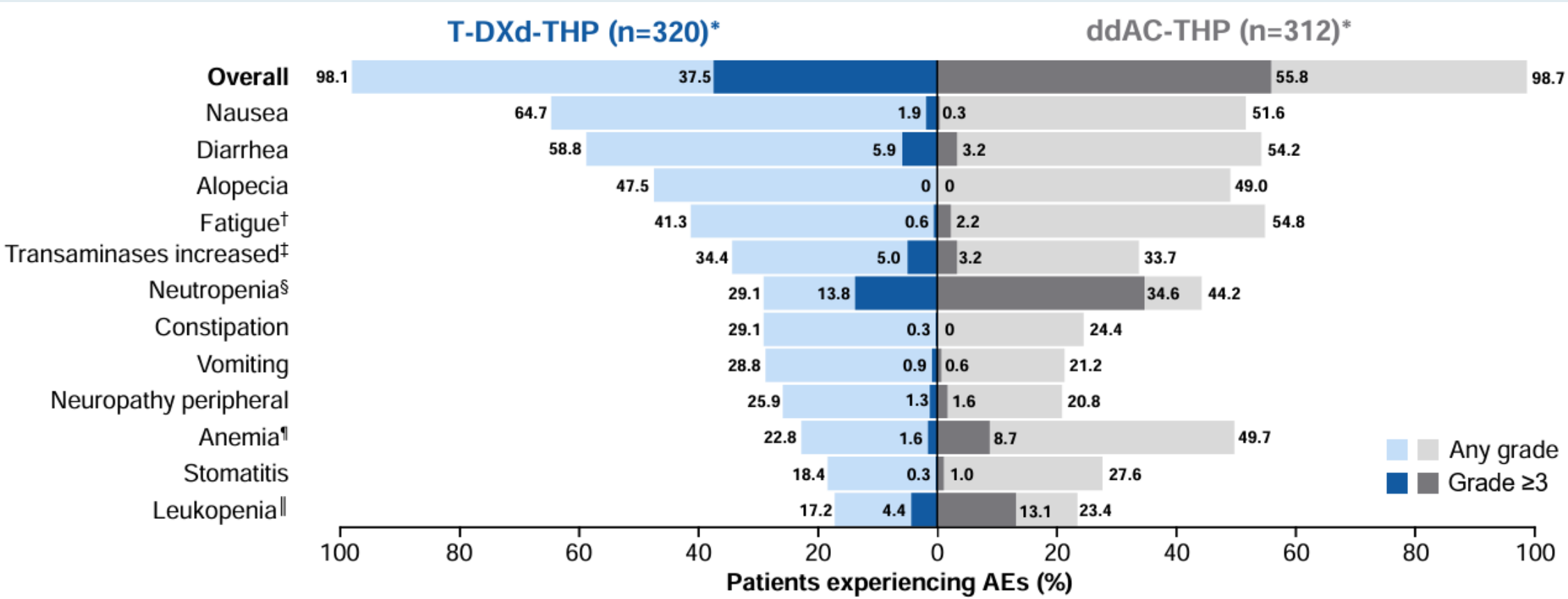
ILD incidence was low and similar in both arms

AE = adverse event; ILD = insterstitial lung disease

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Harbeck N et al. ESMO 2025;Abstract 291O; Harbeck N et al. *Ann Oncol* 2026;37:166-79.

DESTINY-Breast11: Treatment-Emergent AEs in >20% of Patients

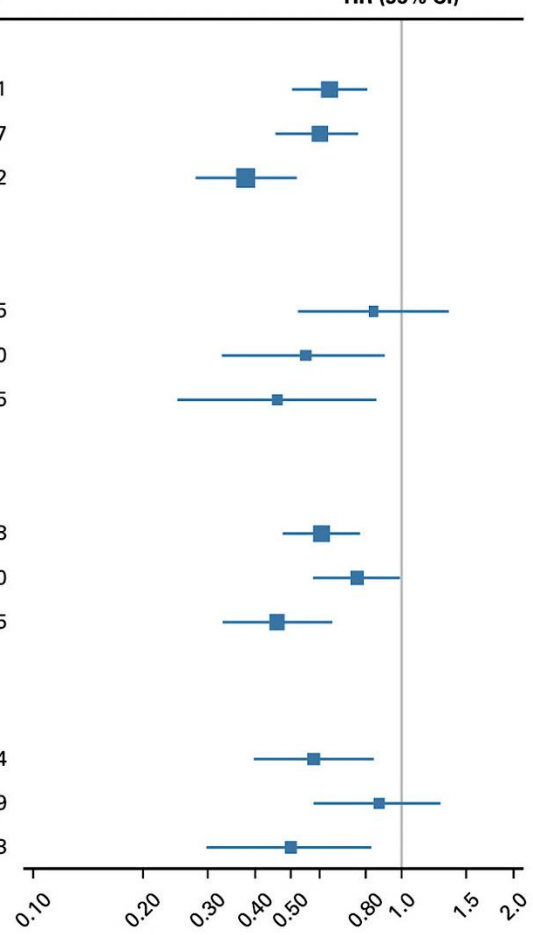


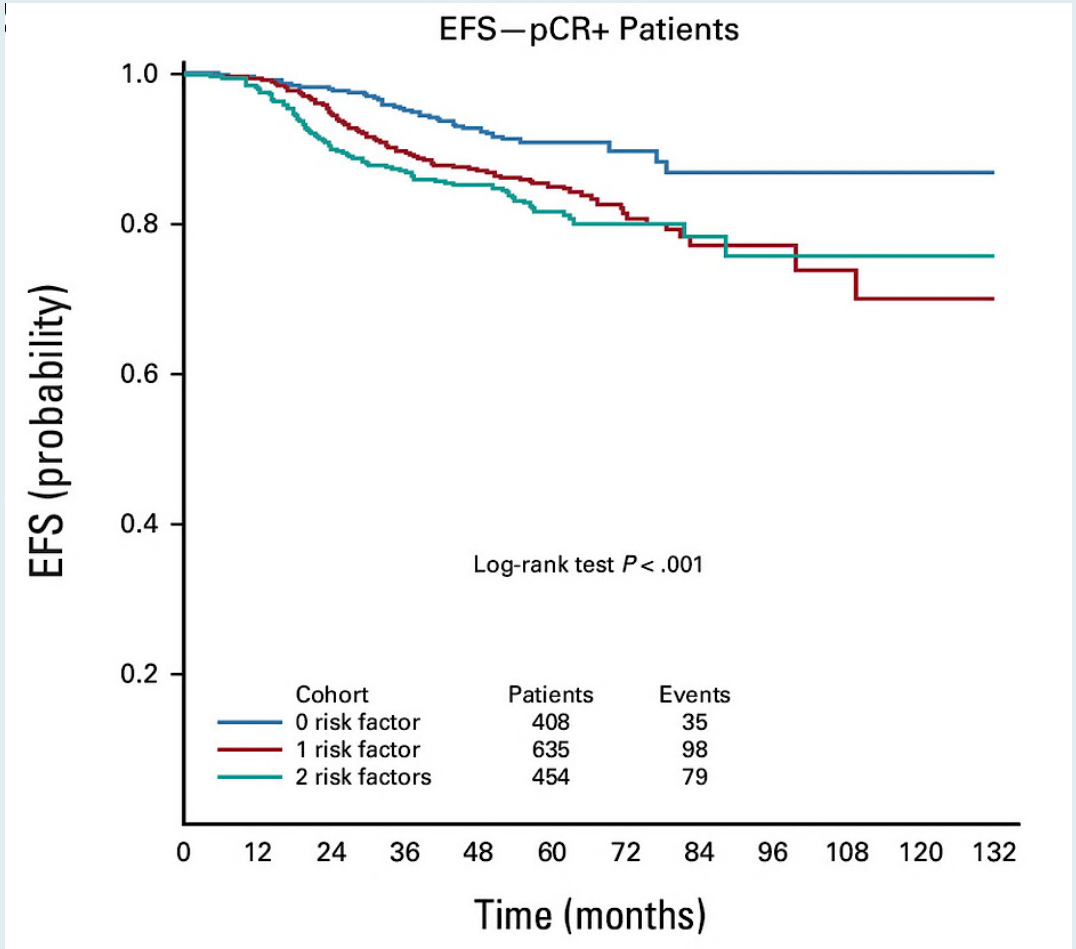
T-DXd-THP had fewer any-grade and Grade ≥3 hematological and fatigue events than ddAC-THP
Aside from nausea, gastrointestinal toxicity was comparable between arms

Harbeck N et al. ESMO 2025;Abstract 291O; Harbeck N et al. *Ann Oncol* 2026;37:166-79.

HER2-Positive Localized Breast Cancer: pCR and Remaining Risk for Recurrence in High-Volume Disease

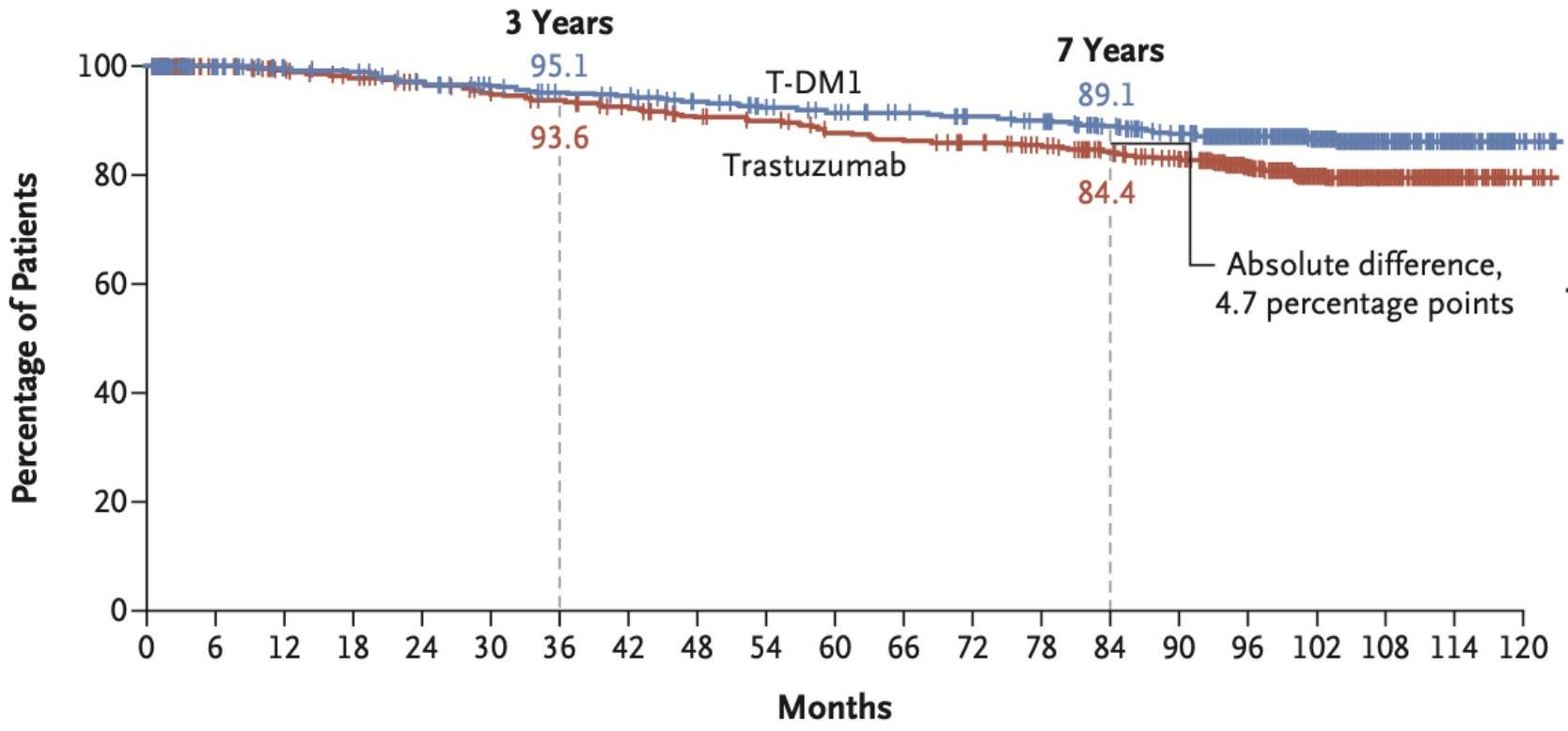
Subgroup	Tumor and Nodal Stage	No.	5-Year Rate, %	HR	95% CI
Hormone receptor+ pCR–	T1-2/N- (reference)	377	84.5		
	T3-4/N-	143	73.2	0.64	0.51-0.81
	T1-2/N+	448	72.1	0.60	0.46-0.77
	T3-4/N+	431	60.9	0.38	0.28-0.52
Hormone receptor+ pCR+	T1-2/N- (reference)	212	91.4		
	T3-4/N-	65	87.0	0.84	0.53-1.35
	T1-2/N+	200	83.6	0.55	0.33-0.90
	T3-4/N+	160	80.4	0.46	0.25-0.85
Hormone receptor– pCR–	T1-2/N- (reference)	140	66.6		
	T3-4/N-	78	59.1	0.61	0.48-0.78
	T1-2/N+	251	64.9	0.76	0.58-1.00
	T3-4/N+	345	45.4	0.46	0.33-0.65
Hormone receptor– pCR+	T1-2/N- (reference)	196	90.3		
	T3-4/N-	90	79.3	0.58	0.40-0.84
	T1-2/N+	280	87.5	0.87	0.58-1.29
	T3-4/N+	294	82.4	0.50	0.30-0.83





van Mackelenbergh MT et al. *J Clin Oncol* 2023;41:2998-3008. Content courtesy of Nadia Harbeck, MD.

KATHERINE Trial: Trastuzumab Emtansine (T-DM1) for Residual HER2-Positive Breast Cancer



	Events *no. (%)*
T-DM1 (N=743)	89 (12.0)
Trastuzumab (N=743)	126 (17.0)

Unstratified hazard ratio for death, 0.66 (95% CI, 0.51–0.87); P=0.003
Boundary for statistical significance, hazard ratio <0.739 or P<0.0263

No. at Risk

T-DM1	743	719	702	695	675	662	649	642	626	614	604	597	585	576	554	530	394	312	158	93	14
Trastuzumab	743	696	677	661	643	625	616	600	586	576	558	549	543	532	511	490	374	280	146	72	9

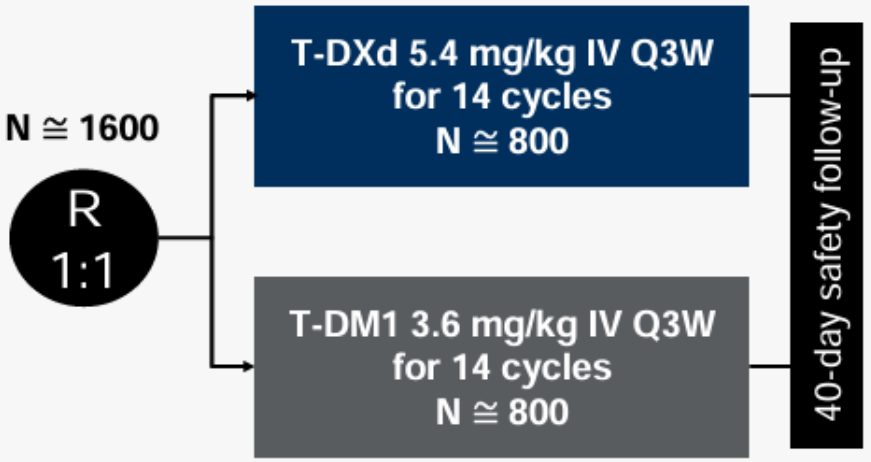
Geyer CE et al. *N Engl J Med* 2025;392(3):249-57.

Phase III DESTINY-Breast05 Study Design

Key Eligibility Criteria

- **Residual invasive disease in the breast and/or axillary lymph nodes** after neoadjuvant chemotherapy with HER2-directed therapy (NAT)[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**
- **Centrally confirmed HER2+** (IHC 3+ or ISH+) eBC
- ECOG PS 0 or 1

Stratification factors
- Extent of disease at presentation (inoperable, operable)
- HER2-targeted NAT (single, dual)
- Hormone receptor status (positive, negative)
- Post-NAT pathologic nodal status (positive, negative)



Primary endpoint
- IDFS

Key secondary endpoint
- DFS

Other secondary endpoints
- OS
- DRFI
- BMFI
- Safety

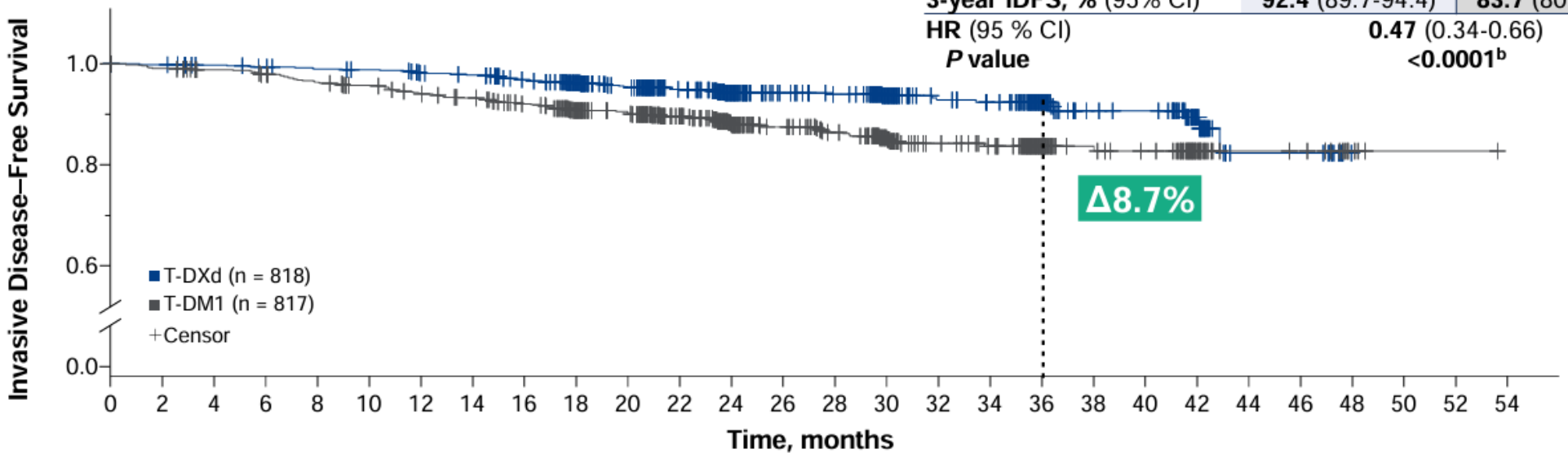
- **Concomitant adjuvant ET was allowed per local practices**
- **If administered, RT could be initiated concurrent with study therapy or completed prior to initiation of study therapy (sequential) per investigator**
- **ILD monitoring program for patients treated with RT**
  - All patients had baseline 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 every 12 weeks while on therapy, and at 40-day follow-up
  - Sequential RT patients had additional LD chest CT after completion of RT prior to start of study therapy

IDFS = invasive disease-free survival; OS = overall survival; BMFI = brain metastasis-free interval; DRFI = distant recurrence-free interval; ET = endocrine therapy; RT = radiation therapy

Geyer CE et al. ESMO 2025;Abstract LBA1; Loibl S et al. *N Engl J Med* 2026;394:845-57.

DESTINY-Breast05: IDFS

	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**[b]	



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

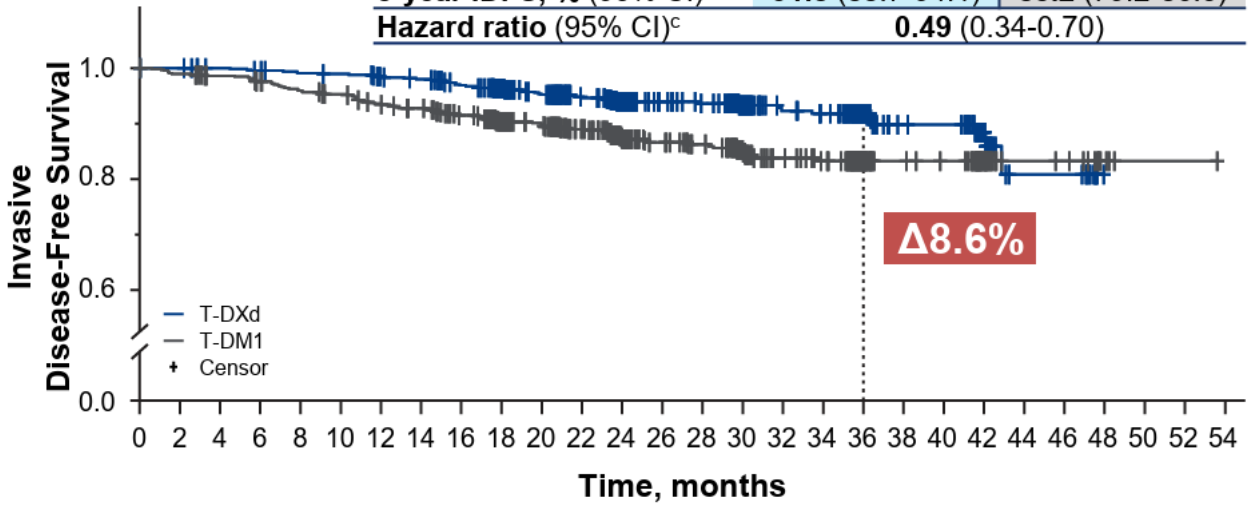
HR, hazard ratio; IDFS, invasive disease–free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Efficacy stopping boundary, *P* = 0.0183.
[a]IDFS is defined as the time from randomization until the date of first occurrence of one of the following events: recurrence of ipsilateral invasive breast tumor, recurrence of ipsilateral locoregional invasive breast cancer, contralateral invasive breast cancer, a distant disease recurrence, or death from any cause. [b]Two-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.

Geyer CE et al. ESMO 2025;Abstract LBA1; Loibl S et al. *N Engl J Med* 2026;394:845-57.

