CASES FROM THE COMMUNITY
Investigators Discuss the Optimal Management of HER2-Positive Breast Cancer

Part 2 of a 3-Part CME Satellite Symposium Series

Wednesday, December 10, 2025
7:00 PM – 9:00 PM CT

Faculty

Professor Giuseppe Curigliano, MD, PhD
Nadia Harbeck, MD, PhD
Ian E Krop, MD, PhD
Nancy U Lin, MD
Joyce O'Shaughnessy, MD

Moderator

Neil Love, MD

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Faculty

Professor Giuseppe Curigliano, MD, PhD
Clinical Director
Division of Early Drug Development for Innovative Therapy
Co-Chair, Cancer Experimental Therapeutics Program
Department of Oncology and Hemato-Oncology
University of Milano
European Institute of Oncology
Milano, Italy

Nadia Harbeck, MD, PhD
Breast Center Director
Department of Obstetrics and Gynecology and Comprehensive Cancer Center Munich
LMU University Hospital
Munich, Germany

Ian E Krop, MD, PhD
Professor of Internal Medicine
Associate Cancer Center Director for Clinical Research
Yale Cancer Center
New Haven, Connecticut

Nancy U Lin, MD
Associate Chief, Division of Breast Oncology
Dana-Farber Cancer Institute
Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Joyce O'Shaughnessy, MD
Celebrating Women Chair in Breast Cancer Research
Baylor University Medical Center
Chair, Breast Disease Committee
Sarah Cannon Research Institute
Dallas, Texas

Moderator

Neil Love, MD
Research To Practice
Miami, Florida

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Prof Curigliano — Disclosures
Faculty

Advisory Committees, Consulting Agreements and Speakers Bureaus	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Gilead Sciences Inc, Lilly, Menarini Group, Novartis, Pfizer Inc
Data and Safety Monitoring Boards/Committees	Roche Laboratories Inc

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Prof Harbeck — Disclosures
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Dr Krop — Disclosures
Faculty

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Contracted Research	Pfizer Inc
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Dr Lin — Disclosures
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Contracted Research	AstraZeneca Pharmaceuticals LP, Genentech, a member of the Roche Group, Merck, Olema Oncology, Pfizer Inc, Seagen Inc, Zion Pharmaceuticals
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Dr O'Shaughnessy — Disclosures
Faculty

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Dr Love — Disclosures

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CASES FROM THE COMMUNITY
Investigators Discuss the Optimal Role of Endocrine-Based and Other Strategies in the Management of HR-Positive Breast Cancer

Part 3 of a 3-Part CME Satellite Symposium Series

Thursday, December 11, 2025

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Angela DeMichele, MD, MSCE
Komal Jhaveri, MD, FACP, FASCO
Erica Mayer, MD, MPH, FASCO
Hope S Rugo, MD
Seth Wander, MD, PhD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Cases from the Community: Investigators Discuss Available Research Guiding the Management of Relapsed/Refractory Multiple Myeloma — What Happened at ASH 2025?

A CME/MOC-Accredited Live Webinar

Monday, December 15, 2025

5:00 PM – 6:00 PM ET

Faculty

Sagar Lonial, MD, FACP, FASCO

María-Victoria Mateos, MD, PhD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Practical Perspectives on the Current and Future Management of Immune Thrombocytopenia — What Happened at ASH 2025?

A CME/MOC-Accredited Live Webinar

Tuesday, December 16, 2025

5:00 PM – 6:30 PM ET

Faculty

Hanny Al-Samkari, MD
Cindy Neunert, MD, MSCS
Francesco Zaja, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Practical Perspectives on the Current Role of Bispecific Antibodies in the Management of Lymphoma — What Happened at ASH 2025?

A CME/MOC-Accredited Live Webinar

Wednesday, December 17, 2025
5:00 PM – 6:00 PM ET

Faculty

Michael Dickinson, MD
Laurie H Sehn, MD, MPH

Moderator

Neil Love, MD

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Expert Second Opinion: Investigators Discuss the Optimal Management of Gastrointestinal Cancers

A CME Symposium Series Held Adjunct to the
2026 ASCO® Gastrointestinal Cancers Symposium

HER2-Positive Gastrointestinal Cancers

Thursday, January 8, 2026

7:15 PM – 8:45 PM PT
(10:15 PM – 11:45 PM ET)

Advanced Gastroesophageal Cancers

Friday, January 9, 2026

6:00 PM – 8:00 PM PT
(9:00 PM – 11:00 PM ET)

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Optimizing Therapy for Patients with Hormone Receptor-Positive Localized Breast Cancer

A CME/MOC-Accredited Interactive Grand Rounds Series

Through April 2026

Faculty

Adam M Brufsky, MD, PhD
Kevin Kalinsky, MD, MS, FASCO
Reshma L Mahtani, DO
Komal Jhaveri, MD, FACP, FASCO
Erica Mayer, MD, MPH, FASCO
Hope S Rugo, MD

Additional faculty to be announced.

Host a 1-hour session at your institution:
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CLL and DLBCL series also available.

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Save The Date

Fifth Annual
National General Medical Oncology Summit

A Multitumor CME/MOC-, NCPD- and ACPE-Accredited Educational Conference Developed in Partnership with Florida Cancer Specialists & Research Institute

Friday to Sunday, April 24 to 26, 2026

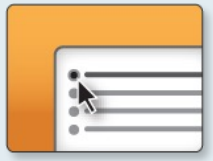
The Ritz-Carlton Orlando, Grande Lakes | Orlando, Florida

Moderated by Neil Love, MD

Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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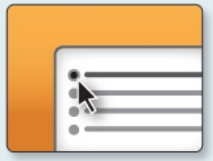
Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get CME Credit: A credit link will be provided in the chat room at the conclusion of the program.

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based program.
  An email will be sent to all attendees when the activity is available.
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RTP Playlist with Neil Love, MD

BREAST CANCER

Dr Hope Rugo: Interview (28 min)

SMALL CELL LUNG CANCER

Drs Stephen Liu and Charles Rudin: Cases (58 min)

GASTROESOPHAGEAL CANCER

Drs Geoffrey Ku and Zev Wainberg: Cases (61 min)

PROSTATE CANCER

Drs Emmanuel Antonarakis and Karim Fizazi: Year in Review (60 min)

ENDOMETRIAL AND OVARIAN CANCER

Dr Shannon Westin: Interview (52 min)

NEUROENDOCRINE TUMORS

Drs Simron Singh and Jonathan Strosberg: Meeting (50 min)

NON-HODGKIN LYMPHOMA

Drs Jeremy Abramson, Joshua Brody, Christopher Flowers, Ann LaCasce and Tycel Phillips: Meeting, cases (59 min)

CHRONIC LYMPHOCYTIC LEUKEMIA

Drs Jennifer Brown and Paolo Ghia: Year in Review (59 min)

ACUTE MYELOID LEUKEMIA

Dr Jorge Cortes: Interview (43 min)

MULTIPLE MYELOMA

Drs Natalie Callander and Sagar Lonial: Patient videos (59 min)

IMMUNE THROMBOCYTOPENIA

Drs Hanny Al-Samkari, James Bussel and Nichola Cooper: Think Tank (117 min)

OCULAR TOXICITES IN ONCOLOGY

Dr Neel Pasricha: Interview (54 min)

Feedback (Please!)
DrNeilLove@ResearchToPractice.com

RTP Playlist with Neil Love, MD

Webinar for patients and families on relapsed multiple myeloma with Drs Natalie Callander and Sagar Lonial.

Relapsed Multiple Myeloma: Where We Were, Where We Are (4 min)

Common Questions from the Beginning (5 min)

Choosing Treatment Options (4 min)

Clinical Research Trials (6 min)

Neuropathy (5 min)

Chimeric Antigen Receptor (CAR) T-Cell Therapy (6 min)

Bispecific Antibodies (8 min)

Antibody-Drug Conjugates: Belantamab Mafadotin (8 min)

Interacting with the Oncology Team (5 min)

Other Questions (4 min)

Recording of Entire Webinar (62 min)

Feedback (Please!)
DrNeilLove@ResearchToPractice.com

ASH and SABCS RTP Video Participants

ASH and SABCS RTP Participating Faculty

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Agenda

Module 1: Considerations in the Care of Patients with Localized HER2-Positive Breast Cancer — Prof Harbeck

Module 2: Previously Untreated HER2-Positive Metastatic Breast Cancer (mBC) — Prof Curigliano

Module 3: Optimal Management of Brain Metastases in Patients with HER2-Positive Breast Cancer — Dr Lin

Module 4: Selection and Sequencing of Therapy for Relapsed/Refractory (R/R) HER2-Positive mBC in the Absence of CNS Involvement — Dr Krop

Module 5: Tolerability Considerations with HER2-Targeted Therapies — Dr O'Shaughnessy

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Contributing General Medical Oncologists

Laila Agrawal, MD
Norton Cancer Institute
Louisville, Kentucky

Kimberly Ku, MD
Illinois CancerCare
Bloomington, Illinois

Alan B Astrow, MD
Weill Cornell Medicine
Brooklyn, New York

Zanetta S Lamar, MD
Florida Oncology and Hematology
Naples, Florida

Justin Favaro, MD, PhD
Oncology Specialists of Charlotte
Charlotte, North Carolina

Yanjun Ma, MD, PhD
Tennessee Oncology
Murfreesboro, Tennessee

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Contributing General Medical Oncologists

Erik Rupard, MD
Penn State Cancer Institute
Reading, Pennsylvania

Richard Zelkowitz, MD
Hartford HealthCare Cancer Institute
Bridgeport, Connecticut

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Agenda

Module 1: Considerations in the Care of Patients with Localized HER2-Positive Breast Cancer — Prof Harbeck

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Module 5: Tolerability Considerations with HER2-Targeted Therapies — Dr O'Shaughnessy

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LMU KLINIKUM
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Considerations in the care of patients

with localized HER2-positive breast cancer

LMU Breast Center | 10.12.25 | Prof. Nadia Harbeck, MD

Brustzentrum im Klinikum der Universität München

CCC MÜNCHEN COMPREHENSIVE CANCER CENTER LMU KLINIKUM

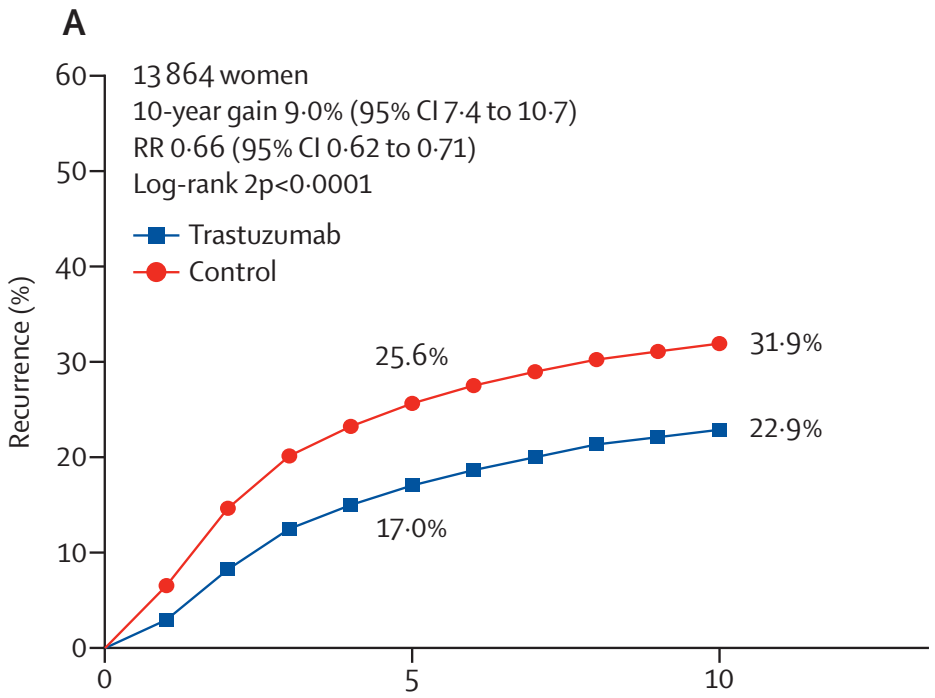
TUMORZENTRUM MÜNCHEN | TZM

Early HER2+ breast cancer

Trastuzumab reduces recurrence and mortality by a third[1]

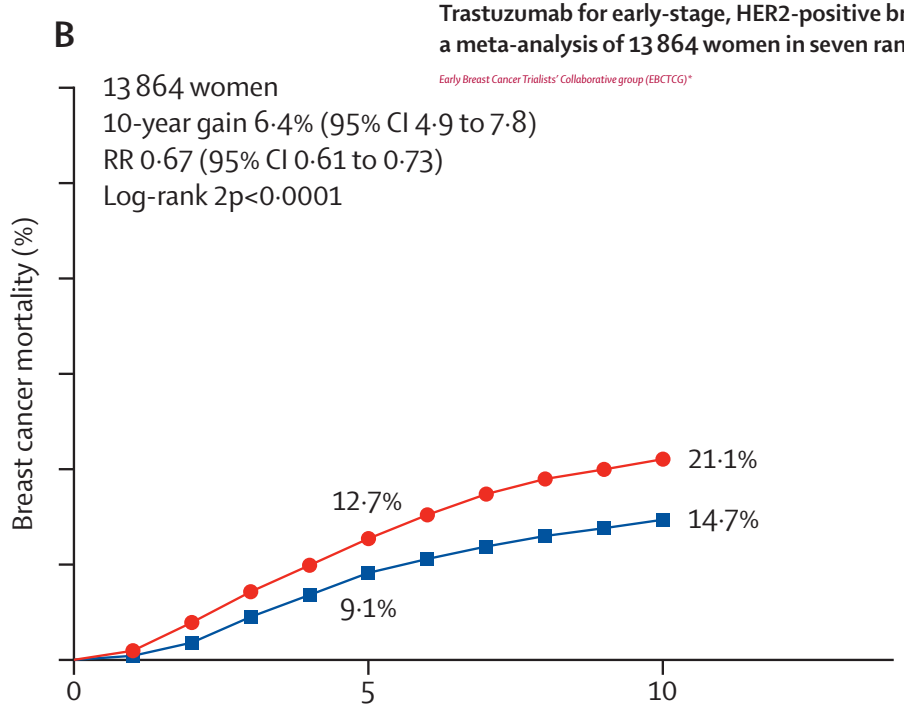
Trastuzumab for early-stage, HER2-positive breast cancer: a meta-analysis of 13 864 women in seven randomised trials

*Early Breast Cancer Trialists' Collaborative group (EBCTCG)**



Recurrence rates per year (% [events/woman-years]) and log-rank analyses

	Years 0–4	Years 5–9	Years ≥10
Trastuzumab	4·10 (1469/35 853)	1·53 (422/27 648)	0·95 (75/7858)
Control	6·24 (1385/22 180)	1·87 (291/15 601)	1·12 (43/3835)
Rate ratio (95% CI)	0·62 (0·58–0·66)	0·83 (0·72–0·95)	0·91 (0·63–1·31)
from (O–E)/V	–284·0/591·3	–29·6/154·9	–2·5/25·3



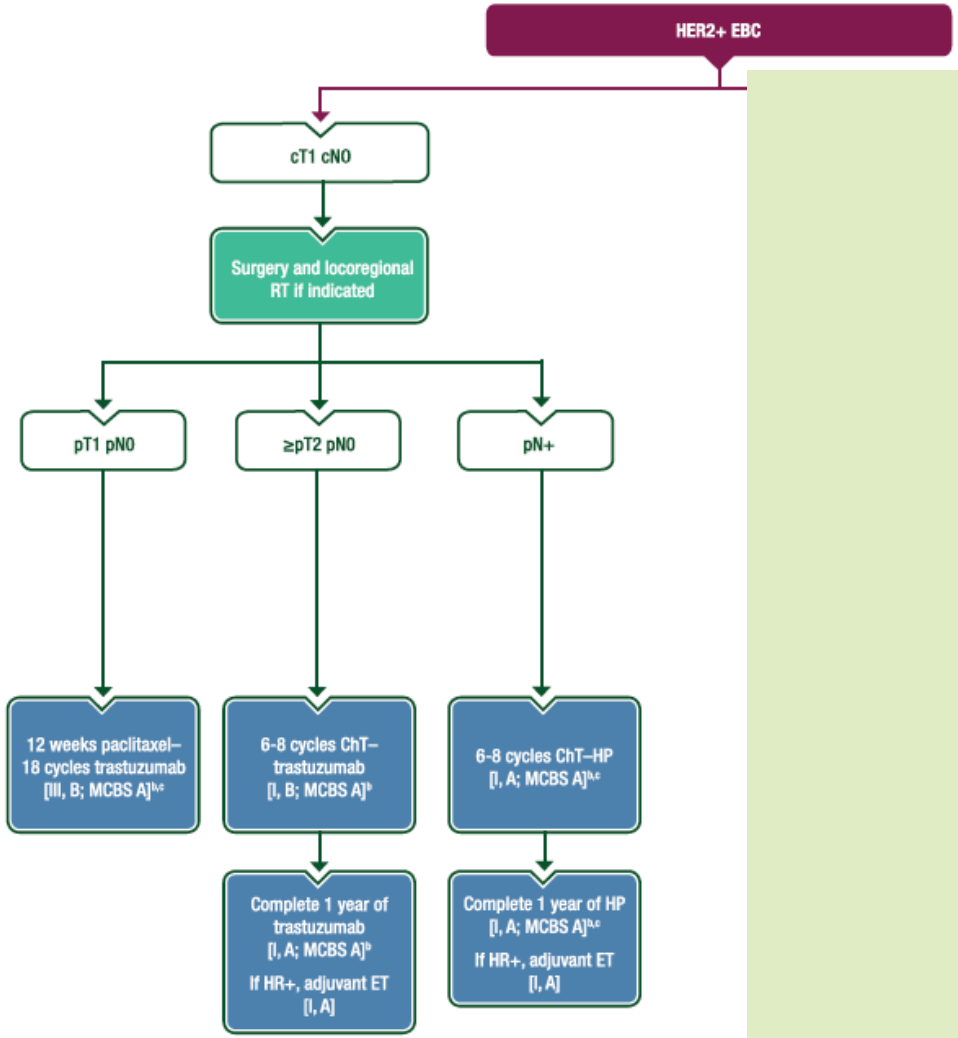
Death rates per year (%; 95% CI) and log-rank analyses

Years 0–4	Years 5–9	Years ≥10
1·99 (1·85–2·13)	1·38 (1·25–1·51)	0·75 (0·57–0·93)
2·73 (2·53–2·94)	2·18 (1·97–2·40)	1·15 (0·83–1·46)
0·70 (0·63–0·76)	0·63 (0·56–0·70)	0·64 (0·47–0·88)
–113·6/312·9	–84·2/179·8	–10·9/24·6

[1]EBCTCG, Lancet Oncol 2021

ESMO *early* breast cancer guidelines

HER2+ [1]



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

S. Loibl[1,2], F. André[3], T. Bachelot[4], C. H. Barrios[5], J. Bergh[6], H. J. Burstein[7], M. J. Cardoso[8,9], L. A. Carey[10], S. Dawood[11], L. Del Mastro[12,13], C. Denkert[14], E. M. Fallenberg[15], P. A. Francis[16], H. Gamal-Eldin[17], K. Gelmon[18], C. E. Geyer[19], M. Gnant[20], V. Guarneri[21,22], S. Gupta[23], S. B. Kim[24], D. Krug[25], M. Martin[26], I. Meattini[27,28], M. Morrow[29], W. Janni[30], S. Paluch-Shimon[31], A. Partridge[7], P. Poortmans[32,33], L. Pusztai[34], M. M. Regan[35], J. Sparano[36], T. Spanic[37], S. Swain[38], S. Tjulandin[39], M. Toi[40], D. Trapani[7], A. Tutt[41,42], B. Xu[43], G. Curigliano[44,45] & N. Harbeck[46], on behalf of the ESMO Guidelines Committee*

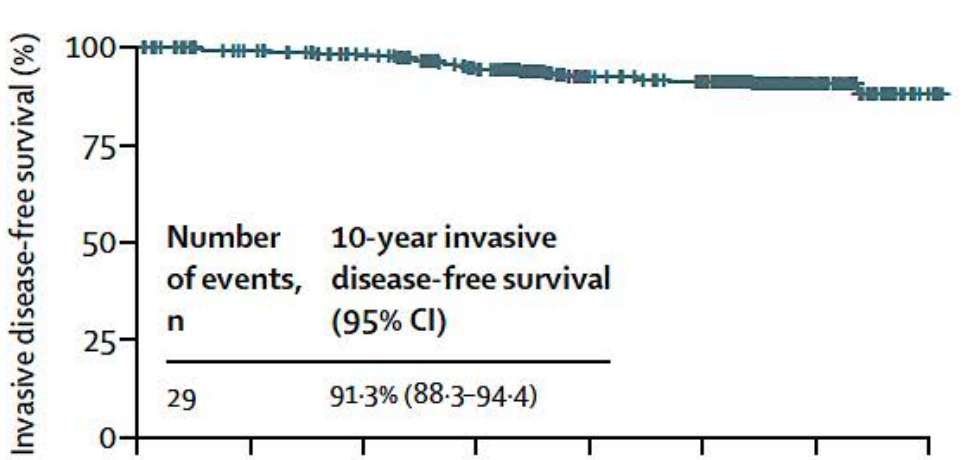
[1]Loibl et al, Annals Oncol 2024; esmo.org

Low-risk HER2+ *early* breast cancer

APT trial[1] – 10-year follow-up

T1mi	10 (2·5%)	1 (0·4%)	3 (1·1%)	1 (0·4%)
T1a	68 (16·7%)	29 (10·4%)	38 (13·4%)	32 (11·3%)
T1b	123 (30·3%)	81 (29·1%)	83 (29·2%)	88 (31·0%)
T1c	169 (41·6%)	137 (49·3%)	132 (46·5%)	132 (46·5%)
T2	36 (8·9%)	30 (10·8%)	28 (9·9%)	31 (10·9%)

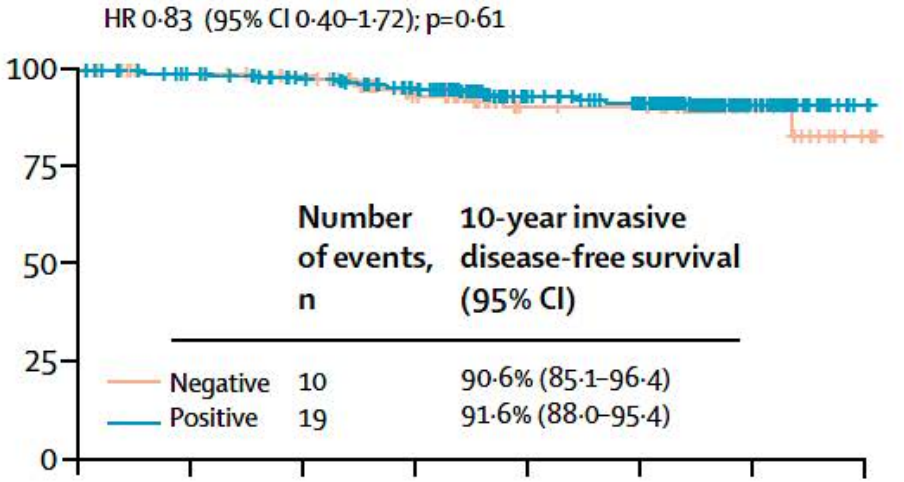
iDFS (overall cohort)



Number at risk (number censored)

	406 (0)	385 (17)	363 (35)	321 (64)	234 (146)	216 (161)	52 (324)	5 (370)

iDFS according to HR status

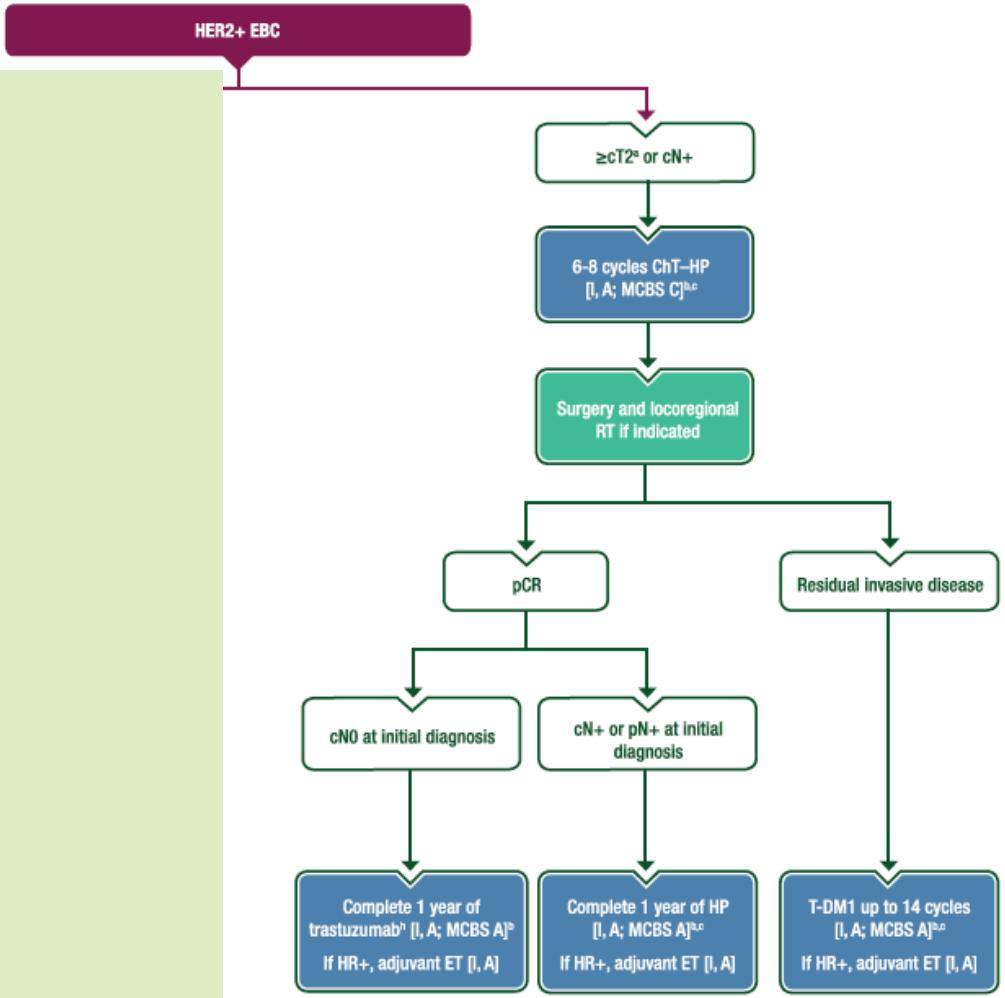


Negative	134 (0)	126 (7)	119 (13)	97 (29)	66 (58)	65 (59)	16 (108)	3 (120)
Positive	272 (0)	259 (10)	244 (22)	224 (35)	168 (88)	151 (102)	36 (216)	2 (250)

[1] Tolaney et al, Lancet Oncology 2023

ESMO *early* breast cancer guidelines

HER2+ [1]



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[1]Loibl et al, Annals Oncol 2024; esmo.org

HER2+ *early* breast cancer

Neoadjuvant chemotherapy: Anthracyclines vs. A-free regimens?[1]

Efficacy of anthracycline-free vs. anthracycline-containing regimens in HER2+ EBC.

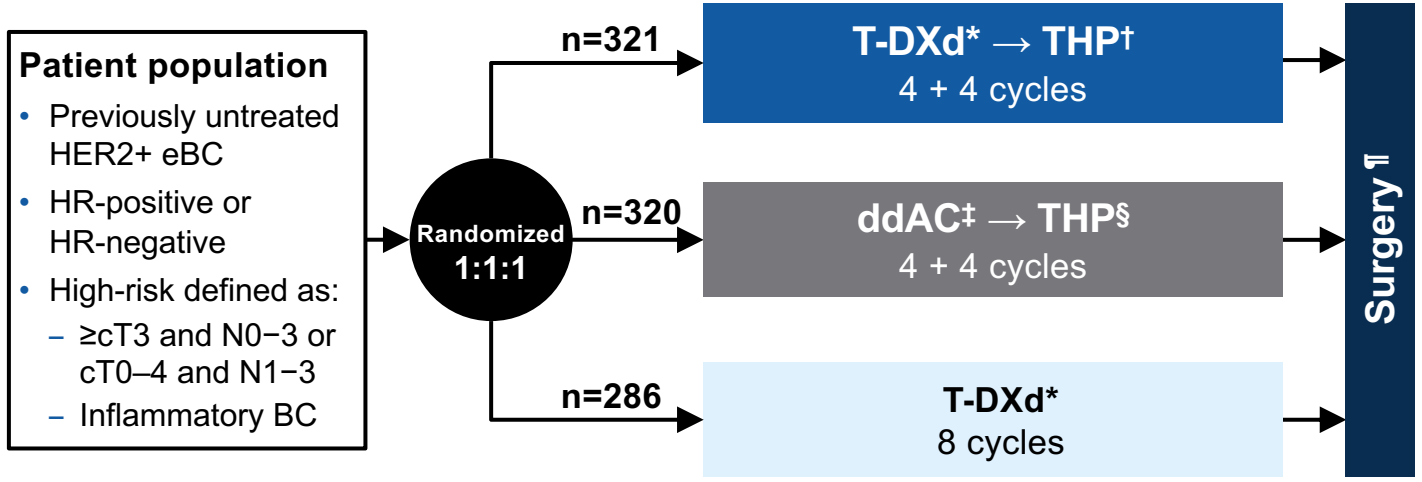
Study	patients	w/o anthracylines	with anthracyclines	w/o anthracylines	with anthracyclines
		pCR	pCR	Survival	Survival
TRYPHAENA [15, 18]	225	ypT0/is: **66.2%** (TCbHP)	ypT0/is: **61.6%** (FEC-HP - > pac-HP) **57.3%** (FEC –> pac-HP)	3y DFS **90%** (T HP)	3y DFS: **87%** (FEC-HP - > T-HP); **88%** (FEC - > T-HP)
TRAIN-2 [16,17]	438	ypT0/is ypN0: **68%** (pacCb-HP)	ypT0/is ypN0: **67%** (FEC-HP - > pacCb-HP)	3y EFS **93.5%** (pacCb - > HP)	3y EFS **92.7%** (FEC-HP - > pacCb-HP)
BCIRG 006 [19]	3222	n.a.	n.a.	5y DFS **81%**; 5y OS **91%** (TCbH)	5y DFS **84%**; 5y OS **92%** (AC - > TH)

FEC = 5-Fluorouracil-Epirubicin-cyclophosphamide; pac = Paclitaxel; T = Docetaxel; Cb = Carboplatin; H = trastuzumab; P = pertuzumab n.a. = not applicable.