DESTINY-Breast05: IDFS Subgroup Analysis

HER2 IHC 3+

	T-DXd n = 676	T-DM1 n = 670
Patients with events, n (%)	**46** (6.8)	**86** (12.8)
3-year IDFS, % (95% CI)	**91.8** (88.7-94.1)	**83.2** (79.2-86.5)
Hazard ratio (95% CI)[c]	**0.49** (0.34-0.70)	

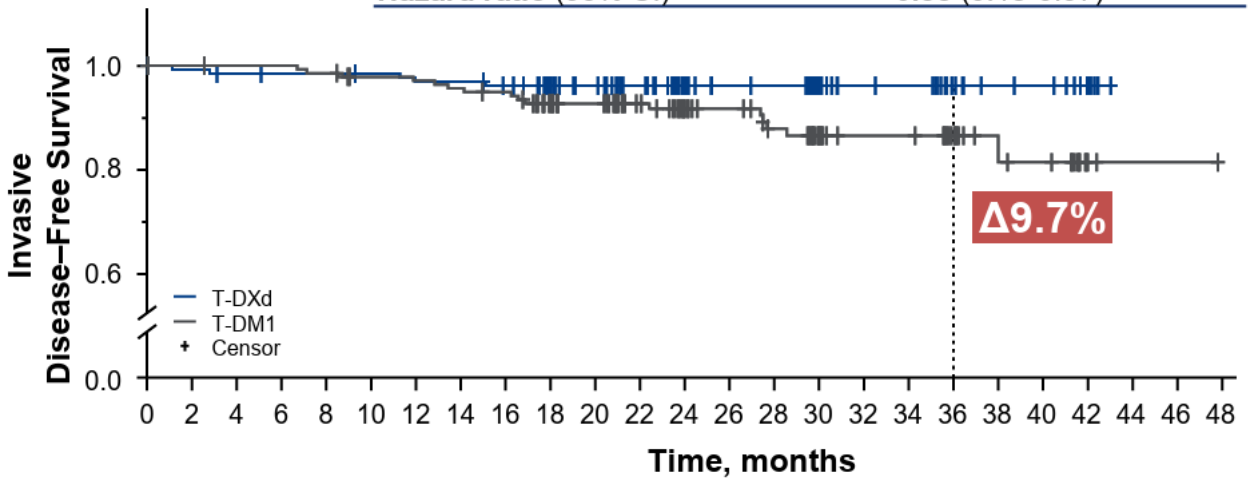


Number at risk

T-DXd	676	655	650	646	641	639	631	626	607	570	532	458	376	329	320	239	239	184	110	80	79	40	14	14	0	0	0	0
T-DM1	670	640	629	620	607	600	586	577	558	515	491	433	339	282	271	189	189	144	97	67	64	34	13	12	4	1	1	0

HER2 ISH+[b]

	T-DXd n = 140	T-DM1 n = 147
Patients with events, n (%)	**5** (3.6)	**16** (10.9)
3-year IDFS, % (95% CI)	**96.2** (91.0-98.4)	**86.5** (78.1-91.8)
Hazard ratio (95% CI)[c]	**0.35** (0.13-0.97)	



Number at risk

T-DXd	140	131	129	128	128	127	125	125	122	112	100	84	62	51	50	36	29	28	19	12	11	6	0	0	0
T-DM1	147	141	140	140	138	134	133	131	129	117	108	94	78	73	66	44	33	33	23	17	15	4	1	1	0

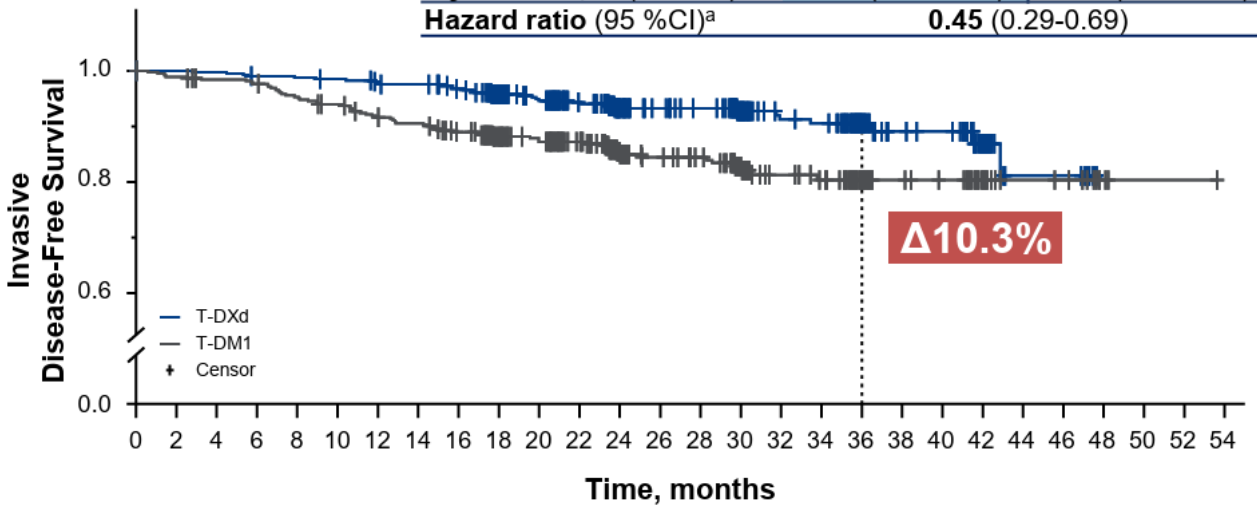
T-DXd demonstrated IDFS benefit over T-DM1 in both the HER2 IHC 3+ and HER2 ISH+ groups

Loibl S et al. San Antonio Breast Cancer Symposium (SABCS) 2025;Abstract RF6-01.

DESTINY-Breast05: IDFS Subgroup Analysis

Prior anthracyclines

	T-DXd n = 423	T-DM1 n = 399
Patients with events, n (%)	**32** (7.6)	**61** (15.3)
3-year IDFS, % (95% CI)	**90.6** (86.1-93.6)	**80.3** (74.8-84.8)
Hazard ratio (95 %CI)[a]	**0.45** (0.29-0.69)	

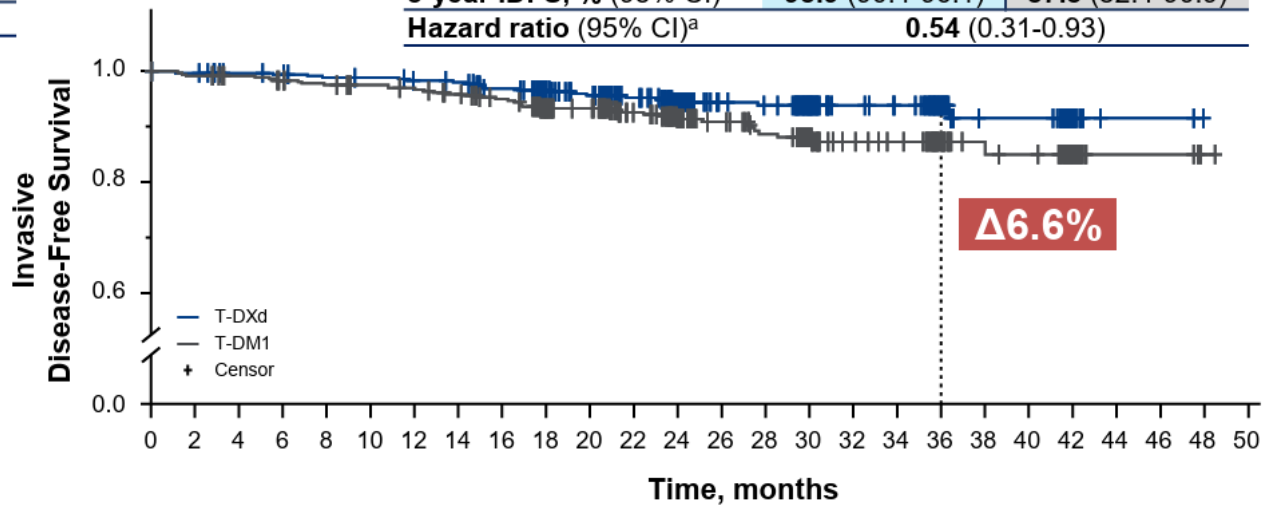


Number at risk

T-DXd	423	412	411	407	406	404	399	397	388	358	334	288	233	211	205	155	124	122	74	55	53	31	12	12	0	0	0	0
T-DM1	399	383	378	375	365	358	347	342	330	304	286	256	196	169	162	117	92	86	61	45	42	21	10	9	3	1	1	0

Prior platinum-based therapy

	T-DXd n = 386	T-DM1 n = 392
Patients with events, n (%)	**20** (5.2)	**37** (9.4)
3-year IDFS, % (95% CI)	**93.9** (90.4-96.1)	**87.3** (82.4-90.9)
Hazard ratio (95% CI)[a]	**0.54** (0.31-0.93)	



Number at risk

T-DXd	386	366	360	358	354	353	349	347	336	316	291	248	198	161	158	115	89	85	51	34	34	14	2	2	0	0	
T-DM1	392	371	365	360	355	351	348	341	332	304	291	253	206	172	161	106	86	82	54	38	36	17	4	5	1	0	

IDFS benefit was observed with T-DXd compared to T-DM1 regardless of prior NAT used

Loibl S et al. SABCS 2025;Abstract RF6-01.

DESTINY-Breast05: Overall Safety Summary

TEAEs, n (%)	T-DXd n = 806[a]	T-DM1 n = 801[a]
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 discontinuation	**144 (17.9)**	**103 (12.9)**
Drug-related ILD/pneumonitis[b]	**87 (10.8)**	**20 (2.5)**
Associated with drug interruptions	400 (49.6)	329 (41.1)
Associated with dose reductions	**213 (26.4)**	**213 (26.6)**
Associated with deaths	**3 (0.4)**	**5 (0.6)**

- **In the T-DXd arm, causes of death (n = 3) were 2 ILD/pneumonitis[c] and respiratory tract infection (adjudicated as not ILD)**
- **In the T-DM1 arm, causes of death (n = 5) were leiomyosarcoma of the uterus, aneurysm, non-neutropenic sepsis, ovarian cancer, and traumatic pneumothorax**

ILD = interstitial lung disease

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Geyer CE et al. ESMO 2025;Abstract LBA1; Loibl S et al. *N Engl J Med* 2026;394:845-57.

DESTINY-Breast05: Adjudicated Drug-Related ILD by Adjuvant Radiation Therapy (RT)

	T-DXd (n = 806)[a]			T-DM1 (n = 801)[a]		
Adjudicated drug-related ILD, any grade, overall, n (%)	77 (9.6)			13 (1.6)		
Adjudicated drug-related ILD, by adjuvant RT, n (%)	**Sequential (n = 319)**	**Concurrent (n = 438)**	**Sequential or concurrent (n = 757)**	**Sequential (n = 270)**	**Concurrent (n = 480)**	**Sequential or concurrent (n = 750)**
Any grade	34 (10.7)	42 (9.6)	76 (10.0)	7 (2.6)	5 (1.0)	12 (1.6)
Grade 1	6 (1.9)	10 (2.3)	16 (2.1)	4 (1.5)	3 (0.6)	7 (0.9)
Grade 2	24 (7.5)	27 (6.2)	51 (6.7)	3 (1.1)	2 (0.4)	5 (0.7)
Grade 3	3 (0.9)	4 (0.9)	7 (0.9)	0	0	0
Grade 4	0	0	0	0	0	0
Grade 5[b]	1 (0.3)	1 (0.2)	2 (0.3)	0	0	0
Grade ≥3	4 (1.3)	5 (1.1)	9 (1.2)	0	0	0
Time to onset, median (range), days[c]	122.0 (36-350)	124.5 (37-326)	123.5 (36-350)	79.0 (36-142)	121.0 (78-130)	121.0 (36-142)
Duration, median (95% CI), days[d,e]	77.0 (41-114)	67.0 (43-107)	74.0 (46-106)	114.0 (22-NE)	142.0 (51-NE)	114.0 (51-235)

- Timing of adjuvant RT did not impact incidence or severity of adjudicated drug-related ILD in either arm
- In the T-DXd arm, adjuvant RT timing had no effect on time to onset or duration of adjudicated drug-related ILD
- Most patients with drug-related ILD had recovered or were recovering at the data cutoff; in the T-DXd arm, the proportion of patients who had recovered from ILD was higher among those who received concurrent RT compared with sequential RT (69.0% vs 58.8%)

Loibl S et al. SABCS 2025;Abstract RF6-01.

DESTINY-Breast05: Radiation Pneumonitis (RP) by Adjuvant RT

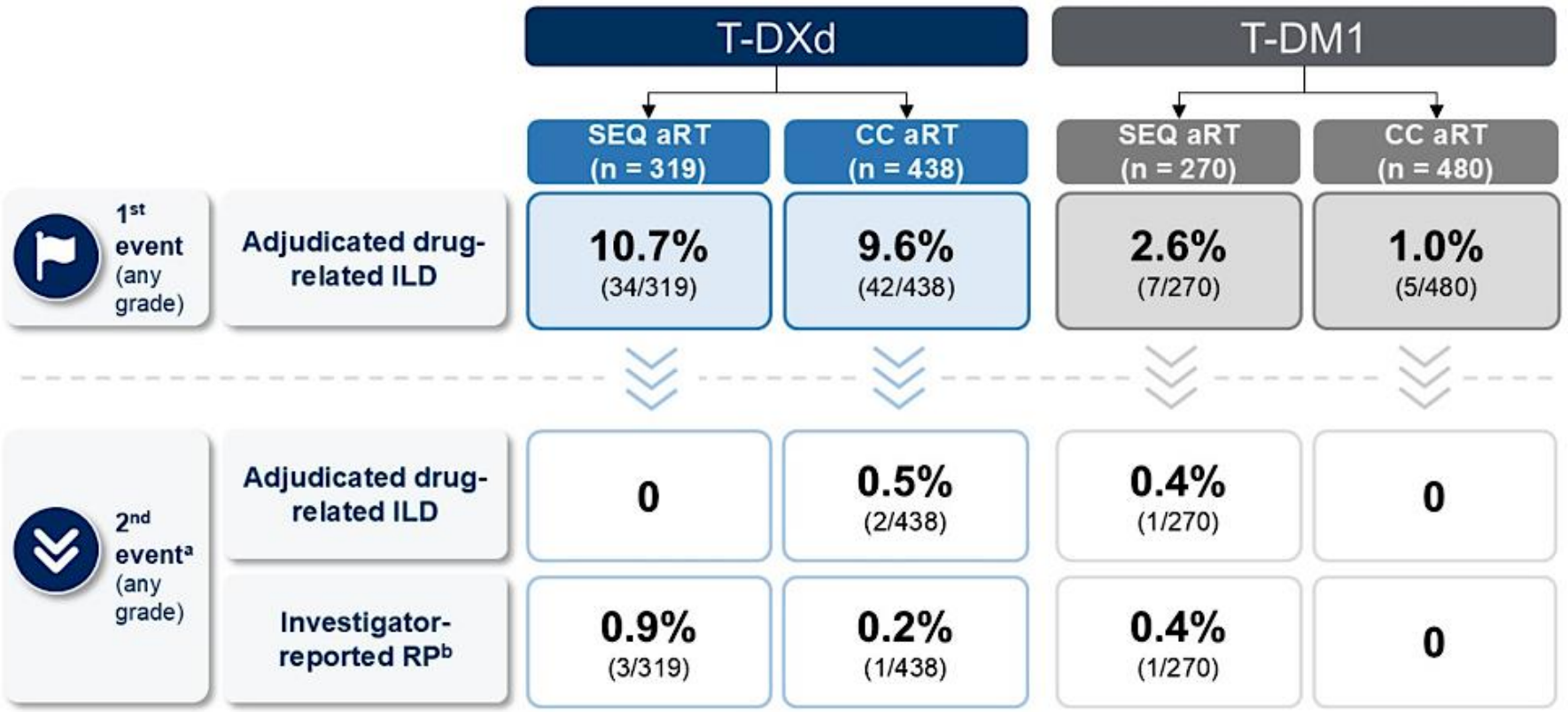
	T-DXd[a]			T-DM1[a]		
	Sequential (n = 319)	Concurrent (n = 438)	Sequential or concurrent (n = 757)	Sequential (n = 270)	Concurrent (n = 480)	Sequential or concurrent (n = 750)
Investigator-reported RP,[b] any grade, n(%)	110 (34.5)	128 (29.2)	238 (31.4)	101 (37.4)	128 (26.7)	229 (30.5)
Grade 1	97 (30.4)	104 (23.7)	201 (26.6)	82 (30.4)	95 (19.8)	177 (23.6)
Grade 2	13 (4.1)	24 (5.5)	37 (4.9)	19 (7.0)	33 (6.9)	52 (6.9)
Grade ≥3	0	0	0	0	0	0
Time to onset, median (range), days[c]	146.5 (46-334)	123.0 (39-353)	124.0 (39-353)	110.0 (56-260)	122.5 (28-232)	120.0 (28-260)
Duration, median (95% CI), days[d,e]	411.0 (336-606)	292.0 (200-370)	352.0 (292-411)	308.0 (288-446)	297.0 (233-394)	306.0 (280-376)

- In both arms, all RP events were grade ≤2, although patients treated with sequential adjuvant RT reported higher incidences of investigator-reported RP than those treated with concurrent adjuvant RT
- Most patients with RP events had recovered or were recovering at data cutoff; rates of unrecovered/unresolved RP were higher among patients who received sequential RT in the T-DXd arm compared with the T-DM1 arm (54.5% vs 39.6%)
- In the T-DXd arm, patients receiving sequential adjuvant RT showed longer time to onset and duration of RP than those who received concurrent adjuvant RT

RTP RESEARCH TO PRACTICE

Loibl S et al. SABCS 2025;Abstract RF6-01.

DESTINY-Breast05: Subsequent Safety Events



- **Adjudicated drug-related ILD did not increase the risk of subsequent adjudicated drug-related ILD or investigator-reported RP**
- Subsequent adjudicated drug-related ILD and investigator-reported RP events were all low grade (grade 1-2)

Untch M et al. ASCO 2026;Abstract 516.

FDA Approves Fam-Trastuzumab Deruxtecan-nxki for 2 Indications in the Treatment of HER2-Positive Localized Breast Cancer

Press Release: May 15, 2026

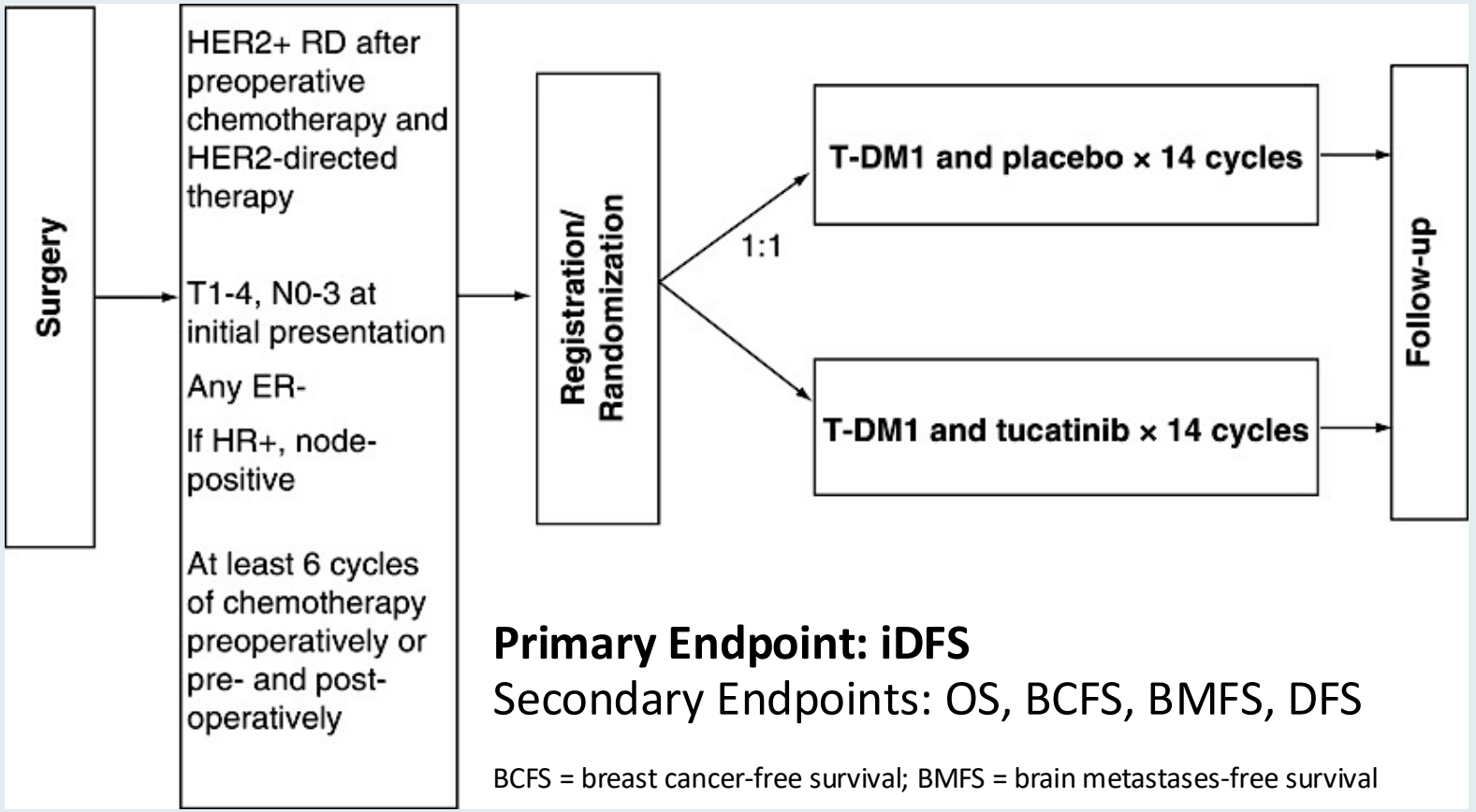
The Food and Drug Administration (FDA) approved fam-trastuzumab deruxtecan-nxki (T-DXd) for 2 separate indications for adults with HER2-positive localized breast cancer.

- T-DXd followed by taxane, trastuzumab and pertuzumab (THP) for the neoadjuvant treatment of HER2-positive (IHC 3+ or ISH+) Stage II or III breast cancer in adult patients
- T-DXd for the adjuvant treatment of HER2-positive (IHC 3+ or ISH+) breast cancer in adult patients who have residual invasive disease following neoadjuvant treatment with trastuzumab (with or without pertuzumab) and taxane-based treatment

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-two-separate-indications-fam-trastuzumab-deruxtecan-nxki-her2-positive-early-stage

RTP RESEARCH TO PRACTICE

Phase III CompassHER2 RD (Alliance A011801) Study Design



Primary Endpoint: iDFS

Secondary Endpoints: OS, BCFS, BMFS, DFS

BCFS = breast cancer-free survival; BMFS = brain metastases-free survival

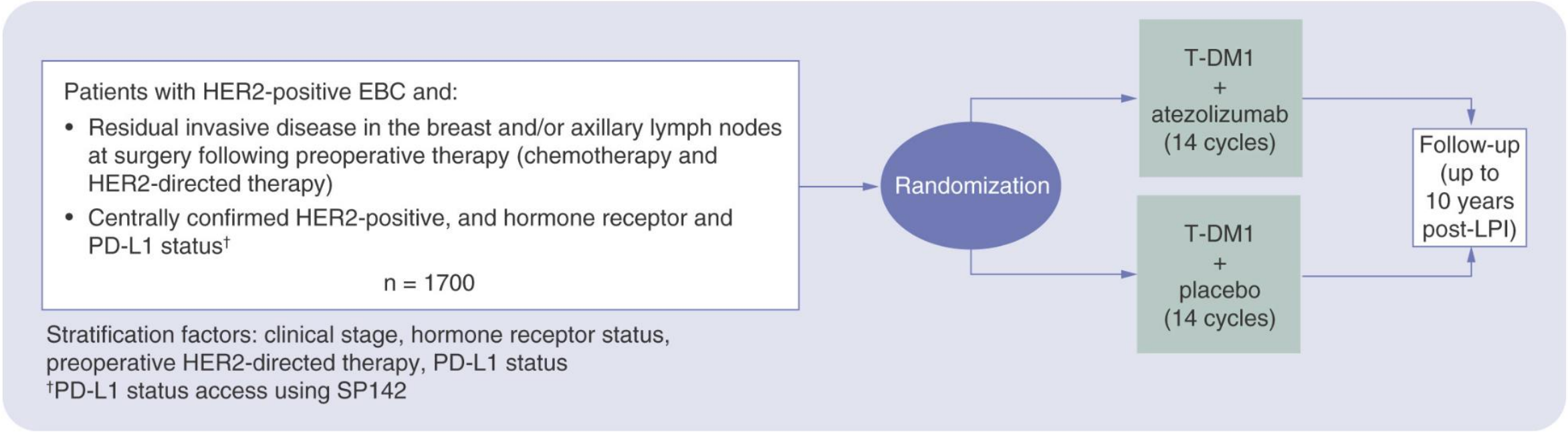
Primary completion
2028-01-31
Study completion
2035-05-31

Eligibility Criteria:

- HER2+ invasive RD (ER-negative, node-positive, or both) after NAST.
- Completion of ≥6 cycles of NAST, including ≥9 weeks of T and H +/- P.
- All neoadjuvant chemotherapy to be completed preoperatively unless participating in EA1181.

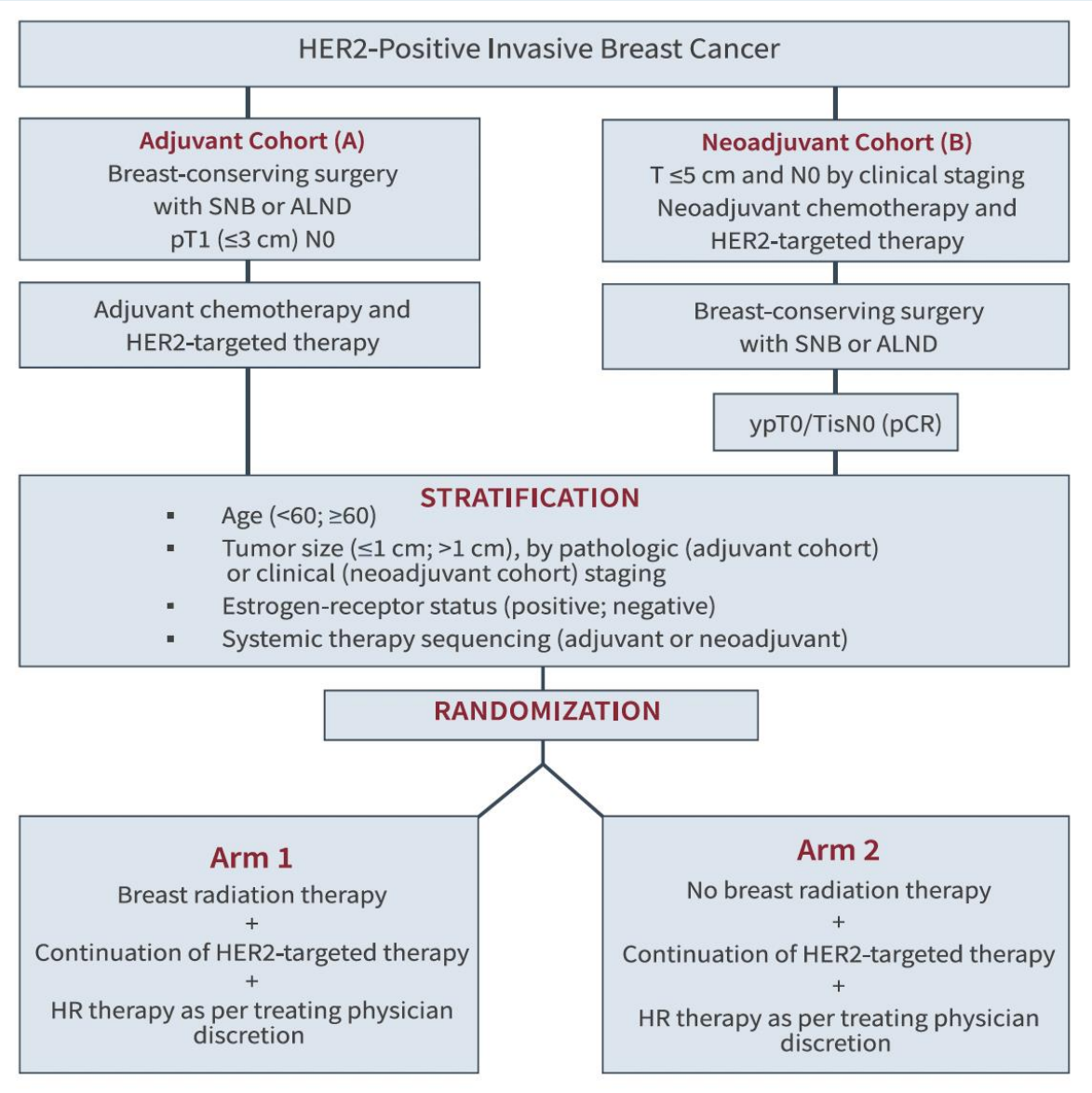
O'Sullivan CC et al. *Future Oncol* 2021;17(34):4665-76.

Phase III ASTEFANIA Study Design



Hurvitz SA et al. *Future Oncol* 2022;18(32):3563-72.

Phase III NRG-BR008/HERO Study Design



Braunstein LZ et al. *Future Oncol* 2025;21(16):2017-25.

Agenda

Module 1: Localized HER2-Positive Breast Cancer (BC)

Module 2: Clinician Survey Results

Module 3: First-Line Treatment of HER2-Positive Metastatic BC (mBC)

Module 4: Clinician Survey Results

Module 5: Maintenance Therapy for HER2-Positive mBC

Module 6: Clinician Survey Results

Module 7: Novel Investigational Strategies for HER2-Positive BC

Module 8: Clinician Survey Results

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A woman presents with a 4.5-cm, HR-negative, HER2-positive, node-negative IDC (cT2N0M0). Regulatory and reimbursement issues aside, which neoadjuvant systemic therapy, if any, would you most likely recommend?

	45-year-old	65-year-old
 Dr Anders	TCHP	TCHP
 Dr Brufsky	THP × 4 cycles	THP × 4 cycles
 Dr Krop	THP → T-DXd with plan to give T-DXd for patient without clinical CR after THP	THP × 4 cycles
 Dr Mahtani	THP × 6 cycles	THP × 6 cycles
 Dr Meisel	THP × 4 and if responding well, complete THP × 6. If not responding well, switch to T-DXd	THP × 6 cycles
 Dr Modi	THP × 6 cycles	THP × 6 cycles
 Dr O'Shaughnessy	T-DXd → THP	T-DXd → THP
 Dr Rimawi	THP × 6 cycles	THP × 6 cycles

IDC = invasive ductal carcinoma; THP = taxane/trastuzumab/pertuzumab

A 65-year-old woman presents with a 2.8-cm, HER2-positive IDC with biopsy-confirmed axillary nodal involvement (cT2N1M0). Regulatory and reimbursement issues aside, which neoadjuvant systemic therapy, if any, would you most likely recommend?

	HR-negative	HR-positive
 Dr Anders	T-DXd → THP	T-DXd → THP
 Dr Brufsky	THP × 4 cycles	THP × 4 cycles
 Dr Krop	THP → T-DXd with plan to give T-DXd for patient without clinical CR after THP	THP → T-DXd with plan to give T-DXd for patient without clinical CR after THP
 Dr Mahtani	T-DXd → THP	T-DXd → THP
 Dr Meisel	T-DXd → THP	T-DXd → THP
 Dr Modi	T-DXd → THP	T-DXd → THP
 Dr O'Shaughnessy	T-DXd → THP	T-DXd → THP
 Dr Rimawi	T-DXd → THP	T-DXd → THP

A woman presents with an HR-negative, HER2-positive IDC with biopsy-confirmed axillary nodal involvement (cT4bN2M0). The disease is considered initially inoperable but is NOT inflammatory. Regulatory and reimbursement issues aside, which neoadjuvant systemic therapy, if any, would you most likely recommend?

	65-year-old	85-year-old (PS 1)
 Dr Anders	T-DXd → THP	THP × 4 cycles
 Dr Brufsky	T-DXd → THP	THP × 4 cycles
 Dr Krop	T-DXd → THP	THP → T-DXd with plan to give T-DXd if disease still not operable after THP
 Dr Mahtani	T-DXd → THP	T-DXd → THP
 Dr Meisel	T-DXd → THP	THP × 4 and if responding well, complete THP × 6. If not responding well, switch to T-DXd
 Dr Modi	T-DXd → THP	THP × 4 cycles
 Dr O'Shaughnessy	T-DXd → THP	T-DXd → THP (reduced doses)
 Dr Rimawi	T-DXd → THP	T-DXd → THP

A 65-year-old woman with a 2.8-cm, HR-negative, HER2-positive IDC with biopsy-confirmed axillary nodal involvement (cT2N1M0) receives neoadjuvant TCHP × 6 cycles. At surgery, she has 1.5 cm of residual invasive disease in the breast and 1 positive axillary node (ypT1cN1). Regulatory and reimbursement issues aside, which adjuvant HER2-directed therapy would you most likely recommend?

 Dr Anders	T-DXd
 Dr Brufsky	T-DM1
 Dr Krop	T-DXd
 Dr Mahtani	T-DXd
 Dr Meisel	T-DXd (with a low threshold to switch to T-DM1 if not tolerated)
 Dr Modi	T-DXd
 Dr O'Shaughnessy	T-DXd
 Dr Rimawi	T-DXd

A 65-year-old woman with HR-positive, HER2-positive inflammatory breast cancer with biopsy-confirmed axillary nodal involvement (cT4dN2M0) receives neoadjuvant T-DXd × 4 cycles followed by THP × 4 cycles. At surgery, she has 2.5 cm of residual invasive disease in the breast and 4 positive axillary nodes (ypT2N2). Regulatory and reimbursement issues aside, which adjuvant HER2-directed therapy would you most likely recommend?

 Dr Anders	T-DM1
 Dr Brufsky	T-DXd
 Dr Krop	T-DXd
 Dr Mahtani	AC → HP
 Dr Meisel	T-DXd
 Dr Modi	T-DXd
 Dr O'Shaughnessy	T-DM1
 Dr Rimawi	T-DXd

A 65-year-old woman with a 5.5-cm, HR-negative, HER2-positive IDC with biopsy-confirmed axillary nodal involvement (cT3N1M0) receives neoadjuvant T-DXd × 4 cycles followed by THP × 4 cycles. At surgery, she has a complete response in the breast and 2 positive axillary nodes (ypT0N1). Regulatory and reimbursement issues aside, which adjuvant HER2-directed therapy would you most likely recommend?

 Dr Anders	T-DXd
 Dr Brufsky	T-DXd
 Dr Krop	T-DXd
 Dr Mahtani	T-DM1
 Dr Meisel	T-DXd (with a low threshold to switch to T-DM1 if not tolerated)
 Dr Modi	T-DXd
 Dr O'Shaughnessy	T-DXd for 4 cycles, then T-DM1 or HP
 Dr Rimawi	T-DXd

HP = trastuzumab/pertuzumab

In which situations, if any, would you continue T-DXd in the adjuvant setting for patients who receive neoadjuvant T-DXd → THP and have residual invasive disease at surgery?

 Dr Anders	If there was a significant response such that not enough pre-op T-DXd was given
 Dr Brufsky	All situations
 Dr Krop	Most pts with ER-negative cancers with T1C or more residual disease and ER-positive cancers with node-positive residual disease
 Dr Mahtani	I would not routinely continue T-DXd in the adjuvant setting after neoadjuvant T-DXd → THP. I would generally favor T-DM1 for residual disease
 Dr Meisel	Patients who had a good response to NACT – ie, were downstaged but not rendered node-negative, or inoperable at diagnosis but became operable
 Dr Modi	If those patients meet DB-05 criteria, I would try to give them a total of 14 cycles of T-DXd, particularly if they had some response to neoadjuvant T-DXd
 Dr O'Shaughnessy	Those with residual nodal disease at surgery who had a very good response to pre-op T-DXd
 Dr Rimawi	If there is high-risk residual disease remaining (RCB II-III)

DB-05 = DESTINY-Breast05 trial

Agenda

Module 1: Localized HER2-Positive Breast Cancer (BC)

Module 2: Clinician Survey Results

Module 3: First-Line Treatment of HER2-Positive Metastatic BC (mBC)

Module 4: Clinician Survey Results

Module 5: Maintenance Therapy for HER2-Positive mBC

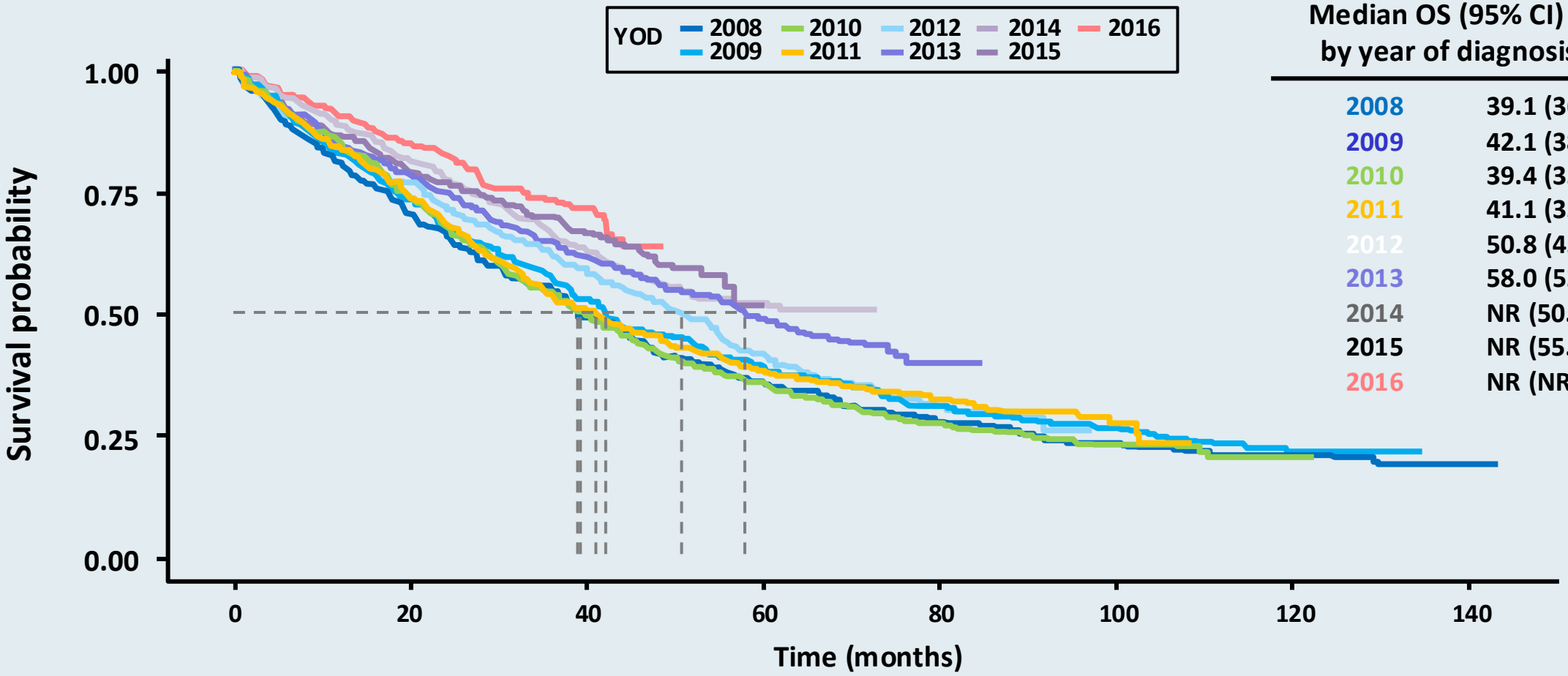
Module 6: Clinician Survey Results

Module 7: Novel Investigational Strategies for HER2-Positive BC

Module 8: Clinician Survey Results

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Overall Survival in HER2-Positive mBC by Year of Diagnosis: ESME-mBC Registry



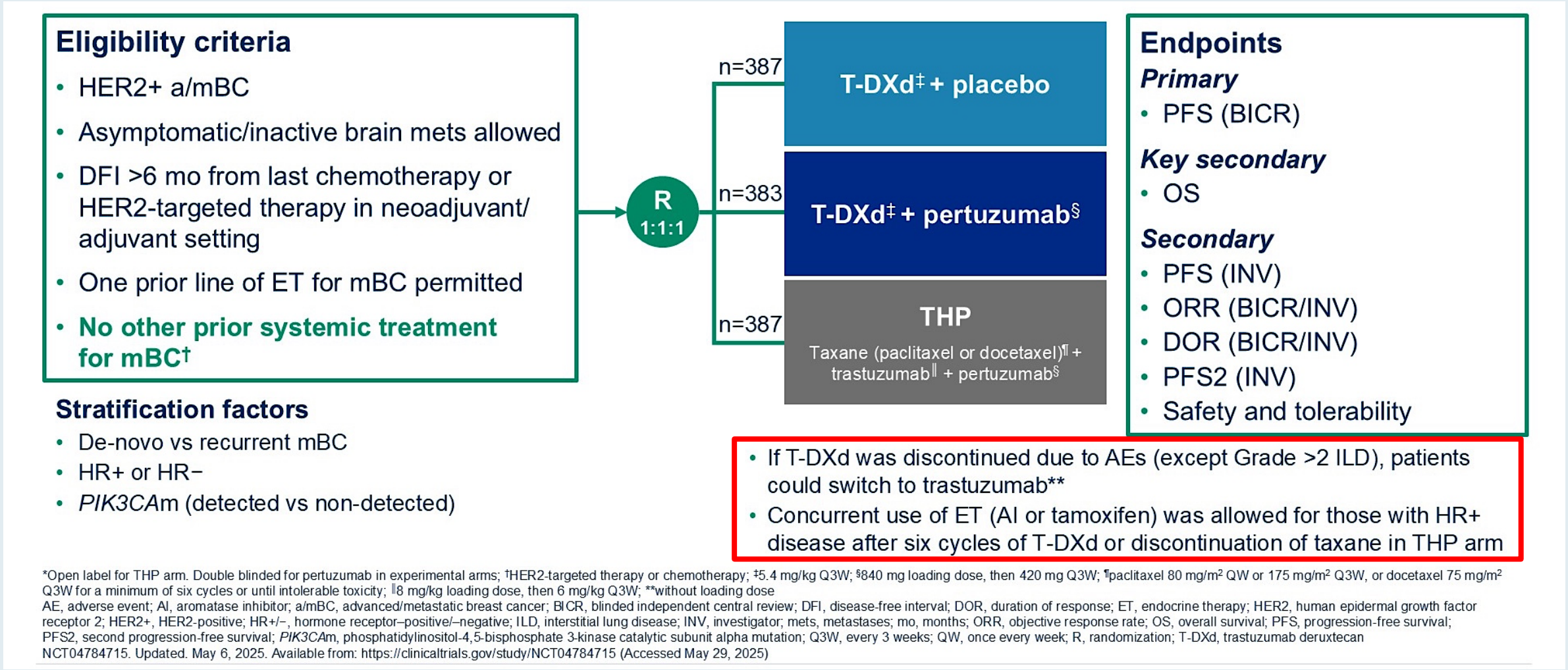
Median OS (95% CI) (months) by year of diagnosis of mBC	
2008	39.1 (36.2–46.5)
2009	42.1 (38.2–50.8)
2010	39.4 (35.9–45.4)
2011	41.1 (35.5–48.3)
2012	50.8 (45.0–55.5)
2013	58.0 (52.0–68.4)
2014	NR (50.6–NR)
2015	NR (55.7–NR)
2016	NR (NR–NR)

ESME-mBC = Epidemio-Strategy-Medico-Economical-mBC; YOD = year of diagnosis; OS = overall survival; NR = not reached

Grinda T et al. *ESMO Open* 2021;6. Content courtesy of Reshma Mahtani, DO.

RTP RESEARCH TO PRACTICE

Phase III DESTINY-Breast09 Study Design



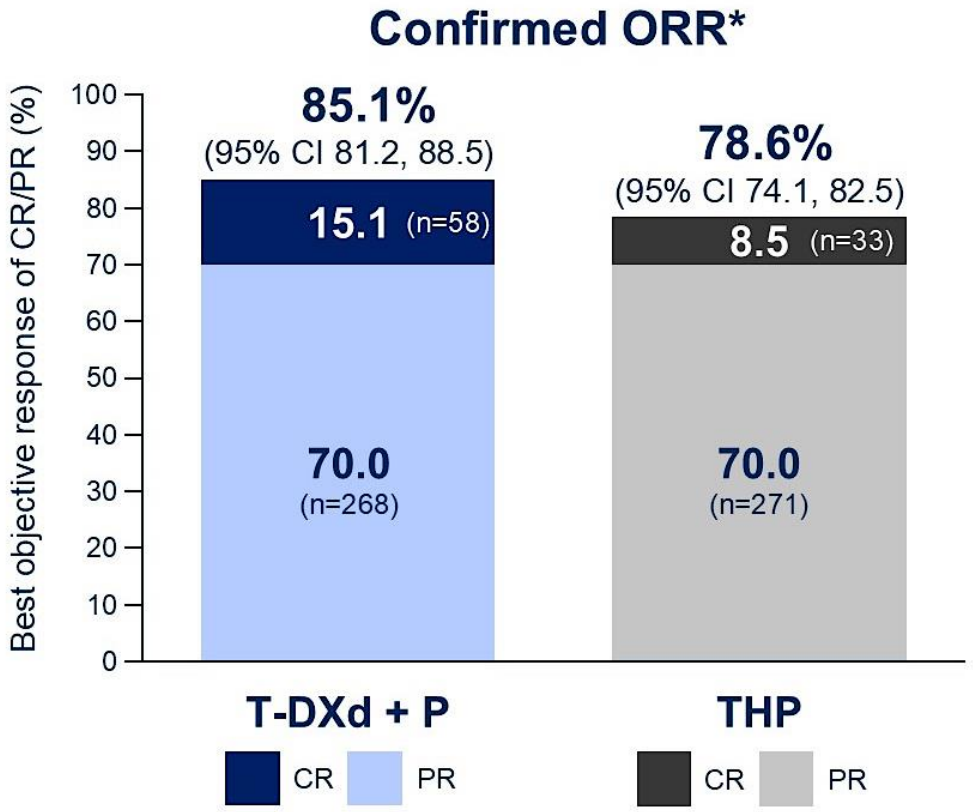
*Open label for THP arm. Double blinded for pertuzumab in experimental arms; †HER2-targeted therapy or chemotherapy; ‡5.4 mg/kg Q3W; §840 mg loading dose, then 420 mg Q3W; ¶paclitaxel 80 mg/m² QW or 175 mg/m² Q3W, or docetaxel 75 mg/m² Q3W for a minimum of six cycles or until intolerable toxicity; ‖8 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)

Tolaney SM et al. ASCO 2025;Abstract LBA1008; Tolaney SM et al. *N Engl J Med* 2026;394;551-62.