[1] Harbeck N, Breast 2022

DESTINY-Breast11 study design

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



Recommended post-neoadjuvant treatment per study protocol‖

pCR: radiotherapy and concomitant trastuzumab ± pertuzumab for up to 1 year

No pCR: radiotherapy and T-DM1 for up to 14 cycles

HR-positive: endocrine therapy

Data cutoff: March 12, 2025

Primary endpoint

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

Secondary endpoints

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

Additional outcome measures

- Residual cancer burden (RCB)

Stratification factors

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

The T-DXd alone arm closed on March 13 2024, following Independent Data Monitoring Committee recommendation
The reasons were multifactorial, including a lower pCR rate, low likelihood that T-DXd alone would be superior to ddAC-THP, and the timing of surgery

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

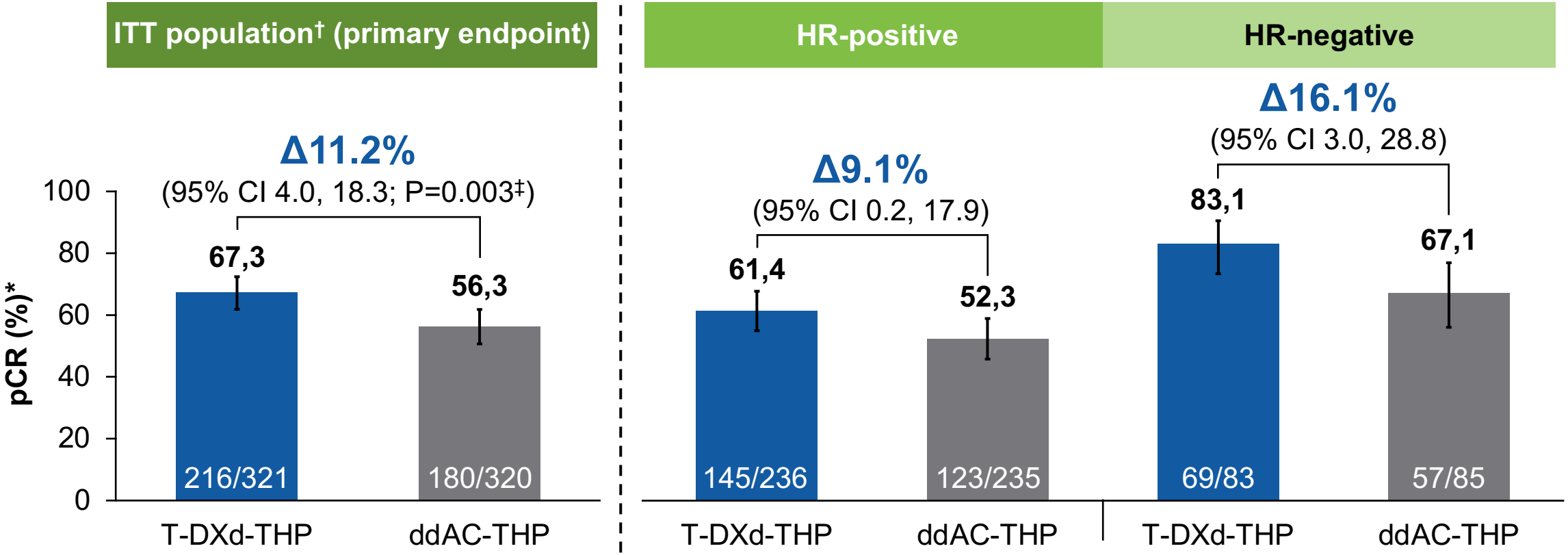
Nadia Harbeck, MD
Abstract 291O

Patient demographics and key baseline characteristics

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

*Brazil, Bulgaria, Peru, Poland, Russia, and Saudi Arabia; †not reported for four patients (1.2%), nine patients (2.8%) and five patients (1.7%) in the T-DXd-THP, ddAC-THP, and T-DXd alone arms, respectively; ‡centrally confirmed. Not categorized for one patient (0.3%) in the T-DXd-THP arm and missing for one patient (0.3%) in the ddAC-THP arm; §the proportion of patients with HR-negative disease was capped at 30% to reflect natural prevalence. Missing for two patients (0.6%) and one patient (0.3%) in the T-DXd-THP and T-DXd alone arms, respectively; ¶ER and/or
PR-positive per electronic case report form data; ‖unknown in eight patients (2.5%), four patients (1.3%), and 12 patients (4.2%) in the T-DXd-THP, ddAC-THP, and T-DXd alone arms, respectively

pCR (ypT0/is ypN0): primary endpoint



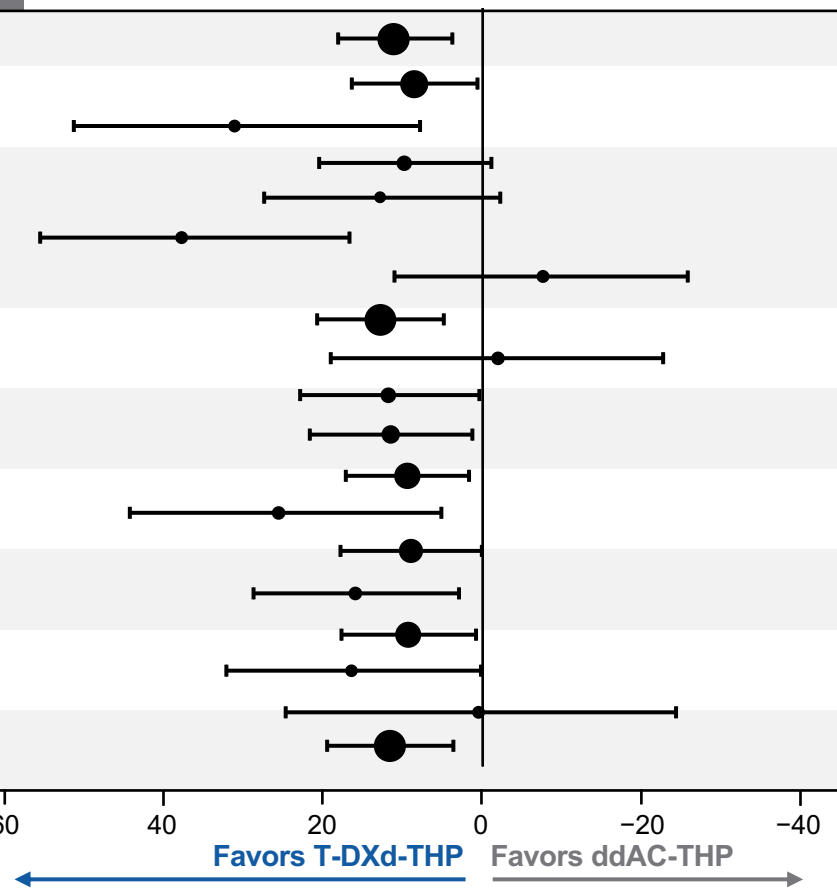
Neoadjuvant T-DXd-THP demonstrated a statistically significant and clinically meaningful improvement in pCR vs ddAC-THP

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

pCR (ypT0/is ypN0) by subgroups

		pCR rate, % (n/N) T-DXd-THP (n=321)	ddAC-THP (n=320)	ΔpCR, % (95% CI)
All patients		67.3 (216/321)	56.3 (180/320)	**11.2** (4.0, 18.3)
Age at baseline	<65 years	66.7 (188/282)	58.0 (167/288)	**8.7** (0.7, 16.5)
	≥65 years	71.8 (28/39)	40.6 (13/32)	**31.2** (8.0, 51.4)
Geographical region	Asia	66.5 (101/152)	56.6 (86/152)	**9.9** (−1.1, 20.6)
	Western Europe	75.4 (52/69)	62.3 (48/77)	**13.0** (−2.2, 27.5)
	North America	74.4 (32/43)	36.6 (15/41)	**37.8** (16.8, 55.7)
	Rest of world*	54.4 (31/57)	62.0 (31/50)	**−7.6** (−25.7, 11.2)
Eastern Cooperative Oncology Group performance status score	0	68.7 (191/278)	55.7 (156/280)	**13.0** (5.0, 20.9)
	1	58.1 (25/43)	60.0 (24/40)	**−1.9** (−22.6, 19.1)
Menopausal status	Post	68.8 (86/125)	56.9 (87/153)	**11.9** (0.5, 23.0)
	Pre	66.9 (123/184)	55.2 (90/163)	**11.6** (1.4, 21.7)
HER2 status	IHC 3+	71.1 (199/280)	61.5 (174/283)	**9.6** (1.8, 17.3)
	Other	42.5 (17/40)	16.7 (6/36)	**25.8** (5.2, 44.4)
HR status	Positive	61.4 (145/236)	52.3 (123/235)	**9.1** (0.2, 17.9)
	Negative	83.1 (69/83)	67.1 (57/85)	**16.1** (3.0, 28.8)
American Joint Committee on Cancer clinical stage	II–IIIA	65.7 (163/248)	56.4 (146/259)	**9.4** (0.9, 17.7)
	IIIB–IIIC	72.2 (52/72)	55.7 (34/61)	**16.5** (0.1, 32.3)
Nodal status	N0	57.7 (15/26)	57.1 (20/35)	**0.6** (−24.2, 24.8)
	N+	68.3 (196/287)	56.6 (159/281)	**11.7** (3.8, 19.5)



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

Size of circle is proportional to the total sample size in a subgroup. *Brazil, Bulgaria, Peru, Poland, Russia, and Saudi Arabia

Nadia Harbeck, MD

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DESTINY-Breast11

BERLIN 2025 ESMO congress

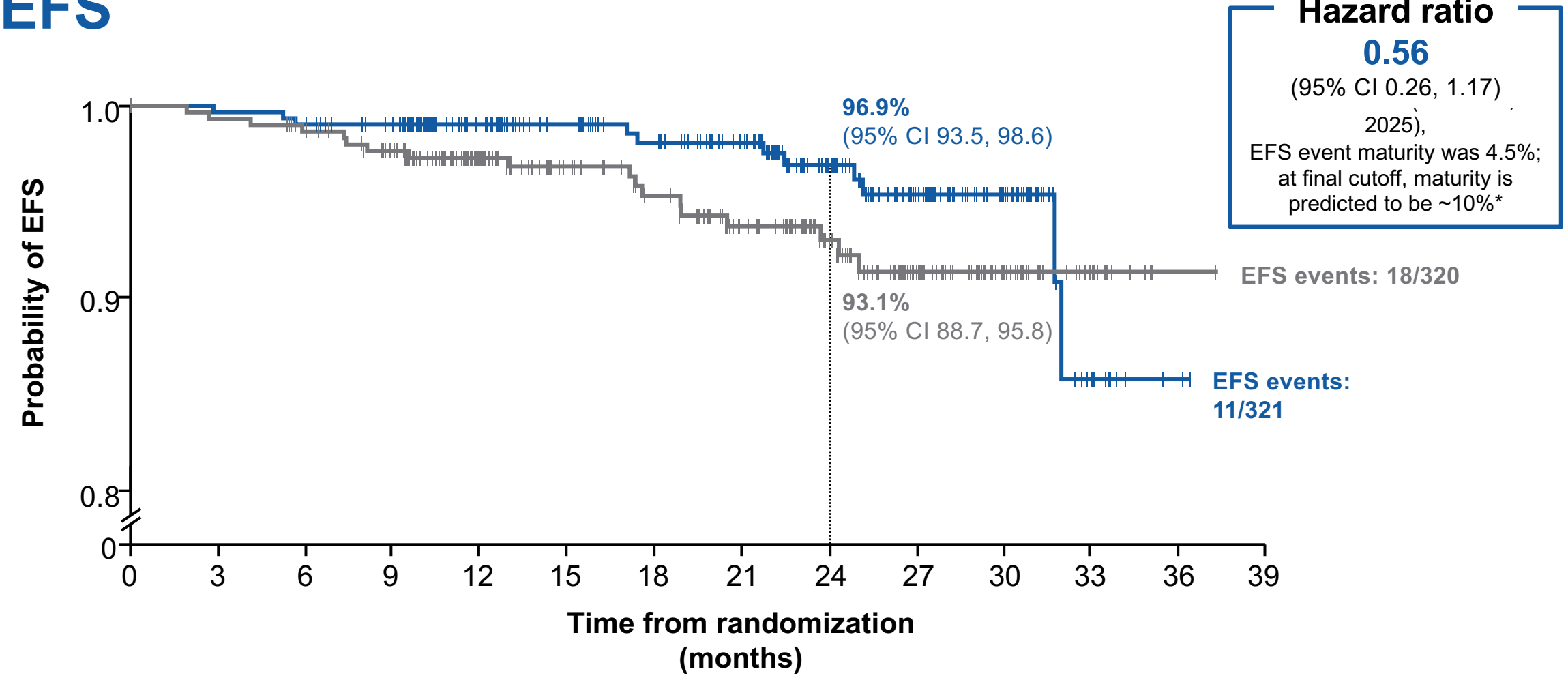
Post-neoadjuvant treatments

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

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

Patients may have had at least one anti-cancer therapy and were counted once per therapy. *By local pCR result; †excludes patients who withdrew consent or did not receive surgery; also excludes treatment given in the metastatic setting

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

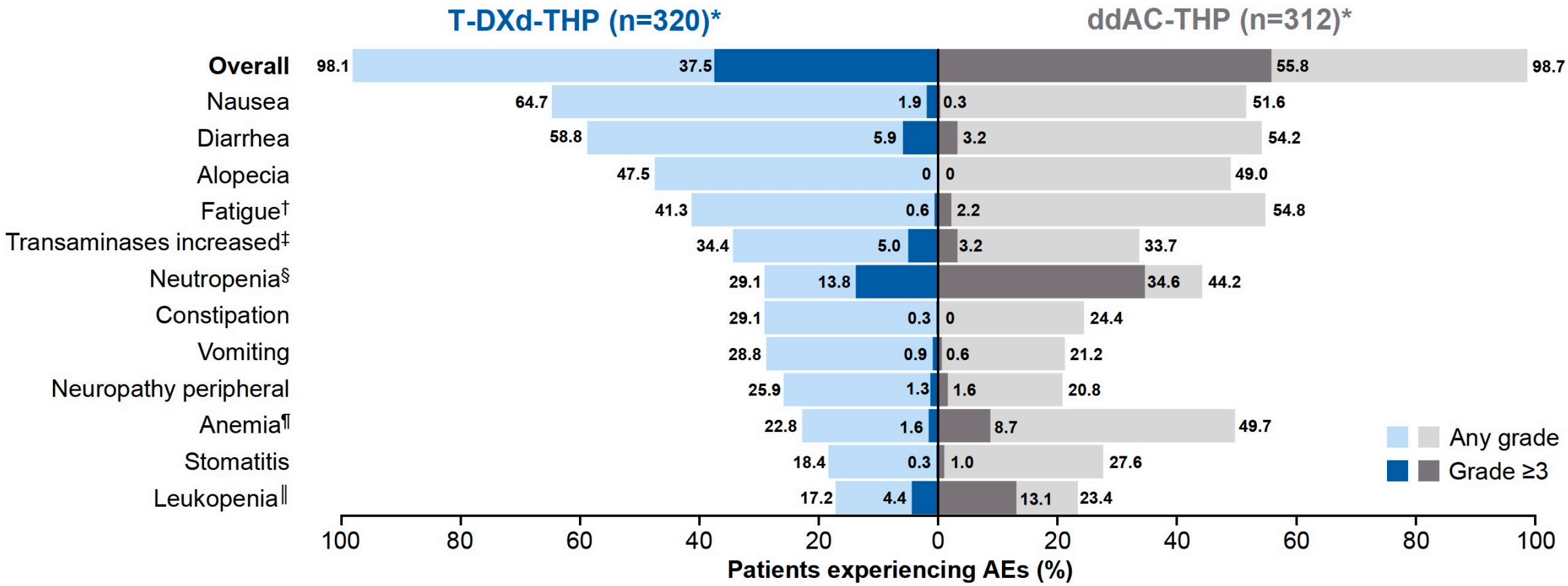
n (%)	T-DXd-THP (n=320)*	ddAC-THP (n=312)*
Any AE	314 (98.1)	308 (98.7)
Grade ≥3	120 (37.5)	174 (55.8)
Any serious AE	34 (10.6)	63 (20.2)
AE leading to any dose reduction	58 (18.1)	60 (19.2)
AE leading to any drug interruption	121 (37.8)	170 (54.5)
AE leading to any treatment discontinuation	45 (14.1)	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)
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

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

TEAEs in at least 20% of patients in either arm



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

*Safety analyses included all patients who received at least one dose of any study treatment; †grouped term: fatigue, asthenia, malaise, and lethargy; ‡grouped term: transaminases increased, aspartate transaminase increased, alanine transaminase increased, gamma-glutamyl transferase increased, liver function test abnormal, hypertransaminasemia, hepatic function abnormal, and liver function test increased; §grouped term: neutrophil count decreased and neutropenia; ¶grouped term: hemoglobin decreased, red blood cell count decreased, and anemia and hematocrit decreased; ‖grouped term: white blood cell count decreased and leukopenia. TEAE, treatment-emergent adverse event

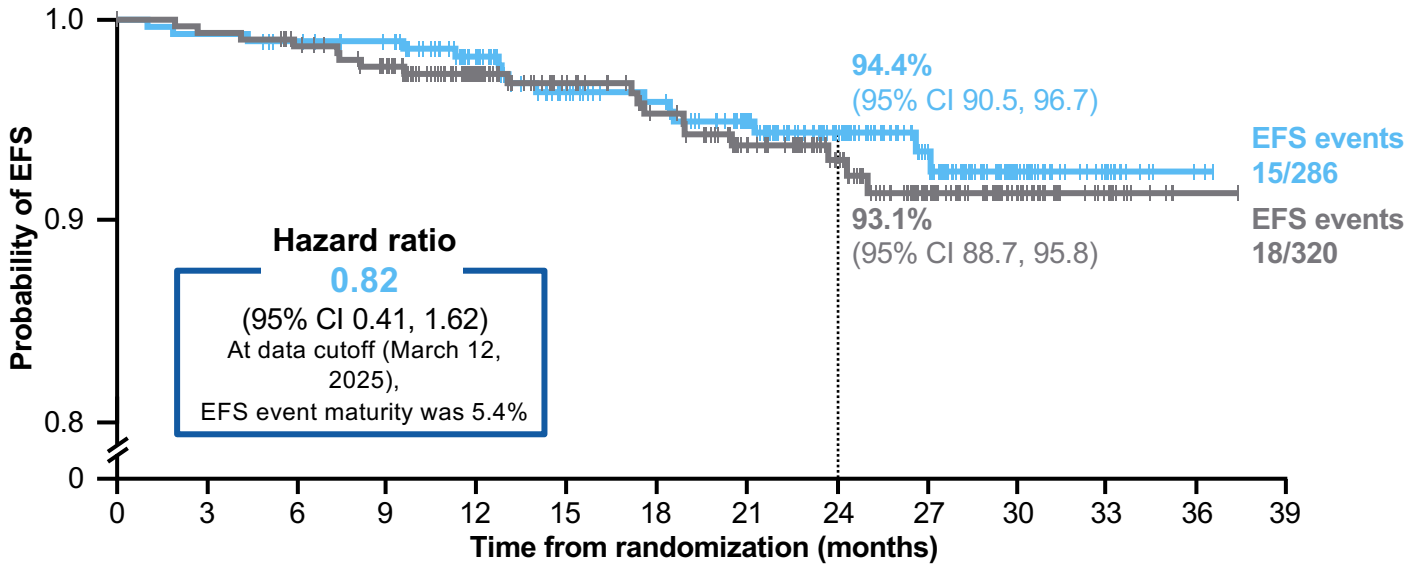
T-DXd alone arm: efficacy summary

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

pCR rate

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

EFS



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

Treatment effects were estimated by the difference in pCR with 95% CIs based on the stratified Miettinen and Nurminen's method, with strata weighting by sample size (ie Mantel–Haenszel weights). Median duration of follow up was 24.9 months (T-DXd) and 23.6 months (ddAC-THP). Analyses are reported in the ITT population. *The reasons were multifactorial, including a lower pCR rate, low likelihood that T-DXd alone would be superior to ddAC-THP, and the timing of surgery; †by blinded central review

T-DXd alone arm: safety summary

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

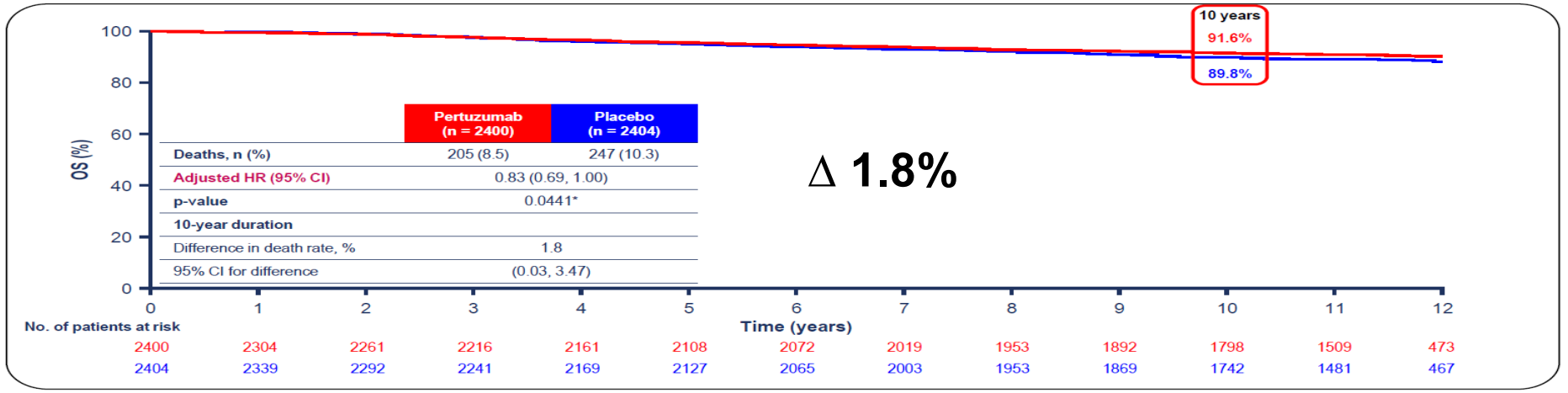
The overall safety profile of T-DXd alone was favorable vs ddAC-THP, with reduced rates of Grade ≥3 AEs, serious AEs, treatment reductions/interruptions, and left ventricular dysfunction

ILD incidence was low and similar in both arms

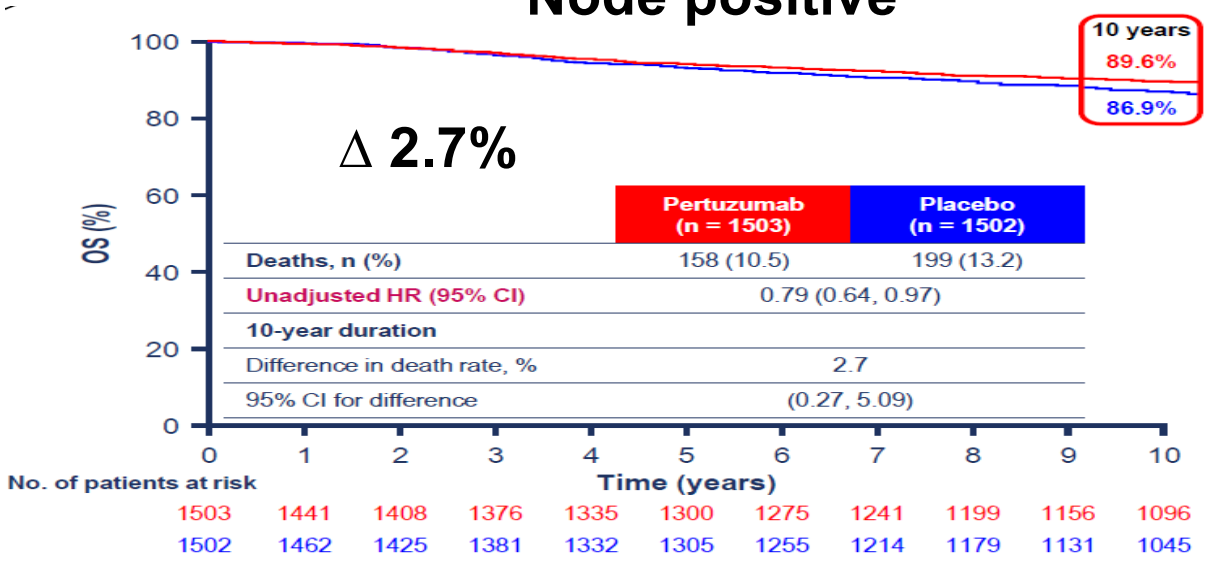
High-resolution computed tomography chest scans were performed every 6 weeks during treatment; if ILD/pneumonitis was suspected while receiving T-DXd, treatment was interrupted and a full investigation completed. Echocardiograms or multigated acquisition scans were performed during screening (<28 days 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 24.0 months (T-DXd) and 21.0 months (ddAC-THP). *Safety analyses included all patients who received at least one dose of any study treatment; †T-DXd alone arm: pulmonary embolism considered by investigator to be unrelated to study treatment (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

Updated results of APHINITY at 11.3 years median follow up (Final OS)

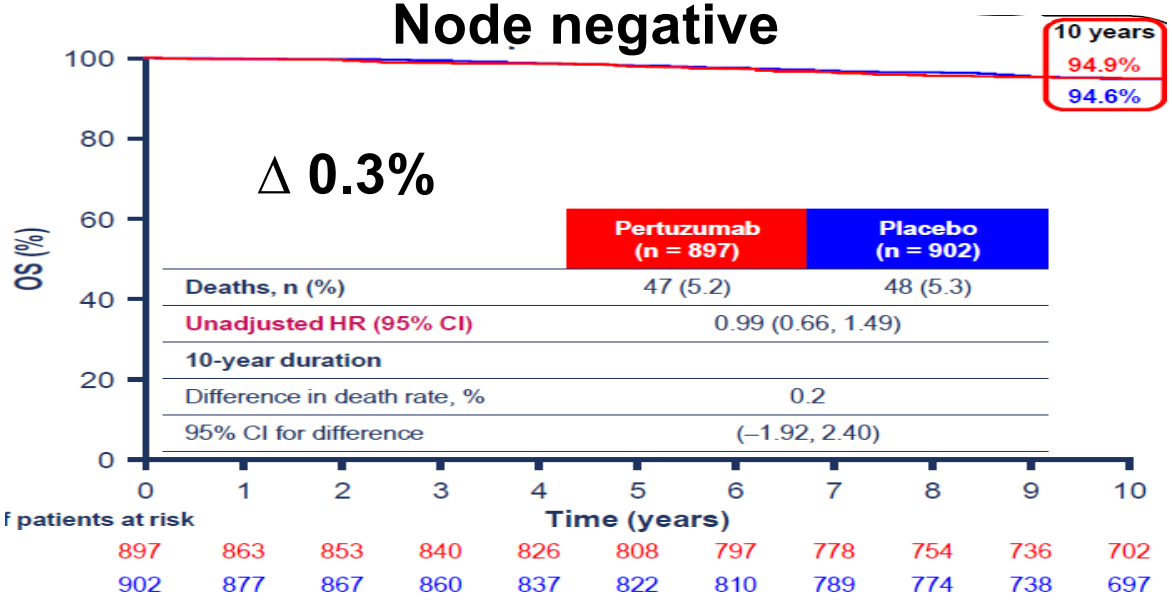
ITT



Node positive



Node negative

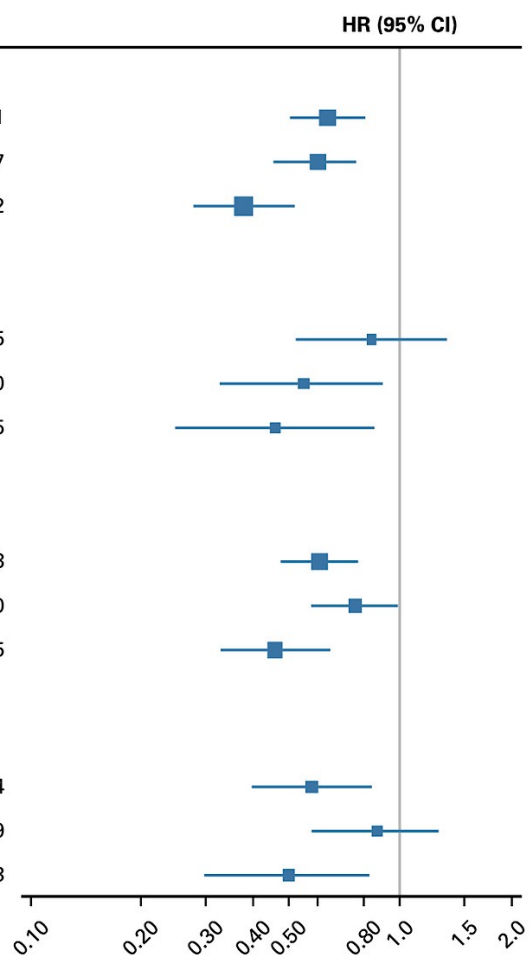


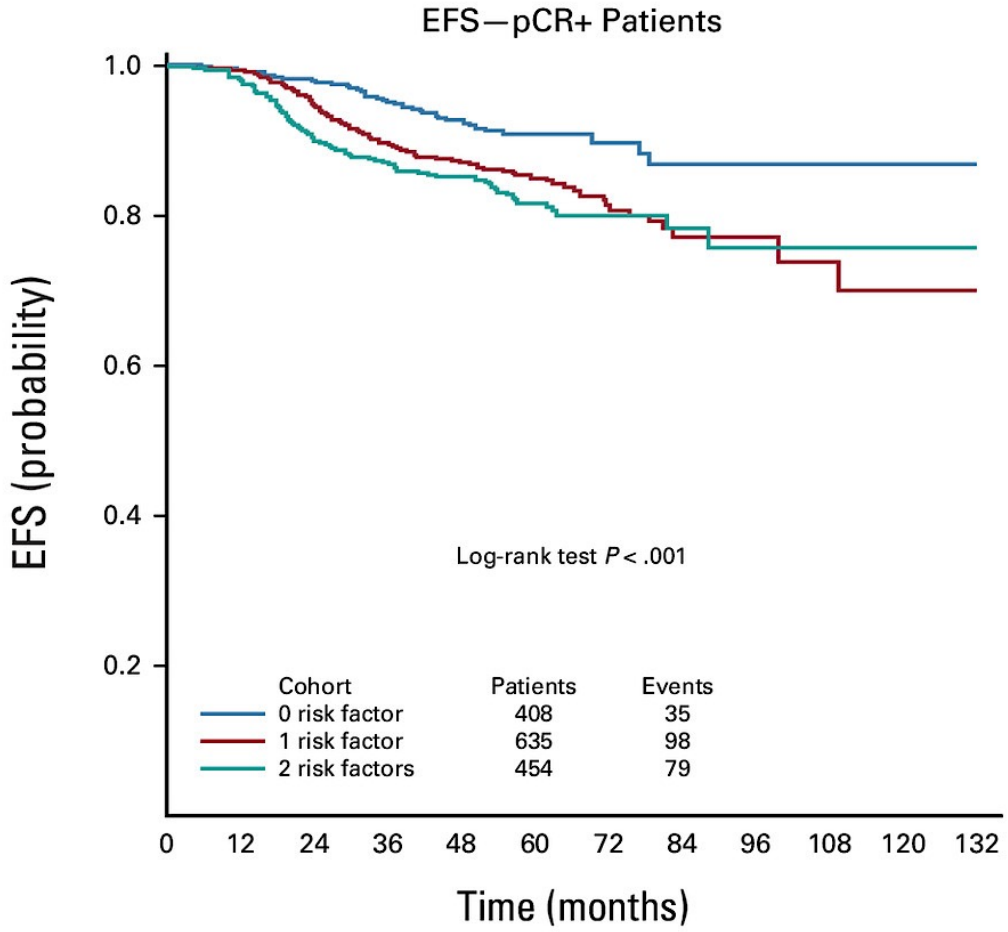
Loibl S, et al. ESMO Breast 2025

HER2+ *early* breast cancer

pCR and remaining risk for recurrence in high volume disease[1]

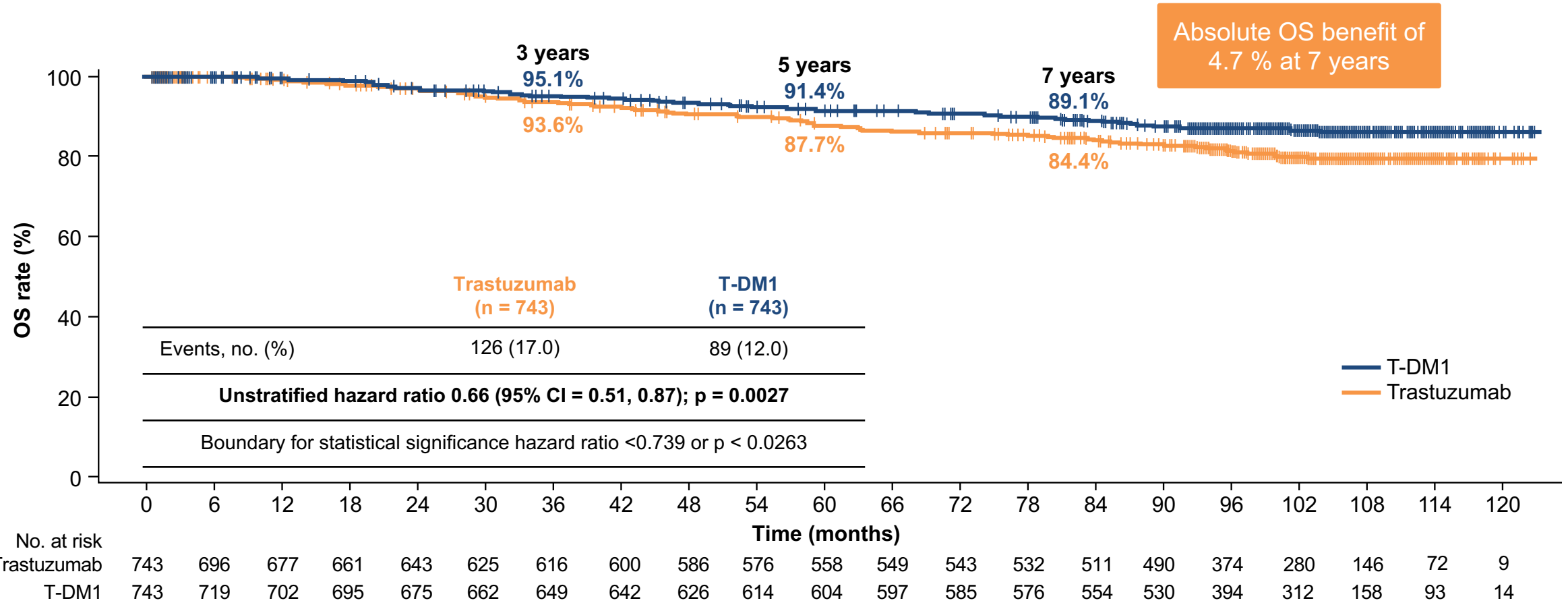
Subgroup	Tumor and Nodal Stage	No.	5-Year Rate, %	HR	95% CI
Hormone receptor+ pCR–	T1-2/N- (reference)	377	84.5		
	T3-4/N-	143	73.2	0.64	0.51-0.81
	T1-2/N+	448	72.1	0.60	0.46-0.77
	T3-4/N+	431	60.9	0.38	0.28-0.52
Hormone receptor+ pCR+	T1-2/N- (reference)	212	91.4		
	T3-4/N-	65	87.0	0.84	0.53-1.35
	T1-2/N+	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





[1] Mackelenbergh et al, JCO 2023

KATHERINE: Adjuvant T-DM1 Improves Overall Survival



Significant reduction in risk of death by 34% with T-DM1

CI, confidence interval; OS, overall survival; T-DM1, ado-trastuzumab emtansine.

Loibl S et al. 2023 SABCS; Geyer et al NEJM 2025

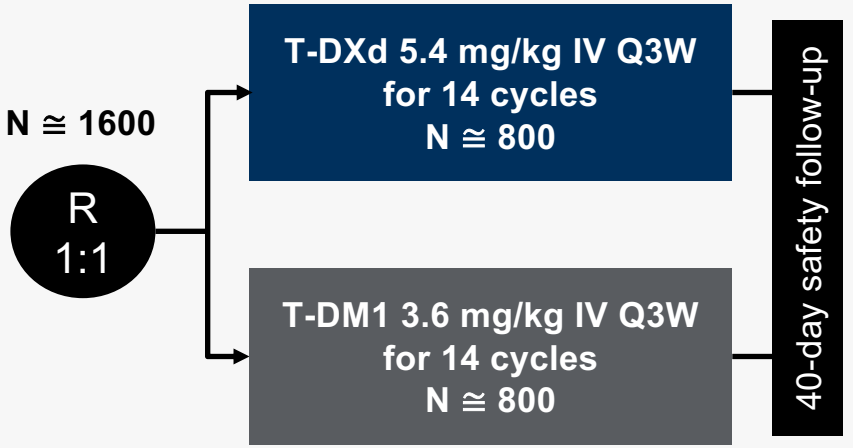
DESTINY-Breast05 study design

A global, multicenter, randomized, open-label, phase 3 trial (NCT04622319)

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

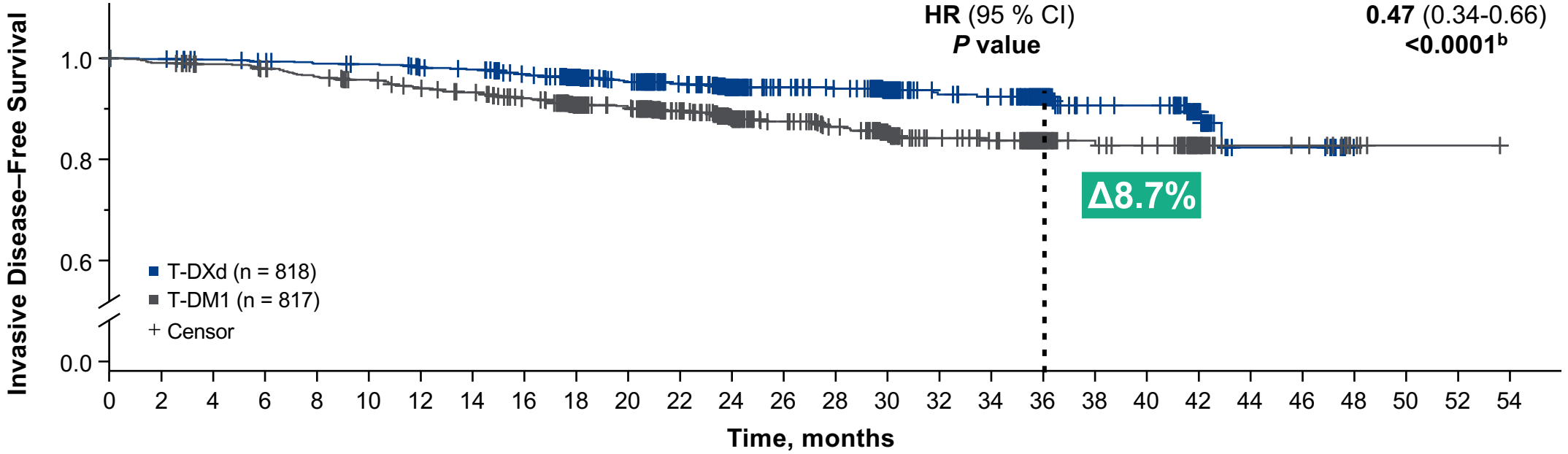
Other secondary endpoints
- OS
- DRFI
- BMFI
- Safety

- **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

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.
[a]NAT is defined as ≥16 weeks' NAT with ≥9 weeks trastuzumab ± pertuzumab and ≥9 weeks taxane-based chemotherapy.

Primary endpoint: IDFS[a]

	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]**	



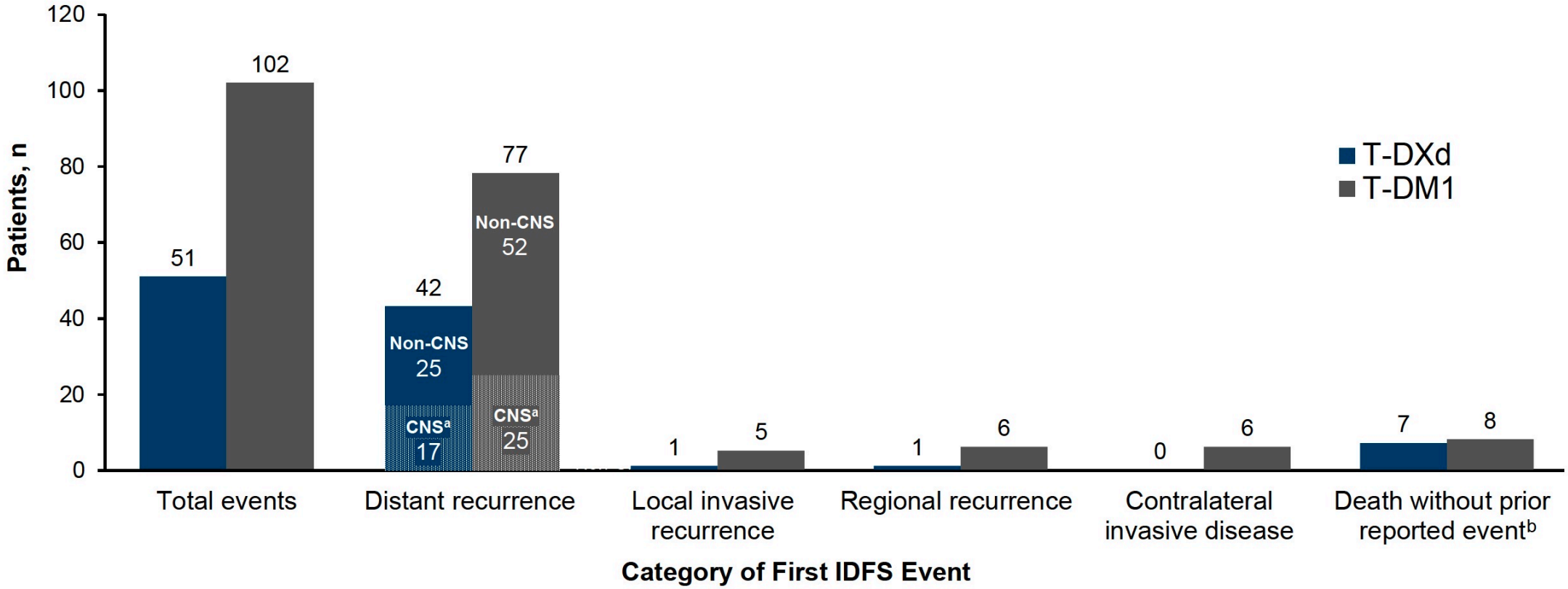
Number at Risk:

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.

Categories of first IDFS events



Lower distant and locoregional recurrences were observed with T-DXd vs T-DM1, including CNS recurrences

IDFS, invasive disease–free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Participants who experienced multiple types of IDFS events within 61 days of their first event are reported in the category according to the following hierarchy: distant recurrence CNS, distant recurrence non-CNS, local invasive recurrence, regional recurrence, contralateral breast cancer, and death without a previous event.
[a]CNS as sole site for distant recurrence or one of multiple distance recurrent sites [b]Causes of death in the T-DXd arm were 2 drug-related ILD, unrelated respiratory tract infection, acute respiratory failure (outside AE reporting period), acute respiratory distress syndrome (outside AE reporting period), and 2 disease progression, and in the T-DM1 arm were drug-related sepsis, unrelated ovarian cancer, unrelated aneurysm, unrelated pneumothorax, unrelated leiomyosarcoma, self-inflicted gun wound, and 2 disease progression.

Dr Charles E Geyer Jr
Abstract LBA1

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

	Adjudicated Drug-related ILD					
n (%)	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

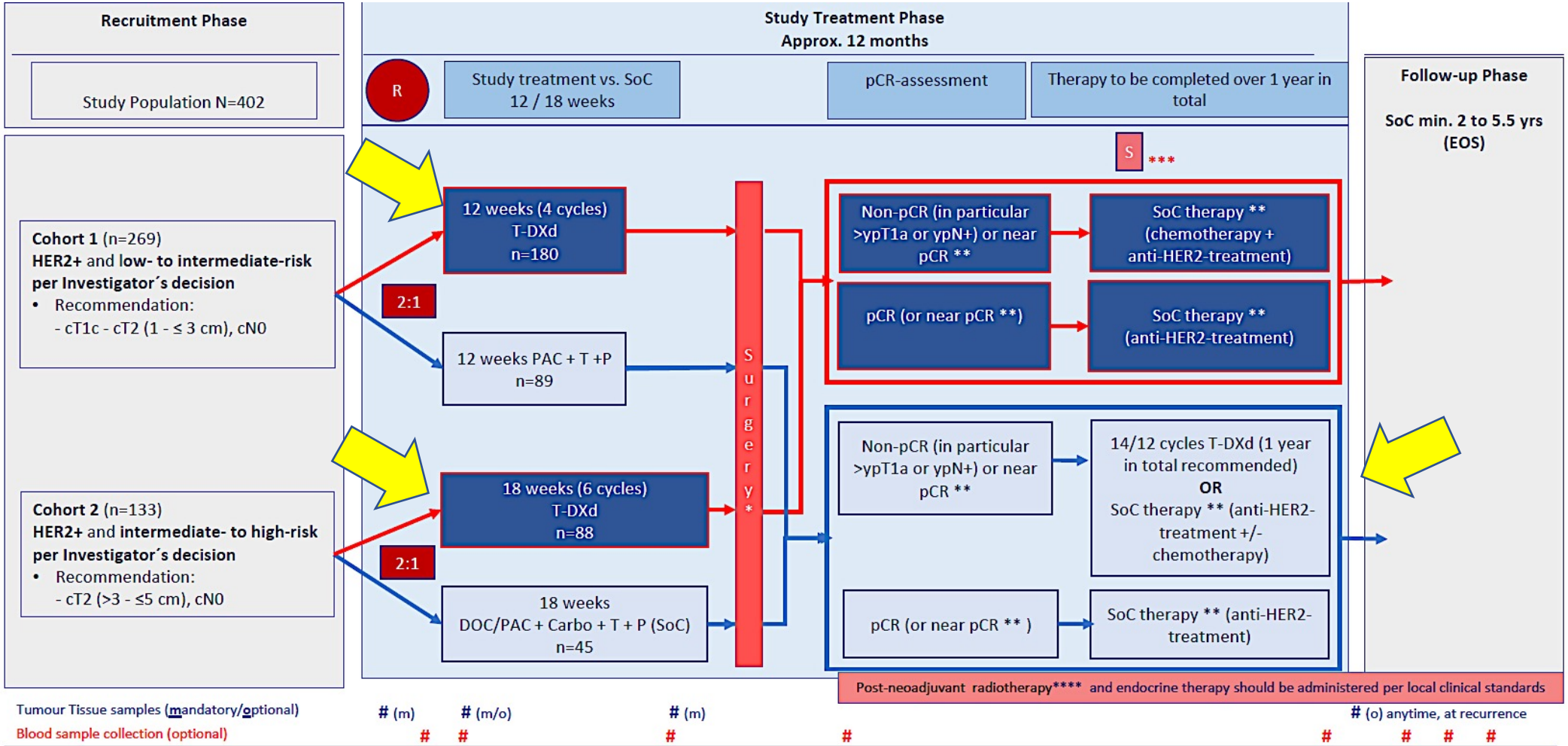
Adjuvant radiotherapy timing (sequential or concurrent) showed no differences in adjudicated drug-related ILD

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)

	LV dysfunction					
n (%)	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.
[a]All patients who received at least 1 dose of study treatment.

TDXd for therapy de-escalation (stage I/II)



Abbreviations: **Carbo** – Carboplatin, **DOC** – Docetaxel, **EOS** – End of Study, **Near pCR**: residual tumor size <5mm (ypT1a), **P** – Pertuzumab, **PAC** – Paclitaxel, **pCR** – pathological complete response, **R** – Randomization, **S** – Surgery / Biopsy, **SoC** – Standard-of-Care, **T** – Trastuzumab, **T-DXd** – Trastuzumab-Deruxtecan

* Surgery strongly recommended. Exceptional core biopsy allowed after consultation with sponsor, if further neo-adjuvant therapy intended.

** Treatment and also classification of near pCR at investigator´s decision according to clinical stage at baseline

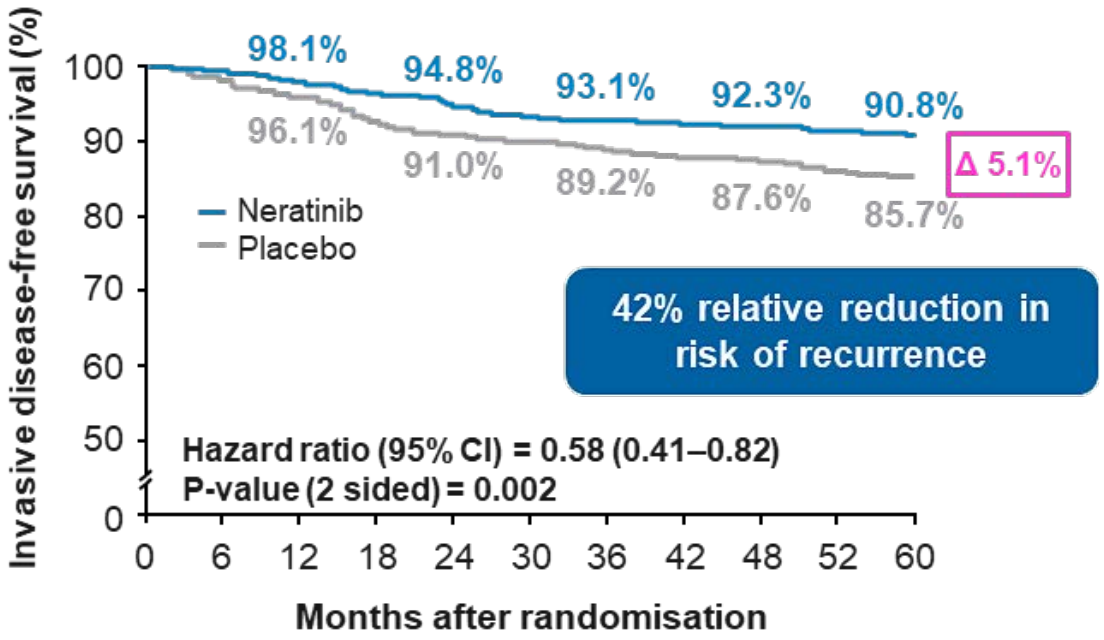
*** Timepoint of definite surgery in case of prolonged neoadjuvant treatment after 12 weeks of further neoadjuvant treatment.

****concurrent in case of anti-HER2-treatment, sequential in case of chemotherapy, prior to T-DXd recommended

Harbeck N et al. ASCO 2024;Abstract TPS631

ExteNET: Neratinib European Label Population
iDFS in the subgroup of pts HR+ and ≤1 Year from Trastuzumab

5 y
ITT
HR+
≤1 year T



No. At risk
HR+/≤1 year from trastuzumab

Neratinib	670	620	599	577	523	469	465	460	457	448	428
Placebo	664	634	609	583	535	481	471	462	458	450	433

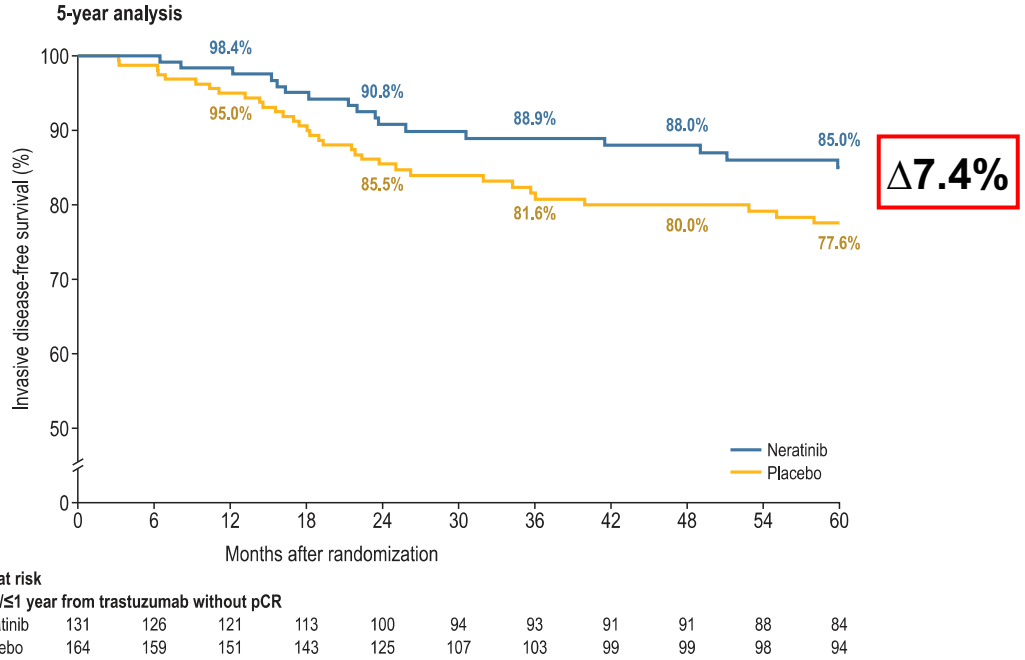
Data cut-off March 2017

Chan A, et al. Clin Breast Cancer. 2021.

95% of the HR+ study population received concomitant endocrine therapy.
CI, confidence interval; HR, hormone response; ITT, intention-to-treat; iDFS, invasive disease-free survival; y, years.

iDFS: invasive disease-free survival. 95% of the HR+ study population received concomitant endocrine therapy.

- Exploratory subset (n=295) with **non-pCR**
- Absolute benefit of **7.4% after 5 years** of follow-up



No. at risk
HR+/≤1 year from trastuzumab without pCR

Neratinib	131	126	121	113	100	94	93	91	91	88	84
Placebo	164	159	151	143	125	107	103	99	99	98	94

No pCR = Residual disease

Gnant M et al. SABCS 2018 #P2-13-01.

HER2+ EBC: Extended adjuvant therapy with neratinib

Real world experience[1]

Table 3: Adherence to neratinib treatment [CS]

	CS, N=279
Median proportion of compliant days, % (IQR)	100.0 (98.6–100.0)
Rate of adherent patients, n (%), [95% CI]	270 (96.8), [94.0–98.5]

Compliant day: intake of at least one tablet of neratinib on days with planned neratinib administration *or* no intake of neratinib on days without planned neratinib administration.
CI, confidence interval; CS, compliance set; IQR, interquartile range.

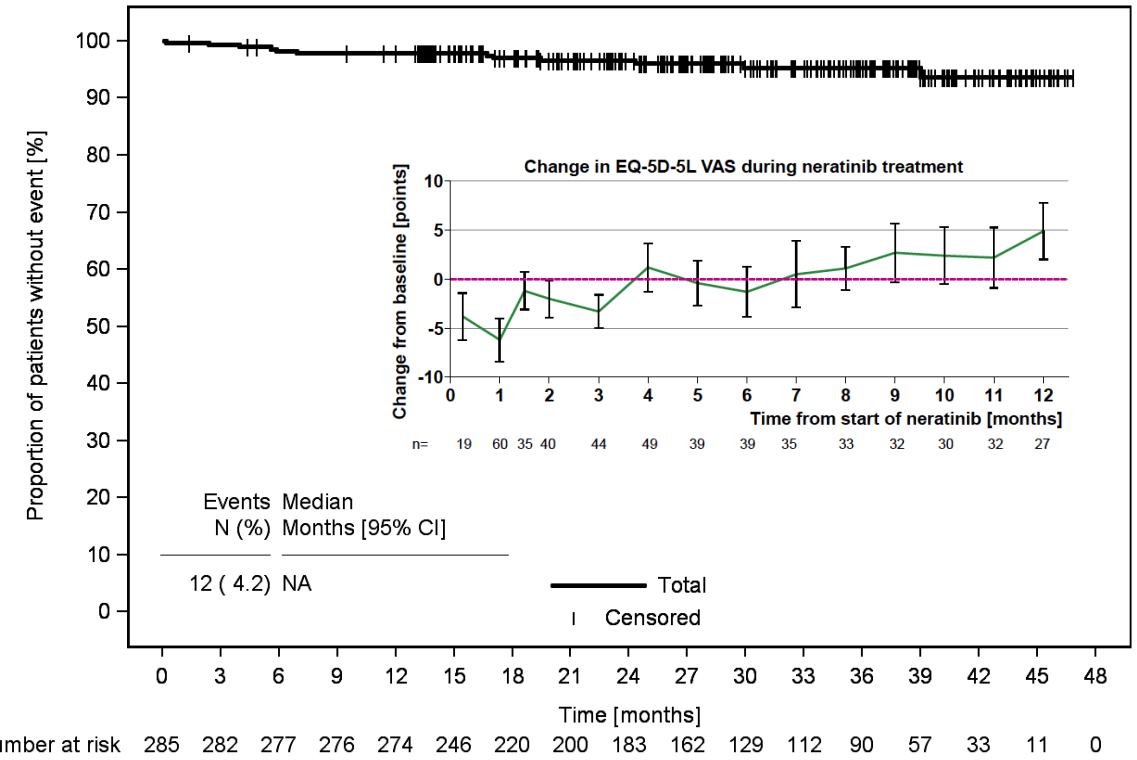
The proportion of pts with grade ≥3 diarrhea was markedly lower when compared indirectly to the ExteNET study (20.6% vs. 39%).[4] This may be a result of an increasing awareness of diarrhea risk leading to a more frequent use of diarrhea prophylaxis (86.4% of pts in ELEANOR) and implementation of the dose escalation approach (44.3% of pts in ELEANOR started with a reduced dose; for 15.0% of those, a grade ≥3 diarrhea was documented).

NCT04388384

ELEANOR

rEal-LifE pAN-HER-blOckade with neRatinib

DFS rate at 6 months, % (95% CI)	98.2 (95.8–99.3)
DFS rate at 12 months, % (95% CI)	97.9 (95.3–99.0)
DFS rate at 24 months, % (95% CI)	96.6 (93.5–98.2)



[1] Lüftner et al, ESMO 2025;Abstract 299P

HER2-positive localized breast cancer

Conclusions

- ✓ **Small N0 tumors**: Primary surgery - if pT1 pN0: 12 weeks of paclitaxel + 1y of trastuzumab (T) (APT)
  - ✓ If > pT1 pN0: Adjuvant Polychemotherapy + 1y T (iN0) or T + pertuzumab (P)) in N+ (APHINITY)
- ✓ **Tumors ≥ 2cm or N+**: **neoadjuvant chemotherapy** + T+P
  - ✓ Anthracycline-free regimens preferred
  - ✓ DB11 demonstrates efficacy and safety of T-DXd-THP in high-risk disease; pCR benefit vs ddAC-THP
- ✓ **pCR:** Continue 1y T (N0) or T+P (N+) (APHINITY)
- ✓ **non-pCR:** 1y of T-DM1 (KATHERINE)
  - ✓ DB05: T-DXd outperforms T-DM1 in high-risk non-pCR
- ✓ ADAPT HER2-IV will provide information on neoadjuvant and post-neoadjuvant T-DXd in stage I-II
- ✓ **Extended adjuvant therapy:** High-risk HR+ after 1y of T-based therapy: Consider 1y neratinib

- ✓ Open clinical questions remain regarding
  - Patient selection for neoadjuvant (DB11) vs. post-neoadjuvant (DB05) T-DXd
  - Post-neoadjuvant therapy after non-pCR with T-DXd-THP
  - De-escalation approaches (e.g. ADAPT HER2-IV, PHERGAIN, TRAIN-3, COMPASS HER2)

CASES FROM THE COMMUNITY
Investigators Discuss the Optimal Management of HER2-Positive Breast Cancer

Part 2 of a 3-Part CME Satellite Symposium Series

Wednesday, December 10, 2025
7:00 PM – 9:00 PM CT

Faculty

Professor Giuseppe Curigliano, MD, PhD
Nadia Harbeck, MD, PhD
Ian E Krop, MD, PhD
Nancy U Lin, MD
Joyce O'Shaughnessy, MD

Moderator

Neil Love, MD

RTP
RESEARCH TO PRACTICE

European Society for Medical Oncology Congress – October 12-17, 2025 – Berlin, Germany – Poster 299P

Extended adjuvant neratinib in HER2+/HR+ early breast cancer in clinical routine – final results from the multi-national, prospective, observational study ELEANOR

Lüftner D[1], Bartsch R[2], Breitenstein U[3], Jackisch C[4], Müller V[5], Schmidt M[6], Balic M[7], Rinnerthaler G[8], Zaman K[9], Schwitter M[10], Wrobel D[11], Guth D[12], Zaiss M[13], Terhaag J[14], Perlova-Griff L[15], Wuerstlein R[16], Schinköthe T[17], Vannier C[18], Harbeck N[16]

[1] Immanuel Campus Rüdersdorf, Medical University of Brandenburg Theodor Fontane, Rüdersdorf bei Berlin, Germany & Immanuel Hospital Märkische Schweiz, Buckow, Germany, [2] Department of Medicine 1, Division of Oncology, Medizinische Universität Wien, Vienna, Austria, [3] Hirslanden Hospital Zurich, Brust-Zentrum, Zurich, Switzerland, [4] Department of Obstetrics and Gynecology / Breast and Gynecologic Cancer Center, Evangelische Kliniken Essen-Mitte gGmbH (KEM), Essen, Germany, [5] Universitätsklinikum Hamburg-Eppendorf, Klinik und Poliklinik für Gynäkologie, Hamburg, Germany, [6] Universitätsmedizin Mainz, Klinik und Poliklinik für Geburtshilfe und Frauengesundheit, Mainz, Germany, [7] Department of Medicine, Division of Oncology, University of Pittsburgh, Pittsburgh, United States of America, [8] Division of Clinical Oncology, Department of Internal Medicine, Medical University of Graz, Graz, Austria, [9] Oncology Department, Lausanne University Hospital CHUV and University of Lausanne, Lausanne, Switzerland, [10] Oncology Department, Cantonal Hospital of Graubünden, Chur, Switzerland, [11] Klinik für Frauenheilkunde und Geburtshilfe, Sozialstiftung Bamberg, Bamberg, Germany, [12] Gyneco-oncological Practice, Dr. med. Dagmar Guth, Plauen, Germany, [13] Oncology Department, Praxis für interdisziplinäre Onkologie und Hämatologie GbR, Freiburg im Breisgau, Germany, [14] Dept. of Gynecology, Rottal/Inn Clinic, Eggenfelden, Germany, [15] Gynecological Practice, Frauenärztinnen-Zentrum Berlin-Zehlendorf, Berlin, Germany, [16] Breast Center, Department of Gynecology and Obstetrics and CCC Munich, LMU University Hospital, Munich, Germany, [17] CANKADO GmbH, Munich, and Research Center Smart Digital Health, University of the Bundeswehr, Munich, Germany, [18] Medical Department, Pierre Fabre Pharma GmbH, Freiburg, Germany.

Background

- Despite modern human epidermal growth factor receptor (HER2)-directed treatment options, relevant recurrence risk persists in patients (pts) with extensive local disease and/or lack of pathologic complete response (pCR) to neoadjuvant therapy.[1,2]
- Neratinib is approved in Europe for extended adjuvant therapy in adult pts with HER2+/hormone receptor positive (HR+) early breast cancer (eBC) who completed adjuvant trastuzumab-based therapy less than one year ago ("EMA-/Swissmedic-label population").[3]
- In this population, the ExteNET study demonstrated a 4.5% absolute improvement in 2-year invasive disease-free survival (2-y iDFS) with neratinib compared to placebo (95.3% vs. 90.8%; hazard ratio (HR) 0.49, 95% confidence interval (CI) 0.30–0.78, p (2-sided)=0.002), and a 5.1% absolute improvement in 5-y iDFS (HR 0.58, 95% CI 0.41–0.82, p (2-sided)=0.002).[4] Exploratory post-hoc analyses demonstrated a more pronounced benefit in pts with residual disease (non-pCR) after neoadjuvant treatment who completed neratinib therapy (i.e., ≥11 months of treatment) (5-y iDFS: Δ11.9%; HR 0.42, 95% CI 0.19–0.83, p (2-sided)=0.016; 8-y overall survival: Δ13.2%; HR 0.29, 95% CI 0.10–0.68, p (2-sided)=0.006).[5]
- In ExteNET, diarrhea was the most common grade 3 adverse event (AE) in the absence of primary diarrhea prophylaxis (neratinib group: 39%, placebo: 1%; no grade 4 events).[4] However, as demonstrated in the CONTROL study, diarrhea can be managed with adequate prophylaxis and treatment management, including a dose escalation approach.[6]
- ELEANOR is the first non-interventional study of the real-world use and management (including dose escalation) of neratinib in the extended adjuvant setting in pts with HER2+/HR+ eBC in Germany, Austria, and Switzerland (NCT04388384) after completion of adjuvant trastuzumab-based therapy, including dual blockade with trastuzumab + pertuzumab or trastuzumab-emtansine (T-DM1). Here, we report the final study results.

Methods

- ELEANOR was a prospective, longitudinal, observational study.
- 300 adult female pts diagnosed with HER2+/HR+ eBC stage I-III, who ended trastuzumab-based adjuvant therapy less than one year ago, were planned to be enrolled in accordance with the EMA/Swissmedic product specifications[3]. Treatment was administered according to local clinical practice.
- **Primary objective** was to assess patient adherence to neratinib (i.e., neratinib intake as planned by the physician on ≥75% of days of the treatment period).
- **Secondary objectives** included patient and tumor characteristics, prior trastuzumab-based treatments and neratinib treatment details, effectiveness, safety, patient-reported outcomes (PRO), and physicians' evaluated treatment satisfaction.

Results

- 298 evaluable pts were enrolled from July 2020 to May 2023 at 66 sites in Germany, Austria, and Switzerland with a minimum follow-up of 13 months.
- 285 of the pts enrolled qualified for the main analysis set (MAS), i.e., they met the eligibility criteria and had at least one documented dose of neratinib.
- 279 pts of the MAS provided at least one patient calendar page and qualified for the compliance set (CS).
- 287 pts had at least one documented dose of neratinib and at least one post-baseline safety assessment and were included in the safety analysis set (SAF).
- 82 pts of the MAS provided an evaluable PRO assessment at baseline and at least two post-baseline questionnaire timepoints for either the STIDAT or the EQ-5D-5L questionnaire and qualified for the patient-reported outcome set (PROS).

References

1. Harbeck N. Neoadjuvant and adjuvant treatment of patients with HER2-positive early breast cancer. Breast. 2022 Mar;62 Suppl 1(Suppl 1):S12–S16.
2. Geyer CE Jr et al. Survival with Trastuzumab Emtansine in Residual HER2-Positive Breast Cancer. N Engl J Med. 2025 Jan 16;392(3):249–257.
3. ema.europa.eu/en/medicines/human/EPAR/nerlynx (05/2023); Swissmedicinfo.ch (12/2024)
4. Chan A et al. Final Efficacy Results of Neratinib in HER2-positive Hormone Receptor-positive Early-stage Breast Cancer From the Phase III ExteNET Trial. Clin Breast Cancer. 2021 Feb;21(1):80–91.e7.
5. Moy B et al. Association between treatment duration and overall survival in early-stage HER2+ breast cancer patients receiving extended adjuvant therapy with neratinib in the ExteNET trial. ASCO 2021. Poster #540. Available at: https://www.pumabiotechnology.com/docs/960421_Puma_ExteNET_Poster_at_ASCO_2021_May_546.pdf
6. Chan A et al. Final findings from the CONTROL trial: Strategies to reduce the incidence and severity of neratinib-associated diarrhea in patients with HER2-positive early-stage breast cancer. Breast. 2023 Feb;67:94–101.

Patient and disease characteristics

- Patient and disease baseline characteristics are summarized in **Tables 1** and **2** [MAS].

Table 1: Patient baseline characteristics [MAS]

	MAS, N=285
Median age (at inclusion) in years (range)	52 (22–81)
Median BMI in kg/m² (IQR)	25.9 (23.0–29.9)
ECOG Performance Status (at inclusion), n (%)	
• 0	210 (73.7)
• 1	57 (20.0)
• 2	5 (1.8)
• Missing	13 (4.6)
Menopausal status (at primary diagnosis), n (%)	
• Premenopausal	131 (46.0)
• Perimenopausal	18 (6.3)
• Postmenopausal	136 (47.7)
Number of concomitant diseases, n (%)	
• 0	118 (41.4)
• 1	62 (21.8)
• 2	51 (17.9)
• ≥3	54 (18.9)

IQR, interquartile range; MAS, main analysis set.

Table 2: Tumor characteristics (at primary diagnosis) and prior treatments [MAS]

	MAS, N=285
WHO tumor type, n (%)	
• Invasive carcinoma of no special type	255 (89.5)
• Invasive lobular carcinoma	18 (6.3)
• Tubular carcinoma	8 (2.8)
• Cribriform carcinoma	1 (0.4)
• Mucinous carcinoma	1 (0.4)
• Other	2 (0.7)
Clinical T-stage, n (%)	
• cT0/cTis	4 (1.4)
• cT1	138 (48.4)
• cT2	112 (39.3)
• cT3	13 (4.6)
• cT4	11 (3.9)
• cTX	7 (2.5)
Clinical N-stage, n (%)	
• cN0/cN1mi	192 (67.4)
• cN1	71 (24.9)
• cN2	15 (5.3)
• cN3	3 (1.1)
• cNX	4 (1.4)
Clinical AJCC stage, n (%)	
• Tis/N0/M0	2 (0.7)
• I	113 (39.6)
• II	130 (45.6)
• III	31 (10.9)
• Not determinable	9 (3.2)
Tumor grading, n (%)	
• G1	5 (1.8)
• G2	127 (44.6)
• G3	142 (49.8)
• GX	11 (3.9)
Positive hormone receptor (i.e., estrogen receptor and/or progesterone receptor) status, n (%)	285 (100)
Ki67 status (local)[a], n (%)	
• High	181 (63.5)
• Low	84 (29.5)
• Unknown / missing	20 (7.0)
Previous anti-neoplastic therapies[b], n (%)	
• Adjuvant	49 (17.2)
• Neoadjuvant	236 (82.8)
• Post-neoadjuvant[c]	235 (82.5)
Pathological response to neoadjuvant treatment, n (%)	
• pCR	119 (50.4)
• non-pCR	116 (49.2)
• Unknown	1 (0.4)
Disease risk profile[d], n (%)	
• Low	71 (24.9)
• Non-low	211 (74.0)
• Unknown	3 (1.1)

[a]High/low classification according to the centers' local standards
[b]Including anti-HER2 therapy and/or chemotherapy
[c]Post-neoadjuvant therapy not documented for one patient
[d]Low risk: AJCC stage I and N0 and pCR (in case of neoadjuvant treatment); non-low risk: AJCC stage >I or N+ or non-pCR (in case of neoadjuvant treatment). Patients with cN1mi were included in the non-low risk group.
MAS, main analysis set; pCR, pathological complete response.

Therapeutic management prior to neratinib

- Prior to neratinib, 38.9% (111/285) of pts received adjuvant/post-neoadjuvant trastuzumab monotherapy, 32.6% (93/285) adjuvant/post-neoadjuvant trastuzumab + pertuzumab, and 23.5% (67/285) post-neoadjuvant T-DM1 (**Figure 1A**) [MAS].
- Anti-HER2 treatments by therapy setting (i.e., adjuvant or post-neoadjuvant) and by pathological response (i.e., pCR or non-pCR) are depicted in **Figure 1B and 1C** [MAS].

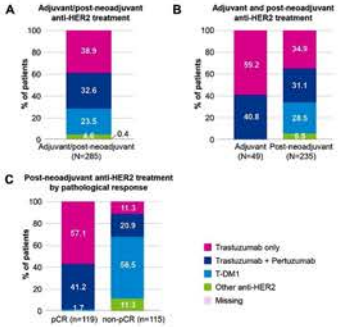


Figure 1: Anti-HER2 agents used in adjuvant (no prior neoadjuvant) and post-neoadjuvant pretreatment settings with/without chemotherapy (A,B) and post-neoadjuvant pretreatment by pathological response (C) [MAS].
"Other anti-HER2" treatments included other combinations and/or sequences of trastuzumab, pertuzumab, and/or T-DM1. Pts without documented adjuvant or post-neoadjuvant anti-HER2 treatment are not depicted in B. Pts without documented post-neoadjuvant anti-HER2 treatment or without documented pathological response are not depicted in C.
MAS, main analysis set; pCR, pathological complete response.

Neratinib treatment management

- Median neratinib treatment duration was 11.9 months (IQR: 4.9–12.0 months) [SAF].
- Neratinib starting dose was <240 mg/day in 44.3% (127/287) of pts; planned dose escalation was the reason for reduced starting dose in 89.8% (114/127) of them and 80.3% (102/127) of them had a documented dose increase (dose escalation strategy) [SAF].
- Median absolute dose intensity was 230.7 mg/day (IQR: 181.5–240.0 mg/day) [SAF].
- 86.4% (248/287) of pts received diarrhea prophylaxis [SAF].
- Reasons for choice of treatment with neratinib and the main reasons for end of treatment with neratinib are depicted in **Figure 2** [MAS].