DESTINY-Breast09: Response Rates and Durability



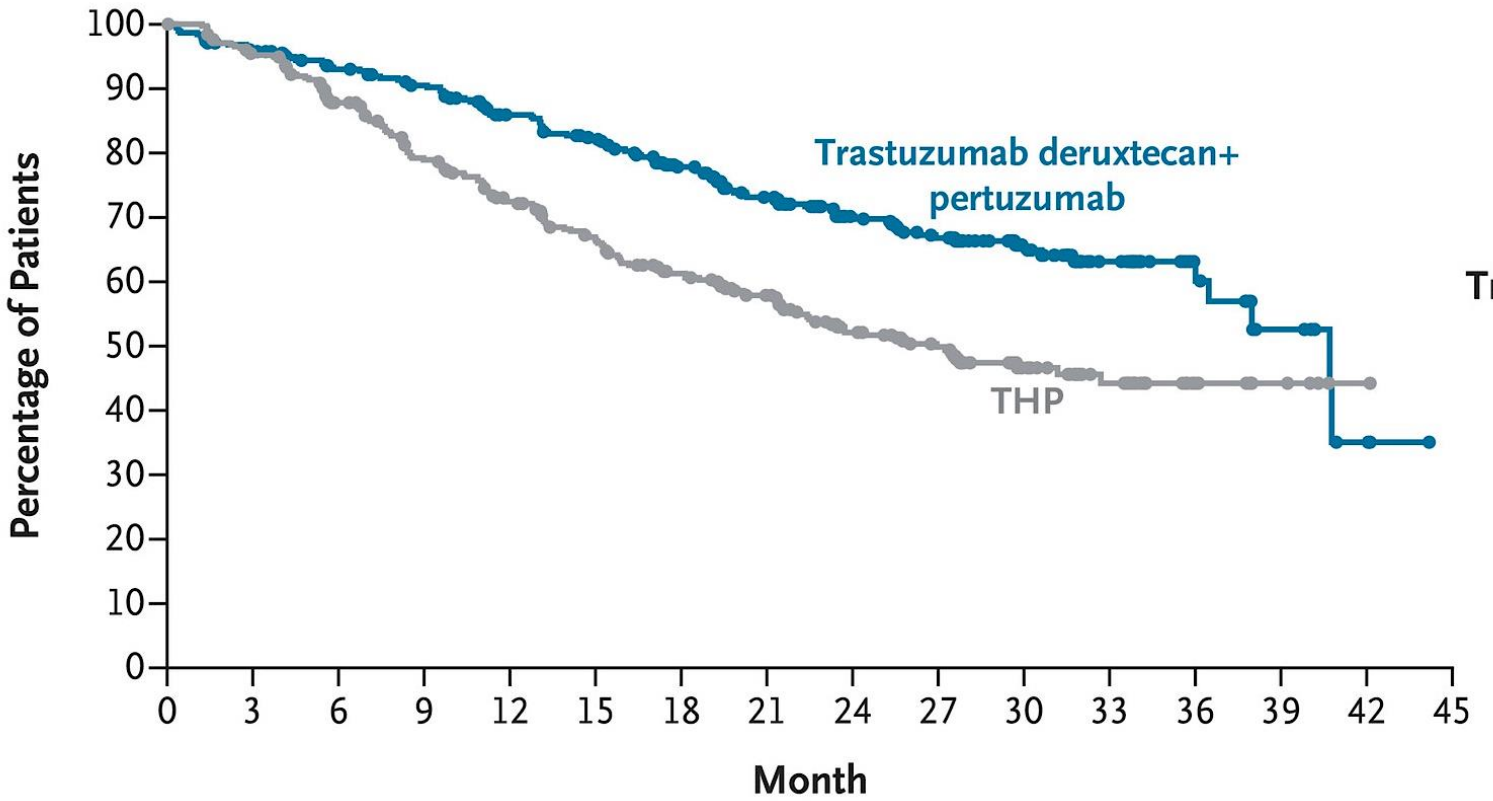
	T-DXd + P (n=383)	THP (n=387)
Median DOR, mo (95% CI)	39.2 (35.1, NC)	26.4 (22.3, NC)
Remaining in response at 24 mo (%)	73.3	54.9
Stable disease, n (%)	38 (9.9)	56 (14.5)

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

Tolaney SM et al. ASCO 2025;Abstract LBA1008; Tolaney SM et al. *N Engl J Med* 2026;394;551-62.

DESTINY-Breast09: Progression-Free Survival by Blinded Independent Central Review

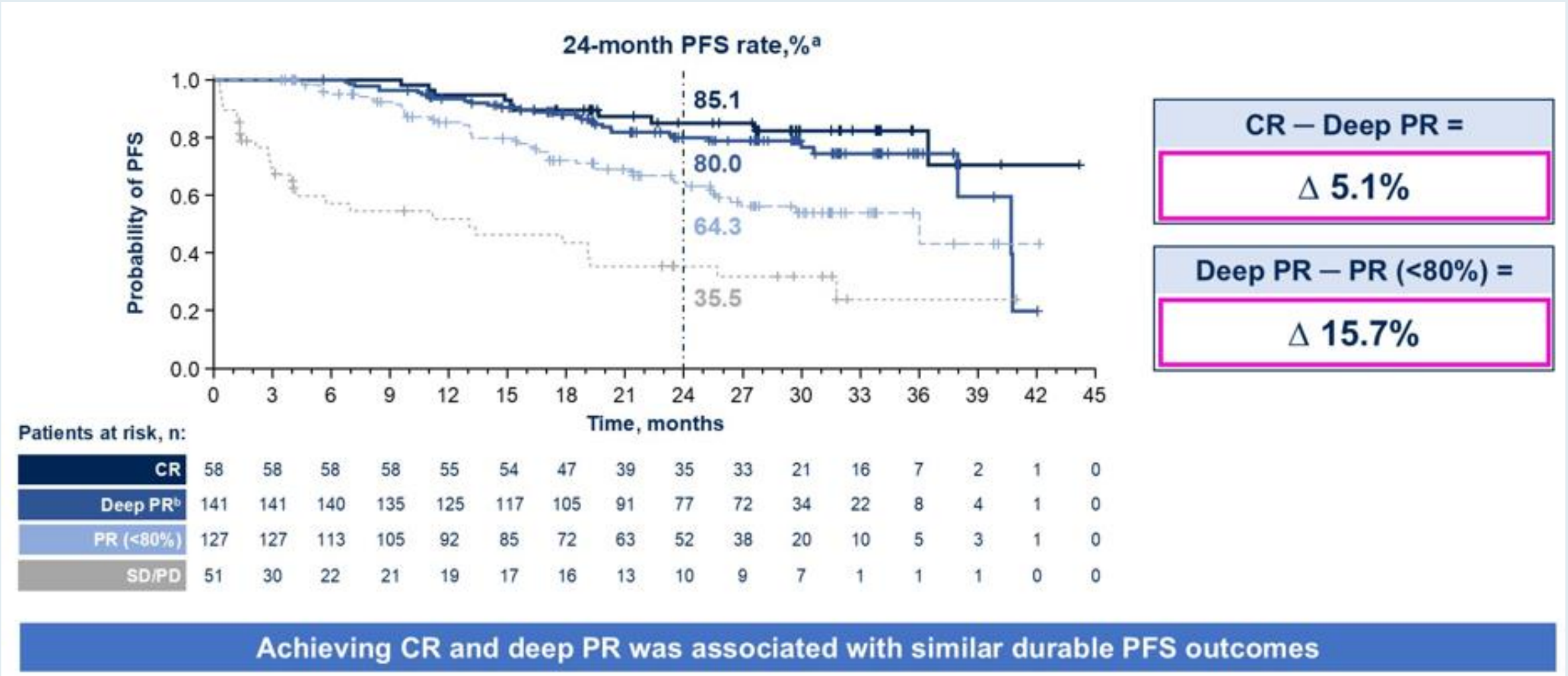


	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Trastuzumab Deruxtecan+ Pertuzumab	383	40.7 (36.5–NC)
THP	387	26.9 (21.8–NC)

Hazard ratio for disease progression or death, 0.56 (95% CI, 0.44–0.71)
P<0.00001 (prespecified P-value boundary for superiority, 0.00043)

Tolaney SM et al. ASCO 2025;Abstract LBA1008; Tolaney SM et al. *N Engl J Med* 2026;394;551-62.

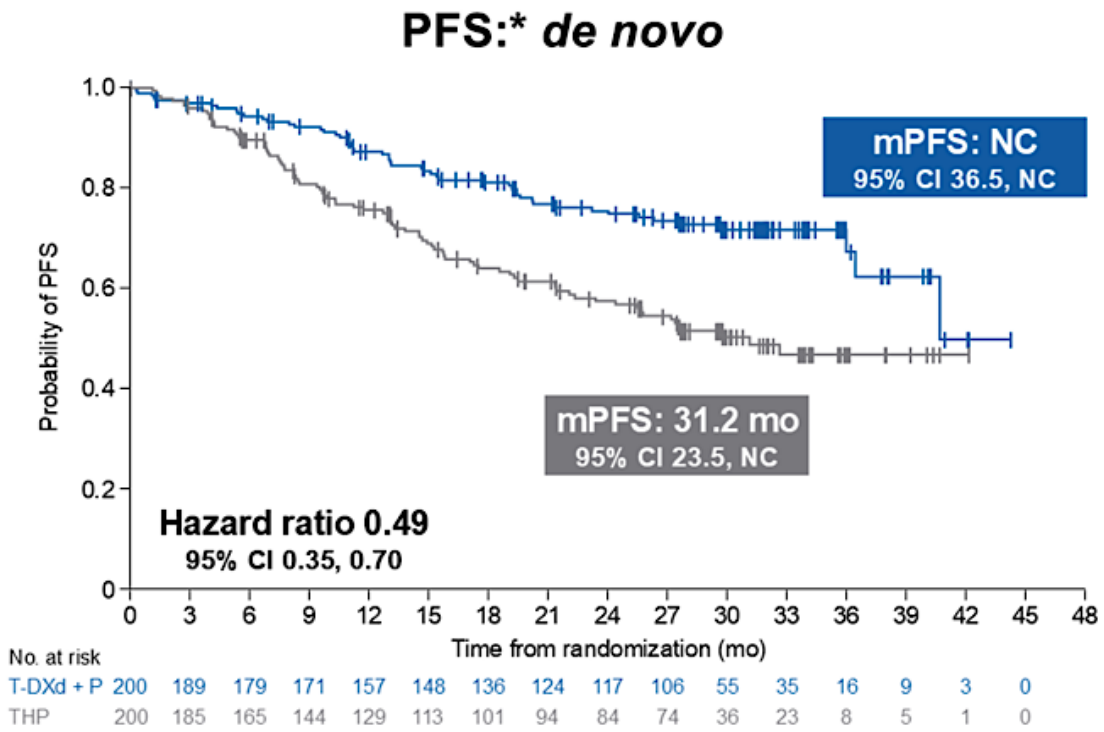
DESTINY-Breast09: Progression-Free Survival (PFS) by Response

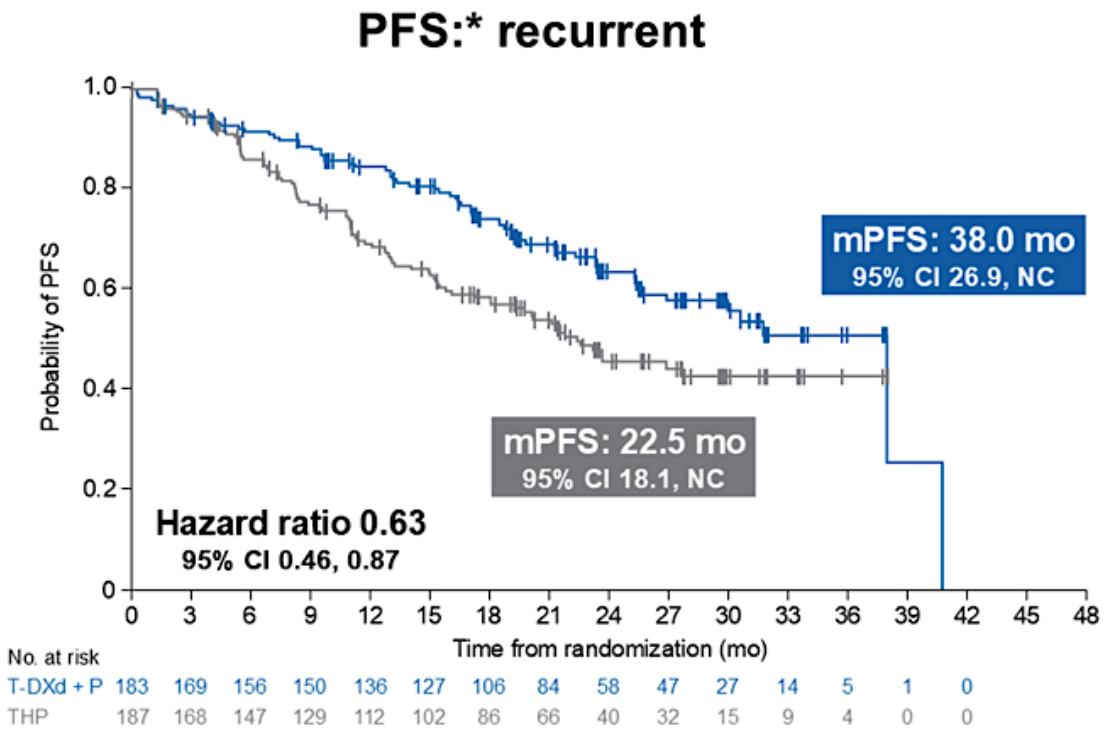


CR = complete response; PR = partial response; SD = stable disease; PD = disease progression

Park YH et al. ASCO 2026;Abstract 1021.

DESTINY-Breast09: PFS by Prior Treatment Status

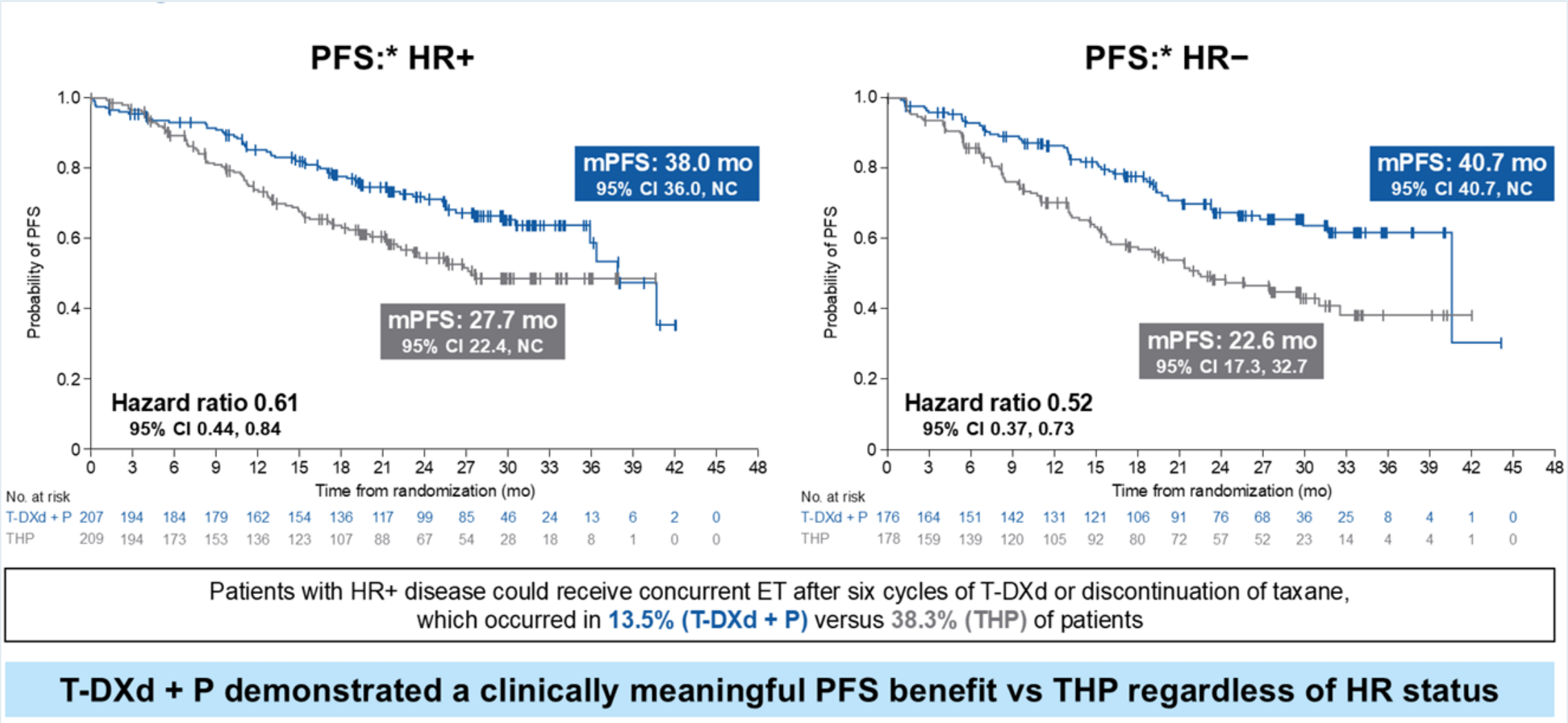




T-DXd + P demonstrated a clinically meaningful PFS benefit vs THP regardless of de-novo or recurrent status

Loibl S et al. ESMO 2025;Abstract LBA18.

DESTINY-Breast09: PFS by Hormone Receptor (HR) Status

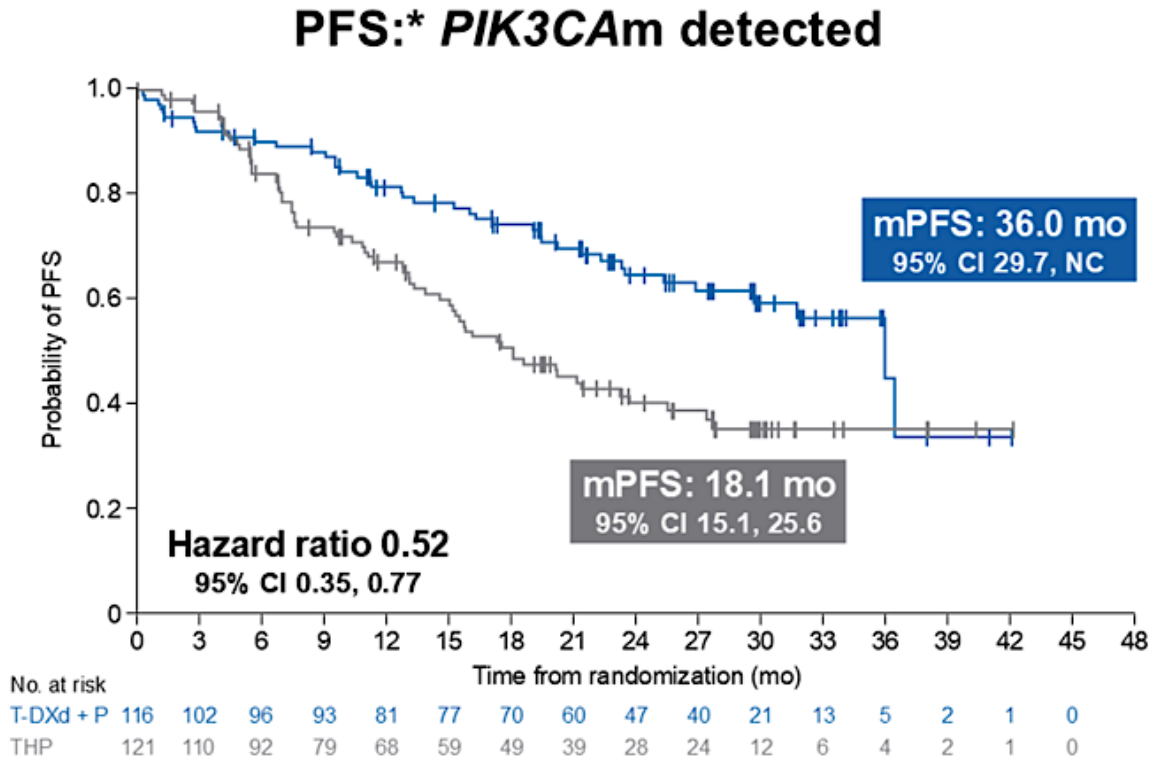


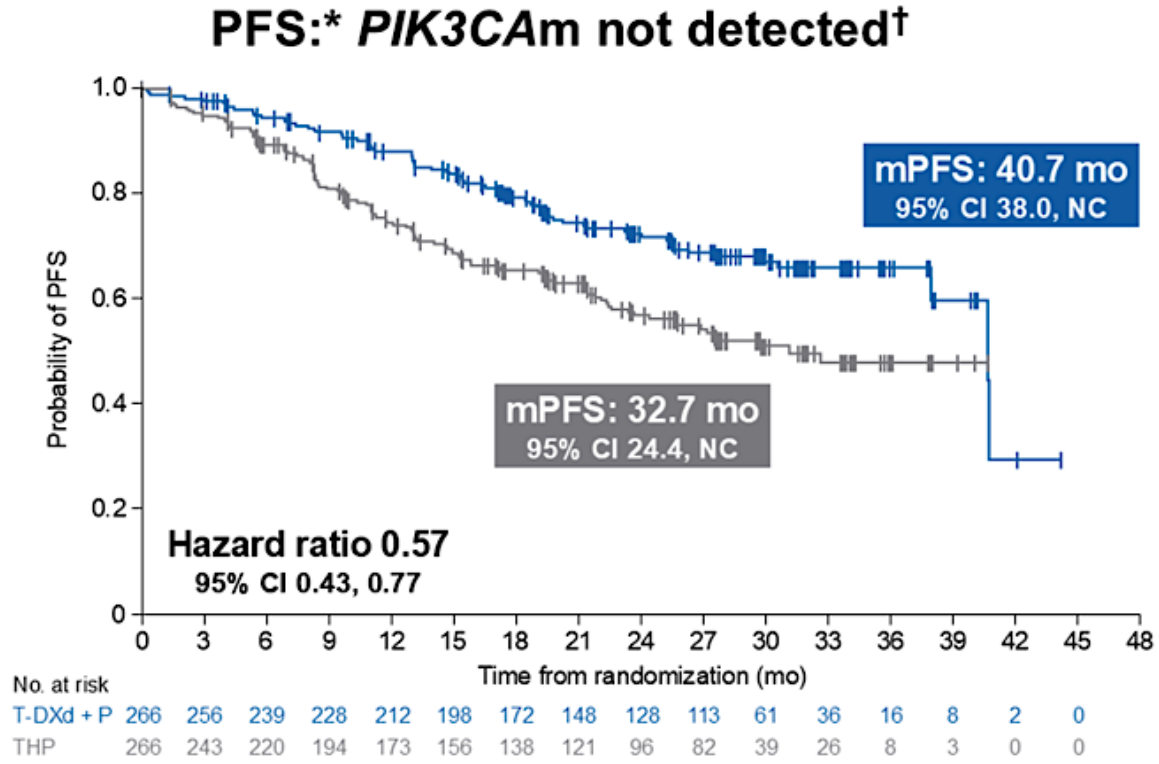
Patients with HR+ disease could receive concurrent ET after six cycles of T-DXd or discontinuation of taxane, which occurred in **13.5% (T-DXd + P)** versus 38.3% (THP) of patients

T-DXd + P demonstrated a clinically meaningful PFS benefit vs THP regardless of HR status

Loibl S et al. ESMO 2025;Abstract LBA18.