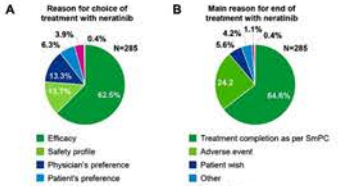


Figure 2: Reason for choice of treatment with neratinib (A) and main reason for end of treatment with neratinib (B) [MAS].
MAS, main analysis set.

Adherence to neratinib treatment (primary endpoint)

- Adherence to neratinib treatment was assessed as:
  - Proportion of compliant days, (i.e., the proportion of days within the treatment period with neratinib intake as planned by the physician)
  - Rate of adherent patients (i.e., the rate of patients with ≥75% of compliant days within the treatment period)
- Adherence rate to neratinib treatment was 96.8% (see **Table 3**).

Table 3: Adherence to neratinib treatment [CS]

	CS, N=279
Median proportion of compliant days, % (IQR)	100.0 (98.6–100.0)
Rate of adherent patients, n (%), [95% CI]	270 (96.8), [94.0–98.5]

Compliant day: intake of at least one tablet of neratinib on days with planned neratinib administration or no intake of neratinib on days without planned neratinib administration.
CI, confidence interval; CS, compliance set; IQR, interquartile range.

Effectiveness

- At an estimated median observation time of 29.1 months (IQR: 20.5–38.3), 3.9% (11/285) of pts experienced a relapse (**Table 4**). Relapse occurred while on neratinib treatment in 3 pts, while for 8 pts, relapse was documented in the follow-up period [MAS]. One patient died without prior relapse (unknown reason of death) after starting neratinib treatment.
- The 24-month DFS rate was 96.6% (95% CI, 93.5–98.2) (**Figure 3**) [MAS].

Table 4: Patients with disease relapse (n=11) [MAS]

Location of first relapse	Disease risk profile*	Pathological response to neoadjuvant treatment	Neratinib treatment duration [days]	Time from end of neratinib treatment to diagnosis of relapse [days]
Distant recurrence, n=8 (2.8%)				
• Brain, bone	Non-low	non-pCR	5	0
• Brain	Non-low	pCR	7	162
• Brain	Non-low	NA	28	490
• Brain, liver, adrenal + retroperitoneal LN	Non-low	non-pCR	71	0
• Liver	Non-low	non-pCR	357	550
• Ovary	Non-low	pCR	359	826
• Lumbar spine, ovary	Non-low	pCR	365	373
• Peritoneal carcinomatosis + ascites	Non-low	pCR	388	202
Local recurrence, n=3 (1.1%)				
• Local relapse	Non-low	pCR	8	169
• Local relapse	Non-low	non-pCR	120	0
• Local relapse	Low	pCR	358	148

* For definition refer to footnote d of Table 2.
LN, lymph nodes; MAS, main analysis set; NA, not applicable (no neoadjuvant treatment received); pCR, pathological complete response.

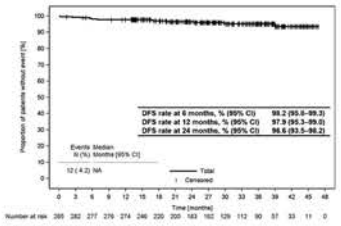


Figure 3: Disease-free survival (DFS) [MAS].
DFS, defined as the time interval measured from the day of first neratinib administration (as intended by the physician) to first relapse (local or distant) or death, whichever came first. DFS was estimated using the Kaplan-Meier method. Pts being event-free at the end of the study (i.e., alive and no relapse documented) were censored with the date of the last documented contact. Due to low frequency of events, median DFS could not be calculated.
CI, confidence interval; MAS, main analysis set; NA, not applicable

Patients' self-rated overall health

- At the start of neratinib treatment, pts' self-rated overall health was 74.9 ± 1.8 points (mean ± SEM) on the EQ-5D-5L Visual Analogue Scale (VAS, range 1 to 100) [PROS].
- Pts' self-rated overall health slightly decreased within the first 3 months of neratinib treatment (max change from baseline: -6.2 ± 2.2 points (mean ± SEM)), recovering thereafter (see **Figure 4**) [PROS].

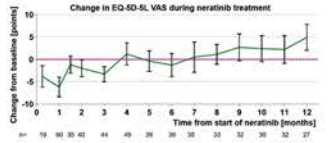


Figure 4: Change in EQ-5D-5L VAS from baseline during treatment with neratinib [PROS].
Time points of evaluation during the first two months of neratinib treatment: week 1, week 2–4, week 5–6 and week 7–8.
n, number of questionnaires at the respective time point; PROS, patient-reported outcome set.

Safety

- Treatment emergent adverse events (TEAEs) were consistent with the known safety profile of neratinib with grade ≥3 diarrhea observed in 20.6% (59/287) of pts.
- The incidence of grade ≥3 diarrhea by worst grade was less common in pts starting on a lower dose of neratinib (15.0% vs. 25.0%) (**Table 5**) [SAF].

Table 5: Safety [SAF][a]

n (%)	SAF, N=287
TEAEs[b], any grade	272 (94.8)
• Grade ≥3[c]	78 (27.2)
• Serious TEAEs	21 (7.3)
• Leading to discontinuation of neratinib	74 (25.8)
TEAEs in ≥10% of pts, any grade	
• Diarrhea	247 (86.1)
• Nausea	68 (23.7)
• Fatigue	66 (23.0)
• Abdominal pain upper	29 (10.1)
Diarrhea by worst grade	
• Grade 1	103 (35.9)
• Grade 2	85 (29.6)
• Grade 3	57 (19.9)
• Grade 4	2 (0.7)
• Grade ≥3 by worst grade and by starting dose	59 (20.6)
◦ Neratinib starting dose <240 mg/day, N=127	19 (15.0)
◦ Neratinib starting dose =240 mg/day, N=160	40 (25.0)
• Leading to treatment	185 (64.5)

[a] Data are retrieved from the AE form; [b] TEAE, treatment emergent adverse event; [c] No fatal TEAEs were reported.
SAF, safety analysis set.

Conclusion

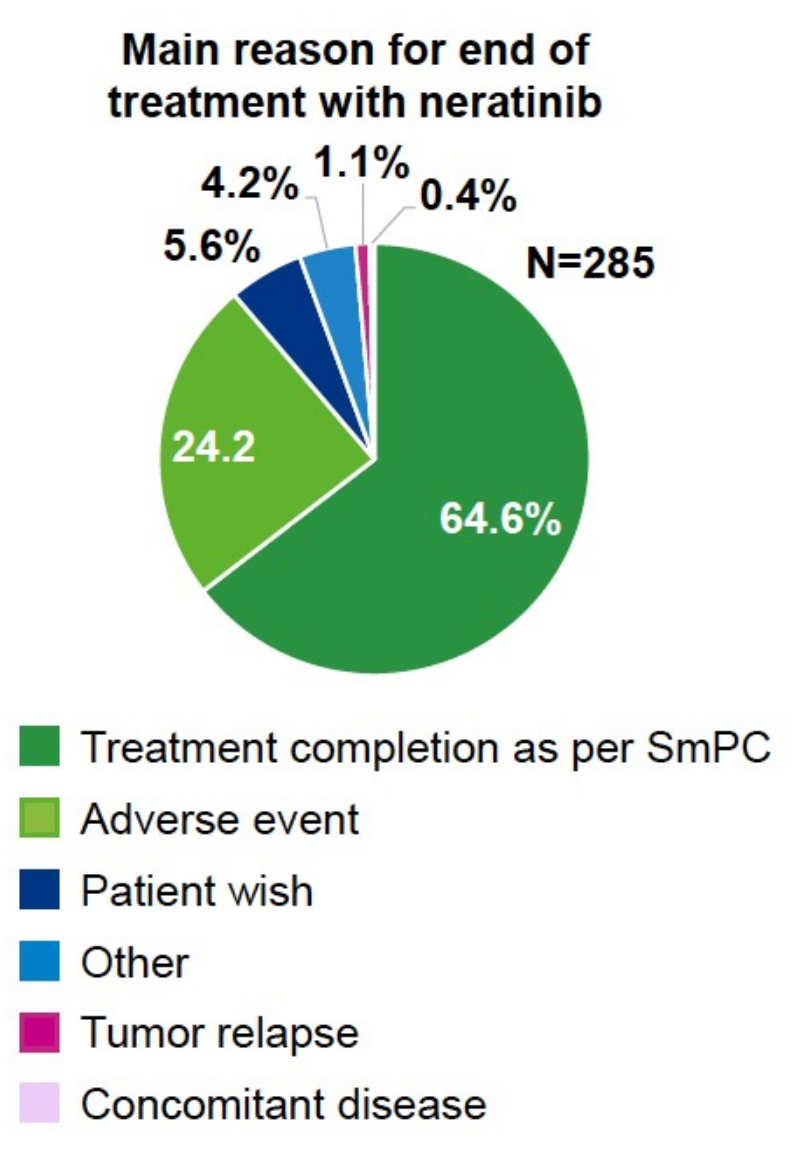
- The final analysis of ELEANOR reflects the use of neratinib in a contemporary cohort of pts with HER2+/HR+ eBC after completion of adjuvant trastuzumab-based regimens including pertuzumab + trastuzumab and T-DM1 in routine practice across Germany, Austria, and Switzerland.
- Pts' adherence to neratinib treatment was high, with 96.8% of pts meeting the predefined primary endpoint of being adherent to prescribed neratinib treatment (i.e., ≥75% of compliant days).
- The 24-month DFS rate of 96.6% appears consistent with previous data.[4]
- The proportion of pts with grade ≥3 diarrhea was markedly lower when compared indirectly to the ExteNET study (20.6% vs. 39%).[4] This may be a result of an increasing awareness of diarrhea risk leading to a more frequent use of diarrhea prophylaxis (86.4% of pts in ELEANOR) and implementation of the dose escalation approach (44.3% of pts in ELEANOR started with a reduced dose; for 15.0% of those, a grade ≥3 diarrhea was documented).

Conflicts of interest (first author)
Advisory Role or Expert Testimony: Amgen, AstraZeneca, BMS, Daiichi Sankyo, Eli Lilly, Exact Sciences, Gilead, GSK, high²md, L'Oréal, MSD, Novartis, onkowissen.de, Pfizer, Roche, Seagen, TEVA.
Honoraria: Amgen, AstraZeneca, BMS, Daiichi Sankyo, Eli Lilly, Exact Sciences, Gilead, GSK, high²md, L'Oréal, MSD, Novartis, onkowissen.de, Pfizer, Roche, Seagen, TEVA.
Financing of Scientific Research: Amgen, Novartis.
Other Financial Relationships: high²md.

Legal entity responsible for the study & study funding
Study sponsored by Pierre Fabre Pharma GmbH (Freiburg, Germany), Pierre Fabre Pharma Austria (Wels, Austria) and Pierre Fabre Pharma AG (Basel, Switzerland). Medical writing assistance was provided by Dr. Katherina Achilles, Alcedis GmbH (Giessen, Germany), funded by Pierre Fabre Pharma GmbH, Pierre Fabre Pharma Austria and Pierre Fabre Pharma AG.

Contact
corinna.vannier@pierre-fabre.com

Phase IV ELEANOR: Reason for End of Treatment with Neratinib — Main Analysis Set



Lüftner D et al. ESMO 2025;Abstract 299P.

Case Presentation: 56-year-old woman presents with locally advanced ER-positive, HER2-positive breast cancer

Dr Alan Astrow (Brooklyn, New York)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

How would you have approached treatment for this patient with extensive localized triple-positive breast cancer?

Based on the DESTINY-Breast11 data, do you believe that neoadjuvant T-DXd will receive FDA approval soon? If so, for which patients with high-risk localized disease will you utilize it? Do you expect it to become standard for HER2-positive breast cancer in the neoadjuvant setting?

For patients with HER2-positive localized breast cancer with post-operative residual disease after neoadjuvant chemotherapy, do you think T-DXd is preferable to T-DM1? What comes next?

Case Presentation: 46-year-old woman with ER-positive, HER2-positive Stage II BC s/p neoadjuvant TCHP with residual disease (13 mm, 1 positive lymph node – 3 mm) receives adjuvant T-DM1 but discontinues due to neuropathy

Dr Laila Agrawal (Louisville, Kentucky)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

For which patients with localized HER2-positive breast cancer are you utilizing post-adjuvant neratinib? Are there patient subgroups that appear to benefit more from this strategy? How important is the improvement in the rate of CNS recurrence in your decision-making?

How do you assess adherence in your patients receiving post-adjuvant neratinib?

What is your approach to monitoring and management of the side effects associated with neratinib?

Agenda

Module 1: Considerations in the Care of Patients with Localized HER2-Positive Breast Cancer — Prof Harbeck

Module 2: Previously Untreated HER2-Positive Metastatic Breast Cancer (mBC) — Prof Curigliano

Module 3: Optimal Management of Brain Metastases in Patients with HER2-Positive Breast Cancer — Dr Lin

Module 4: Selection and Sequencing of Therapy for Relapsed/Refractory (R/R) HER2-Positive mBC in the Absence of CNS Involvement — Dr Krop

Module 5: Tolerability Considerations with HER2-Targeted Therapies — Dr O'Shaughnessy

RTP RESEARCH TO PRACTICE

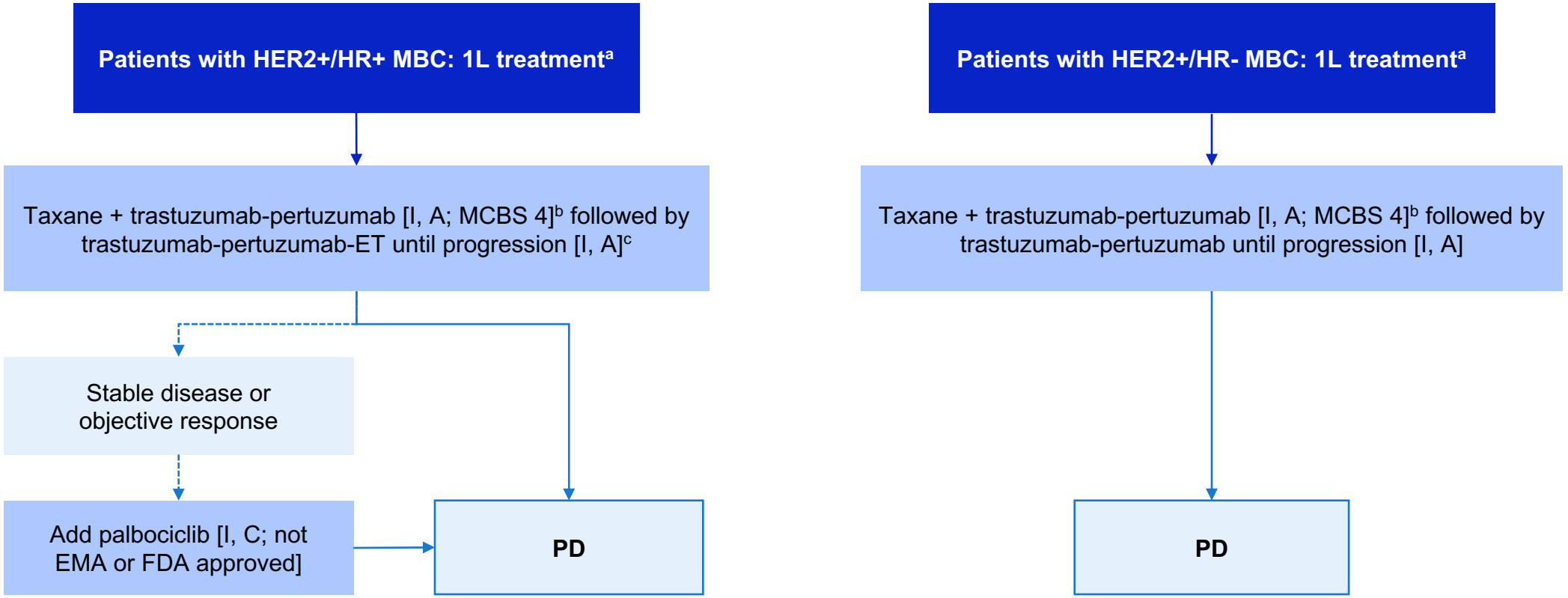
Previously untreated HER2 positive metastatic breast cancer

Giuseppe Curigliano, MD, PhD
University of Milano and Istituto Europeo di Oncologia
Milano, Italia

UNIVERSITÀ DEGLI STUDI DI MILANO

IEO
Istituto Europeo di Oncologia

ESMO Guideline Treatment Recommendations: 1L HER2+ MBC[1,2]



Adapted from Curigliano G, et al. ESMO Metastatic Breast Cancer Living Guidelines, v1.2 April 2025.

As per EMA, palbociclib is approved for the treatment of HR+/HER2- locally advanced or MBC in combination with an aromatase inhibitor or in combination with fulvestrant in women who have received prior ET. In pre- or perimenopausal women, the ET should be combined with a luteinizing hormone-releasing hormone agonist.[3]

[a] For *ERBB2*-amplifications [ESCAT score: I-A] (Mosele, 2024). [b] The MCBS score only applies to the combination with docetaxel. [c] Ovarian function suppression should also be added for pre- and perimenopausal women [I, A].

1L, first line; EMA, European Medicines Agency; ESCAT, ESMO scale for the clinical actionability of molecular targets; ESMO, European Society for Medical Oncology; ET, endocrine therapy; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MBC, metastatic breast cancer; MCBS, magnitude of clinical benefit scale; PD, progressive disease; SmPC, Summary of Product Characteristics.

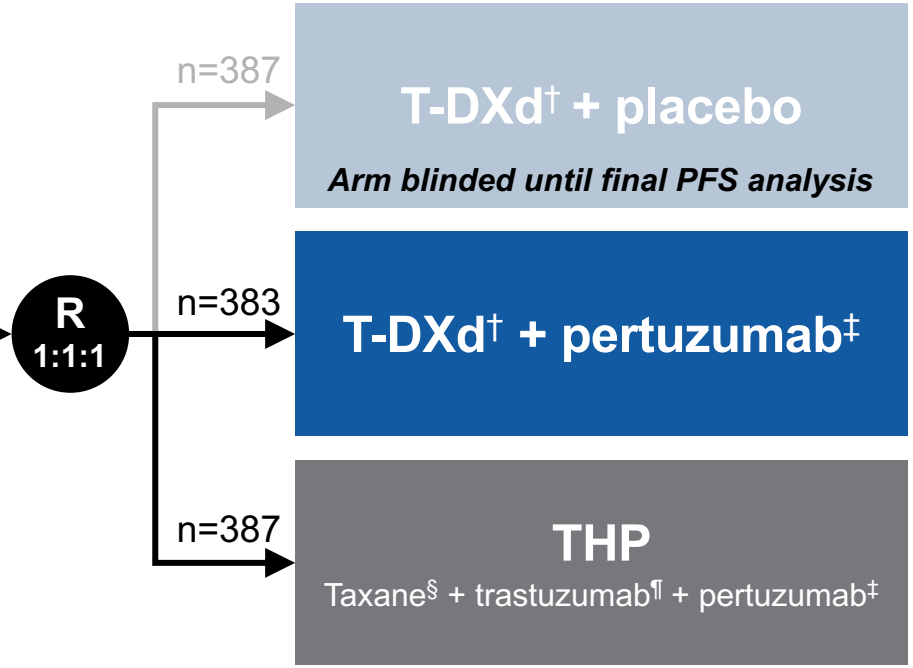
1. Gennari A, et al. *Ann Oncol*. 2021;32(12):1475-1495; 2. Curigliano G, et al. ESMO Metastatic Breast Cancer Living Guidelines. v1.2 April 2025. Accessed August 2025; 3. IBRANCE (palbociclib) [SmPC]. EMA. Accessed August 2025.

DESTINY-Breast09 study design

A randomized, multicenter, open-label,* Phase 3 study (NCT04784715)[1,2]

Patient population

- 1L HER2+ a/mBC
- DFI >6 mo from last (neo)adjuvant therapy
- One prior line of ET for a/mBC permitted
- Asymptomatic BMs allowed



Endpoints

Primary

- PFS (BICR)

Key secondary

- OS

Secondary

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

Stratification factors

- **De-novo (~52%) vs recurrent a/mBC**
- **HR+ (~54%) or HR−**
- ***PIK3CA*m detected (~31%) vs not detected**

- If T-DXd was discontinued owing to AEs (except Grade >2 ILD), patients could switch to trastuzumab‖
- Concurrent use of ET (aromatase inhibitor or tamoxifen) was allowed for those with HR+ disease after six cycles of T-DXd or discontinuation of taxane

*Open label for THP arm, double blinded for pertuzumab in experimental arms; †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

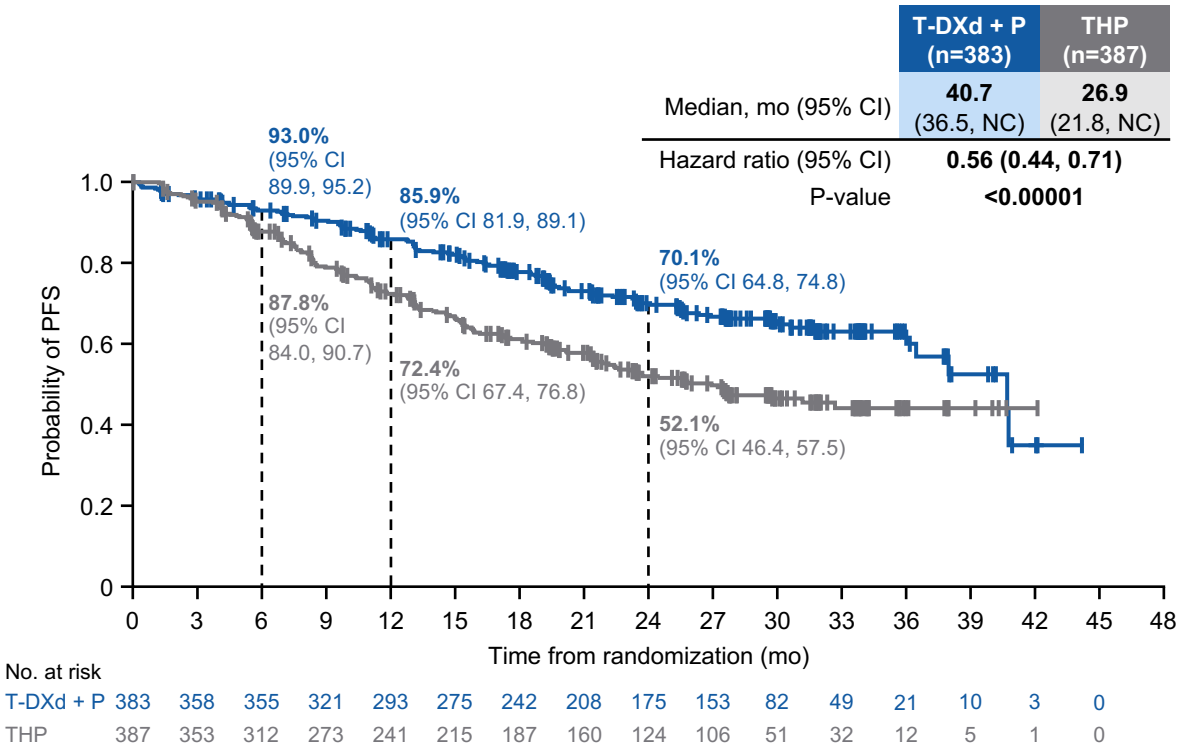
1L, first-line; AE, adverse event; a/mBC, advanced/metastatic breast cancer; BICR, blinded independent central review; BM, brain metastasis; DFI, disease-free interval; DOR, duration of response; ET, endocrine therapy; HER2+, human epidermal growth factor receptor 2–positive; HR+/−, hormone receptor–positive/–negative; ILD, interstitial lung disease; INV, investigator; mo, months; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival; *PIK3CA*m, *PIK3CA* mutation; Q3W, every 3 weeks; QW, once weekly; R, randomization; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

1. Tolaney SM, et al. Oral presentation at ASCO 2025 (Abstract LBA1008); 2. NCT04784715. Updated. August 1, 2025. Available from: https://clinicaltrials.gov/study/NCT04784715 (Accessed October 15, 2025)

Background: DESTINY-Breast09 primary results

- T-DXd + P demonstrated a statistically significant and clinically meaningful **improvement in PFS by BICR vs THP**[1]
- Early OS data suggest a positive trend favoring T-DXd + P, with a **supportive hazard ratio of 0.60 for PFS2**[1]
- A consistent PFS benefit with T-DXd + P was also observed across **stratification factors**[1]
  - **Recurrent disease / prior treatment** (~50% of patients in this setting[2])
  - **HR-negative status** (~50% of patients[3])
  - ***PIK3CA* mutation** (~30% of patients[4,5])
- T-DXd + P safety data were consistent with known profiles of individual treatments[1]

DESTINY-Breast09 interim analysis (DCO February 26, 2025)
PFS by BICR: primary endpoint[1]



BICR, blinded independent central review; CI, confidence interval; DCO, data cutoff; HR, hormone receptor; mo, months; NC, not calculable; OS, overall survival; P, pertuzumab; PFS, progression-free survival; PFS2, second progression-free survival; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

1. Tolaney SM, et al. Oral presentation at ASCO 2025 (Abstract LBA1008); 2. Tripathy D, et al. *Oncologist.* 2020;25:e214–e222; 3. Baselga J, et al. *N Engl J Med.* 2012;366:109–119; 4. Baselga J, et al. *J Clin Oncol.* 2014;32:3753–3761; 5. Swain S, et al. *Cancer Res.* 2023;83(Suppl. 5):P2-11-07 (Abstract)

Sibylle Loibl, MD, PhD

DESTINY-Breast09

BERLIN 2025 ESMO congress

Key baseline disease characteristics by subgroup

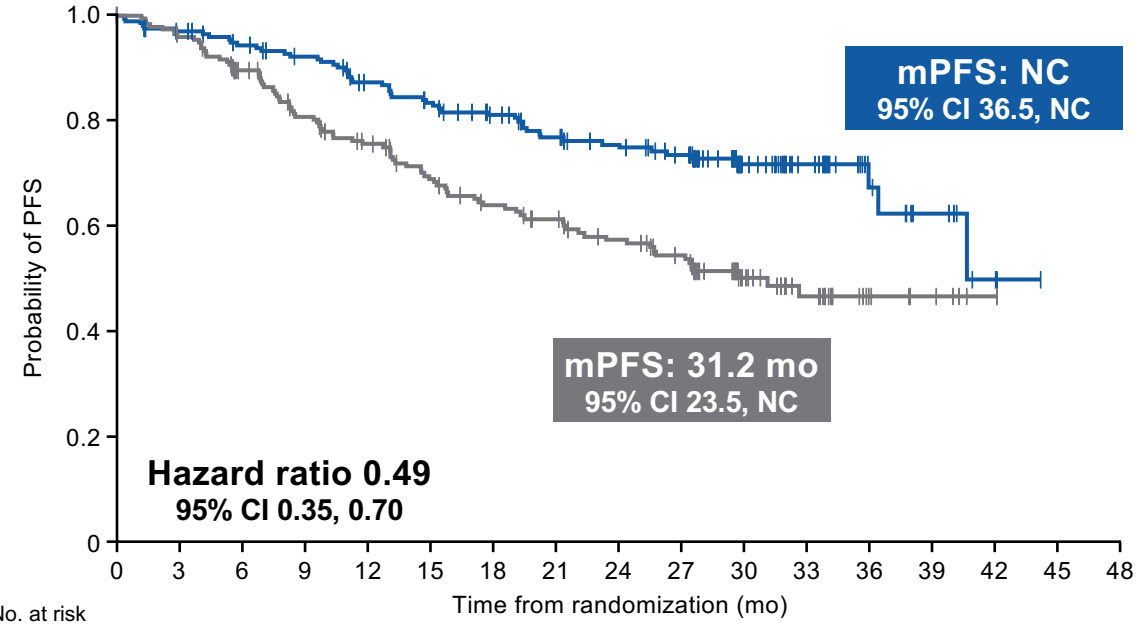
	Prior treatment status				HR status				*PIK3CA*m status			
	De novo		Recurrent		HR+		HR−		Detected		Not detected	
n (%)	T-DXd + P (n=200)	THP (n=200)	T-DXd + P (n=183)	THP (n=187)	T-DXd + P (n=207)	THP (n=209)	T-DXd + P (n=176)	THP (n=178)	T-DXd + P (n=116)	THP (n=121)	T-DXd + P (n=266)*	THP (n=266)
ECOG PS score												
0	136 (68.0)	121 (60.5)	120 (65.6)	125 (66.8)	141 (68.1)	129 (61.7)	115 (65.3)	117 (65.7)	71 (61.2)	76 (62.8)	185 (69.5)	170 (63.9)
1	64 (32.0)	79 (39.5)	63 (34.4)	62 (33.2)	66 (31.9)	80 (38.3)	61 (34.7)	61 (34.3)	45 (38.8)	45 (37.2)	81 (30.5)	96 (36.1)
Brain mets†	10 (5.0)	7 (3.5)	15 (8.2)	15 (8.0)	10 (4.8)	7 (3.3)	15 (8.5)	15 (8.4)	8 (6.9)	6 (5.0)	17 (6.4)	16 (6.0)
Visceral mets	146 (73.0)	137 (68.5)	135 (73.8)	131 (70.1)	147 (71.0)	141 (67.5)	134 (76.1)	127 (71.3)	75 (64.7)	77 (63.6)	205 (77.1)	191 (71.8)
Prior treatment status												
De novo					112 (54.1)	106 (50.7)	88 (50.0)	94 (52.8)	54 (46.6)	55 (45.5)	146 (54.9)	145 (54.5)
Recurrent					95 (45.9)	103 (49.3)	88 (50.0)	84 (47.2)	62 (53.4)	66 (54.5)	120 (45.1)	121 (45.5)
HR status												
Positive‡	112 (56.0)	106 (53.0)	95 (51.9)	103 (55.1)					61 (52.6)	64 (52.9)	146 (54.9)	145 (54.5)
Negative	88 (44.0)	94 (47.0)	88 (48.1)	84 (44.9)					55 (47.4)	57 (47.1)	120 (45.1)	121 (45.5)
***PIK3CA*m status**												
Detected	54 (27.0)	55 (27.5)	62 (33.9)	66 (35.3)	61 (29.5)	64 (30.6)	55 (31.3)	57 (32.0)				

Treatment arms were well balanced according to key disease characteristics

*One patient had missing *PIK3CA*m status; †participants were eligible if they had brain metastases that were clinically inactive or treated/asymptomatic; ‡defined as estrogen receptor–positive and/or progesterone receptor–positive (≥1%)
CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR(+/−), hormone receptor(–positive/–negative); mets, metastases; mo, months; NC, not calculable; P, pertuzumab; *PIK3CA*m, *PIK3CA* mutation; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

PFS by prior treatment status

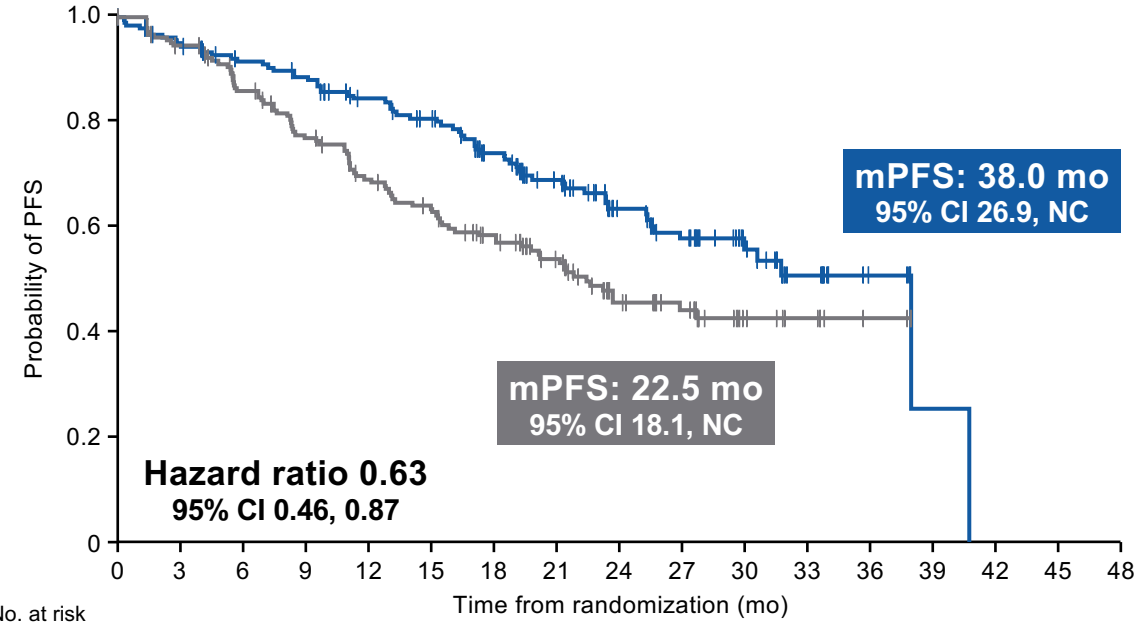
PFS:* *de novo*



No. at risk

T-DXd + P	200	189	179	171	157	148	136	124	117	106	55	35	16	9	3	0
THP	200	185	165	144	129	113	101	94	84	74	36	23	8	5	1	0

PFS:* recurrent



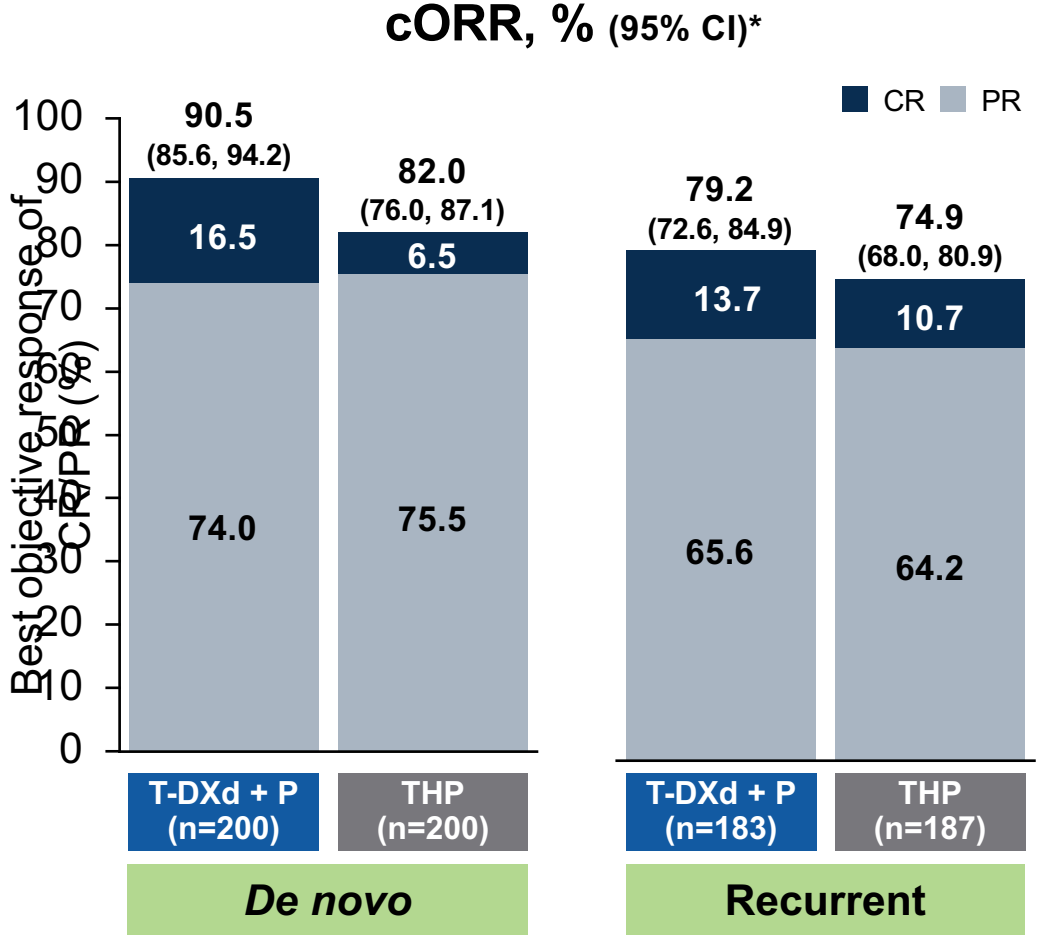
No. at risk

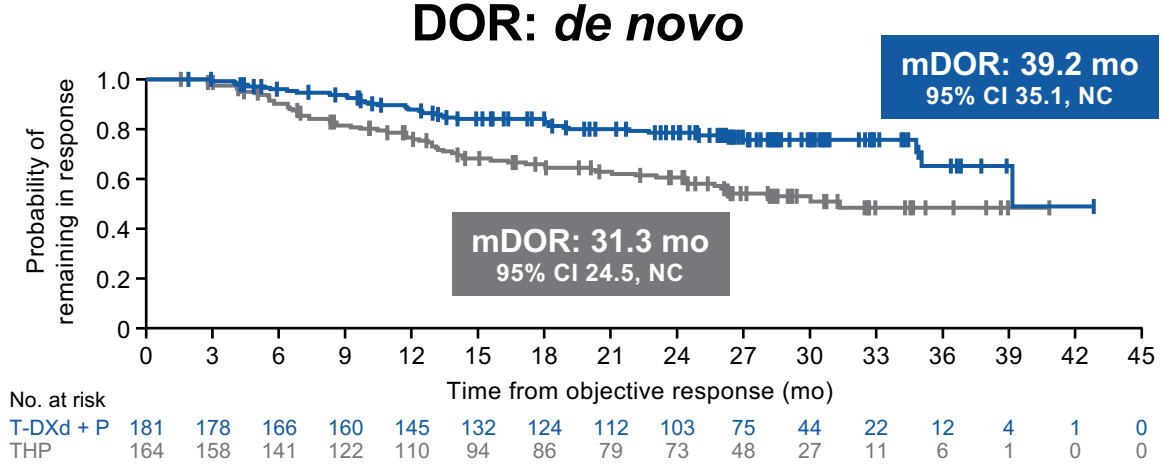
T-DXd + P	183	169	156	150	136	127	106	84	58	47	27	14	5	1	0	
THP	187	168	147	129	112	102	86	66	40	32	15	9	4	0	0	

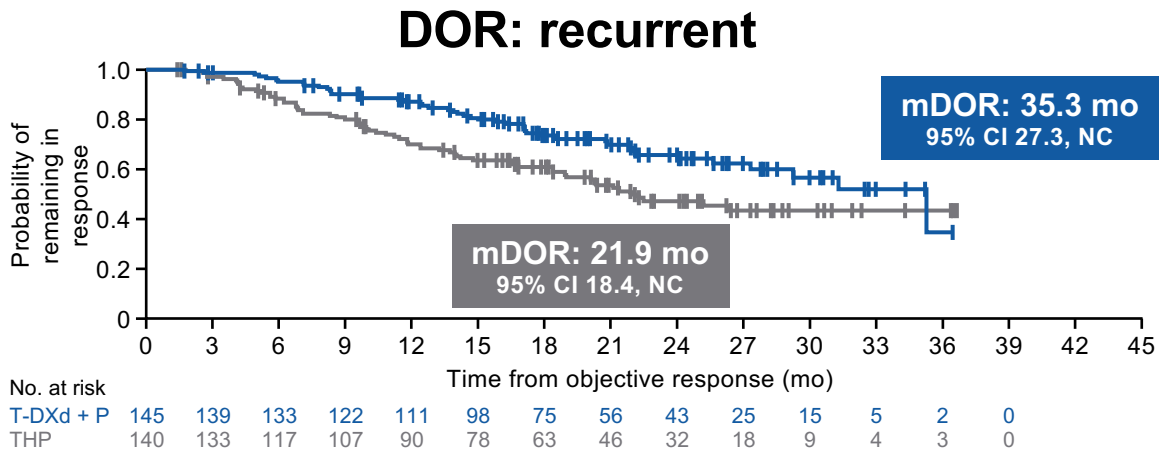
T-DXd + P demonstrated a clinically meaningful PFS benefit vs THP regardless of de-novo or recurrent status

*By blinded independent central review
CI, confidence interval; mPFS, median progression-free survival; mo, months; NC, not calculable; P, pertuzumab; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

cORR and DOR by prior treatment status







CR rates and DOR favored T-DXd + P vs THP regardless of prior treatment status

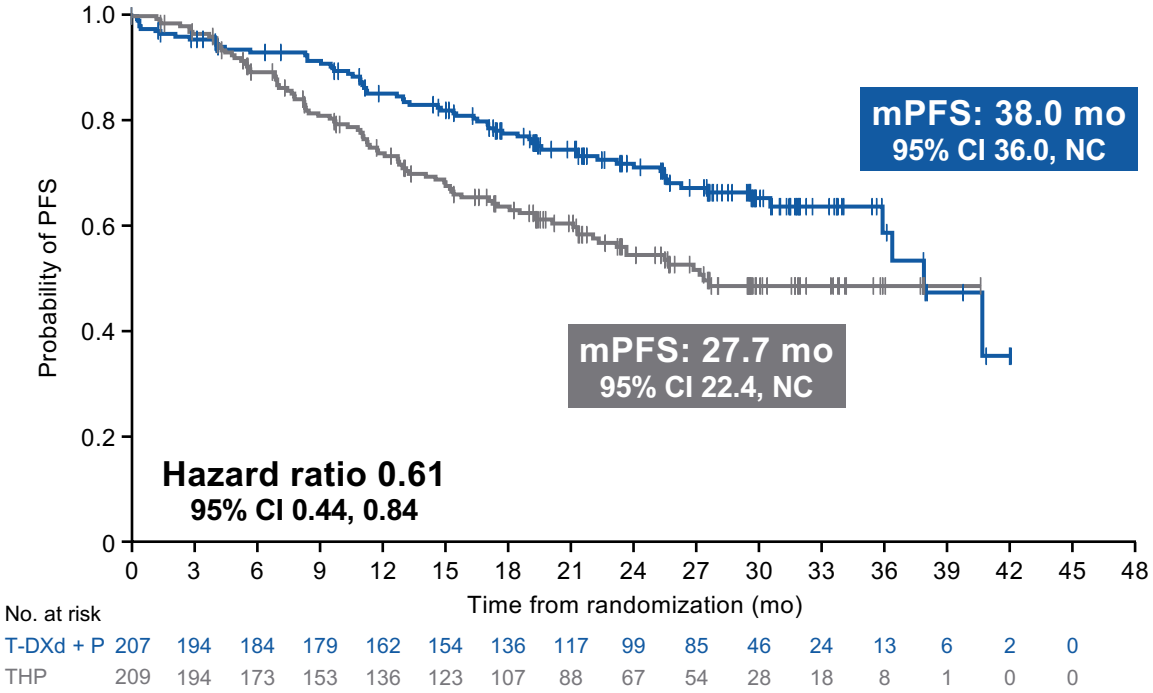
*By blinded independent central review

CI, confidence interval; cORR, confirmed objective response rate; CR, complete response; DOR, duration of response; mDOR, median duration of response; mo, months; NC, not calculable; P, pertuzumab; PR, partial response; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

Sibylle Loibl, MD, PhD

PFS by HR status

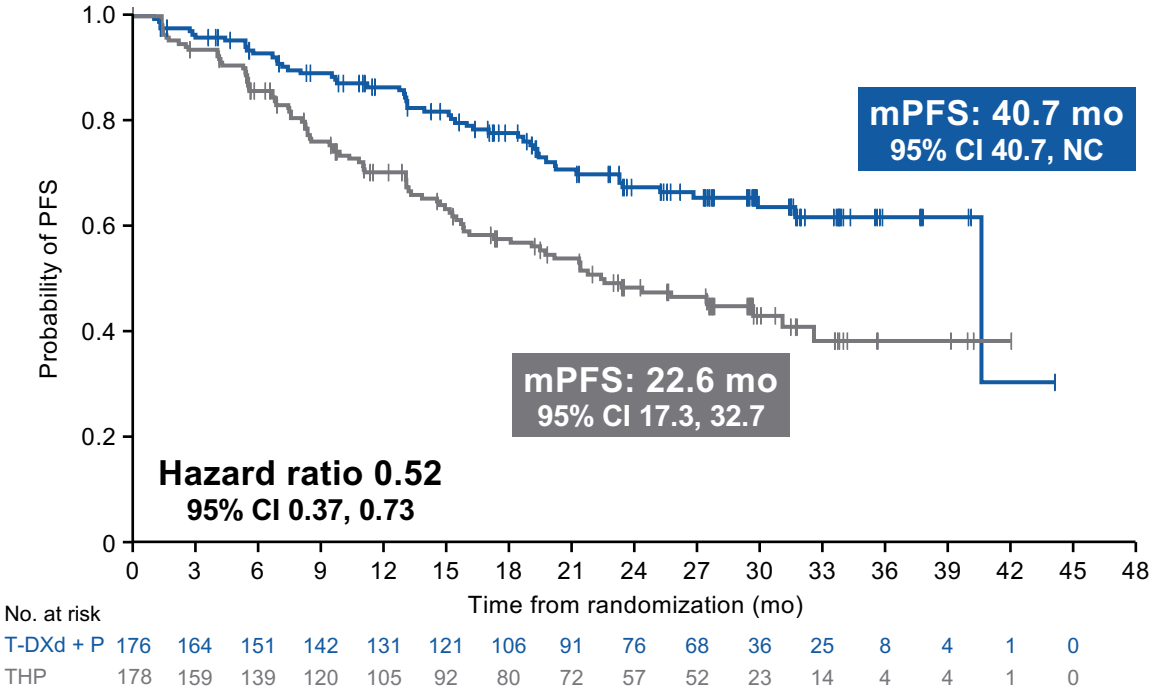
PFS:* HR+



No. at risk

T-DXd + P	207	194	184	179	162	154	136	117	99	85	46	24	13	6	2	0
THP	209	194	173	153	136	123	107	88	67	54	28	18	8	1	0	0

PFS:* HR−



No. at risk

T-DXd + P	176	164	151	142	131	121	106	91	76	68	36	25	8	4	1	0
THP	178	159	139	120	105	92	80	72	57	52	23	14	4	4	1	0

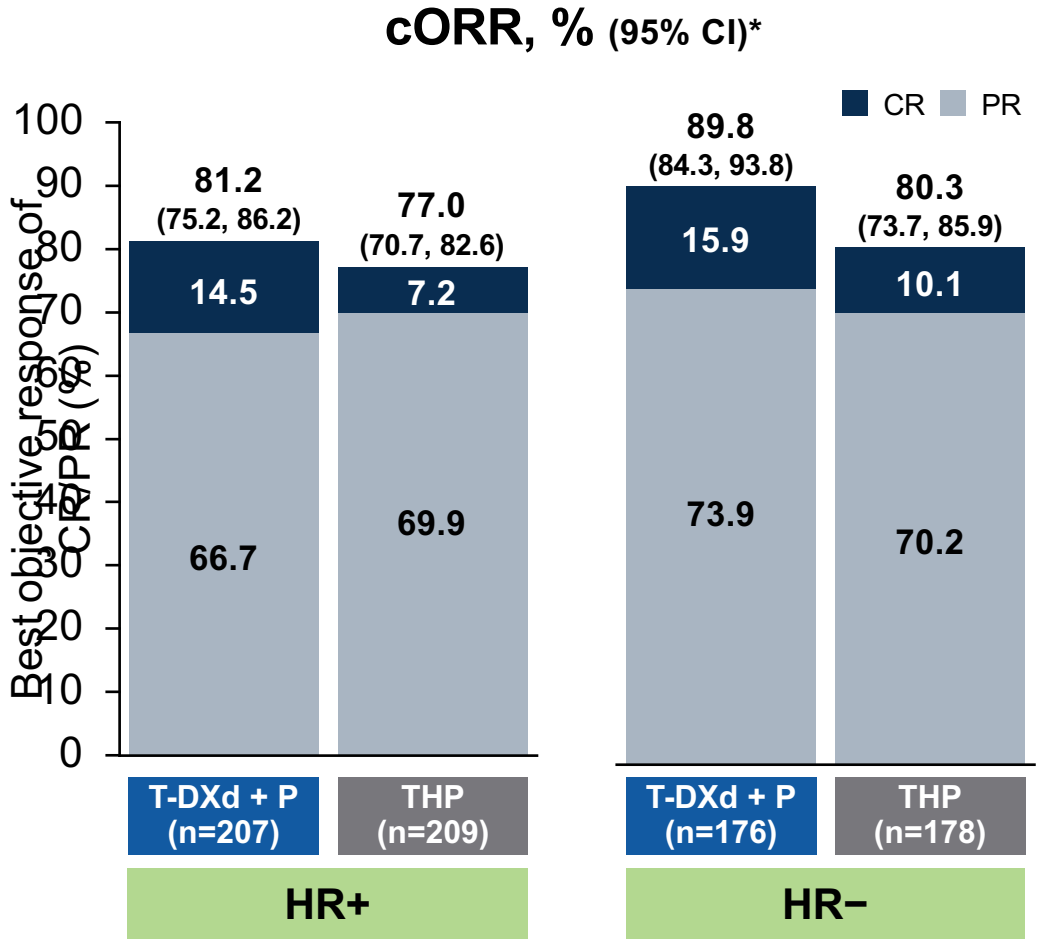
Patients with HR+ disease could receive concurrent ET after six cycles of T-DXd or discontinuation of taxane, which occurred in **13.5% (T-DXd + P)** versus **38.3% (THP)** of patients

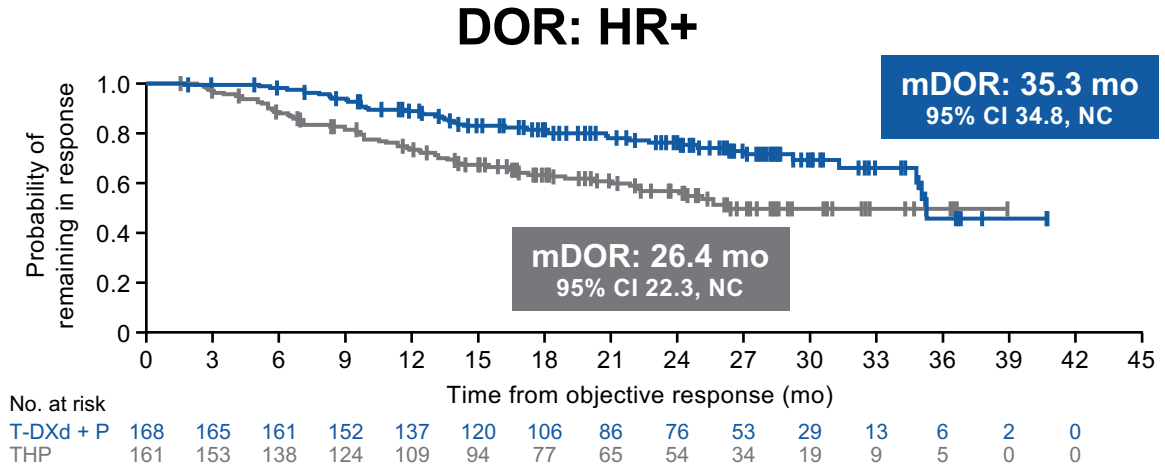
T-DXd + P demonstrated a clinically meaningful PFS benefit vs THP regardless of HR status

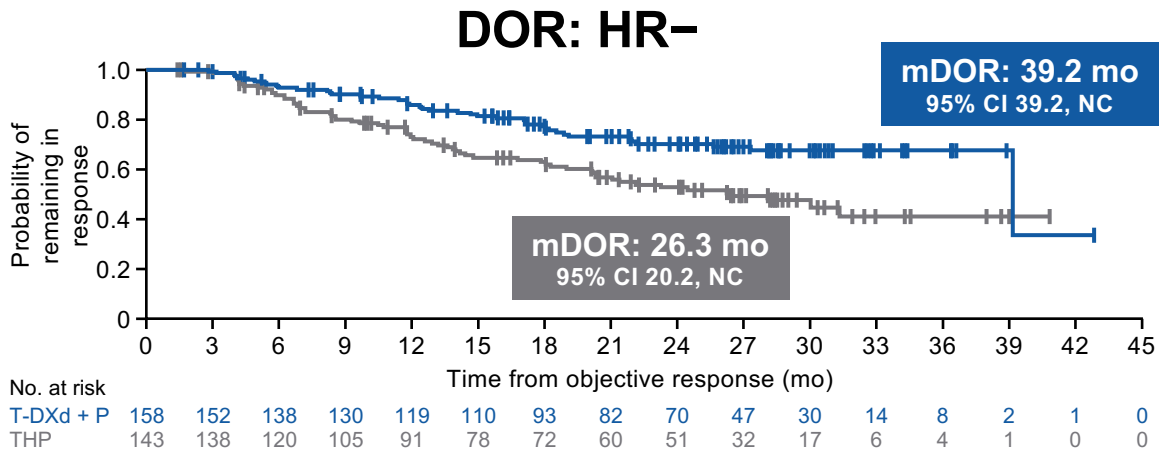
*By blinded independent central review
CI, confidence interval; ET, endocrine therapy; HR(+/−), hormone receptor(–positive/–negative); mPFS, median progression-free survival; mo, months; NC, not calculable; P, pertuzumab; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

Sibylle Loibl, MD, PhD

cORR and DOR by HR status







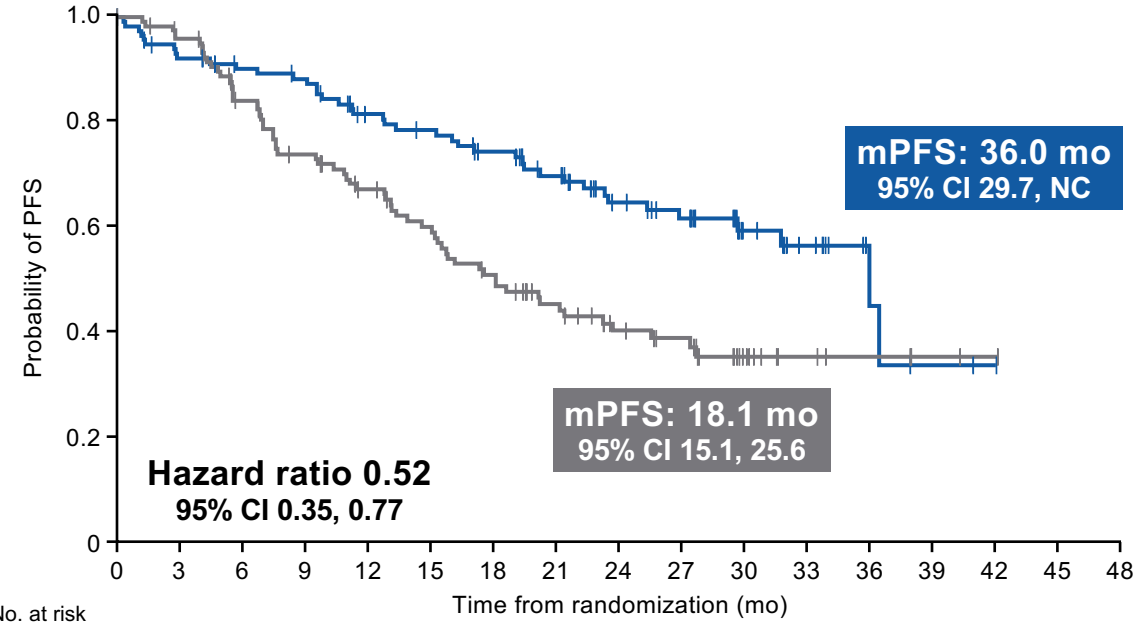
CR rates and DOR favored T-DXd + P vs THP regardless of HR status

*By blinded independent central review

CI, confidence interval; cORR, confirmed objective response rate; CR, complete response; DOR, duration of response; HR(+/−), hormone receptor(–positive/–negative); mDOR, median duration of response; mo, months; NC, not calculable; P, pertuzumab; PR, partial response; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

PFS by *PIK3CA*m status

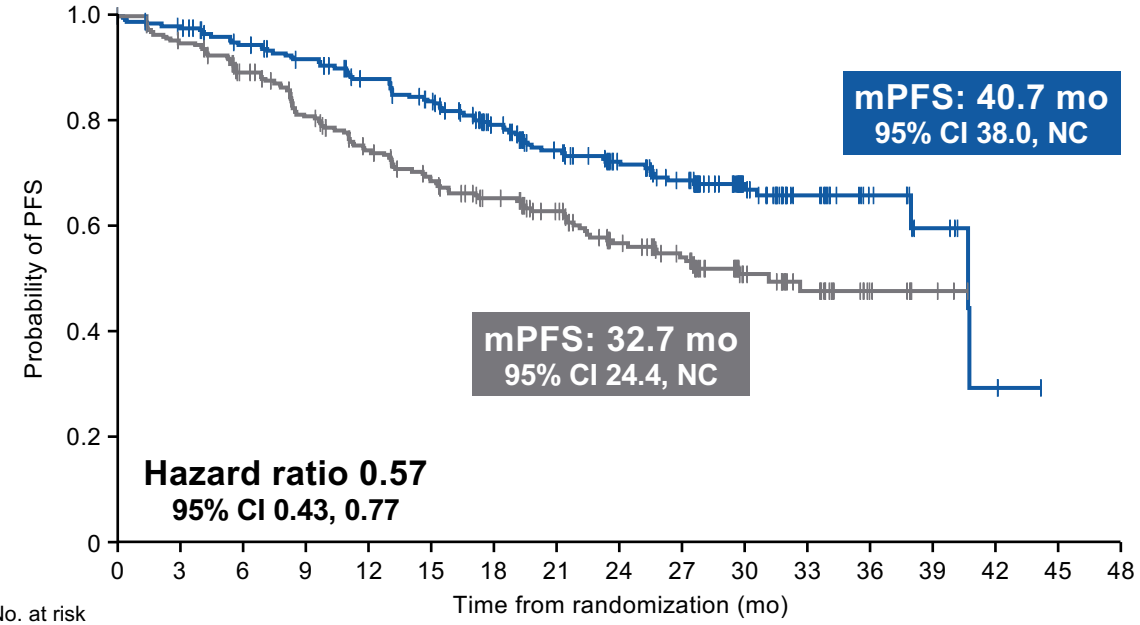
PFS:* *PIK3CA*m detected



No. at risk

T-DXd + P	116	102	96	93	81	77	70	60	47	40	21	13	5	2	1	0
THP	121	110	92	79	68	59	49	39	28	24	12	6	4	2	1	0

PFS:* *PIK3CA*m not detected†



No. at risk

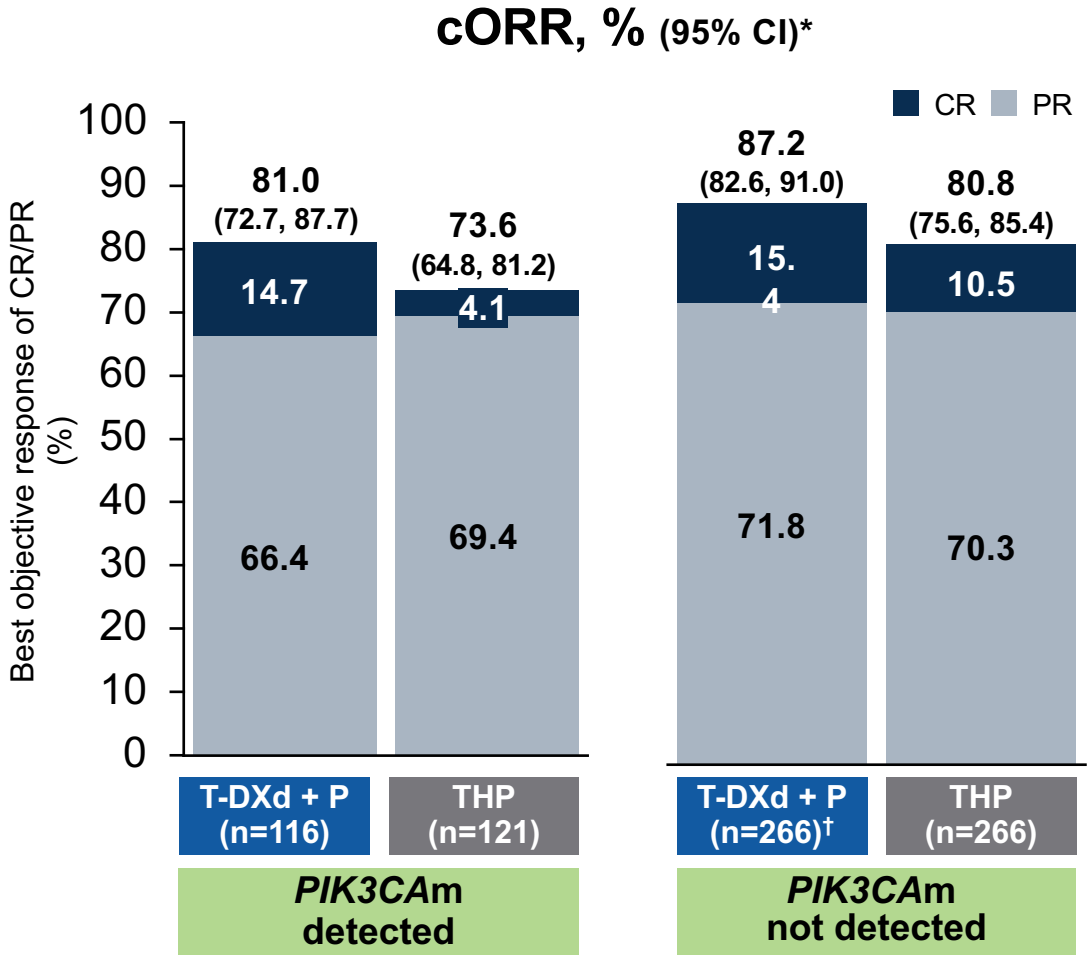
T-DXd + P	266	256	239	228	212	198	172	148	128	113	61	36	16	8	2	0
THP	266	243	220	194	173	156	138	121	96	82	39	26	8	3	0	0

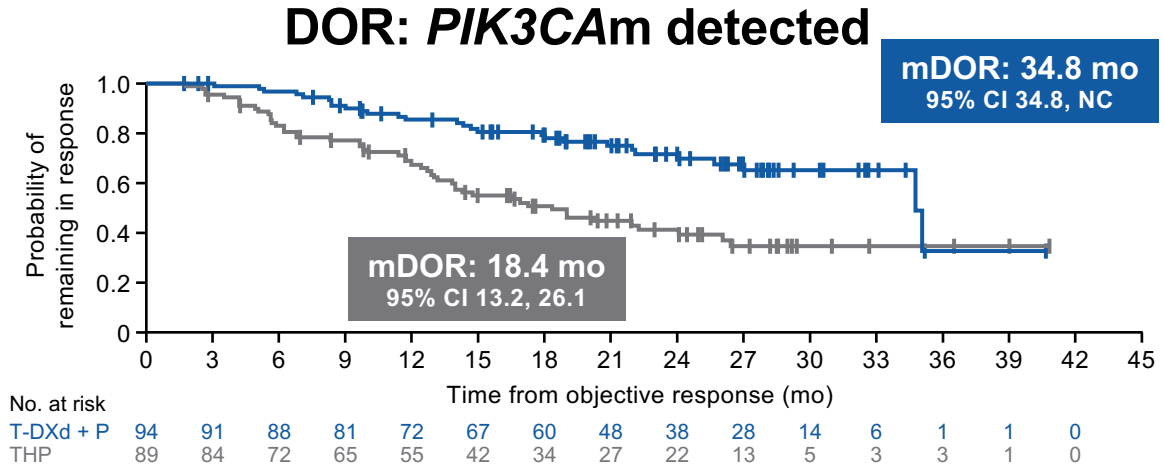
T-DXd + P demonstrated a clinically meaningful PFS benefit vs THP regardless of *PIK3CA*m status

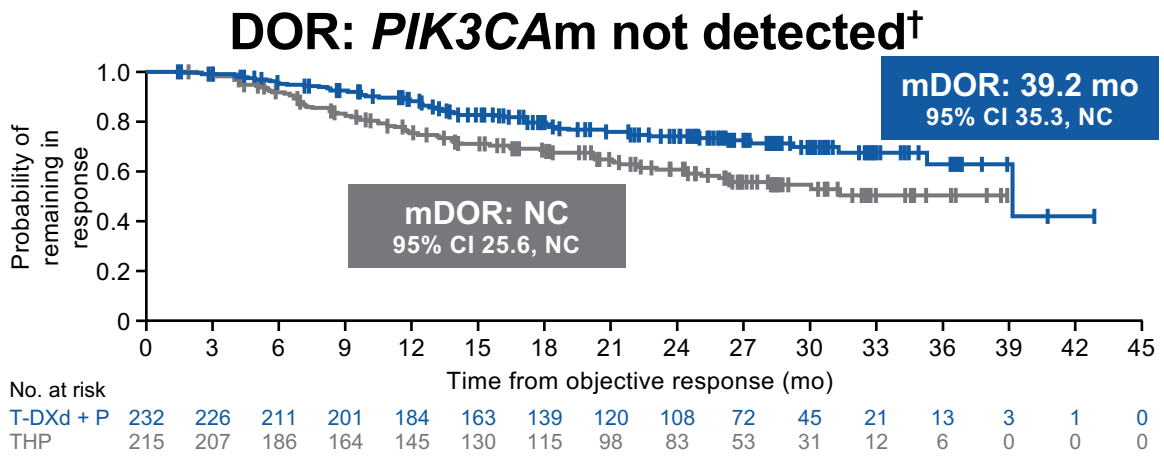
*By blinded independent central review; †one patient in the T-DXd + P arm had missing *PIK3CA*m status
CI, confidence interval; mo, months; mPFS, median progression-free survival; NC, not calculable; P, pertuzumab; PFS, progression-free survival; *PIK3CA*m, *PIK3CA* mutation; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

Sibylle Loibl, MD, PhD

cORR and DOR by *PIK3CA*m status







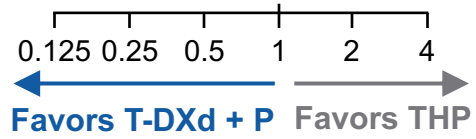
CR rates and DOR favored T-DXd + P vs THP regardless of *PIK3CA*m status

*By blinded independent central review; †one patient in the T-DXd + P arm had missing *PIK3CA*m status
CI, confidence interval; cORR, confirmed objective response rate; CR, complete response; DOR, duration of response; mDOR, median duration of response; mo, months; NC, not calculable; P, pertuzumab; *PIK3CA*m, *PIK3CA* mutation; PR, partial response; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

Sibylle Loibl, MD, PhD

PFS2 by subgroup

	No. of events / no. of patients		mPFS2, mo (95% CI)		Hazard ratio (95% CI)
	T-DXd + P	THP	T-DXd + P	THP	
Prior treatment status					
De novo	38/200	59/200	NC	37.4 (36.1, NC)	0.55 (0.36, 0.83)
Recurrent	41/183	56/187	NC	36.5 (30.2, NC)	0.66 (0.44, 0.99)
HR status					
Positive	38/207	62/209	NC	NC (33.2, NC)	0.54 (0.36, 0.81)
Negative	41/176	53/178	NC (39.6, NC)	36.5 (33.1, NC)	0.67 (0.44, 1.01)
***PIK3CA*m status**					
Detected	29/116	44/121	NC	33.2 (24.2, NC)	0.57 (0.35, 0.91)
Not detected	49/266*	71/266	NC (39.6, NC)	37.4 (36.1, NC)	0.61 (0.42, 0.87)