DESTINY-Breast09: PFS by PIK3CA Mutation (PIK3CAm) Status

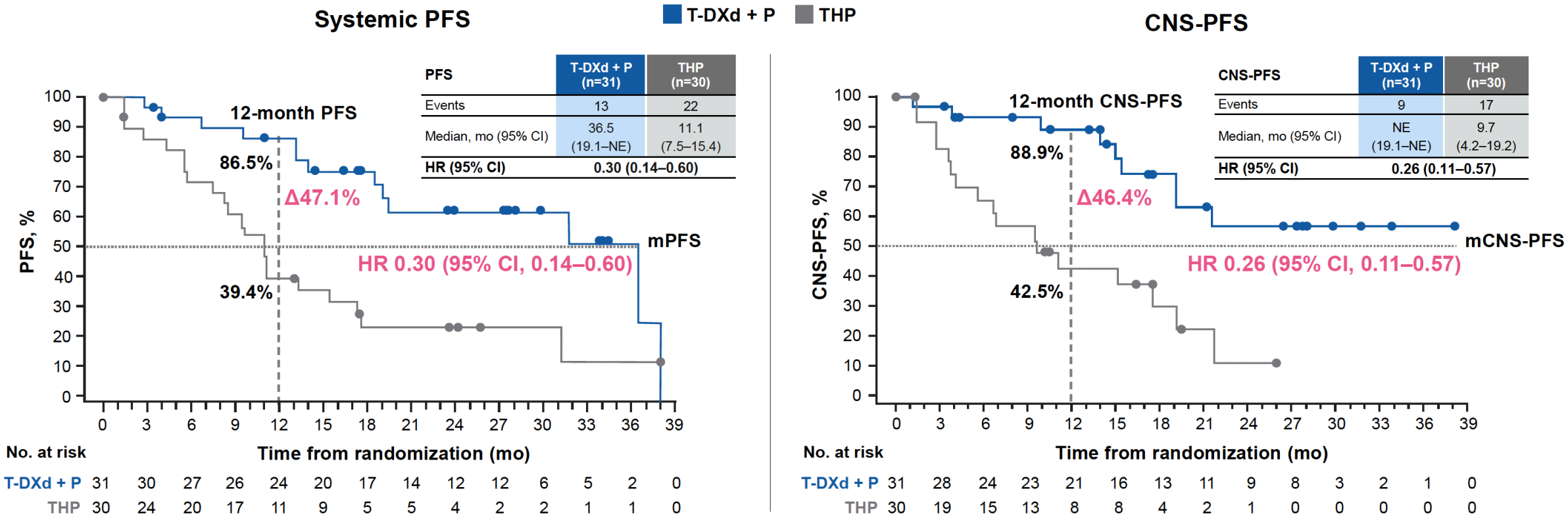




T-DXd + P demonstrated a clinically meaningful PFS benefit vs THP regardless of *PIK3CA*m status

Loibl S et al. ESMO 2025;Abstract LBA18.

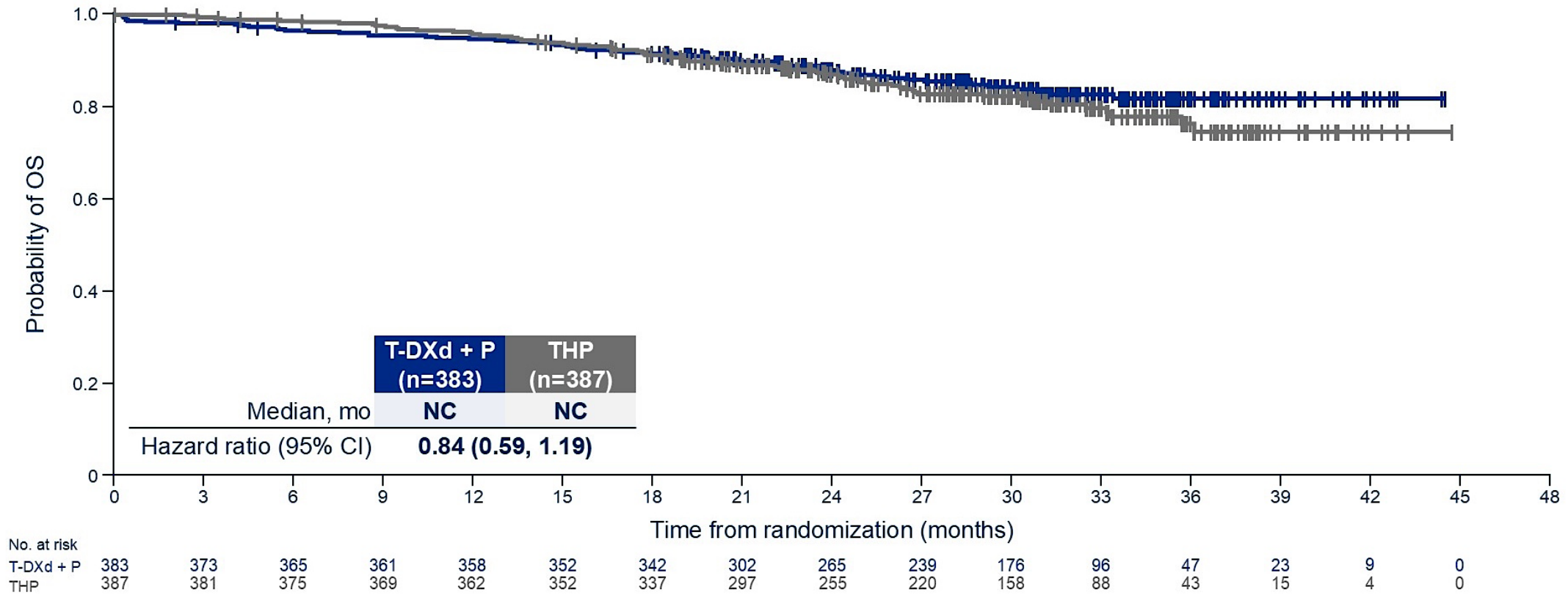
DESTINY-Breast09: PFS in Patients with Baseline Brain Metastases



Patients with BMs at BL in the T-DXd + P arm had substantially longer systemic PFS and CNS-PFS than those in the THP arm

Saura C et al. ESMO 2026;Abstract LBA49.

DESTINY-Breast09: Overall Survival (16% Maturity)



Early OS data suggest a positive trend favoring T-DXd + P over THP

CI, confidence interval; OS, overall survival; NC, not calculable; P, pertuzumab; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

Tolaney SM et al. ASCO 2025;Abstract LBA1008; Tolaney SM et al. *N Engl J Med* 2026;394;551-62.

DESTINY-Breast09: Overall Safety Summary

	Safety analysis set*	
	T-DXd + P (n=381)	THP (n=382)
Total exposure, patient years	659.7	564.0
Any TEAE, n (%)	380 (99.7)	378 (99.0)
Possibly treatment-related TEAEs (investigator assessed), n (%)	373 (97.9)	369 (96.6)
Grade ≥3	209 (54.9)	200 (52.4)
Serious TEAEs, n (%)	103 (27.0)	96 (25.1)
TEAEs associated with any treatment discontinuation,† n (%)	79 (20.7)	108 (28.3)
TEAEs associated with any dose interruptions,† n (%)	262 (68.8)	187 (49.0)
TEAEs associated with any dose reductions,† n (%)	175 (45.9)	76 (19.9)
TEAEs with outcome of death, n (%)	13 (3.4)	3 (0.8)
Possibly treatment related (investigator assessed)‡	5 (1.3)	1 (0.3)

Median total treatment 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 treatment duration for taxanes:

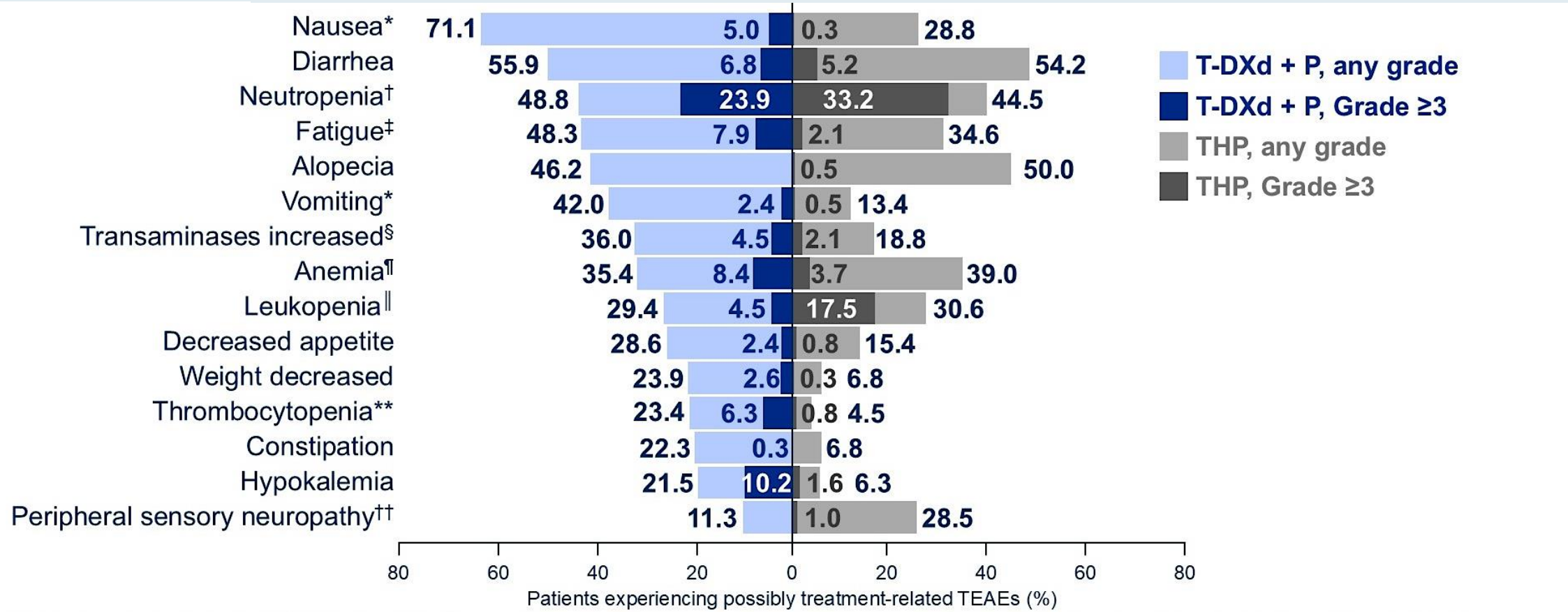
- Docetaxel: 5.5 mo (range 0.7–37.4)
- Paclitaxel: 4.4 mo (range 0.2–30.7)

Median number of cycles for taxanes:

- Docetaxel: 8 (range 1–51)
- Paclitaxel: 6 (range 1–42)

Tolaney SM et al. ASCO 2025;Abstract LBA1008; Tolaney SM et al. *N Engl J Med* 2026;394;551-62.

DESTINY-Breast09: Common Adverse Events



*Antiemetic prophylaxis was recommended but not mandated by protocol; †neutropenia (grouped term) includes: neutropenia and neutrophil count decreased; ‡fatigue (grouped term) includes: fatigue, asthenia, malaise, and lethargy; §transaminases increased (grouped term) includes: transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hepatic function abnormal, and liver function test increase; ¶anemia (grouped term) includes: anemia, hemoglobin decreased, hematocrit decreased, and red blood cell count decreased; ‖leukopenia (grouped term) includes: leukopenia and white blood cell count decreased; **thrombocytopenia (grouped term) includes: platelet count decreased and thrombocytopenia; ††peripheral sensory neuropathy (grouped term) includes: neuropathy peripheral, peripheral sensory neuropathy, and polyneuropathy
P, pertuzumab; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; THP, taxane + trastuzumab + pertuzumab

Tolaney SM et al. ASCO 2025;Abstract LBA1008; Tolaney SM et al. *N Engl J Med* 2026;394;551-62.

DESTINY-Breast09: 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

Tolaney SM et al. ASCO 2025;Abstract LBA1008; Tolaney SM et al. *N Engl J Med* 2026;394;551-62.

FDA Approves Fam-Trastuzumab Deruxtecan-nxki with Pertuzumab for Unresectable or Metastatic HER2-Positive Breast Cancer

Press Release: December 15, 2025

"On December 15, 2025, the Food and Drug Administration approved fam-trastuzumab deruxtecan-nxki in combination with pertuzumab for the first-line treatment of adults with unresectable or metastatic HER2-positive (IHC 3+ or ISH+) breast cancer as determined by an FDA-approved test.

Efficacy was evaluated in DESTINY-Breast09 (NCT04784715), a randomized, three-arm, multicenter, global trial that enrolled 1157 adults with HER2-positive advanced or metastatic breast cancer who had not received prior chemotherapy or HER2-targeted therapy or had received neoadjuvant or adjuvant HER2-targeted therapy more than six months before the diagnosis of advanced or metastatic disease."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-fam-trastuzumab-deruxtecan-nxki-pertuzumab-unresectable-or-metastatic-her2-positive

RTP RESEARCH TO PRACTICE

Agenda

Module 1: Localized HER2-Positive Breast Cancer (BC)

Module 2: Clinician Survey Results

Module 3: First-Line Treatment of HER2-Positive Metastatic BC (mBC)

Module 4: Clinician Survey Results

Module 5: Maintenance Therapy for HER2-Positive mBC

Module 6: Clinician Survey Results

Module 7: Novel Investigational Strategies for HER2-Positive BC

Module 8: Clinician Survey Results

RTP RESEARCH TO PRACTICE

A 65-year-old woman (PS 0) presents with de novo HR-negative, HER2-positive metastatic breast cancer (mBC). Regulatory and reimbursement issues aside, which first-line anti-HER2 therapy would you most likely recommend for each of the following scenarios?

	Asymptomatic bone metastases	Symptomatic liver metastases	Multiple brain metastases
 Dr Anders	Trastuzumab/pertuzumab /taxane	T-DXd/pertuzumab	T-DXd/pertuzumab
 Dr Brufsky	T-DXd/pertuzumab	T-DXd/pertuzumab	T-DXd/pertuzumab
 Dr Krop	Trastuzumab/pertuzumab /taxane	T-DXd/pertuzumab	T-DXd/pertuzumab
 Dr Mahtani	T-DXd/pertuzumab	T-DXd/pertuzumab	T-DXd/pertuzumab
 Dr Meisel	Trastuzumab/pertuzumab /docetaxel	T-DXd/pertuzumab	T-DXd/pertuzumab
 Dr Modi	T-DXd/pertuzumab	T-DXd/pertuzumab	T-DXd/pertuzumab
 Dr O'Shaughnessy	T-DXd/pertuzumab	T-DXd/pertuzumab	T-DXd/pertuzumab
 Dr Rimawi	Trastuzumab/pertuzumab /paclitaxel	T-DXd/pertuzumab	T-DXd/pertuzumab

A 85-year-old woman (PS 1) presents with de novo HR-negative, HER2-positive metastatic breast cancer (mBC). Regulatory and reimbursement issues aside, which first-line anti-HER2 therapy would you most likely recommend for each of the following scenarios?

	Asymptomatic bone metastases	Symptomatic liver metastases	Multiple brain metastases
 Dr Anders	Trastuzumab/pertuzumab /taxane	Trastuzumab/pertuzumab /taxane	Trastuzumab/pertuzumab /taxane
 Dr Brufsky	Trastuzumab/pertuzumab /paclitaxel	Trastuzumab/pertuzumab /paclitaxel	T-DXd/pertuzumab
 Dr Krop	Trastuzumab/pertuzumab /taxane	Trastuzumab/pertuzumab /taxane	Trastuzumab/pertuzumab /taxane
 Dr Mahtani	Trastuzumab/pertuzumab /paclitaxel	T-DXd/pertuzumab	T-DXd/pertuzumab
 Dr Meisel	Trastuzumab/pertuzumab /docetaxel	Trastuzumab/pertuzumab /docetaxel	T-DXd/pertuzumab
 Dr Modi	Trastuzumab/pertuzumab /paclitaxel	Trastuzumab/pertuzumab /paclitaxel	Tucatinib/trastuzumab /capecitabine
 Dr O'Shaughnessy	Trastuzumab/pertuzumab /docetaxel	T-DXd/pertuzumab	T-DXd/pertuzumab
 Dr Rimawi	Trastuzumab/pertuzumab /paclitaxel	T-DXd/pertuzumab	T-DXd/pertuzumab

A 65-year-old woman (PS 0) with localized HR-negative, HER2-positive breast cancer receives neoadjuvant TCHP. At surgery, she has residual invasive disease and receives adjuvant T-DXd. The patient now presents 1 year later after completing adjuvant T-DXd with metastatic disease, and repeat biomarker analysis confirms HR negativity and HER2 positivity (IHC 3+). Regulatory and reimbursement issues aside, which first-line anti-HER2 therapy would you most likely recommend for each of the following scenarios?

	Asymptomatic bone metastases	Symptomatic liver metastases	Multiple brain metastases
 Dr Anders	Trastuzumab/pertuzumab /taxane	T-DXd/pertuzumab	T-DXd/pertuzumab
 Dr Brufsky	T-DXd/pertuzumab	T-DXd/pertuzumab	T-DXd/pertuzumab
 Dr Krop	Tucatinib/trastuzumab /capecitabine	T-DXd/pertuzumab	T-DXd/pertuzumab
 Dr Mahtani	Tucatinib/trastuzumab /capecitabine	Tucatinib/trastuzumab /capecitabine	Tucatinib/trastuzumab /capecitabine
 Dr Meisel	Trastuzumab/pertuzumab /paclitaxel	Trastuzumab/pertuzumab /paclitaxel	Tucatinib/trastuzumab /capecitabine
 Dr Modi	T-DXd/pertuzumab	T-DXd/pertuzumab	T-DXd/pertuzumab
 Dr O'Shaughnessy	T-DXd/pertuzumab	T-DXd/pertuzumab	Tucatinib/trastuzumab /capecitabine
 Dr Rimawi	Trastuzumab/pertuzumab /paclitaxel	T-DXd/pertuzumab	Tucatinib/trastuzumab /capecitabine

A 65-year-old woman (PS 0) with localized HR-negative, HER2-positive breast cancer receives neoadjuvant TCHP. At surgery, she has residual invasive disease and receives adjuvant T-DXd. The patient now presents 5 years later after completing adjuvant T-DXd with metastatic disease, and repeat biomarker analysis confirms HR negativity and HER2 positivity (IHC 3+). Regulatory and reimbursement issues aside, which first-line anti-HER2 therapy would you most likely recommend for each of the following scenarios?

	Asymptomatic bone metastases	Symptomatic liver metastases	Multiple brain metastases
 Dr Anders	Trastuzumab/pertuzumab /taxane	T-DXd/pertuzumab	T-DXd/pertuzumab
 Dr Brufsky	T-DXd/pertuzumab	T-DXd/pertuzumab	T-DXd/pertuzumab
 Dr Krop	Tucatinib/trastuzumab /capecitabine	T-DXd/pertuzumab	T-DXd/pertuzumab
 Dr Mahtani	T-DXd/pertuzumab	T-DXd/pertuzumab	T-DXd/pertuzumab
 Dr Meisel	T-DXd/pertuzumab	T-DXd/pertuzumab	T-DXd/pertuzumab
 Dr Modi	T-DXd/pertuzumab	T-DXd/pertuzumab	T-DXd/pertuzumab
 Dr O'Shaughnessy	T-DXd/pertuzumab	T-DXd/pertuzumab	T-DXd/pertuzumab
 Dr Rimawi	Trastuzumab/pertuzumab /paclitaxel	T-DXd/pertuzumab	T-DXd/pertuzumab

A 65-year-old woman (PS 0) with localized HR-negative, HER2-positive breast cancer receives neoadjuvant T-DXd → THP. At surgery, she has a pathologic complete response and receives adjuvant trastuzumab/pertuzumab. Three years later, the patient presents with metastatic disease, and repeat biomarker analysis confirms HR negativity and HER2 positivity (IHC 3+). Regulatory and reimbursement issues aside, which first-line anti-HER2 therapy would you most likely recommend for each of the following scenarios?

	Asymptomatic bone metastases	Symptomatic liver metastases	Multiple brain metastases
 Dr Anders	Trastuzumab/pertuzumab /taxane	T-DXd/pertuzumab	T-DXd/pertuzumab
 Dr Brufsky	T-DXd/pertuzumab	T-DXd/pertuzumab	T-DXd/pertuzumab
 Dr Krop	Tucatinib/trastuzumab /capecitabine	T-DXd/pertuzumab	T-DXd/pertuzumab
 Dr Mahtani	T-DXd/pertuzumab	T-DXd/pertuzumab	T-DXd/pertuzumab
 Dr Meisel	T-DXd/pertuzumab	T-DXd/pertuzumab	T-DXd/pertuzumab
 Dr Modi	T-DXd/pertuzumab	T-DXd/pertuzumab	T-DXd/pertuzumab
 Dr O'Shaughnessy	T-DXd/pertuzumab	T-DXd/pertuzumab	T-DXd/pertuzumab
 Dr Rimawi	Trastuzumab/pertuzumab /paclitaxel	T-DXd/pertuzumab	T-DXd/pertuzumab

Agenda

Module 1: Localized HER2-Positive Breast Cancer (BC)

Module 2: Clinician Survey Results

Module 3: First-Line Treatment of HER2-Positive Metastatic BC (mBC)

Module 4: Clinician Survey Results

Module 5: Maintenance Therapy for HER2-Positive mBC

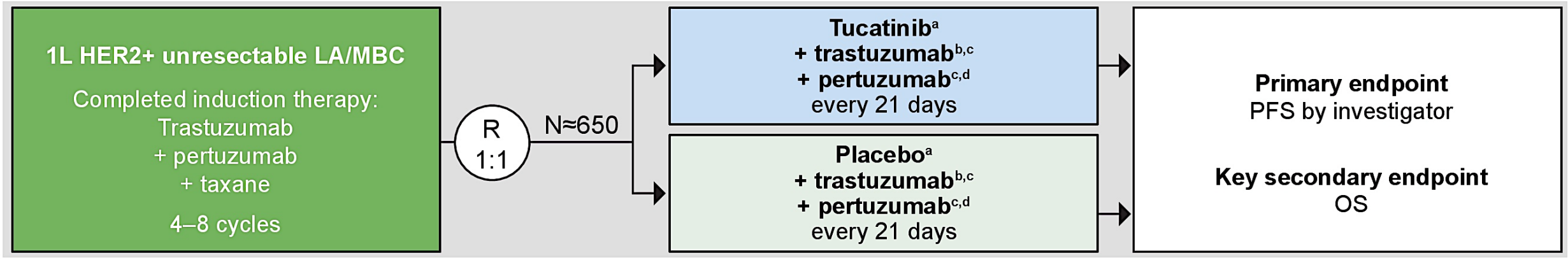
Module 6: Clinician Survey Results

Module 7: Novel Investigational Strategies for HER2-Positive BC

Module 8: Clinician Survey Results

RTP RESEARCH TO PRACTICE

Phase III HER2CLIMB-05 Study Design



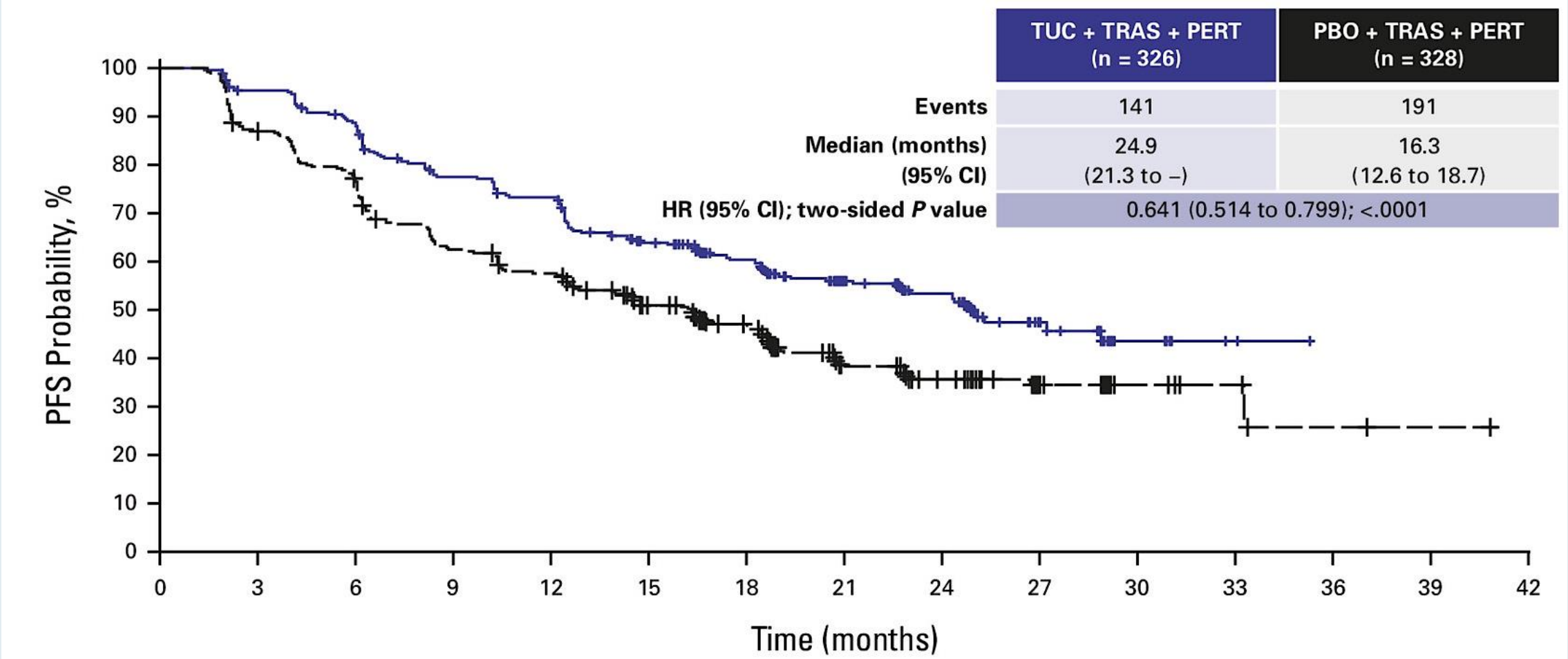
Randomization will be stratified by diagnosis (de novo vs recurrent MBC), hormone receptor status (positive vs negative), and presence or history of BMs (yes vs no).

Patients are permitted to receive up to 2 cycles of carboplatin during the start of induction therapy in combination with trastuzumab, pertuzumab, and taxane.

[a]Tucatinib/placebo 300 mg will be administered PO from Cycle 1 Day 1 onward, BID on each day of study treatment. [b]IV trastuzumab will be given at a dose of 6 mg/kg once every 21 days. Alternatively, trastuzumab may be administered as an SC dose, at a fixed dose of 600 mg once every 21 days. SC trastuzumab does not require a loading dose. [c]A fixed dose of trastuzumab + pertuzumab (600 mg pertuzumab, 600 mg trastuzumab, and 20,000 units hyaluronidase) can be administered every 21 days by SC administration, in lieu of trastuzumab and pertuzumab administered IV individually. [d]Pertuzumab 420 mg will be administered every 21 days intravenously over 30-60 minutes.

Hamilton EP et al. ASCO 2023;Abstract TPS1115.

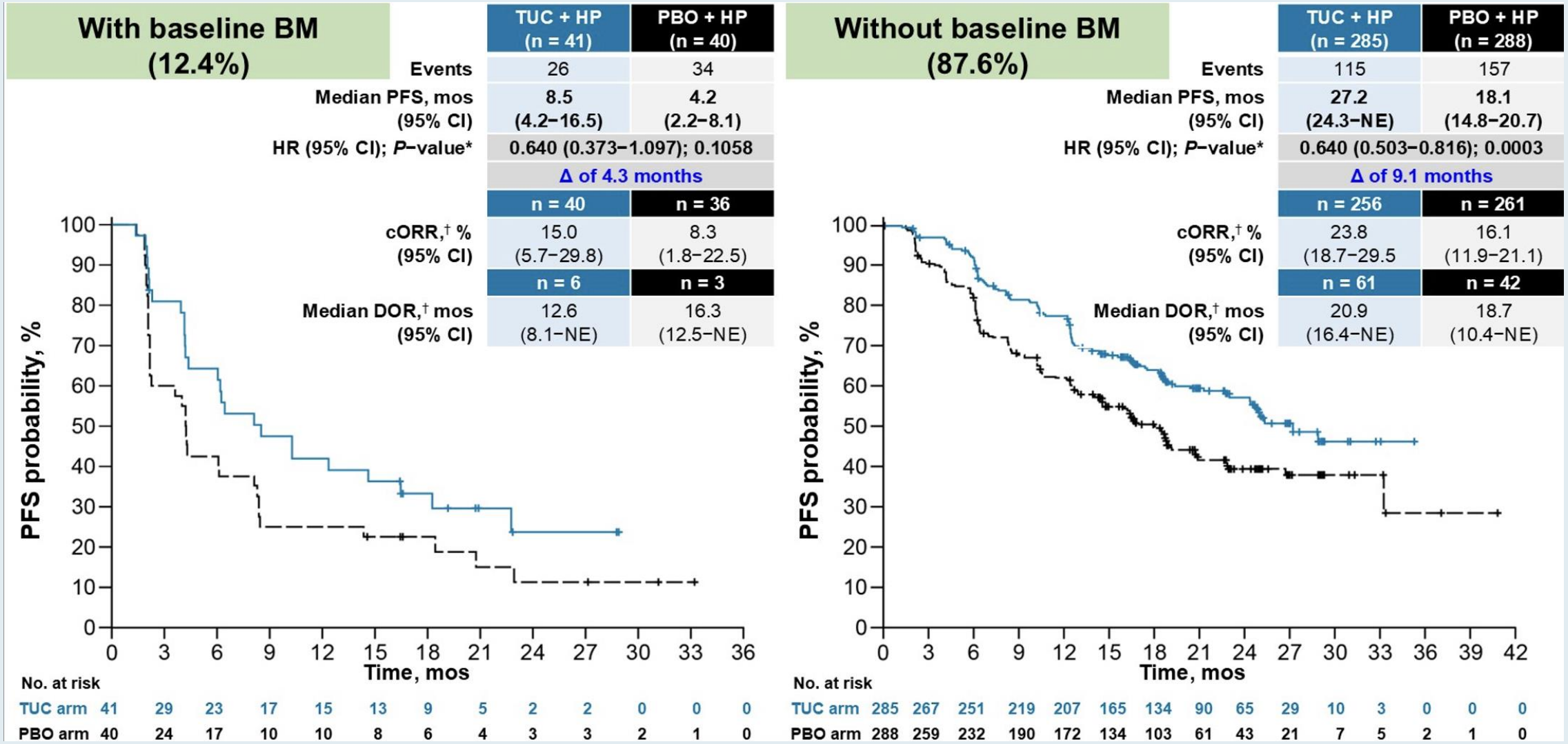
HER2CLIMB-05: Investigator-Assessed PFS in the Intent-to-Treat Population



TUC = tucatinib; TRAS = trastuzumab; PERT = pertuzumab; PBO = placebo

Dieras V et al. *J Clin Oncol* 2026;44:1597-607.

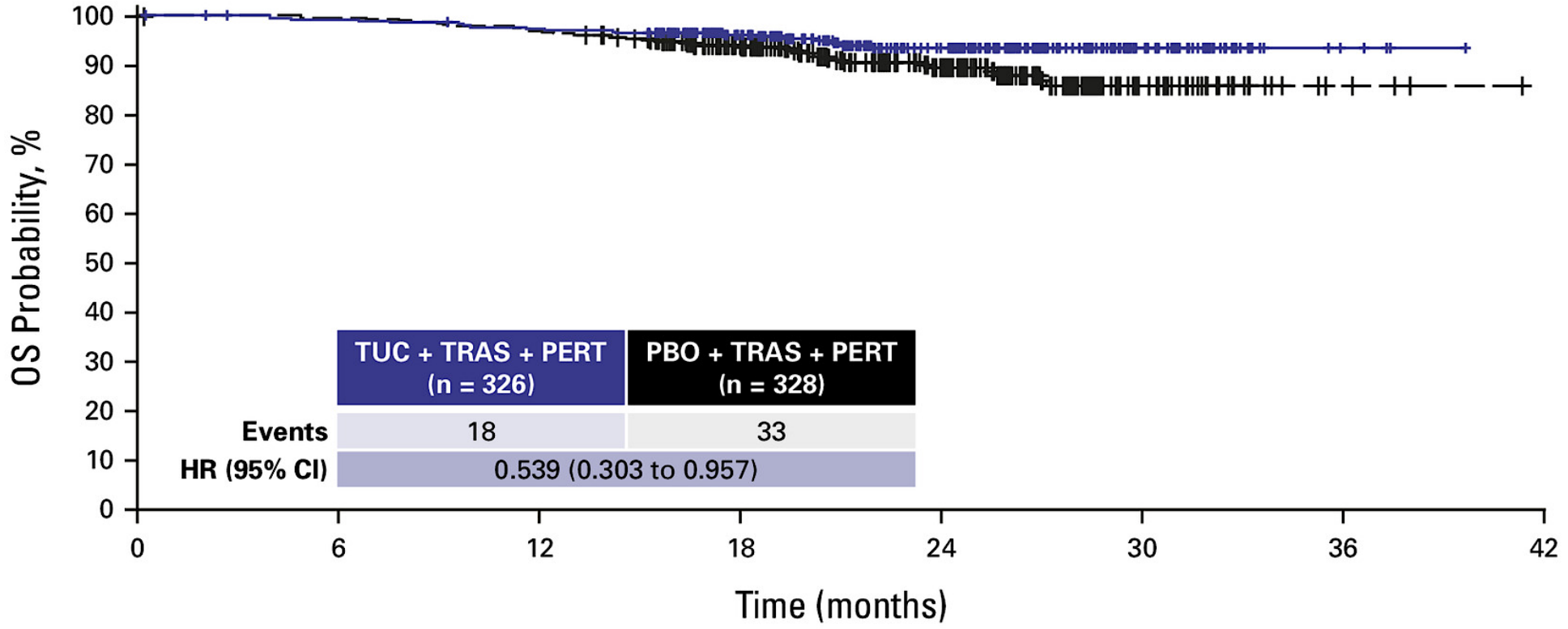
HER2CLIMB-05: PFS by Brain Metastases (BM) at Baseline



DOR = duration of response

Hamilton E et al. ASCO 2026;Abstract 1005.

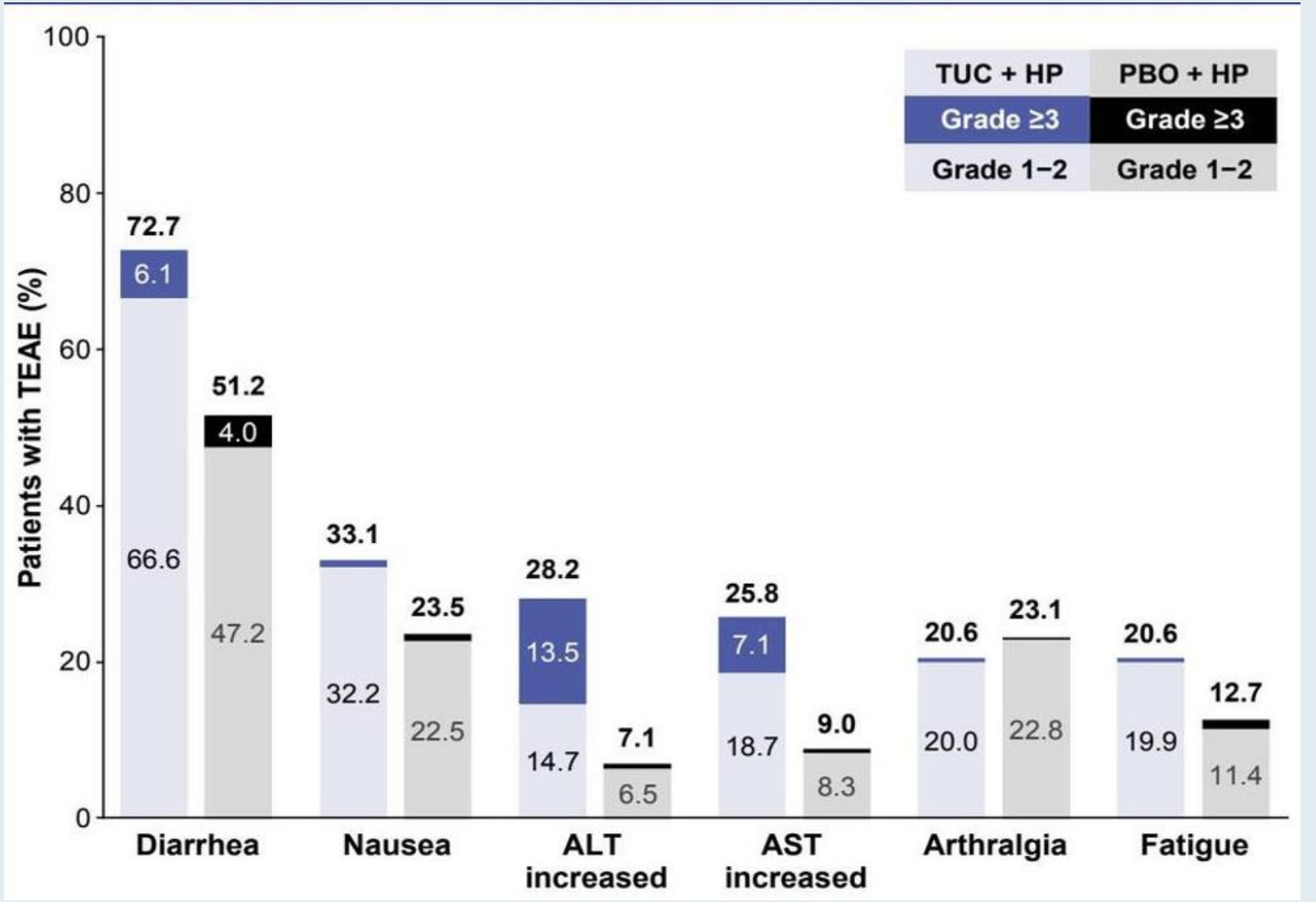
HER2CLIMB-05: Overall Survival (OS) Outcomes in the Intent-to-Treat Population



TUC + TRAS + PERT								
No. at risk	326	321	314	255	152	43	4	0
No. censored	0	3	4	59	156	265	304	308
PBO + TRAS + PERT								
No. at risk	328	326	317	249	151	41	4	0
No. censored	0	1	1	60	148	254	291	295

Dieras V et al. *J Clin Oncol* 2026;44:1597-607.

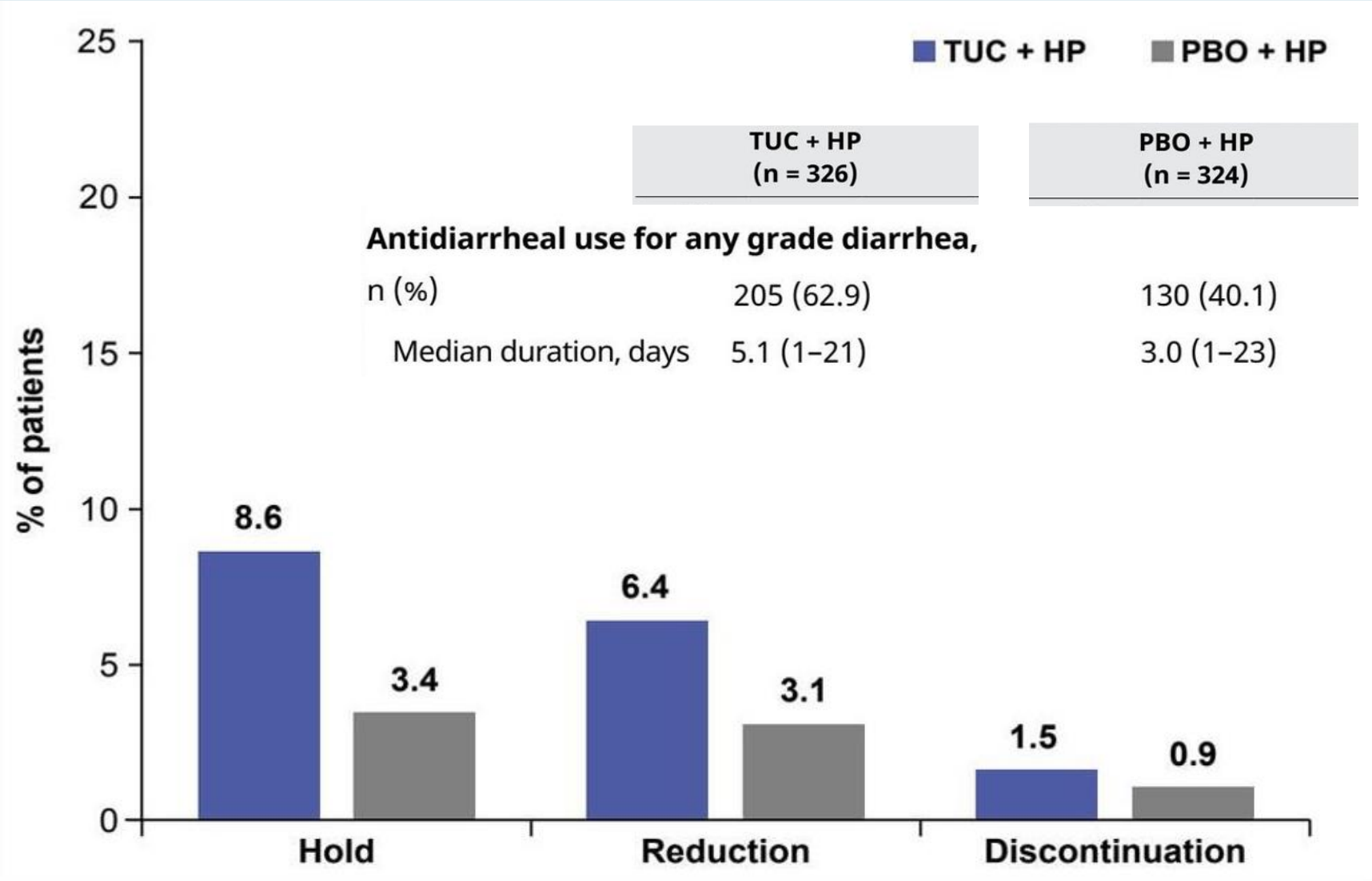
HER2CLIMB-05: Safety Overview



TEAE = treatment-emergent adverse event; ALT = alanine transaminase; AST = aspartate transferase

Dieras VC et al. ASCO 2026;Abstract 1042.

HER2CLIMB-05: Dose Modifications Due to Diarrhea



	TUC + HP (n = 326)	PBO + HP (n = 324)
Antidiarrheal use for any grade diarrhea,		
n (%)	205 (62.9)	130 (40.1)
Median duration, days	5.1 (1–21)	3.0 (1–23)

Dieras VC et al. ASCO 2026;Abstract 1042.

FDA Approves Tucatinib with Trastuzumab and Pertuzumab for the Maintenance Treatment of HER2-Positive Breast Cancer

Press Release: October 7, 2026

"On October 7, 2026, the Food and Drug Administration approved tucatinib in combination with trastuzumab and pertuzumab for the maintenance treatment of adults with unresectable locally advanced or metastatic HER2-positive breast cancer following induction treatment.