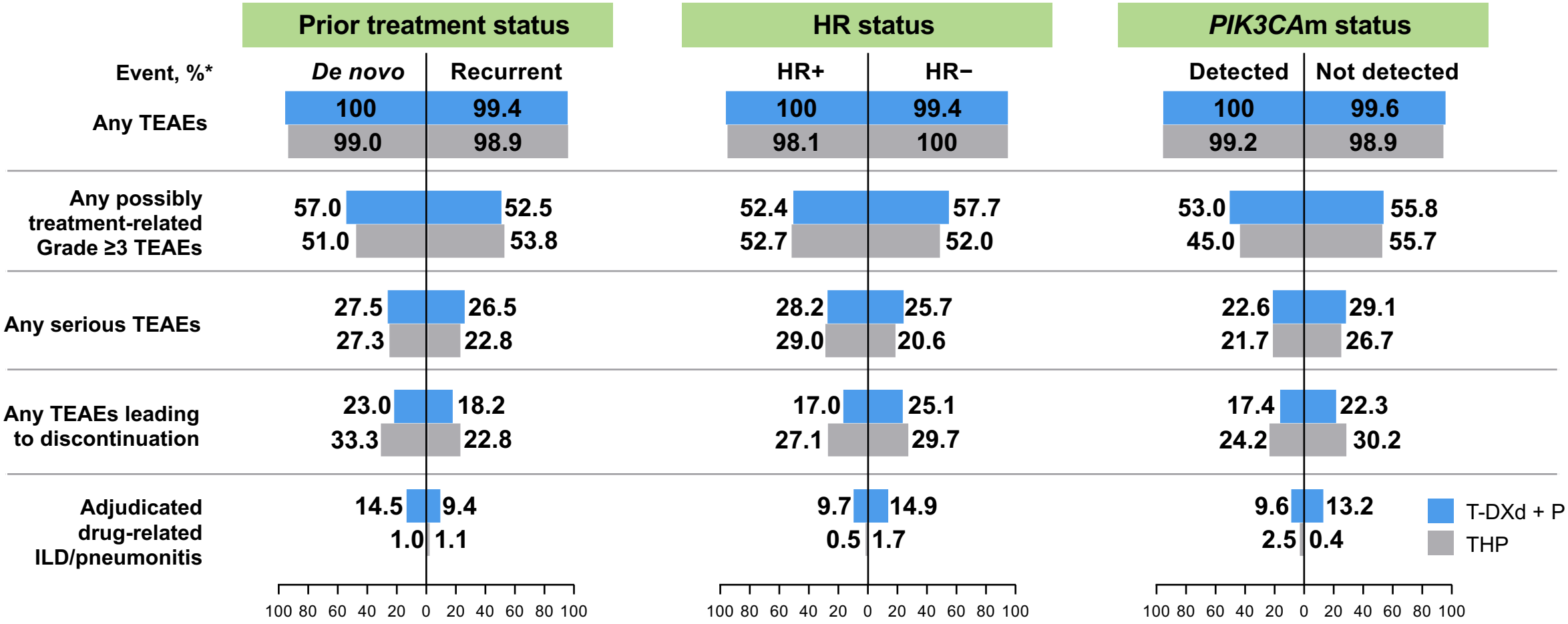


Clinically meaningful improvement in PFS2 with T-DXd + P vs THP across subgroups

*One patient in the T-DXd + P arm had missing *PIK3CA*m status. Size of circle is proportional to the number of events. PFS2 was defined by investigators according to local standard clinical practice as the time from randomization to second progression (earliest progression event following first subsequent therapy) or death
CI, confidence interval; HR, hormone receptor; mo, months; mPFS2, median second progression-free survival; NC, not calculable; P, pertuzumab; PFS2, second progression-free survival; *PIK3CA*m, *PIK3CA* mutation; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

Sibylle Loibl, MD, PhD

Safety summary by subgroup



Safety profiles in subgroups were in line with the overall safety population

*Includes TEAEs with an onset date on or after the date of first dose and up to and including 47 days following the date of last dose of study medication or before the initiation of the first subsequent cancer therapy (whichever occurs first). Safety analyses included all patients who received at least one dose of study medication (at least one study drug). HR(+/−), hormone receptor(–positive/–negative); ILD, interstitial lung disease; P, pertuzumab; *PIK3CA*m, *PIK3CA* mutation; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; THP, taxane + trastuzumab + pertuzumab

Conclusions

- In this subgroup analysis of DESTINY-Breast09, 1L treatment with T-DXd + P demonstrated a clinically meaningful PFS benefit vs THP regardless of prior treatment, HR, or *PIK3CA*m status, reflecting results in the overall population
- DOR consistently favored T-DXd + P (**median of ~3 years**), and CR rates were higher with T-DXd + P (**13.7–16.5%**) than THP (**4.1–10.7%**) in all subgroups
- No new safety signals were identified for T-DXd + P; safety outcomes for each arm were broadly similar across subgroups and in line with the overall population

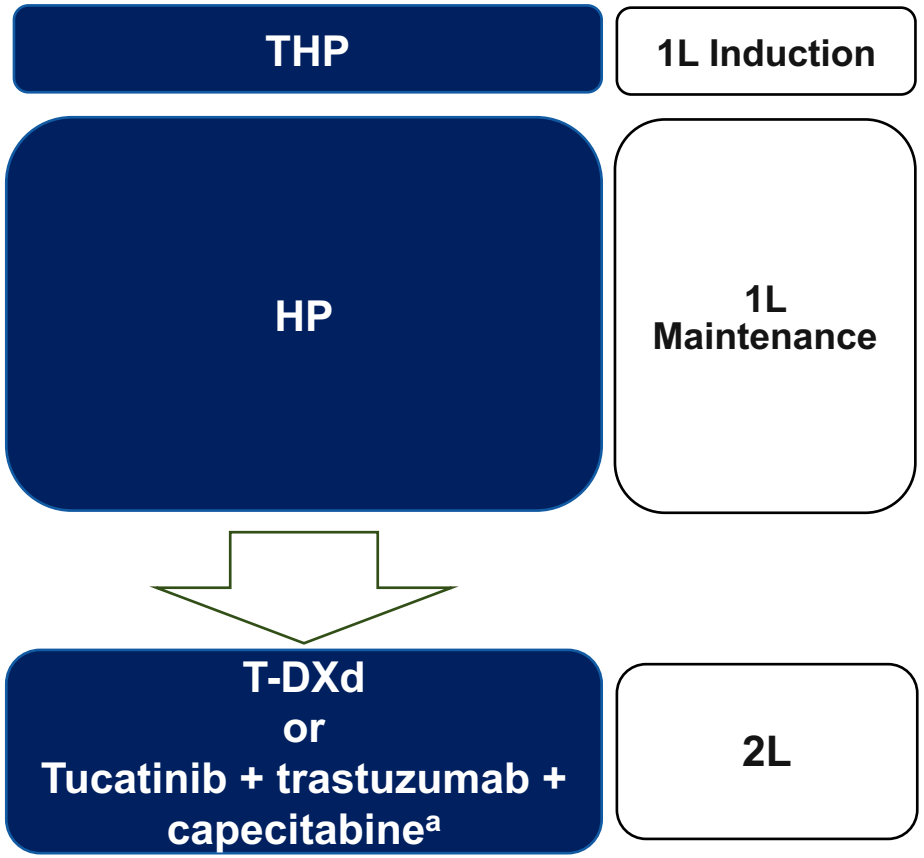
T-DXd + P represents an effective 1L treatment for patients with HER2+ a/mBC, regardless of prior treatment, HR, or *PIK3CA*m status

1L, first-line; a/mBC, advanced/metastatic breast cancer; CR, complete response; DOR, duration of response; HER2+, human epidermal growth factor receptor 2–positive; HR, hormone receptor; P, pertuzumab; PFS, progression-free survival; *PIK3CA*m, *PIK3CA* mutation; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

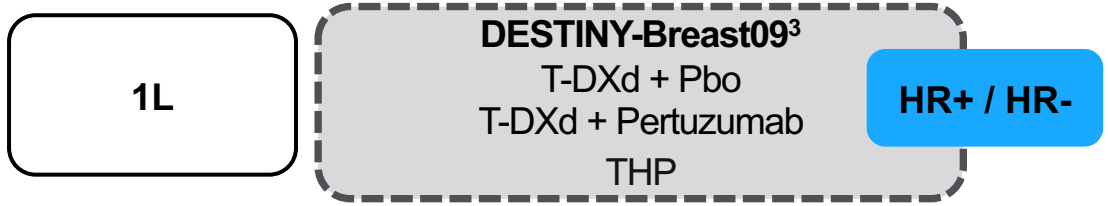
Sibylle Loibl, MD, PhD

Potential Practice-Changing Studies in the 1L HER2+ MBC Treatment Landscape

Current Treatment Algorithm[1,2]



Ongoing or Recently Reported Pivotal Trials: How to Deal With Complex Treatment Decisions?



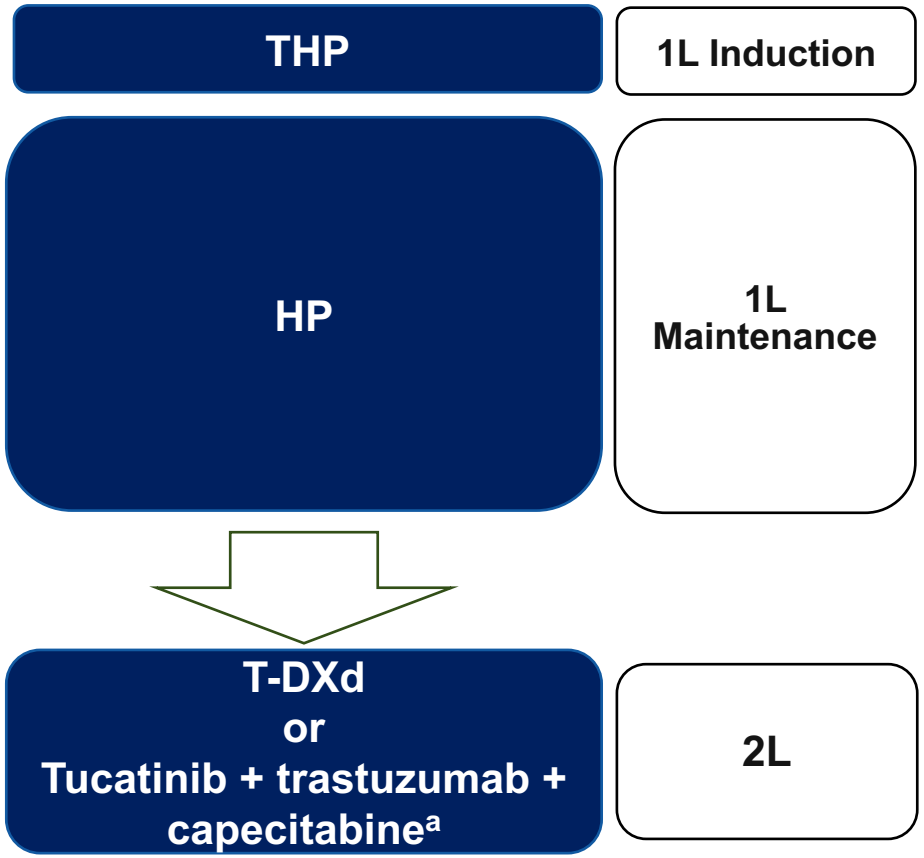
[a] Tucatinib is indicated in combination with trastuzumab and capecitabine for the treatment of adult patients with HER2+ locally advanced or MBC who have received at least 2 prior anti-HER2 treatment regimens.[4]

1L, first line; 2L, second line; EMA, European Medicines Agency; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HP, trastuzumab, pertuzumab; HR, hormone receptor; MBC, metastatic breast cancer; Pbo, placebo; T-DXd, trastuzumab deruxtecan; THP, docetaxel, trastuzumab, pertuzumab.

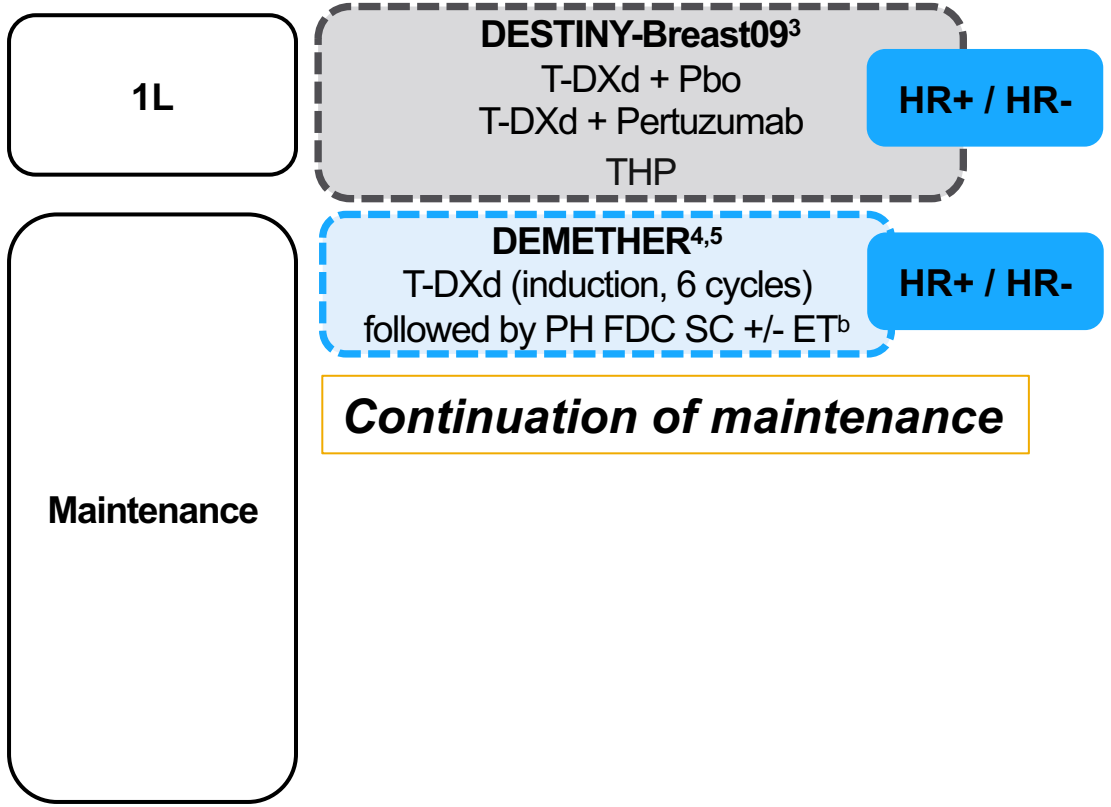
1. Gennari A, et al. *Ann Oncol*. 2021;32(12):1475-1495; 2. Curigliano G, et al. ESMO Metastatic Breast Cancer Living Guidelines, v1.2 April 2025. Accessed August 2025; 3. ClinicalTrials.gov. NCT04784715; 4. TUKYSA (tucatinib) [SmPC]. EMA. April 2025.

Potential Practice-Changing Studies in the 1L HER2+ MBC Treatment Landscape

Current Treatment Algorithm[1,2]

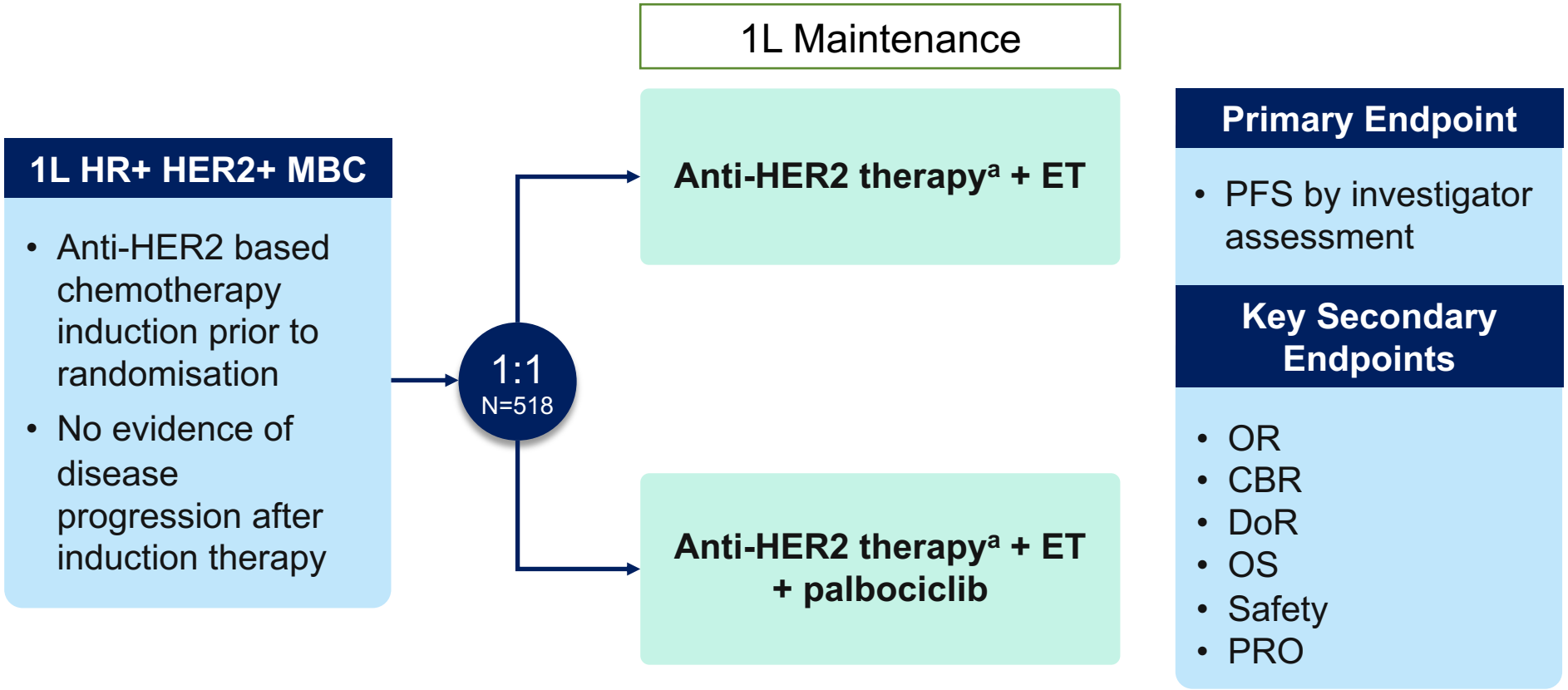


Ongoing or Recently Reported Pivotal Trials: How to Deal With Complex Treatment Decisions?



[a] Tucatinib is indicated in combination with trastuzumab and capecitabine for the treatment of adult patients with HER2+ locally advanced or MBC who have received at least 2 prior anti-HER2 treatment regimens.[6]
[b] One prior line of endocrine therapy is allowed for MBC.
1L, first line; 2L, second line; EMA, European Medicines Agency; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HP, trastuzumab, pertuzumab; HR, hormone receptor; MBC, metastatic breast cancer; Pbo, placebo; PH FDC SC, fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection; T-DXd, trastuzumab deruxtecan; THP, docetaxel, trastuzumab, pertuzumab.
1. Gennari A, et al. *Ann Oncol.* 2021;32(12):1475-1495; 2. Curigliano G, et al. ESMO Metastatic Breast Cancer Living Guidelines, v1.2 April 2025. Accessed August 2025; 3. ClinicalTrials.gov. NCT04784715; 4. ClinicalTrials.gov. NCT06172127; 5. Cortes J, et al. Poster presentation P5-03-11. SABCS 2024; 6. TUKYSA (tucatinib) [SmPC]. EMA. April 2025.

PATINA



Created from ClinicalTrials.gov. NCT02947685.

As per EMA, palbociclib is not approved as 1L maintenance therapy in HR+ HER2+ MBC.[2]

[a] Anti-HER2 therapy options are trastuzumab + pertuzumab or trastuzumab only. The same anti-HER2 regimen should be used pre- and post-randomisation. [b] Palbociclib is given at a starting dose of 125 mg as capsules taken orally once per day for 21 days followed by 7 days off to complete a 28-day cycle. Trastuzumab dosing is determined based on a loading dose on cycle 1 day 1 of 8 mg per kilogram of body weight every 3 weeks or a maintenance dose of 6 mg per kilogram of body weight every 3 weeks. Pertuzumab is administered at a loading dose of 840 mg infusion and then a maintenance dose of 420 mg every 3 weeks.

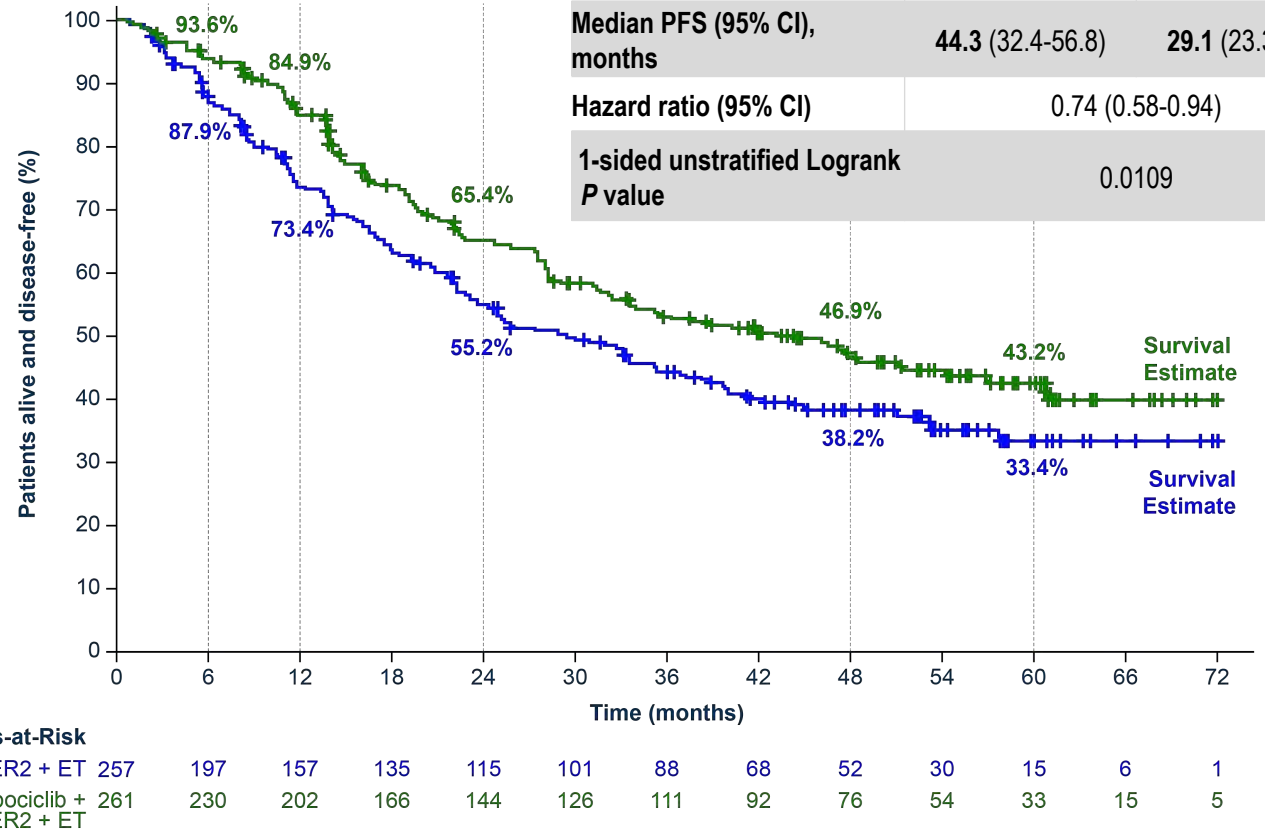
1L, first line; CBR, clinical benefit rate; DoR, duration of response; EMA, European Medicines Agency; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MBC, metastatic breast cancer; OR, objective response; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome.

1. ClinicalTrials.gov. NCT02947685; 2. IBRANCE (palbociclib) [SmPC]. EMA. March 2025. Accessed August 2025.

PATINA: Primary Results

Primary Endpoint
Investigator-Assessed PFS[1]

	Palbociclib+ anti-HER2 + ET	Anti-HER2 + ET
Events	127/261	135/257
Median PFS (95% CI), months	**44.3** (32.4-56.8)	**29.1** (23.3-38.6)
Hazard ratio (95% CI)	0.74 (0.58-0.94)	
1-sided unstratified Logrank *P* value	0.0109	



Patients-at-Risk

Anti-HER2 + ET	257	197	157	135	115	101	88	68	52	30	15	6	1
Palbociclib + anti-HER2 + ET	261	230	202	166	144	126	111	92	76	54	33	15	5

Median follow-up on patients who are alive and disease-free: 53.5 months

- Safety was consistent with the known toxicities of the individual agents.
- Grade ≥3 AEs reported more frequently (≥5% higher absolute difference) in palbociclib arm than in the control arm included neutropenia, diarrhea, fatigue, and leukopenia.
- Most AEs were manageable by dosing interruption and/or dose reduction.
- No treatment-related deaths were reported in either arm of the study.

AE, adverse event; CI, confidence interval; ET, endocrine therapy; HER2, human epidermal growth receptor-2; PFS, progression-free survival.

Reference: 1. Metzger O, *et al*. SABCS 2024. Presentation GS2-12.

Ines Vaz-Luis, MD

HER2CLIMB-05: Study Design

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

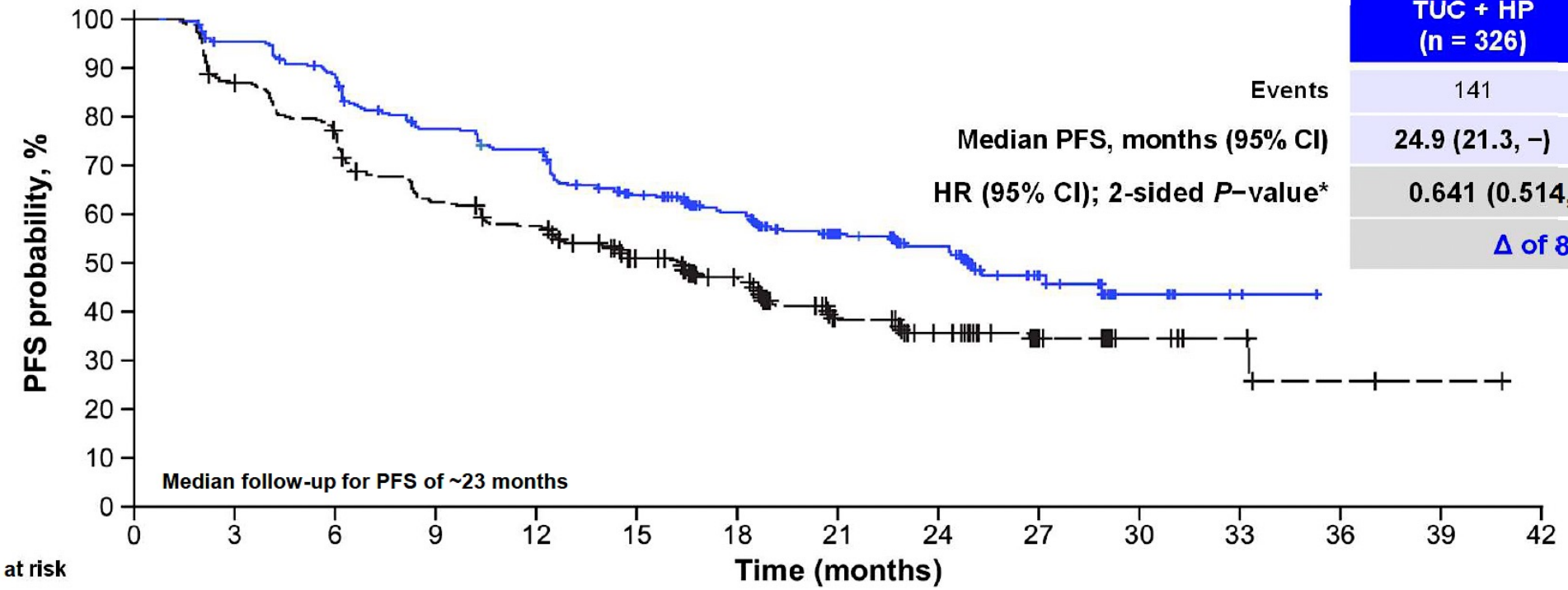
Primary
- Investigator-assessed PFS per RECIST v1.1

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).
1L = first-line; BICR = blinded independent central review; BM = brain metastases; CNS-PFS = central nervous system progression-free survival; ECOG PS = Eastern Cooperative Oncology Group performance status; ET = endocrine therapy; H = trastuzumab; HER2+ = human epidermal growth factor receptor 2-positive; HRQoL = health-related quality of life; IV = intravenous; MRI = magnetic resonance imaging; OS = overall survival; P = pertuzumab; PBO = placebo; PFS = progression-free survival; PO BID = orally twice a day; R = randomization; RECIST = Response Evaluation Criteria in Solid Tumors; SC = subcutaneous; T = taxane; TUC = tucatinib.

Hamilton E et al. SABCS 2025;Abstract GS1-01; Dieras V et al. *J Clin Oncol* 2025; Dec 10 [online ahead of print].

HER2CLIMB-05 Primary Endpoint: INV-Assessed PFS



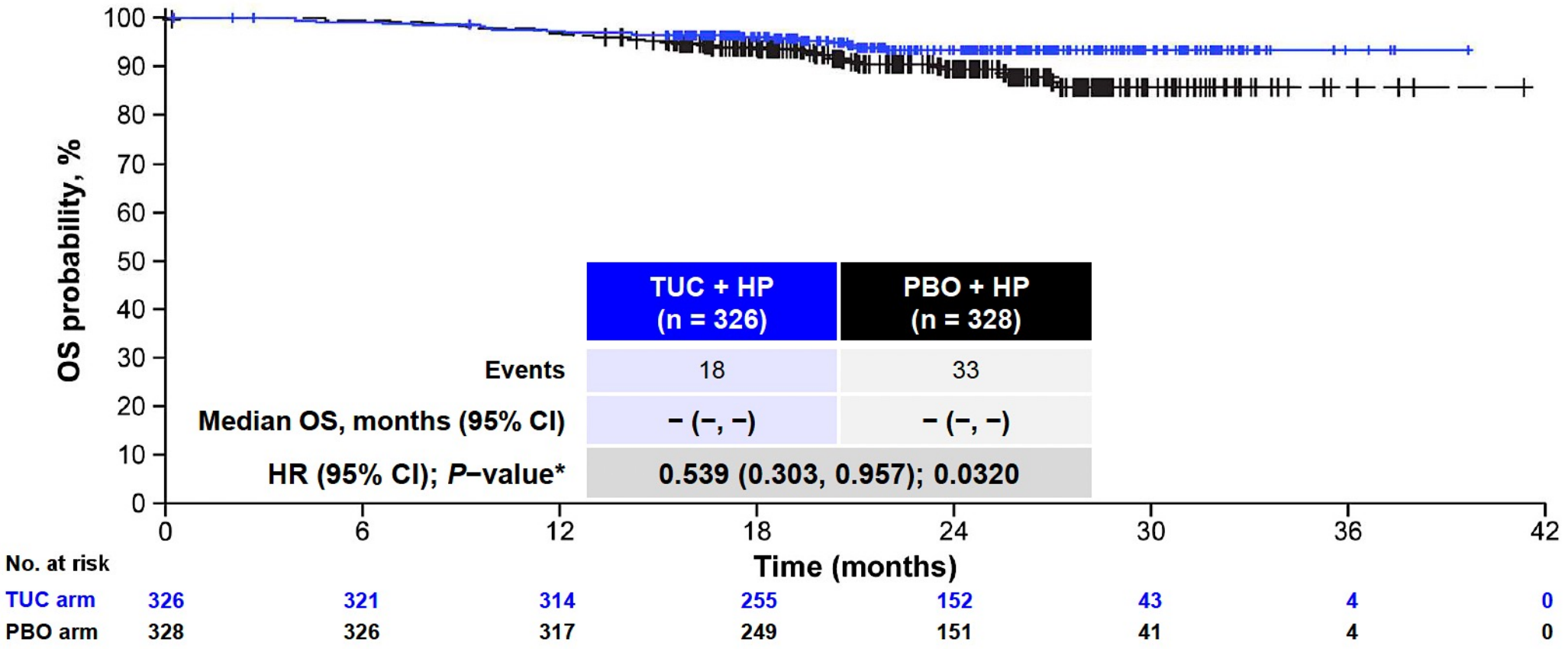
	TUC + HP (n = 326)	PBO + HP (n = 328)
Events	141	191
Median PFS, months (95% CI)	24.9 (21.3, –)	16.3 (12.6, 18.7)
HR (95% CI); 2-sided *P*–value*	0.641 (0.514, 0.799); < 0.0001	
	Δ of 8.6 months	

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.

Data cutoff of date: September 5, 2025. *Two-sided *P*-value based on stratified log-rank test.
CI = confidence interval; H = trastuzumab; HER2+ = human epidermal growth factor receptor 2-positive; HR = hazard ratio; MBC = metastatic breast cancer; P = pertuzumab; PBO = placebo; PFS = progression-free survival; TUC = tucatinib.

Hamilton E et al. SABCS 2025;Abstract GS1-01; Dieras V et al. *J Clin Oncol* 2025; Dec 10 [online ahead of print].

HER2CLIMB-05 Key Secondary Endpoint: OS



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

At the data cutoff of September 5, 2025, a total of 51 deaths have occurred.
*Two-sided *P*-value based on stratified log-rank test.
CI = confidence interval; H = trastuzumab; HR = hazard ratio; OS = overall survival; P = pertuzumab; PBO = placebo; TUC = tucatinib.

Hamilton E et al. SABCS 2025;Abstract GS1-01; Dieras V et al. *J Clin Oncol* 2025; Dec 10 [online ahead of print].

HER2CLIMB-05: Hepatic and Diarrhea TEAEs

Hepatic TEAEs	TUC + HP (n = 326)	PBO + HP (n = 324)
Any, n (%)	142 (43.6)	51 (15.7)
Grade 1	51 (15.6)	35 (10.8)
Grade 2	32 (9.8)	12 (3.7)
Grade 3	50 (15.3)	4 (1.2)
Grade 4	8 (2.5)	0
Grade 5	1 (0.3)*	0
Days to grade ≥3 onset, median	40.0	386.5
Days to grade ≥3 resolution, median	40.0	10.0
Dose modification due to any, n (%)		
TUC/PBO dose hold	63 (19.3)	8 (2.5)
TUC/PBO dose reduction	53 (16.3)	3 (0.9)
TUC/PBO discontinuation	25 (7.7)	0

Diarrhea TEAEs†	TUC + HP (n = 326)	PBO + HP (n = 324)
Any, n (%)	237 (72.7)	166 (51.2)
Grade 1	114 (35.0)	110 (34.0)
Grade 2	103 (31.6)	43 (13.3)
Grade 3	20 (6.1)	13 (4.0)
Grade 4	0	0
Grade 5	0	0
Days to grade 3 onset, median	49.5	149.0
Days to grade 3 resolution, median	8.0	14.0
Dose modification due to any, n (%)		
TUC/PBO dose hold	28 (8.6)	11 (3.4)
TUC/PBO dose reduction	21 (6.4)	10 (3.1)
TUC/PBO discontinuation	5 (1.5)	3 (0.9)

*A single grade 5 case of severe DILI was reported; however, the event was complicated by several confounding factors and was ultimately assessed as highly probable DILI with metamizole identified as the most likely causative agent.
†Prophylactic use of antidiarrheal medications was not required.
DILI = drug-induced liver injury; H = trastuzumab; P = pertuzumab; PBO = placebo; TEAE = treatment-emergent adverse event; TUC = tucatinib.

Hamilton E et al. SABCS 2025;Abstract GS1-01; Dieras V et al. *J Clin Oncol* 2025; Dec 10 [online ahead of print].

HER2CLIMB-05: Conclusions

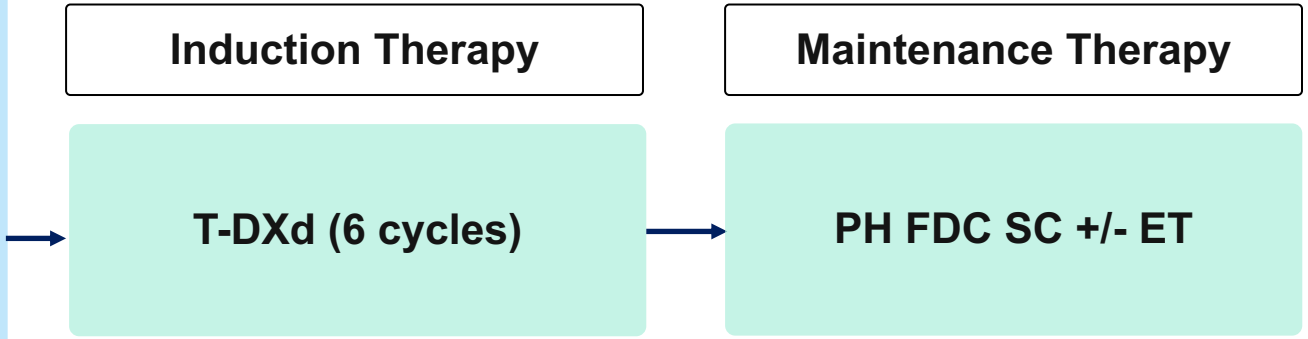
- In HER2CLIMB-05, the addition of TUC to 1L maintenance therapy with HP demonstrated a statistically significant and clinically meaningful PFS benefit in patients with HER2+ MBC.
  - 36% reduction in risk of disease progression or death
  - Median PFS: 24.9 vs 16.3 months; an 8.6-month improvement
  - Benefit was observed across all patient subgroups
- Preliminary OS data suggest a positive trend favoring TUC + HP.
- The TUC + HP combination showed a manageable safety profile, with diarrhea, nausea, and elevated liver enzymes, mostly of low grade, being the most common adverse events.
- HER2CLIMB-05 has demonstrated that addition of TUC to HP represents an enhanced 1L maintenance therapy option for patients with HER2+ MBC, providing an opportunity to prolong time to disease progression and time off chemotherapy.

Hamilton E et al. SABCS 2025;Abstract GS1-01.

DEMETHER

1L HER2+ MBC[1]

- No prior systemic therapy for advanced disease (one prior line of ET for advanced breast cancer)
- Participants may have received CT or/and 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



Primary Endpoints

- 1-year PFS[a]
- 3-year OS

Created from Cortes J, et al. SABCS 2025. Poster Presentation P5-03-11.

T-DXd will be administered at a dose of 5.4 mg/kg intravenously on day 1 of each 21-day cycle. The subcutaneous fixed-dose combination of pertuzumab and trastuzumab will be administered each 21-day cycle until disease progression.

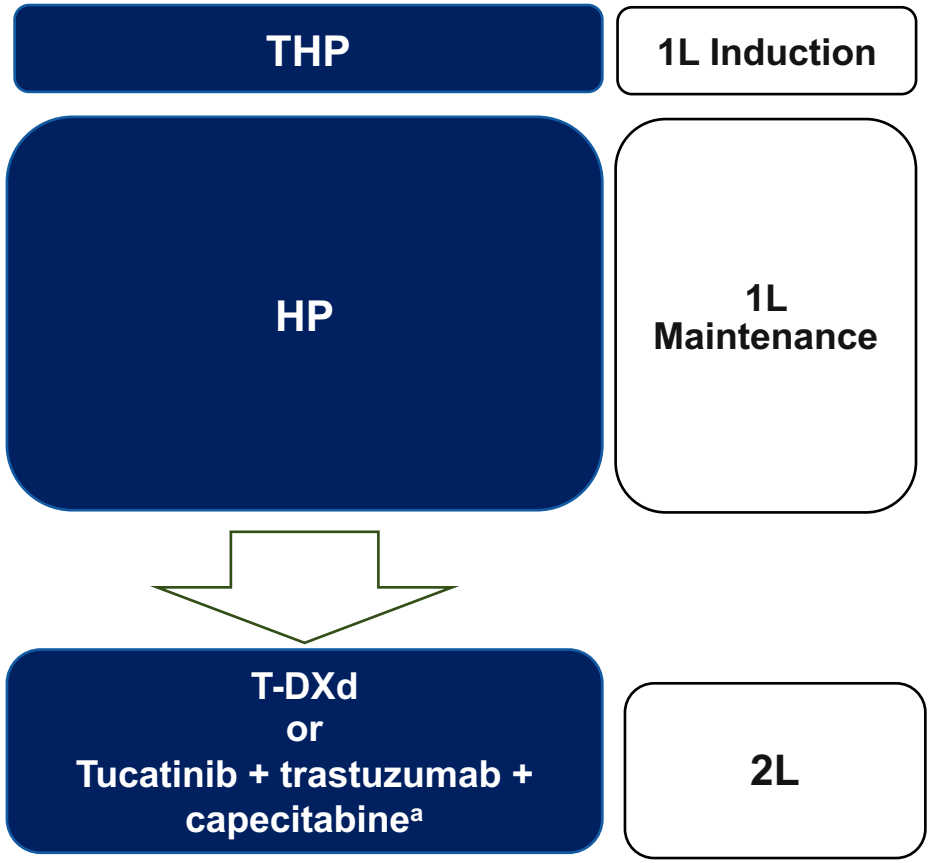
[a] Locally determined by the Investigator according to RECIST v1.1.

1L, first line; CT, chemotherapy; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; PH FDC SC, fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection; T-DXd, trastuzumab deruxtecan.

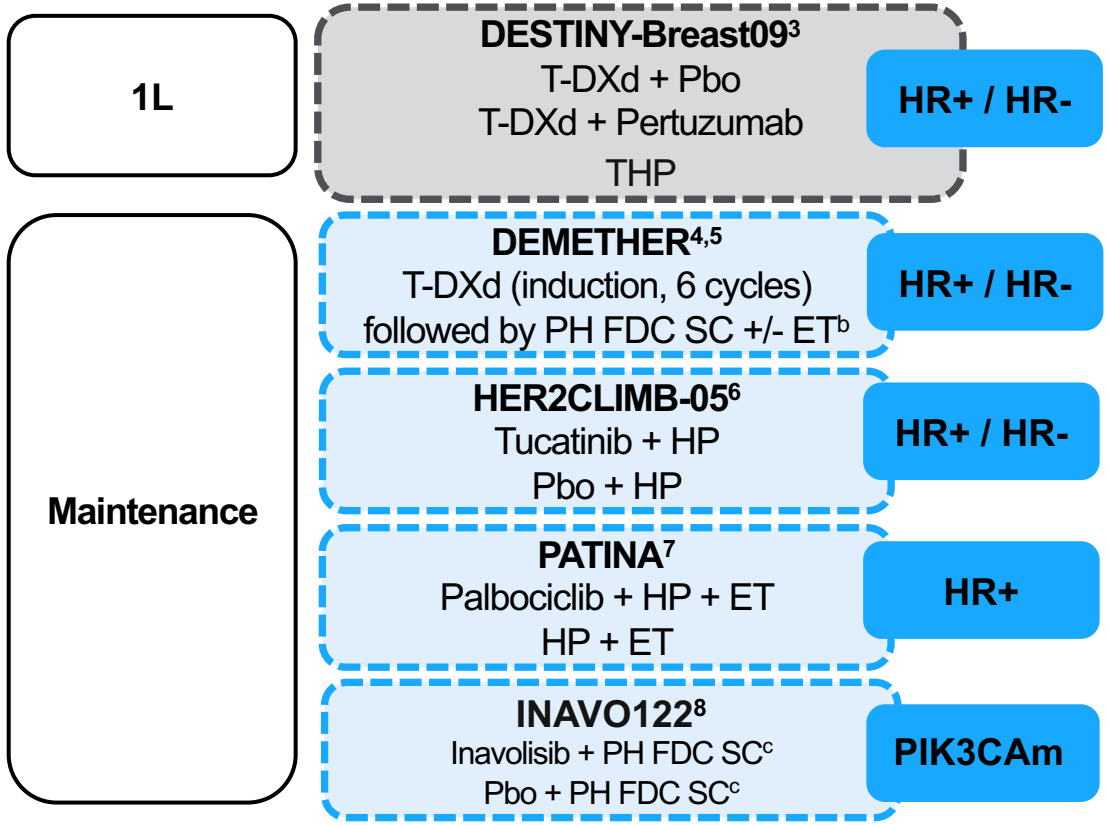
Cortes J, et a. SABCS 2025. Poster Presentation P5-03-11.

Potential Practice-Changing Studies in the 1L HER2+ MBC Treatment Landscape

Current Treatment Algorithm[1,2]



Ongoing or Recently Reported Pivotal Trials: How to Deal With Complex Treatment Decisions?[3-8]



As per EMA, palbociclib is not approved as 1L maintenance therapy in HR+ HER2+ MBC.[9] As per EMA, tucatinib is not approved as 1L maintenance therapy in HER2+ MBC.[10]

[a] Tucatinib is indicated in combination with trastuzumab and capecitabine for the treatment of adult patients with HER2+ locally advanced or MBC who have received at least 2 prior anti-HER2 treatment regimens.[9] [b] One prior line of endocrine therapy is allowed for MBC. [c] Fixed-dose combination of pertuzumab plus trastuzumab and rHuPH20 injection for subcutaneous use.[8,11]

1L, first line; 2L, second line; EMA, European Medicines Agency; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HP, trastuzumab, pertuzumab; HR, hormone receptor; MBC, metastatic breast cancer; Pbo, placebo; PH FDC SC, fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection; T-DXd, trastuzumab deruxtecan; THP, docetaxel, trastuzumab, pertuzumab.

1. Gennari A, et al. *Ann Oncol*. 2021;32(12):1475-1495; 2. Curigliano G, et al. ESMO Metastatic Breast Cancer Living Guidelines, v1.2 April 2025. Accessed August 2025; 3. ClinicalTrials.gov. NCT04784715; 4. ClinicalTrials.gov. NCT06172127; 5. Cortes J, et al. Poster presentation P5-03-11. SABCS 2024; 6. ClinicalTrials.gov. NCT05132582; 7. ClinicalTrials.gov. NCT02947685; 8. ClinicalTrials.gov. NCT05894239; 9. IBRANCE (palbociclib) [SmPC]. EMA. March 2025; 10. TUKYSA (tucatinib) [SmPC]. EMA. April 2025; 11. Swain SM, et al. *J Clin Oncol*. 2024;42(16_suppl):TPS1124-TPS1124.

Case Presentation: 82-year-old woman presents with de novo metastatic (bone-only) ER-positive, HER2-positive breast cancer

Dr Zanetta Lamar (Naples, Florida)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

For which patients with HER2-positive mBC would you prioritize T-DXd/pertuzumab in the first-line setting? Would it be a consideration for older patients like this?

How are you most likely to approach maintenance therapy when employing first-line T-DXd/pertuzumab? Will you continue T-DXd/pertuzumab indefinitely or switch to an alternative maintenance approach after a certain duration?

If a patient with HR-positive, HER2-positive mBC received first-line T-DXd/pertuzumab, would you consider using a CDK4/6 inhibitor as a component of maintenance therapy?

Agenda

Module 1: Considerations in the Care of Patients with Localized HER2-Positive Breast Cancer — Prof Harbeck

Module 2: Previously Untreated HER2-Positive Metastatic Breast Cancer (mBC) — Prof Curigliano

Module 3: Optimal Management of Brain Metastases in Patients with HER2-Positive Breast Cancer — Dr Lin

Module 4: Selection and Sequencing of Therapy for Relapsed/Refractory (R/R) HER2-Positive mBC in the Absence of CNS Involvement — Dr Krop

Module 5: Tolerability Considerations with HER2-Targeted Therapies — Dr O'Shaughnessy

Optimal Management of Brain Metastases in Patients with HER2-Positive Breast Cancer

Nancy U. Lin, MD

Dana-Farber Cancer Institute

Boston, MA USA

December 10, 2025

Dana-Farber Cancer Institute

Incidence of Brain Metastases in Pts with MBC

RWD from U.S. Flatiron Database

Line of therapy	HR+, HER2- positive	HR–, HER2- positive	HR+, HER2– [HR+, HER2-low]	TNBC [HR–, HER2-low]
Number of pts, n				
1	3062	902	12331 [7062]	1780 [725]
2	1936	478	8120 [4721]	972 [422]
3	1232	281	5303 [3101]	526 [240]
4	761	159	3454 [2002]	283 [129]
5+	453	103	2191 [1276]	141 [70]
Prevalence of BM, %				
1	193 (6.3)	101 (11.2)	134 (2.5) [199 (2.8)]	109 (10.3) [88 (12.1)]
2	341 (17.6)	149 (31.2)	150 (4.4) [275 (5.8)]	97 (17.6) [73 (17.3)]
3	265 (21.5)	102 (36.3)	125 (6.7) [231 (7.4)]	63 (22.0) [50 (20.8)]
4	199 (26.1)	59 (37.1)	104 (7.2) [189 (9.4)]	38 (24.7) [36 (27.9)]
5+	120 (26.5)	38 (36.9)	78 (8.5) [134 (10.5)]	23 (32.4) [18 (25.7)]

Data from 18,075 patients with MBC in the Flatiron database who had initiated a 1L of therapy up to March 1, 2021 to allow at least 2y follow-up

By 3L of therapy, **21.5%** of HR+/HER2+, **36.3%** of HR-/HER2+ have developed brain metastases

Older data from the HERA trial (Pestalozzi et al, Lancet Oncol 2013) where HER2+ pts were followed until death reported that **47%** of trastuzumab-treated pts eventually developed brain mets

Sammons et al, JNCI 2025

Prospective study of screening brain MRI in HER2+ or TN MBC

Brain MRI at baseline, end of 1L, end of 2L systemic therapy

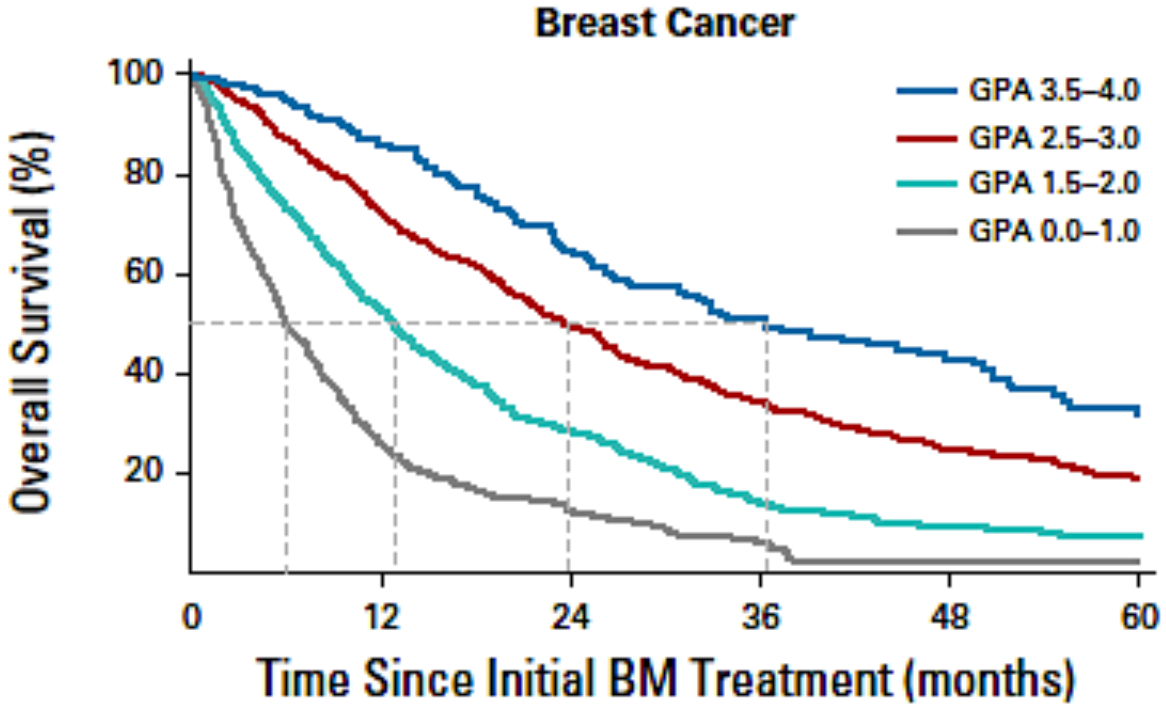
	TNBC	ER-/HER2+	ER+/HER2+
	N=75	N=43	N=29
Initial BM	8 (10.7)	5 (11.6)	1 (3.4)
Asymptomatic BM	18 (24.0)	6 (14.0)	6 (20.7)
Symptomatic BM	11 (14.7)	8 (18.6)	2 (6.9)
All BM	29 (38.7)	14 (32.6)	8 (27.6)

Initial tx: SRS (58.8%), WBRT (27.5%), surgery (3.9%), no treatment (11.8%)
Median OS after BM dx: 23.7 mo in asymptomatic vs 7.3 mo in symptomatic (HR 0.41, p=0.04)

Kim et al, SABCS 2023

Survival after BM is most favorable in HER2+ MBC

OS by DS-GPA in Multi-Institutional Academic Database



No. at risk:					
GPA 3.5–4.0	173	141	88	60	45
GPA 2.5–3.0	654	449	262	149	92
GPA 1.5–2.0	769	369	162	69	38
GPA 0.0–1.0	376	85	32	13	3

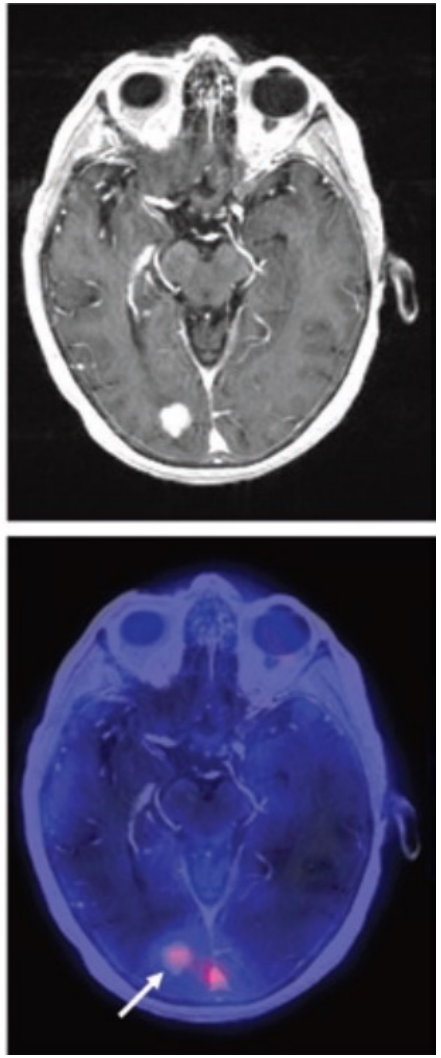
Prognostic Factor by Cancer Type	GPA 0	0.5	1.0	1.5	2.0	Patient Score
Breast cancer						
KPS	≤ 60	70-80	90-100	NA	NA	
Age, years	≥ 60	< 60	NA	NA	NA	
No. of BM	≥ 2	1	NA	NA	NA	
ECM	Present	Absent	NA	NA	NA	
Subtype	Basal	Luminal A	NA	Her2 or Luminal B	NA	
					Sum =	MS (months) by GPA: 0-1 = 6; 1.5-2.0 = 13; 2.5-3.0 = 24; 3.5-4.0 = 36

Note: These data do not reflect widespread adoption of tucatinib and T-DXd. There is a plan to re-update the breast cancer database for the next Breast GPA update in 2026 to reflect patients dx'd 2018-2025

Sperduto et al, J Clin Oncol 2020

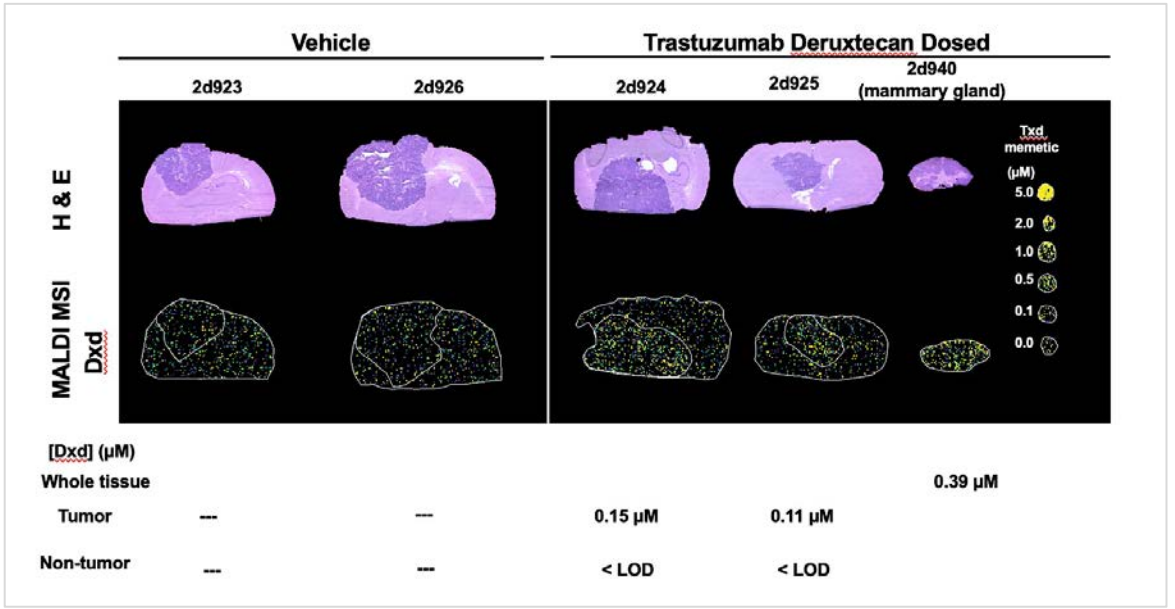
The Blood-Tumor Barrier is leaky

Provides a therapeutic window for ADCs in the CNS



Biodistribution of 89Zr-trastuzumab and PET Imaging of HER2-Positive Lesions in Patients With Metastatic Breast Cancer

EC Dijkers, et al
Clinical pharmacology & Therapeutics
2010

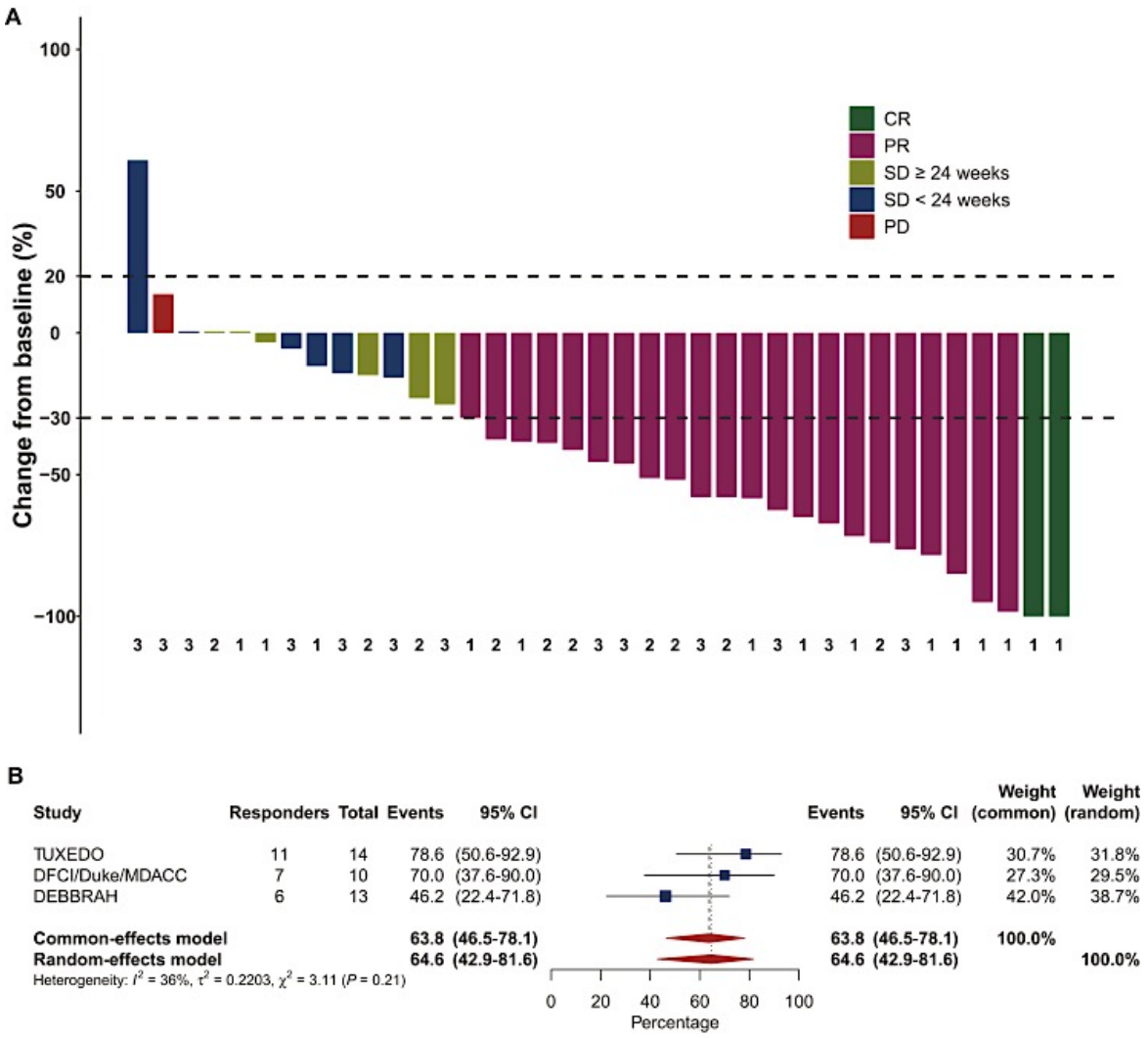


DXd payload achieves therapeutic levels in PDX models of breast cancer BM

N. Agar laboratory, unpublished data

Pooled Analysis: TUXEDO-1, DEBBRAH, & US Case Series

Inclusion for pooled cohort – Active, measurable, parenchymal BM received T-DXd



N=37

CNS ORR = **64.9%**

CNS CBR (CR, PR, SD ≥ 24 wks) = **81.1%**

Median PFS **13.3 months**

Median OS **22.5 months**

100% prior trastuzumab, 78.4% prior pertuzumab, 64.9% prior T-DM1, 51.4% prior lapatinib.
Median of 2 prior lines in TUXEDO-1; 4 prior lines in DEBBRAH and the DFCI/Duke/MDACC cohorts

Bartsch et al, ESMO Open 2025

Pooled Analysis: DESTINY-Breast01, -02, -03

Brain metastasis inclusion and definitions

Inclusion Criteria	
DESTINY-Breast01[1]	**DESTINY-Breast02 and DESTINY-Breast03**[2-4]
• Patients with *asymptomatic, previously locally treated, and stable* BMs	• Initially, patients with *previously untreated and asymptomatic* BM were eligible • After protocol amendments, only patients with *treated, asymptomatic* BMs were allowed

BM status was according to the following definitions by the US FDA Clinical Trial Eligibility Criteria:

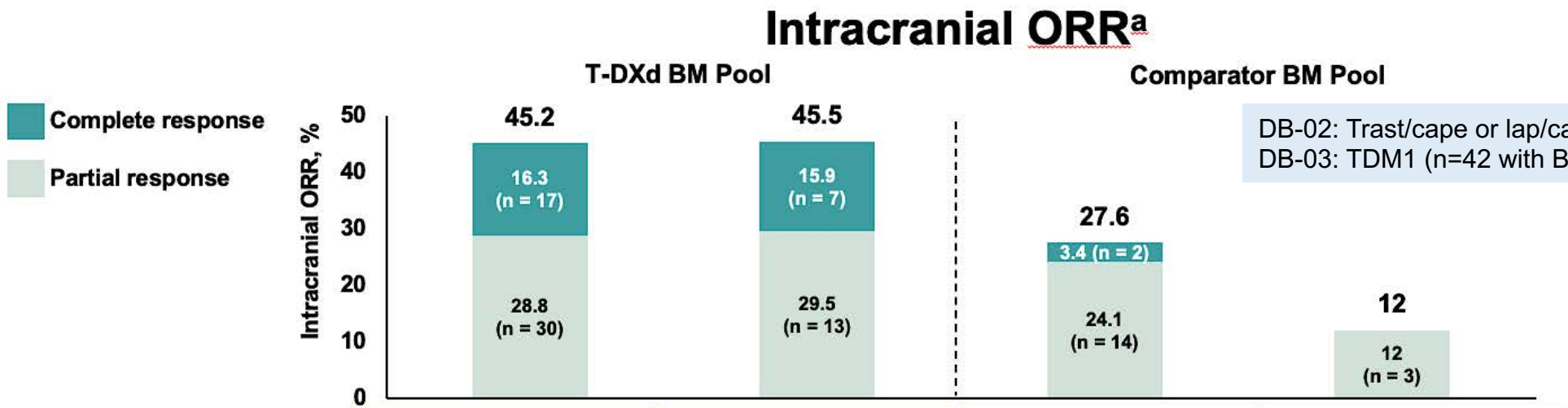
- **Treated/stable BMs:** Patients have received prior CNS-directed therapy for their BMs, and their CNS disease is stable
- **Untreated/active BMs:** Patients have new BMs or progressive BMs that have not been subjected to CNS-directed therapy since documented progression

The population of patients with baseline BMs from DESTINY-Breast02 and -03 therefore consists of a mix of treated/stable and untreated/active metastases

Hurvitz et al, ESMO 2023
Andre et al, Ann Oncol 2024

Pooled Analysis: DESTINY-Breast01, -02, -03

Exploratory Best IC Response, IC-ORR and IC-DoR by BICR



DB-02: Trast/cape or lap/cape (n=41 with BM)
DB-03: TDM1 (n=42 with BM)

	Treated/stable BMs (n = 104)	Untreated/active BMs (n = 44)	Treated/stable BMs (n = 58)	Untreated/active BMs (n = 25)
Best overall IC response, n (%)				
Stable disease	48 (46.2)	15 (34.1)	28 (48.3)	15 (60.0)
Progressive disease	3 (2.9)	1 (2.3)	7 (12.1)	5 (20.0)
Not evaluable/Missing	6 (5.8)	8 (18.2)	7 (12.1)	2 (8.0)
IC-DoR, median, months (95% CI)	12.3 (9.1-17.9)	17.5 (13.6-31.6)	11.0 (5.6-16.0)	NA[b]

- **T-DXd consistently demonstrated superior rates of IC responses over comparator in patients with treated/stable and untreated/active BMs**
- **A trend in prolonged median IC-DoR was most pronounced in the untreated/active BMs subgroup**

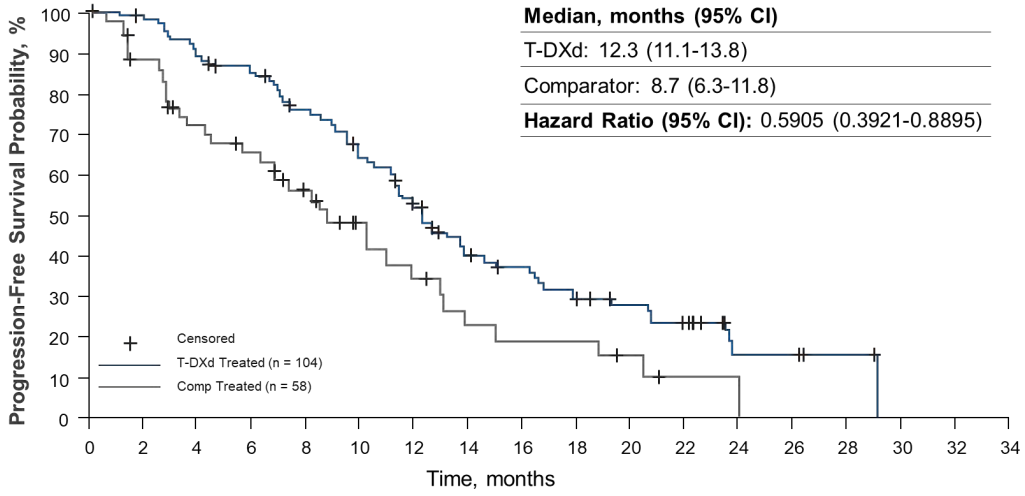
BM, brain metastasis; BICR, blinded independent central review; DoR, duration of response; IC, intracranial; NA, not available; ORR, objective response rate; T-DXd, trastuzumab deruxtecan.
This table considers both target and non-target lesions at baseline. Lesions in previously irradiated areas were not considered measurable target lesions unless there was demonstrated progression in the lesion.
[a]IC-ORR was assessed per RESIST v1.1. [b]IC-DoR NA due to small number of responders (n < 10).