Efficacy was evaluated in 654 adult patients in HER2CLIMB-05 (NCT05132582), a randomized, double-blind, placebo-controlled trial. Eligible patients were required to have HER2-positive, unresectable locally advanced or metastatic breast cancer, with or without brain metastases, and no evidence of disease progression by investigator assessment after induction treatment with 4-8 cycles of trastuzumab, pertuzumab, and a taxane. Patients received tucatinib 300 mg or placebo orally twice daily with trastuzumab and pertuzumab intravenously, or with a fixed-dose combination of trastuzumab, pertuzumab, and hyaluronidase administered subcutaneously. Patients with hormone receptor positive disease were permitted to continue endocrine therapy. Patients were treated until disease progression or unacceptable toxicity."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tucatinib-trastuzumab-and-pertuzumab-maintenance-treatment-her2-positive-breast-cancer

RTP RESEARCH TO PRACTICE

Phase III PATINA Study Design

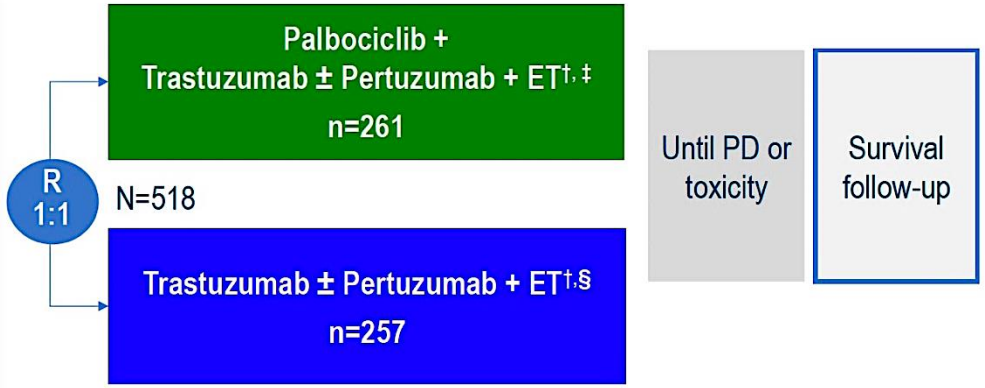
Objective: To evaluate the addition of palbociclib to anti-HER2 and ET for patients with HR+/HER2+ breast cancer

REGISTRATION

- Histologically confirmed HR+/HER2+ aBC
- 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)



Primary Outcome

- Investigator-assessed PFS

Secondary Outcomes

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

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)‖
- Response to induction therapy (CR or PR vs SD) by investigator assessment‖
- Type of ET (fulvestrant vs aromatase inhibitor)

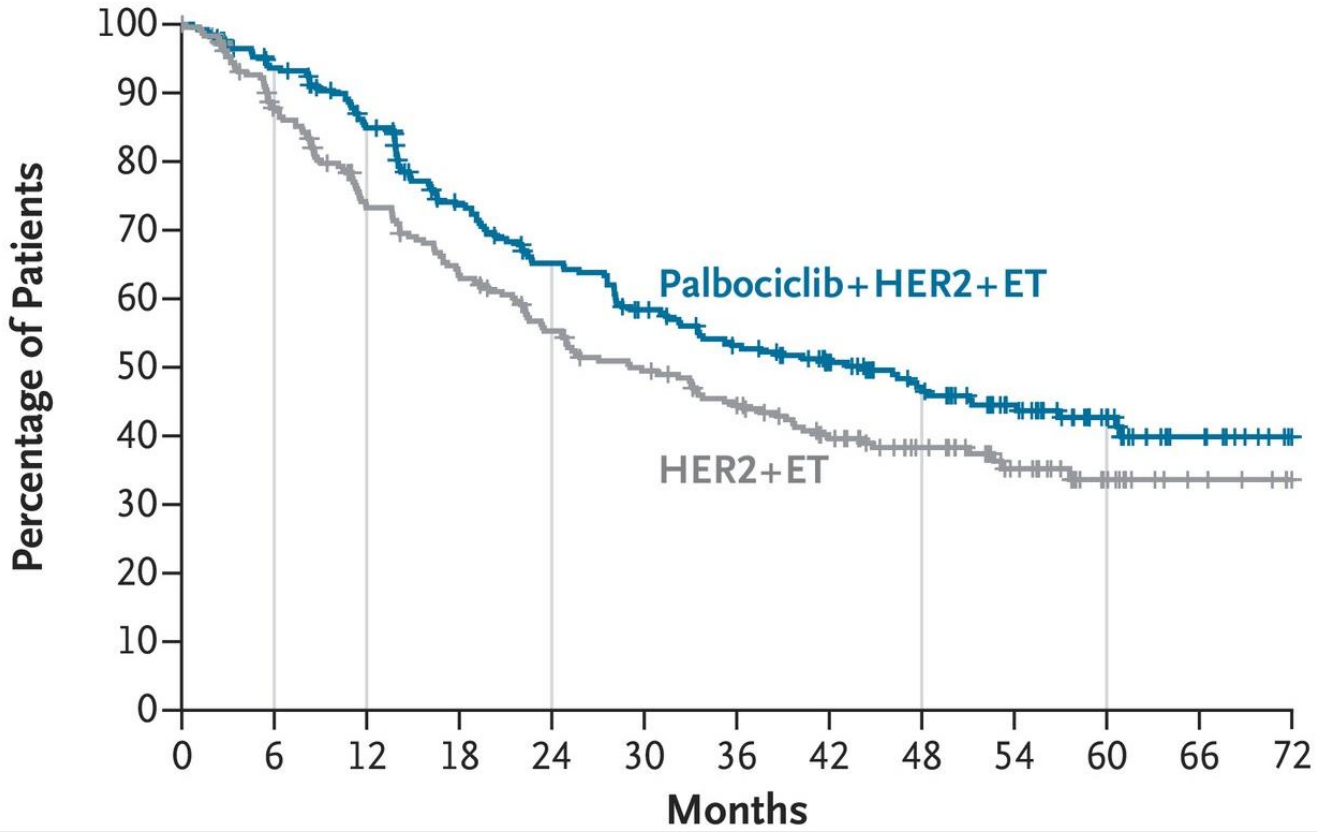
Data cutoff for final PFS analysis: October 15, 2024.

*Study enrollment period was June 2017 until 2021 across the United States, France, Germany, Italy, Portugal, Spain, Australia, and New Zealand. DSMB recommendation to release study data occurred on December 2, 2024. †Trastuzumab and pertuzumab were administered per SOC. ET options included an aromatase inhibitor or fulvestrant. ‡All patients included in the primary and secondary analyses. §Nine patients withdrew before starting treatment and were not included in the safety analysis. All patients were included in the ITT analysis. ‖Factors used in stratified analyses. CBR, clinical benefit rate; CNS, central nervous system; CR=complete response; DOR, duration of response; DSMB=Data and Safety Monitoring Board; ET=endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; mBC, metastatic breast cancer; mets, metastases; OS, overall survival; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; PRO, patient-reported outcome; R, randomization; SD, stable disease; SOC, standard of care.

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

Vaz-Luis I et al. ESMO 2025;Abstract 485MO.

PATINA: PFS Outcomes in the Intent-to-Treat Population



	No. of Events/Total No. of Patients	Median Progression-free Survival (95% CI)
		mo
Palbociclib+HER2+ET	127/261	44.3 (32.4–56.8)
HER2+ET	135/257	29.1 (23.3–38.6)

Hazard ratio for disease progression or death, 0.75 (95% CI, 0.59–0.96)
Two-sided unstratified P=0.02 by log-rank test

Metzger O et al. *N Engl J Med* 2026;394(5):451-62.

PATINA: Cumulative Incidence of CNS Progression or Death Among Patients without CNS Metastases at Baseline

	Palbociclib + anti-HER2 + ET (n = 250)	Anti-HER2 + ET (n = 248)
CNS PFS event (n)	35	48
Death	3	1
CNS progression	32	47
Cumulative risk of CNS progression or death (%)		
12 months	4.6%	6.9%
24 months	9.7%	15.7%
36 months	13.0%	19.2%

ET = endocrine therapy

RTP RESEARCH TO PRACTICE

Metzger O et al. SABCS 2025;Abstract RF4-01.

PATINA: Safety Profile

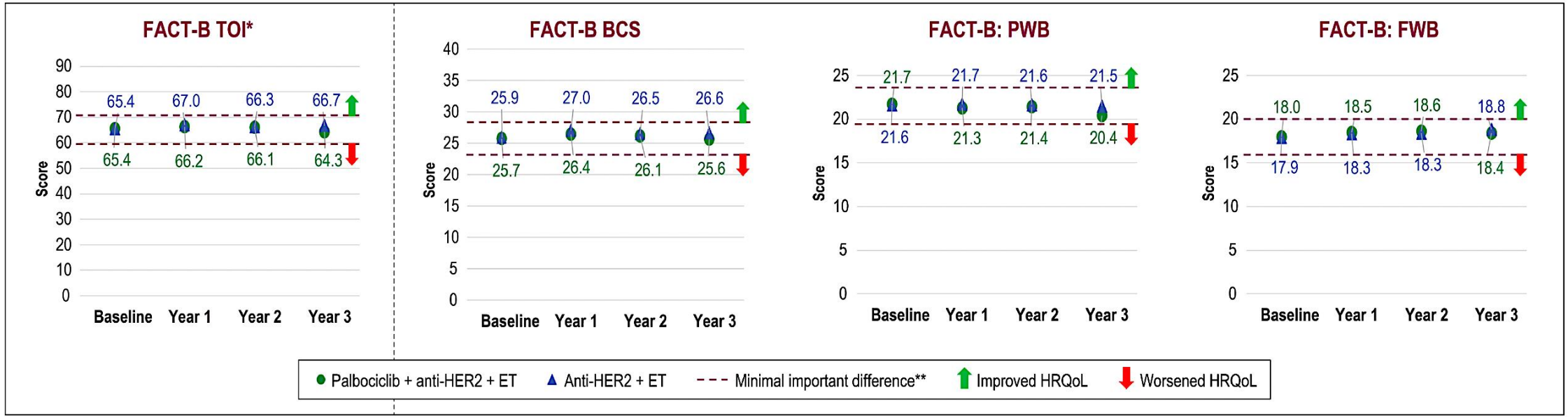
Adverse Events, n (%)*	**Palbociclib + anti-HER2 and ET (N=261)**			**Anti-HER2 and ET (N=248)**		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Neutropenia	52 (19.9)	165 (63.2)	12 (4.6)	10 (4.0)	11 (4.4)	0 (0.0)
White blood cell count decreased	30 (11.5)	30 (11.5)	1 (0.4)	2 (0.8)	0 (0.0)	0 (0.0)
Fatigue	60 (22.9)	14 (5.4)	0 (0.0)	32 (12.9)	0 (0.0)	0 (0.0)
Stomatitis	45 (17.2)	11 (4.2)	0 (0.0)	3 (1.2)	0 (0.0)	0 (0.0)
Diarrhea	69 (26.4)	29 (11.1)	0 (0.0)	26 (10.5)	4 (1.6)	0 (0.0)
Upper respiratory tract infection	30 (11.5)	1 (0.4)	0 (0.0)	16 (6.5)	0 (0.0)	0 (0.0)
Urinary tract infection	26 (10.0)	2 (0.8)	0 (0.0)	19 (7.7)	1 (0.4)	0 (0.0)
Arthralgia	23 (8.8)	4 (1.5)	0 (0.0)	44 (17.7)	3 (1.2)	0 (0.0)
Ejection fraction decreased	22 (8.4)	1 (0.4)	0 (0.0)	21 (8.5)	8 (3.2)	0 (0.0)
Cardiac heart failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	0 (0.0)

- The incidence of grade ≥4 adverse events regardless of treatment attribution was similar across study arms (12.3% vs 8.9% for palbociclib-containing arm vs control; *P*=0.21)
- Treatment discontinuation due to AEs were reported in 14 (7.5%) of patients in the palbociclib arm
- No treatment-related deaths were reported in either arm of the study

Metzger O et al. SABCS 2024;Abstract GS2-12.

PATINA: HRQoL Analysis

FACT-B



HRQoL showed stability from baseline over time with **no significant or clinically meaningful differences** between treatment arms.

Global health status from EQ-5D-5L showed a similar pattern with **no significant or clinically meaningful differences**^ between treatment arms.

*Minimal important differences: FACT-B TOI (5 points); FACT-B Subscales (2 points); BCS (2 points).[1]

^Data not shown

BCS, Breast Cancer Subscale; EQ-5D, EuroQol 5 Dimension; ET, endocrine therapy; FACT-B TOI, Functional Assessment of Cancer Therapy-Breast Trial Outcome Index; FWB, Functional well-being; HER2, human epidermal growth factor receptor 2; HRQoL, health-related quality of life; PWB, Physical well-being.

Vaz-Luis I et al. ESMO 2025;Abstract 485MO.

FDA Approves Palbociclib with Trastuzumab, with or without Pertuzumab, and Endocrine Therapy for the Maintenance Treatment of HR-Positive, HER2-Positive Metastatic Breast Cancer

Press Release: June 24, 2026

"…the Food and Drug Administration approved palbociclib in combination with trastuzumab, with or without pertuzumab, and endocrine therapy for the maintenance treatment of adults with HR-positive, HER2-positive locally advanced or metastatic breast cancer following induction treatment.

Efficacy was evaluated in PATINA (NCT02947685), a randomized, open-label trial in 518 patients with HR-positive, HER2-positive locally advanced or metastatic breast cancer who had no evidence of disease progression after induction treatment with a taxane and trastuzumab, with or without pertuzumab, for their advanced disease."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-palbociclib-trastuzumab-or-without-pertuzumab-and-endocrine-therapy-maintenance

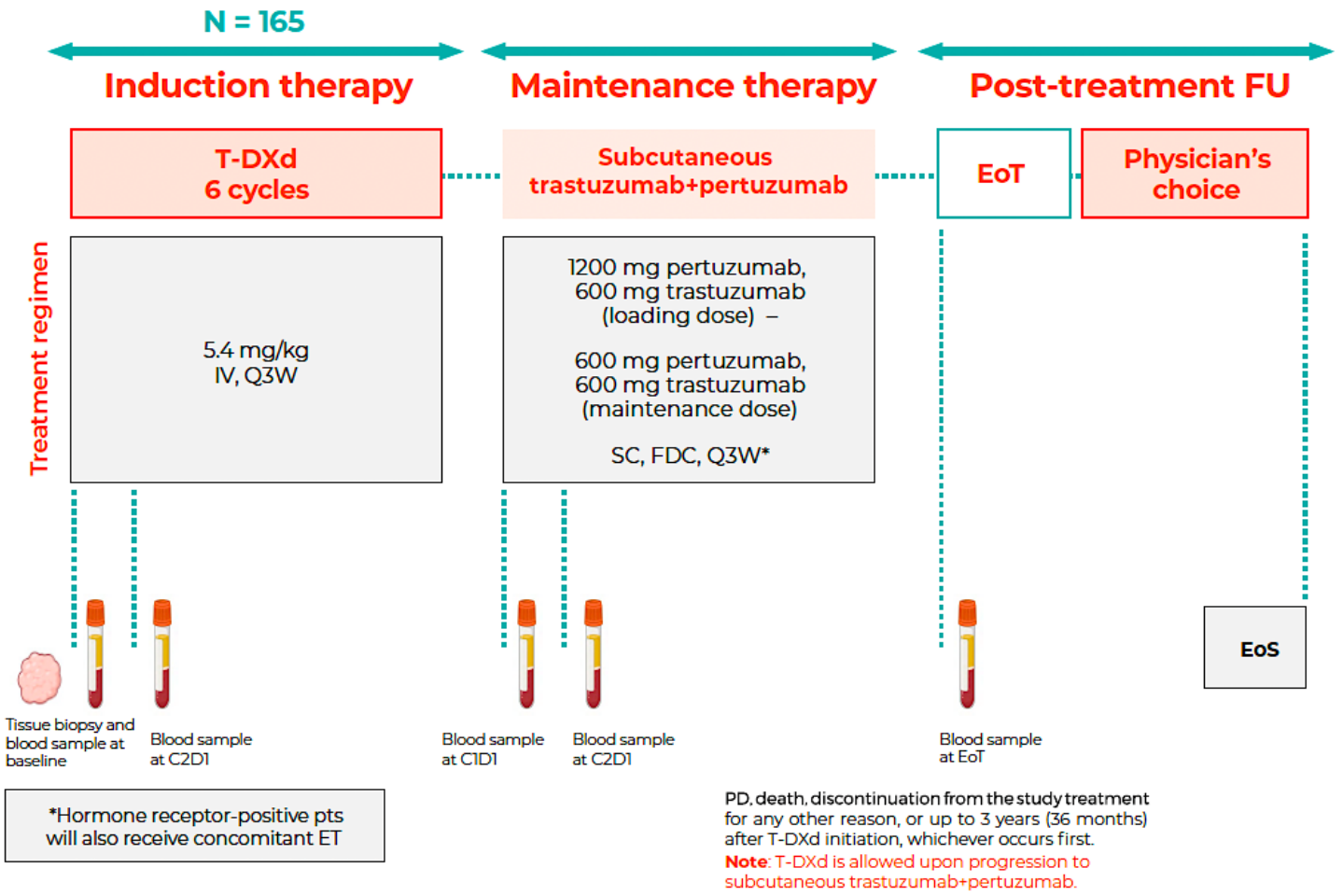
RTP RESEARCH TO PRACTICE

DEMETHER: A Phase II Study of Maintenance Pertuzumab and Trastuzumab After Induction T-DXd

KEY INCLUSION CRITERIA

- ≥18 years of age.
- Centrally-confirmed HER2[+] (IHC 3+, IHC 2+ & ISH+) ABC.
- Stable brain metastasis allowed.
- No prior systemic treatment for advanced disease (one prior line of ET is allowed for ABC).
- Participants may have received CT or HER2-targeted therapy in the (neo)adjuvant setting with a disease-free interval from completion of the systemic treatment (excluding ET) to metastatic diagnosis ≥ 12 months.
- No prior treatment with T-DXd in the (neo)adjuvant setting.
- Evaluable disease according to RECIST v.1.1.
- ECOG PS 0-1.
- LVEF ≥ 55% (ECHO or MUGA scan)
- Adequate hematologic and organ function

*An **interim analysis** will be performed on the first 62 pts with measurable lesions; if at least 44 pts show objective response, the trial will continue.

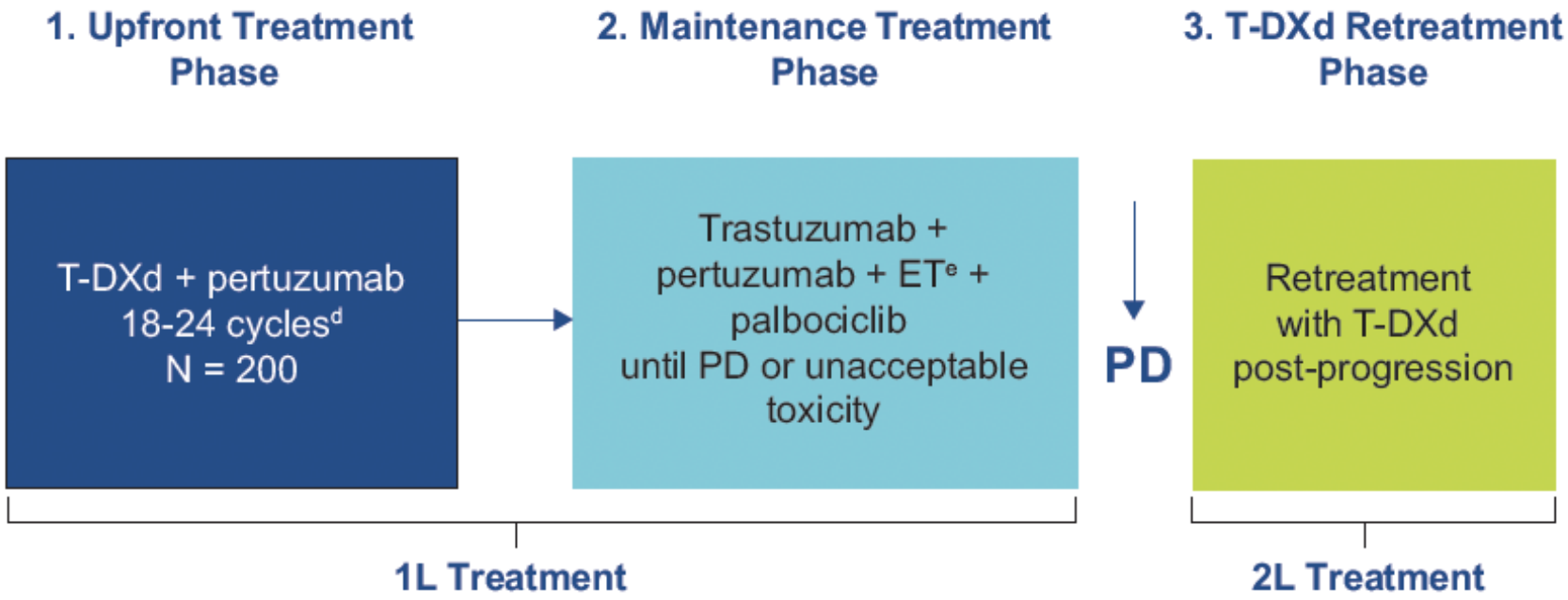


Cortes J et al. SABCS 2024;Abstract P5-03-11.

DESTINY-Breast Guide: A Phase III Study of First-Line T-DXd-Based Therapy Followed by Palbociclib, Endocrine Therapy and Dual HER2 Blockade and Re-treatment with T-DXd

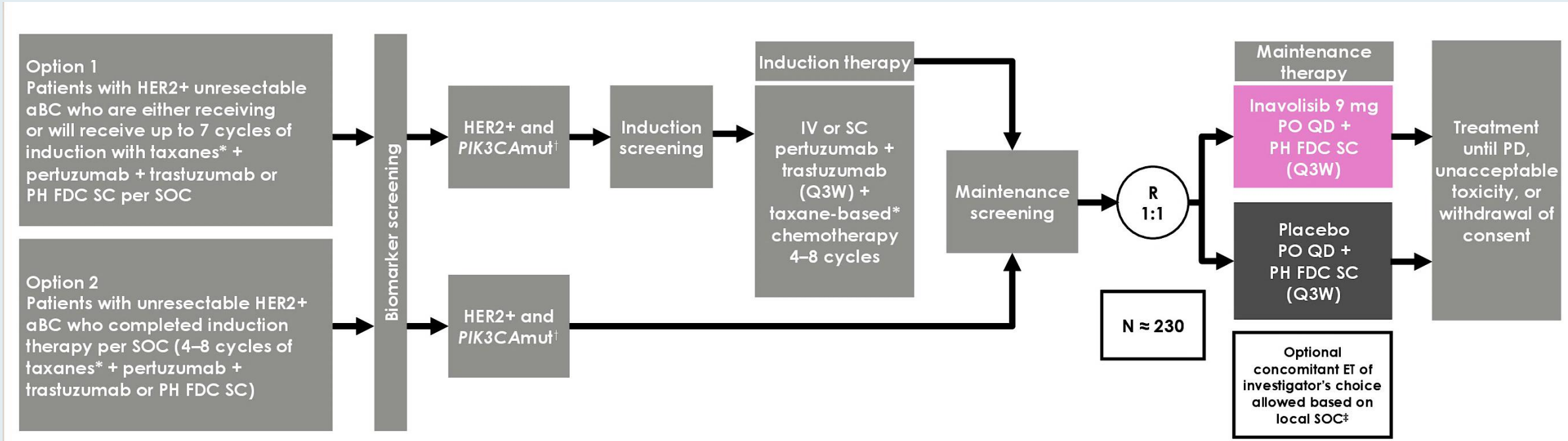
Key Eligibility Criteria

- Patients aged ≥18 years
- HER2+ (IHC 3+ or IHC 2+/ISH+)[a]/HR+, de novo or recurrent mBC
- No prior chemotherapy or HER2-targeted therapy for advanced or mBC[b]
- ECOG PS 0 or 1
- DFI >6 months[c]
- Asymptomatic brain metastases allowed



Sammons S et al. ESMO 2026;Abstract 1795TiP.

INAVO122: A Phase III Study of Maintenance Inavolisib with Pertuzumab and Trastuzumab After Induction with Paclitaxel, Trastuzumab and Pertuzumab for PIK3CA-Mutated, HER2-Positive mBC



Stratification factors

- *De novo* HER2+ unresectable advanced vs. recurrent disease
- HR+ vs. HR– tumor status
- Objective response after induction therapy: PR/CR vs. SD (or non-CR/non-PD for patients with non-measurable disease)

Primary endpoint

- Investigator-assessed progression-free survival, defined as the time from randomization to the first occurrence of PD (per RECIST v1.1), or death from any cause (whichever occurs first)

Secondary endpoints

- Overall survival
- Investigator-assessed objective response rate
- Investigator-assessed duration of response
- Investigator-assessed clinical benefit rate
- Investigator-assessed time to second disease progression
- Patient-reported outcomes/health-related quality of life
- Safety
- Pharmacokinetics

Swain SM et al. ASCO 2024;Abstract TPS1124.

Agenda

Module 1: Localized HER2-Positive Breast Cancer (BC)

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RTP RESEARCH TO PRACTICE

A 65-year-old woman with de novo HR-negative, HER2-positive mBC receives T-DXd/pertuzumab as first-line therapy and achieves a complete response (CR) with good tolerability. Regulatory and reimbursement issues aside, which maintenance regimen would you recommend?

 Dr Anders	Switch to trastuzumab/pertuzumab + tucatinib at CR or near CR
 Dr Brufsky	Switch to trastuzumab/pertuzumab after CR x 2 cycles
 Dr Krop	Switch to trastuzumab/pertuzumab after 2 years
 Dr Mahtani	Continue T-DXd/pertuzumab indefinitely
 Dr Meisel	Switch to trastuzumab/pertuzumab + tucatinib after CR
 Dr Modi	Continue T-DXd/pertuzumab indefinitely
 Dr O'Shaughnessy	Continue T-DXd/pertuzumab indefinitely
 Dr Rimawi	Continue T-DXd/pertuzumab indefinitely

A 65-year-old woman with de novo HR-negative, HER2-positive mBC receives T-DXd/pertuzumab as first-line therapy and achieves a partial response (PR) with good tolerability. Regulatory and reimbursement issues aside, which maintenance regimen would you recommend?

 Dr Anders	Continue T-DXd/pertuzumab indefinitely
 Dr Brufsky	Switch to trastuzumab/pertuzumab + tucatinib after stable disease for at least 2 cycles after 6 to 8 cycles
 Dr Krop	Switch to trastuzumab/pertuzumab after 3 years
 Dr Mahtani	Continue T-DXd/pertuzumab indefinitely
 Dr Meisel	Continue T-DXd/pertuzumab indefinitely
 Dr Modi	Switch to trastuzumab/pertuzumab + tucatinib after 2 sequential scans show a plateau in response
 Dr O'Shaughnessy	Continue T-DXd/pertuzumab indefinitely
 Dr Rimawi	Continue T-DXd/pertuzumab indefinitely

A 65-year-old woman with de novo HR-positive, HER2-positive mBC receives T-DXd/pertuzumab as first-line therapy and achieves a CR with good tolerability. Regulatory and reimbursement issues aside, which maintenance regimen would you recommend?

 Dr Anders	Switch to trastuzumab/pertuzumab and add ET and palbociclib at CR
 Dr Brufsky	Switch to trastuzumab/pertuzumab and add ET and palbociclib after about 12 months
 Dr Krop	Switch to trastuzumab/pertuzumab and add ET after 2 years
 Dr Mahtani	Continue T-DXd/pertuzumab indefinitely and add ET
 Dr Meisel	Switch to trastuzumab/pertuzumab and add ET and palbociclib after 6 cycles
 Dr Modi	Switch to trastuzumab/pertuzumab and add ET and palbociclib; switch dependent on disease-free interval and negative ctDNA
 Dr O'Shaughnessy	Continue T-DXd/pertuzumab indefinitely and add ET
 Dr Rimawi	Continue T-DXd/pertuzumab indefinitely

ET = endocrine therapy; ctDNA = circulating tumor DNA

A 65-year-old woman with de novo HR-positive, HER2-positive mBC receives T-DXd/pertuzumab as first-line therapy and achieves a PR with good tolerability. Regulatory and reimbursement issues aside, which maintenance regimen would you recommend?

 Dr Anders	Continue T-DXd/pertuzumab indefinitely and add ET
 Dr Brufsky	Continue T-DXd/pertuzumab indefinitely
 Dr Krop	Switch to trastuzumab/pertuzumab and add ET after 3 years
 Dr Mahtani	Continue T-DXd/pertuzumab indefinitely and add ET
 Dr Meisel	Switch to trastuzumab/pertuzumab and add ET and palbociclib after 6 cycles
 Dr Modi	Switch to trastuzumab/pertuzumab and add ET and palbociclib after plateau in response on at least two scans
 Dr O'Shaughnessy	Continue T-DXd/pertuzumab indefinitely and add ET
 Dr Rimawi	Continue T-DXd/pertuzumab indefinitely

A 65-year-old woman is diagnosed with de novo HR-negative, HER2-positive mBC with multiple brain metastases. The patient undergoes stereotactic radiosurgery, receives T-DXd/pertuzumab as first-line therapy and achieves a CR with good tolerability. Regulatory and reimbursement issues aside, which maintenance regimen would you recommend?

 Dr Anders	Continue T-DXd/pertuzumab indefinitely
 Dr Brufsky	Switch to trastuzumab/pertuzumab + tucatinib immediately
 Dr Krop	Switch to trastuzumab/pertuzumab + tucatinib after 2 years
 Dr Mahtani	Continue T-DXd/pertuzumab indefinitely
 Dr Meisel	Continue T-DXd/pertuzumab indefinitely
 Dr Modi	Continue T-DXd/pertuzumab indefinitely
 Dr O'Shaughnessy	Continue T-DXd/pertuzumab indefinitely
 Dr Rimawi	Continue T-DXd/pertuzumab indefinitely

A 65-year-old woman with HR-positive, HER2-positive mBC receives first-line T-DXd/pertuzumab and achieves a CR with good tolerability. She is switched to maintenance therapy with palbociclib/ET/ trastuzumab/pertuzumab but after 10 months develops limited disease progression with minimally symptomatic bone metastases. Regulatory and reimbursement issues aside, which systemic treatment would you recommend as second-line therapy?

 Dr Anders	Retreatment with T-DXd
 Dr Brufsky	Retreatment with T-DXd
 Dr Krop	Retreatment with T-DXd
 Dr Mahtani	Retreatment with T-DXd
 Dr Meisel	Look for ESR1 mutation, consider switching from palbociclib/AI to abemaciclib/imlunestrant and continuing HP if tolerable/possible
 Dr Modi	Retreatment with T-DXd
 Dr O'Shaughnessy	Retreatment with T-DXd
 Dr Rimawi	Retreatment with T-DXd

AI = aromatase inhibitor; HP = trastuzumab/pertuzumab

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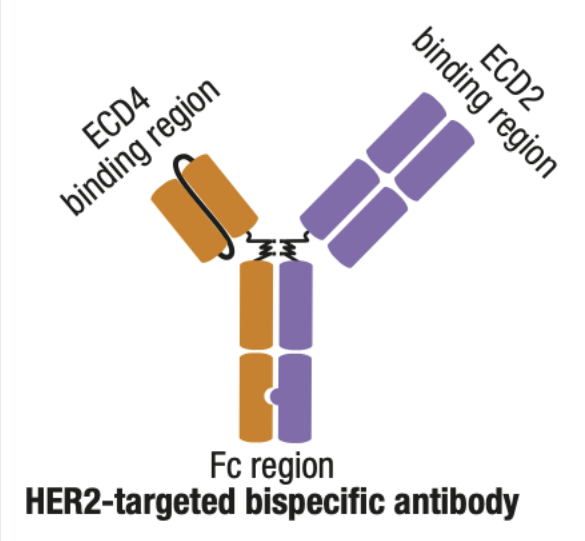
Module 6: Clinician Survey Results

Module 7: Novel Investigational Strategies for HER2-Positive BC

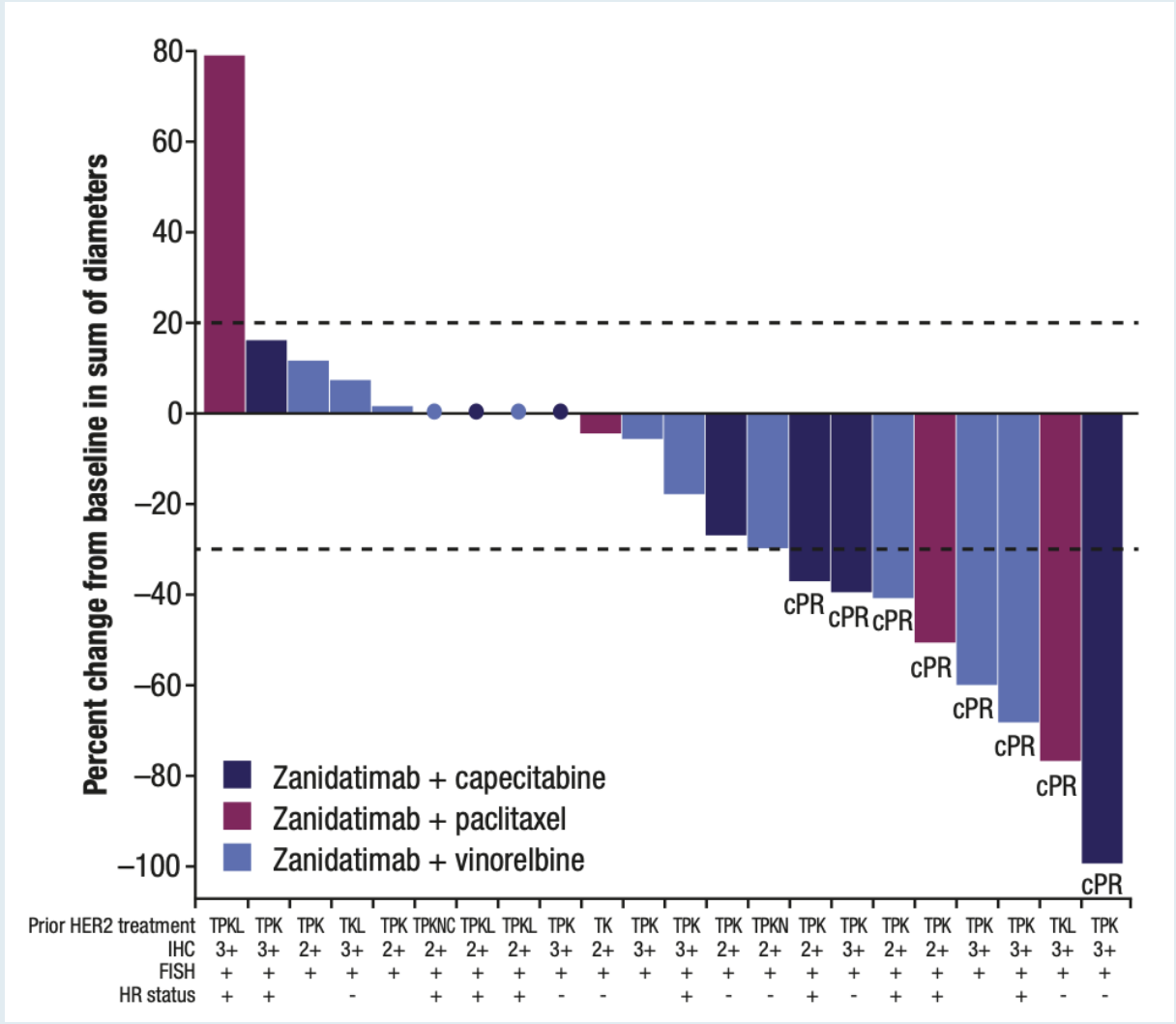
Module 8: Clinician Survey Results

RTP RESEARCH TO PRACTICE

Phase I Study of Zanidatamab/Chemotherapy for Relapsed/Refractory HER2-Positive mBC

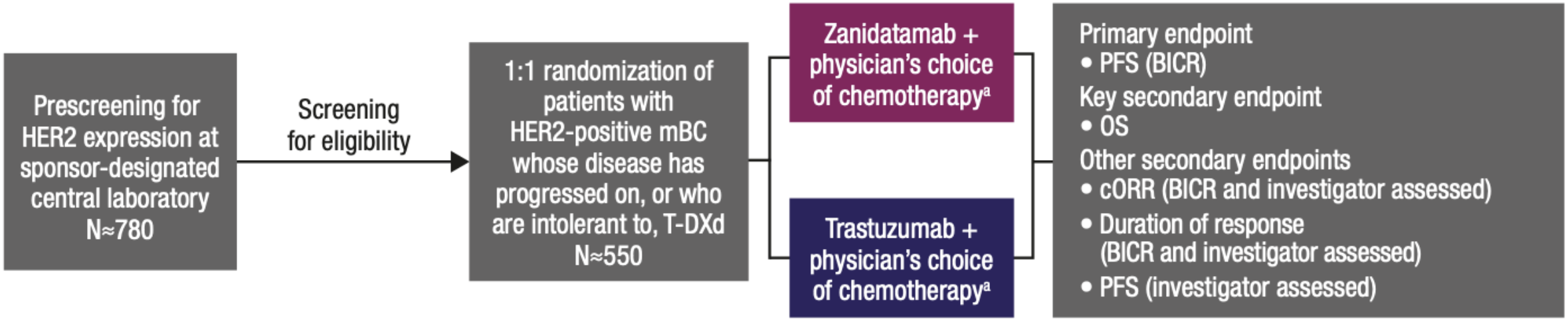


Disease Response Endpoint	n=22
cORR, % (95% CI)	36.4 (13.9, 54.9)
Duration of response, months (range)	NA (1.6-22.1+)
mPFS, months (95% CI)	7.3 (3.6, NE)



Bedard PL et al. SABCS 2021;Abstract P2-13-07. Tolaney SM et al. AACR 2025;Abstract CT256.

EmpowHER-303: A Phase III Study of Zanidatamab/Chemotherapy versus Trastuzumab/Chemotherapy for HER2-Positive mBC That Progressed on T-DXd



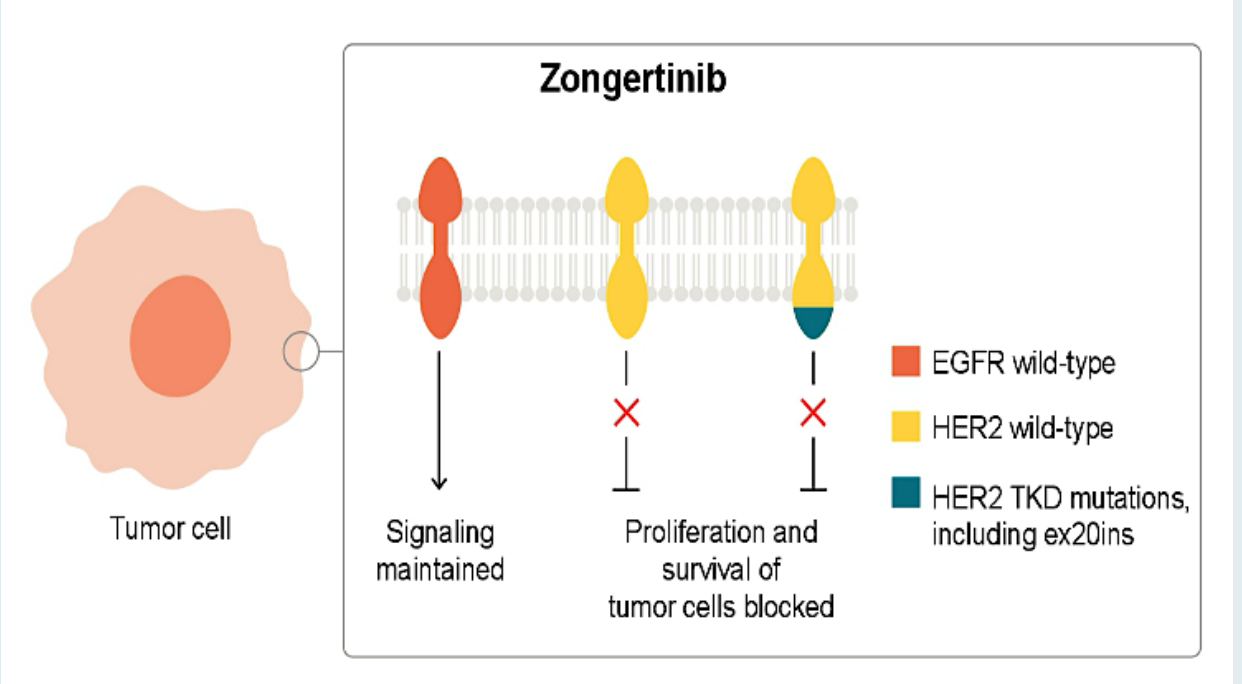
Prescreening and HER2 testing to be done within 6 months of randomization

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

[a]If a patient received and whose disease progressed on a prior line of therapy with either an eribulin-, vinorelbine-, gemcitabine-, or capecitabine-containing regimen in the metastatic setting for the treatment of HER2-positive breast cancer, the patient may not receive the same chemotherapy combination with trastuzumab or zanidatamab in this study.

Tolaney SM et al. AACR 2025;Abstract CT256.

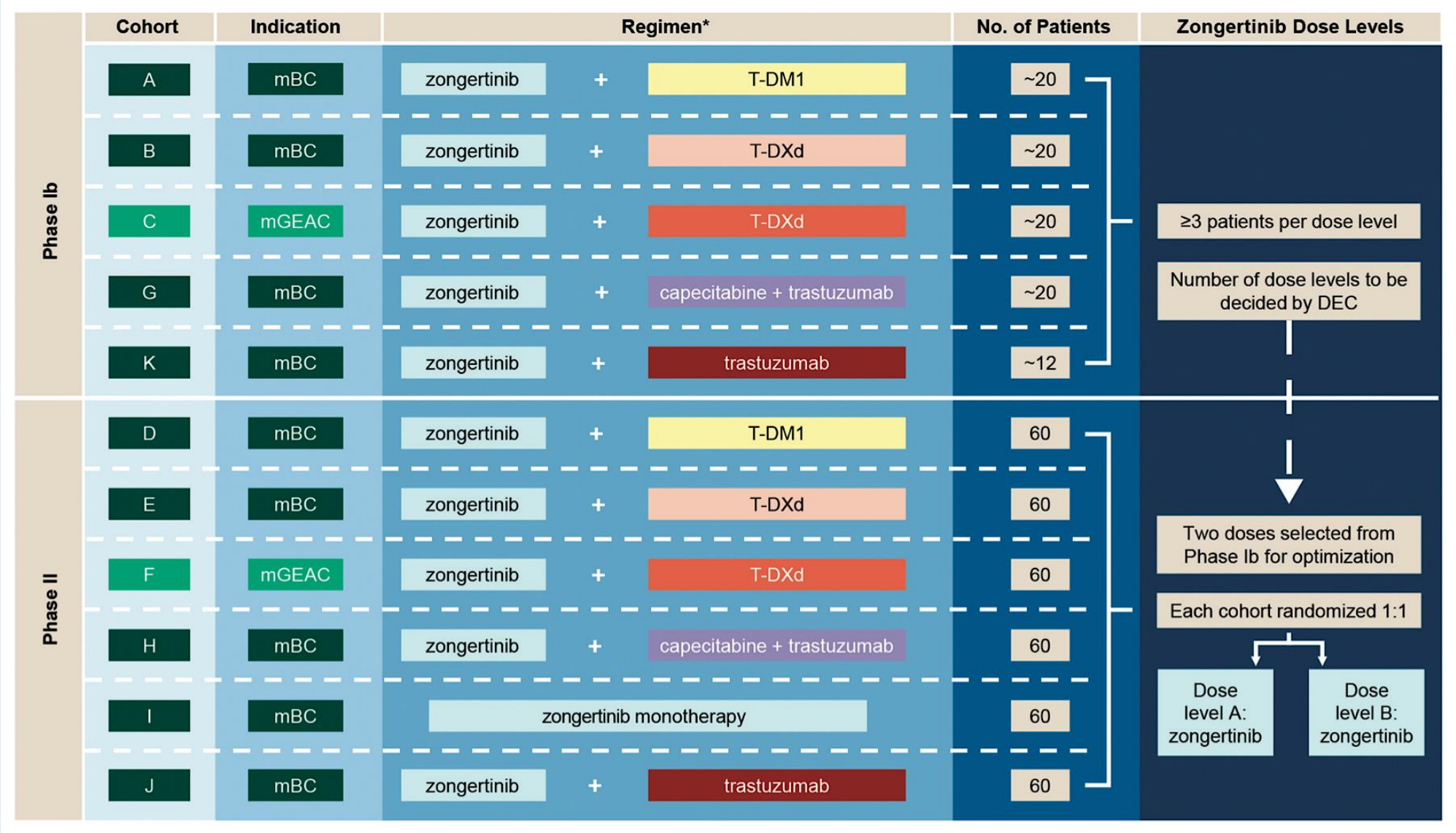
Zongertinib: A HER2 Tyrosine Kinase Domain (TKD) Inhibitor



FDA grants accelerated approval to zongertinib for unresectable or metastatic non-squamous non-small cell lung cancer

Nakayama I et al. Gastrointestinal Cancers Symposium 2025;Abstract TPS509.

Beamion BCGC-1: A Phase Ib/II Study of Zongertinib for Advanced HER2-Positive Breast or Gastroesophageal Cancers



Hurvitz S et al. *Future Oncol* 2025;21(26):3385-93.

DEC = dose escalation commitee

RTP RESEARCH TO PRACTICE

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RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, would you offer T-DXd to a patient with mBC that is HER2-negative by IHC but has a HER2 TKD mutation?

 Dr Anders	Yes
 Dr Brufsky	Yes
 Dr Krop	Yes
 Dr Mahtani	Yes
 Dr Meisel	Yes
 Dr Modi	Yes
 Dr O'Shaughnessy	Yes
 Dr Rimawi	Yes

IHC = immunohistochemistry

Regulatory and reimbursement issues aside, what other HER2-targeted therapies (eg, neratinib, HER2 TKIs approved for lung cancer, such as zongertinib and sevabertinib) would you offer to a patient with mBC that is HER2-negative by IHC but has a HER2 TKD mutation?

 Dr Anders	Neratinib, zongertinib or IAM1363
 Dr Brufsky	Neratinib
 Dr Krop	Neratinib, tucatinib or zongertinib
 Dr Mahtani	Tucatinib, neratinib, zongertinib or sevabertinib
 Dr Meisel	All would be reasonable — it would depend on what other options the patient had at their disposal
 Dr Modi	Any one of the TKIs: neratinib, sevabertinib or zongertinib
 Dr O'Shaughnessy	Tucatinib, neratinib or zongertinib
 Dr Rimawi	Neratinib mostly since it has data in breast cancer but would also consider other TKIs like zongertinib and sevabertinib

TKIs = tyrosine kinase inhibitors

Questions?