Hurvitz et al, ESMO 2023
Andre et al, Ann Oncol 2024

Pooled Analysis: DESTINY-Breast01, -02, -03

PFS in patients with BM in TDXd treated vs Comparator Pool

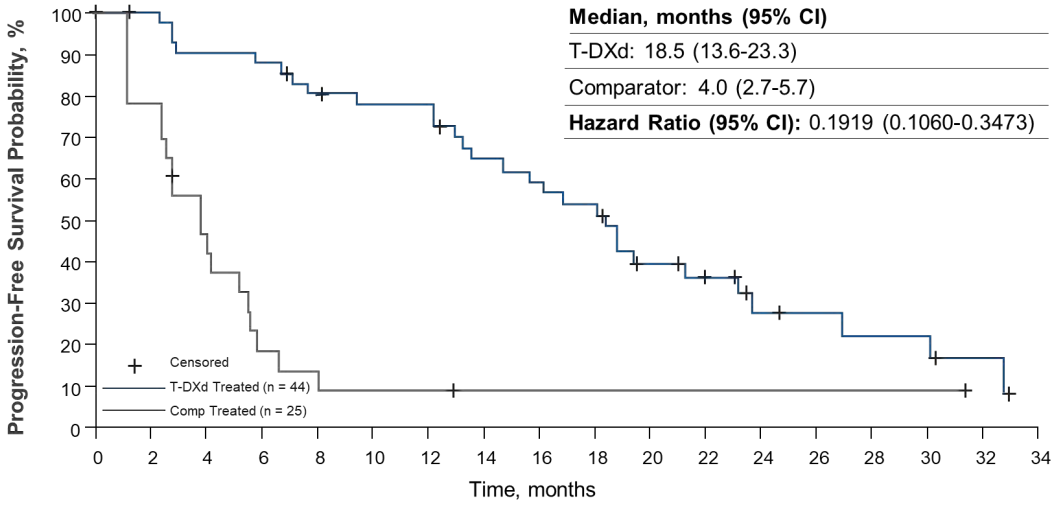
Treated/Stable BM



Patients still at risk

T-DXd Treated (n = 104)	104	100	89	83	72	58	46	32	28	21	18	12	4	4	2	0	0	0
Comparator Treated (n = 58)	58	44	33	29	22	14	10	6	5	5	3	1	0	0	0	0	0	0

Active BM



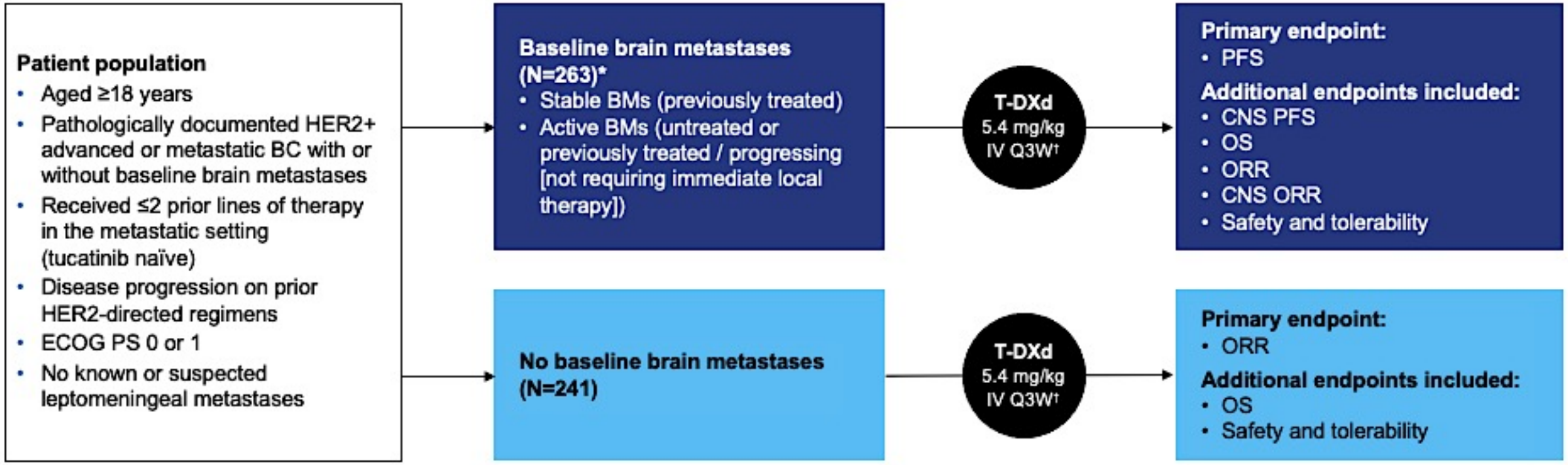
Patients still at risk

T-DXd Treated (n = 44)	44	41	37	36	32	30	30	24	22	20	13	11	6	5	4	4	2	0
Comparator Treated (n = 25)	25	18	11	5	3	2	2	1	1	1	1	1	1	1	1	1	0	0

Hurvitz et al, ESMO 2023
Andre et al, Ann Oncol 2024

DESTINY-Breast12

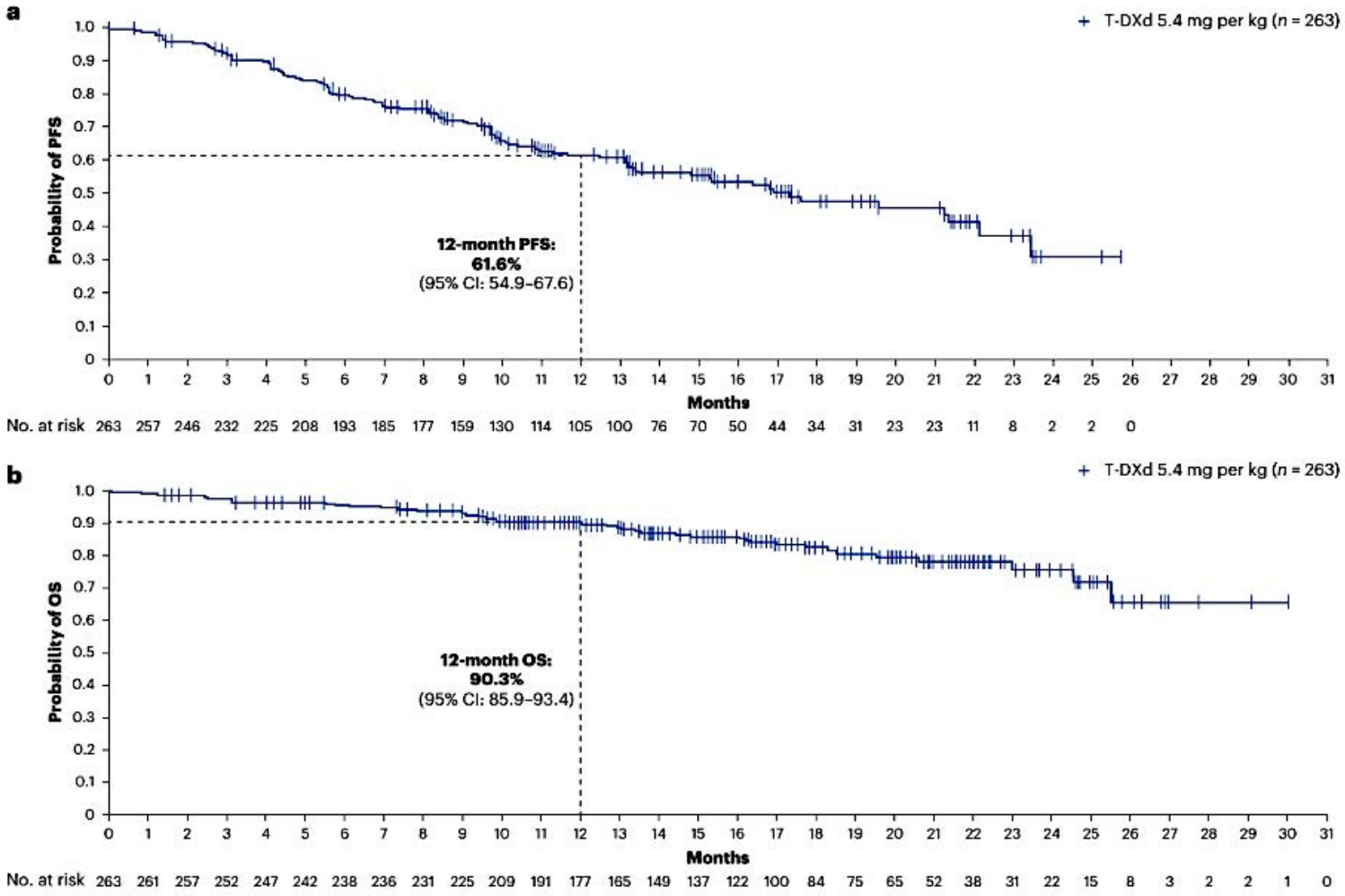
Phase 3b/4, multicenter, single-arm, two-cohort, open-label study of T-DXd in previously treated HER2+ mBC with and without brain metastases (BMs); the largest prospective study of T-DXd in patients with stable or active BMs



Lin et al, ESMO 2024

DESTINY-Breast12

PFS and OS in BM Cohort



Brain Metastases Cohort (n=263)

Median PFS **17.3** months

12-month PFS **61.6%**

12-month CNS PFS **58.9%**

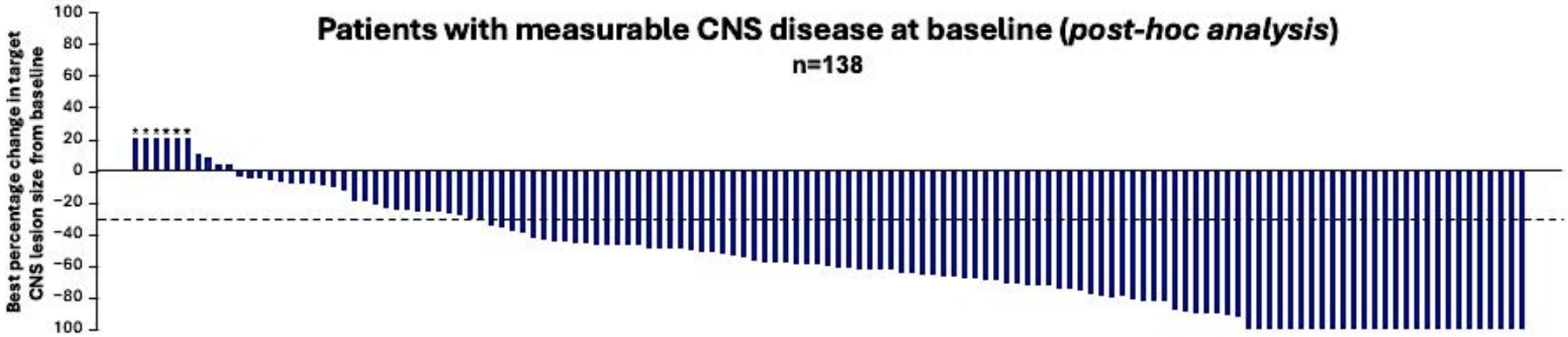
12-month OS **90.3%**

Prior lines: 1 prior (7.6%), 1 prior (50.2%), 2 prior (41.4%)

Harbeck et al, Nat Med 2024

DESTINY-Breast12

Intracranial ORR with T-DXd



Measurable CNS disease at baseline	All patients (n=138)	Stable BMs (n=77)	Active BMs subgroups: Active BMs (n=61)	Active BMs subgroups: Untreated (n=23) *Post-hoc analysis*	Active BMs subgroups: Previously treated / progressing (n=38) *Post-hoc analysis*
Confirmed CNS ORR, % (95% CI)	**71.7 (64.2, 79.3)**	79.2 (70.2, 88.3)	62.3 (50.1, 74.5)	82.6 (67.1, 98.1)	50.0 (34.1, 65.9)

T-DXd showed substantial CNS responses in the overall BMs population, including patients with stable and active BMs

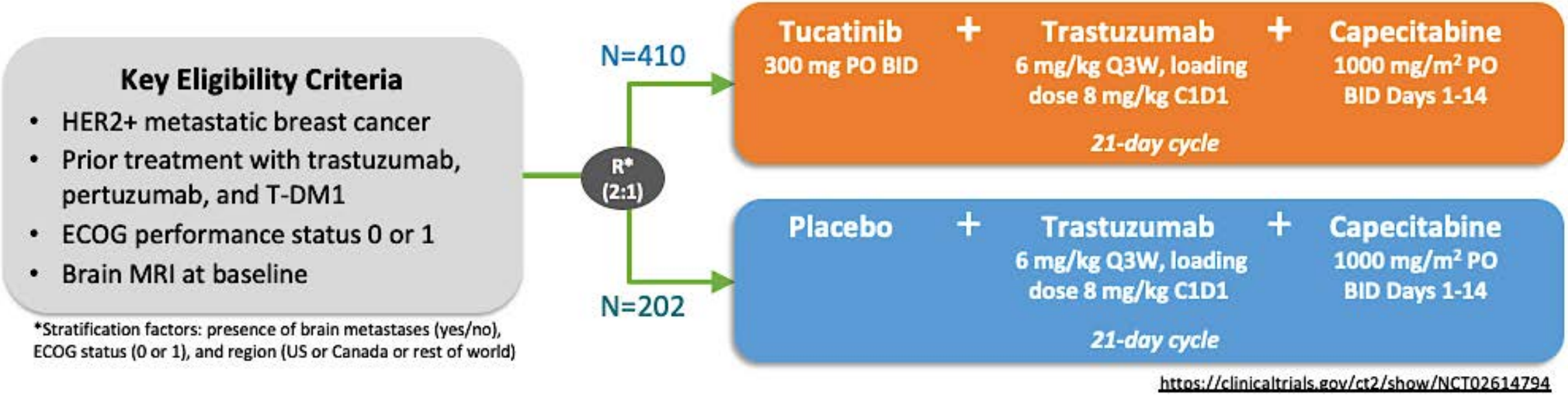
*Imputed values: a value of +20% was imputed if best percentage change could not be calculated because of missing data if: a patient had a new lesion or progression of non-target lesions or target lesions, or had withdrawn because of PD and had no evaluable target lesion data before or at PD

BM, brain metastasis; CI, confidence interval; CNS, central nervous system; ORR, objective response rate; PD, progressive disease; PR, partial response; T-DXd, trastuzumab deruxtecan

Harbeck N et al. Nat Med 2024

HER2CLIMB

Randomized trial including patients with stable or active BM



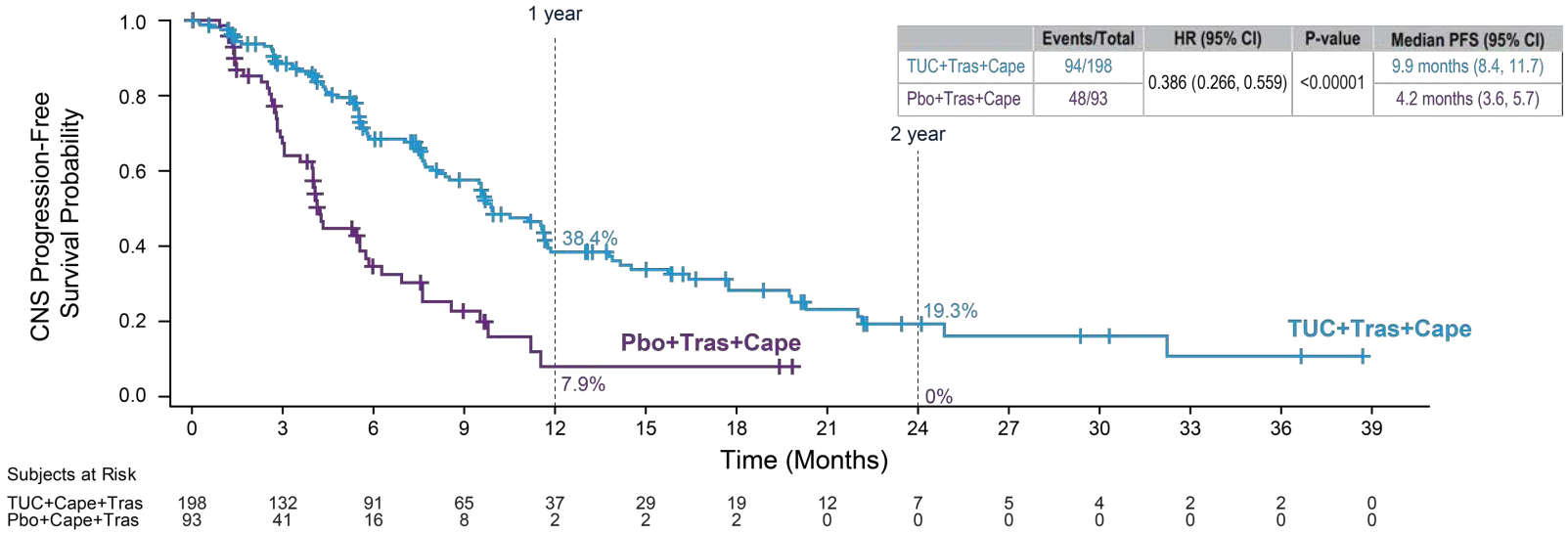
Patients with or without brain mets
PFS HR 0.54; medians 5.6 vs 7.8 months; p <0.001
OS HR 0.66; medians 17.4 months vs 21.9 months; p=0.005

Patients with brain mets
PFS HR 0.48; medians 5.4 vs 7.6 months; p <0.001

Murthy et al, NEJM 2019

HER2CLIMB

CNS outcomes in patients with BM



	Events/Total	HR (95% CI)	P-value	Median PFS (95% CI)
TUC+Tras+Cape	94/198	0.386 (0.266, 0.559)	<0.00001	9.9 months (8.4, 11.7)
Pbo+Tras+Cape	48/93			4.2 months (3.6, 5.7)

CNS PFS: 9.9 vs 4.2 mo

CNS ORR: 47.3% vs 20.0%

DoR-IC: medians 8.6 mo vs 3.0 mo

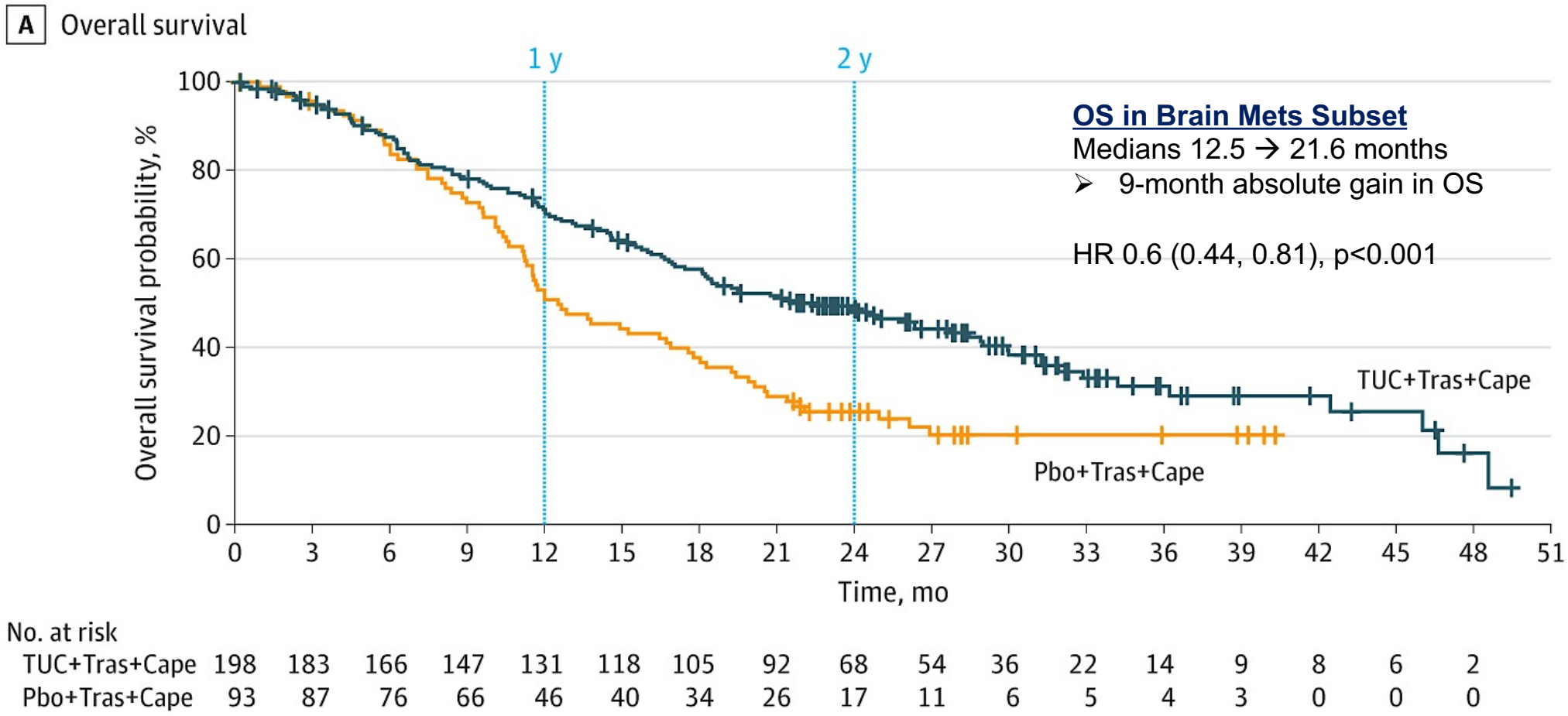
Very few pts (3.6%) with PD as best response

SUBGROUP	TREATMENT	EVENTS	HR (95% CI)	P value	Median CNS-PFS (95% CI)
Patients with active brain metastases	TUC+Tras+Cape	69/118	0.339 (0.215, 0.536)	<0.00001	9.6 months (7.6, 11.1)
	Pbo+Tras+Cape	35/56			4.0 months (2.9, 5.6)
Patients with treated stable brain metastases	TUC+Tras+Cape	25/80	0.406 (0.194, 0.850)	0.01	13.9 months (9.7, 24.9)
	Pbo+Tras+Cape	13/37			5.6 months (3.0, –)

Lin et al, SABCS 2021
Lin et al, JAMA Oncol 2023

HER2CLIMB

Overall survival in BM subset



OS in Brain Mets Subset

Medians 12.5 → 21.6 months

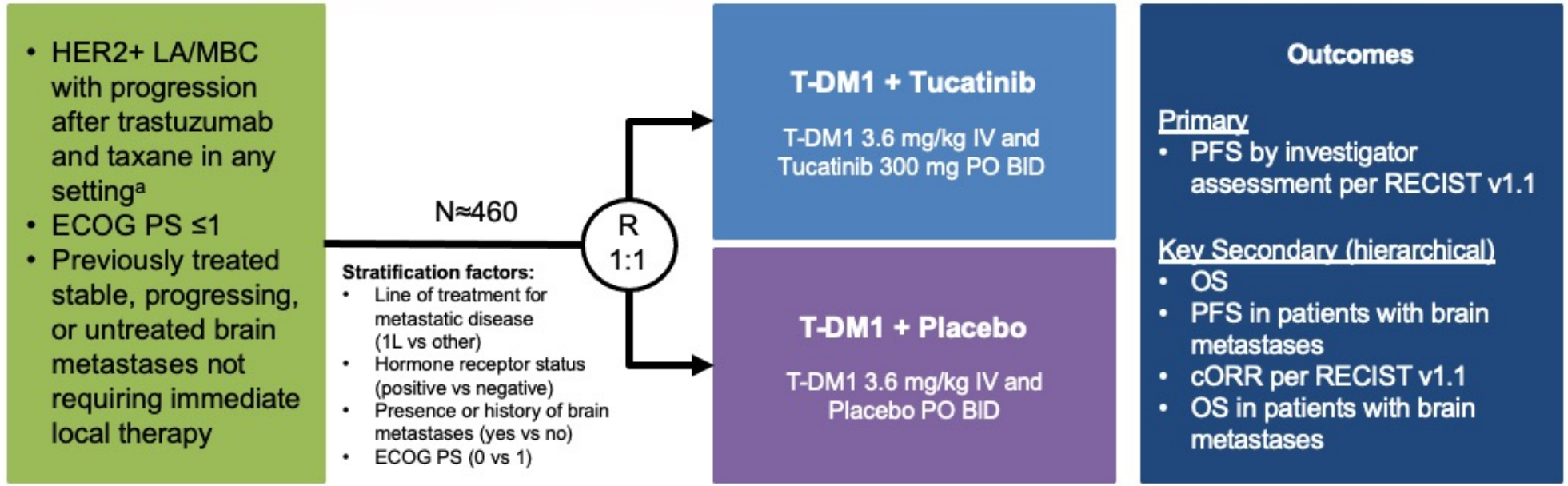
- 9-month absolute gain in OS

HR 0.6 (0.44, 0.81), p<0.001

Lin et al, SABCS 2021
Lin et al, JAMA Oncol 2023

HER2CLIMB-02

Does tucatinib add to T-DM1 for HER2+ MBC?



The primary analysis for PFS was planned after ≈331 PFS events to provide 90% power for hazard ratio of 0.7 at two-sided alpha level of 0.05. The first of two interim analyses for OS was planned at the time of the primary PFS analysis, if the PFS result was significantly positive[b].

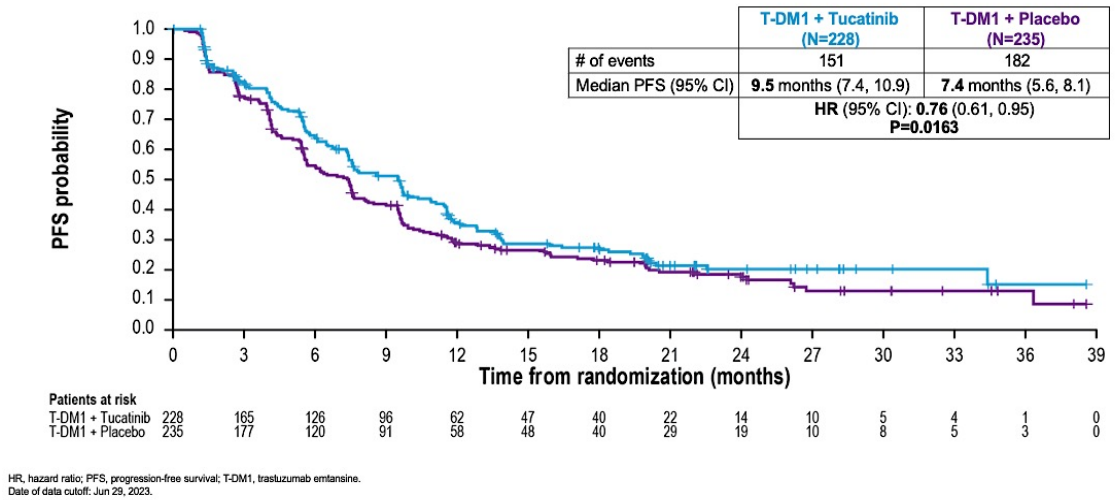
	T-DM1 + Tucatinib (N=228)	T-DM1 + Placebo (N=235)
Presence or history of brain metastases, n (%)		
Yes	99 (43.4)	105 (44.7)
Active	50 (21.9)	57 (24.3)
Treated stable	49 (21.5)	48 (20.4)
No[a]	129 (56.6)	130 (55.3)

Hurvitz et al, SABCS 2023

HER2CLIMB-02

Tucatinib prolongs PFS when added to T-DM1

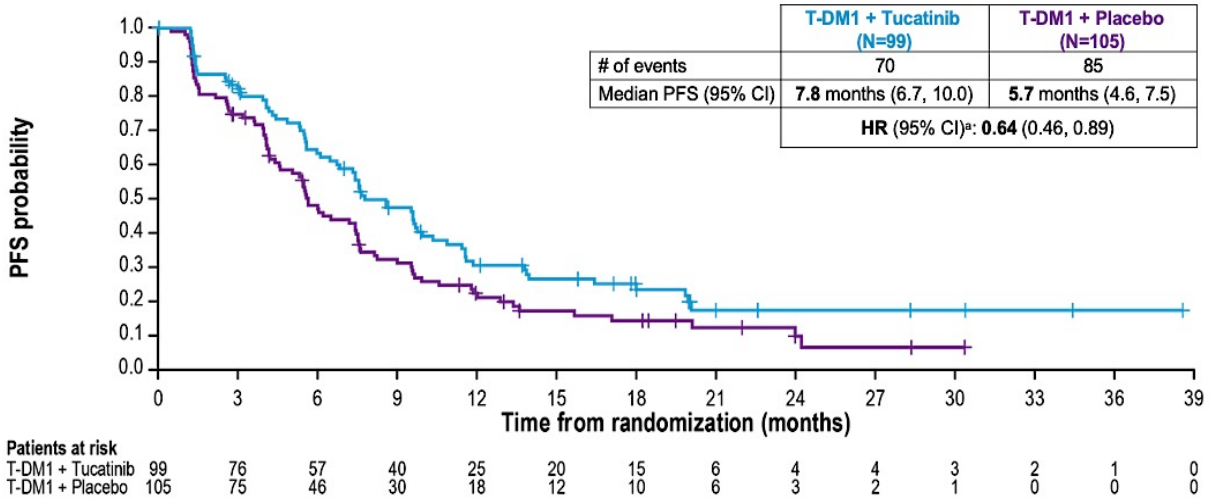
Progression-Free Survival: ITT Population



	T-DM1 + Tucatinib (N=228)	T-DM1 + Placebo (N=235)
# of events	151	182
Median PFS (95% CI)	**9.5** months (7.4, 10.9)	**7.4** months (5.6, 8.1)
	HR (95% CI): **0.76** (0.61, 0.95) **P=0.0163**	

HR, hazard ratio; PFS, progression-free survival; T-DM1, trastuzumab emtansine.
Date of data cutoff: Jun 29, 2023.

Progression-Free Survival: BM Subset



	T-DM1 + Tucatinib (N=99)	T-DM1 + Placebo (N=105)
# of events	70	85
Median PFS (95% CI)	**7.8** months (6.7, 10.0)	**5.7** months (4.6, 7.5)
	HR (95% CI)[a]: **0.64** (0.46, 0.89)	

a The outcome was not formally tested.
HR, hazard ratio; PFS, progression-free survival; T-DM1, trastuzumab emtansine.
Date of data cutoff: Jun 29, 2023.

Overall ORR 36.1% vs 42.0% favoring the combination

CNS-ORR not reported

OS, no difference at median f/u 24.4 months; await more mature data

Hurvitz et al, SABCS 2023
Hurvitz et al, Ann Oncol 2025

Summary of studies

Study	DB-01/02/03 Pooled Analysis	DESTINY-Breast12	HER2CLIMB	HER2CLIMB-02
Regimen	T-DXd	T-DXd	Tucatinib, trastuzumab, capecitabine	Tucatinib, TDM1
BM inclusion	Stable/treated Active (previously untreated asymptomatic only) in DB-02 and DB-03	Stable or active	Stable or active	Stable or active
Prior therapy	Varied by study	0-2 lines for MBC	Prior trastuzumab, pertuzumab and TDM1 required	Prior trastuzumab and taxane
CNS ORR	45.2% stable/treated BM 45.5% active/untreated BM	79.2% stable/treated BM 62.3% active BM (82.6% in prev untreated)	47.3% active BM	Not reported
CNS DoR	12.3 mo stable/treated BM 17.5 mo active/untreated BM	Not reported	8.6 mo	Not reported
CNS PFS	12.3 mo stable/treated BM 18.5 mo active/untreated BM	58.9% at 12 months	13.9 mo stable/treated BM 9.6 mo active BM	Not reported
PFS in BM pts	Not reported in pooled analysis	17.3 mo across all BM pts	7.6 mo	7.8 mo
OS in BM pts	Not reached, stable/treated BM 30.2 mo active/untreated	90.3% at 12 months	21.6 months	Not reported

Practical Questions in Clinic ….

- In what sequence should we offer T-DXd vs tucatinib for pts with BM?
- Is there value in continuing tucatinib beyond progression and switching out the partner?
- How should we weigh whether to switch systemic therapy vs offering local therapy?
- What CNS-active systemic therapies can we offer after T-DXd and tucatinib?

Weighing Local Therapy Versus Systemic Therapy

FAVORS LOCAL THERAPY

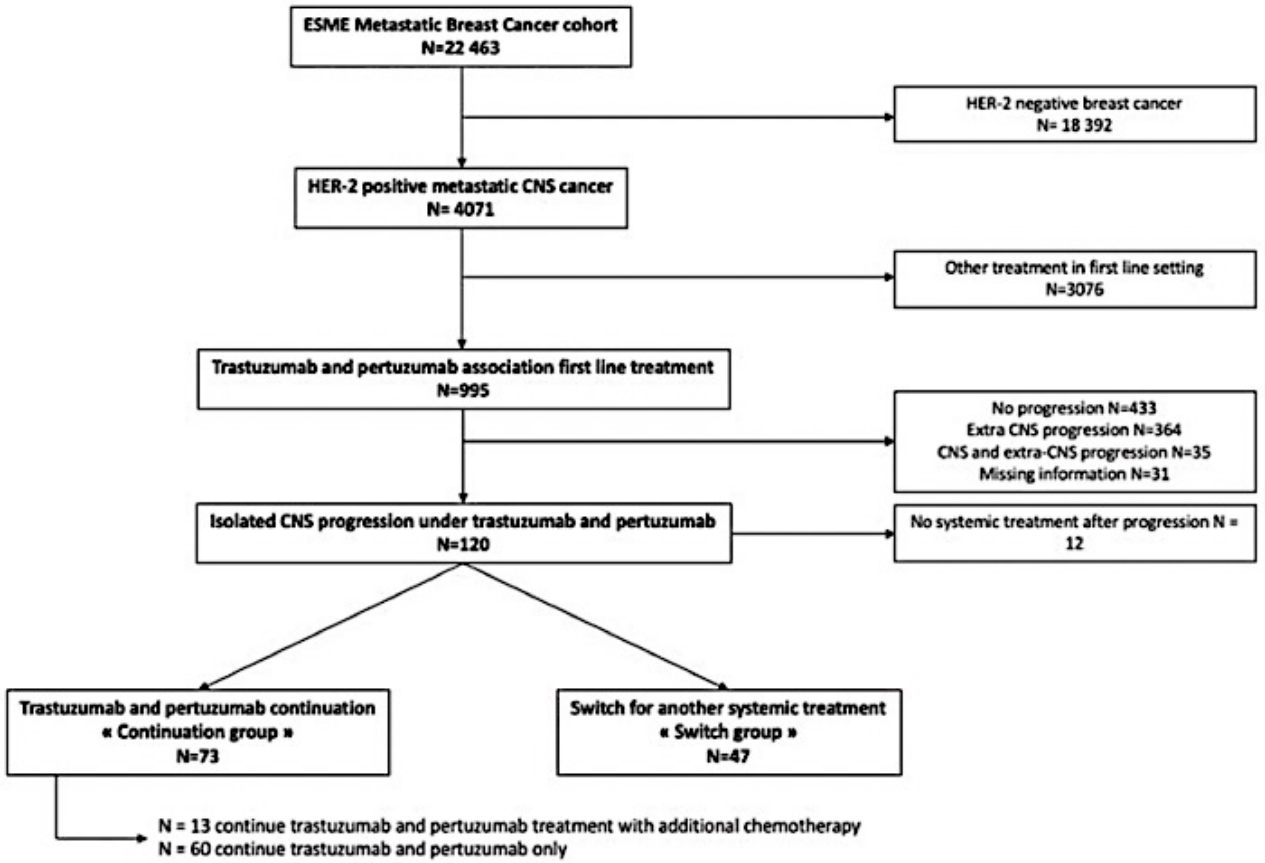
- Controlled extracranial disease
- Desire to maintain systemic regimen
- Symptomatic lesions
- Low brain met velocity
- Disease amenable to SRS
- Less confidence in systemic tx

FAVORS SYSTEMIC THERAPY

- Progressive extracranial disease
- Need to switch systemic regimen
- Less symptomatic lesions
- High brain met velocity
- Concern for RT toxicity
- More confidence in systemic tx

Should systemic therapy be routinely switched after local therapy to BM?

Isolated CNS PD on 1L HP-based regimen



	Continued HP N=73	Switched systemic therapy N=47
Local therapy	WBRT (n=43) SRS (n=20) Surgery (n=13)	WBRT (n=16) SRS (n=8) Surgery (n=1)
Systemic therapy	HP (n=60) HP + taxane (n=7) HP + capecitabine (n=3) HP + TDM1 (n=2) HP + lapatinib (n=1)	TDM1 (n=27) Trastuzumab + chemo (n=17) Lapatinib-based (n=10)

Factors associated with longer OS:

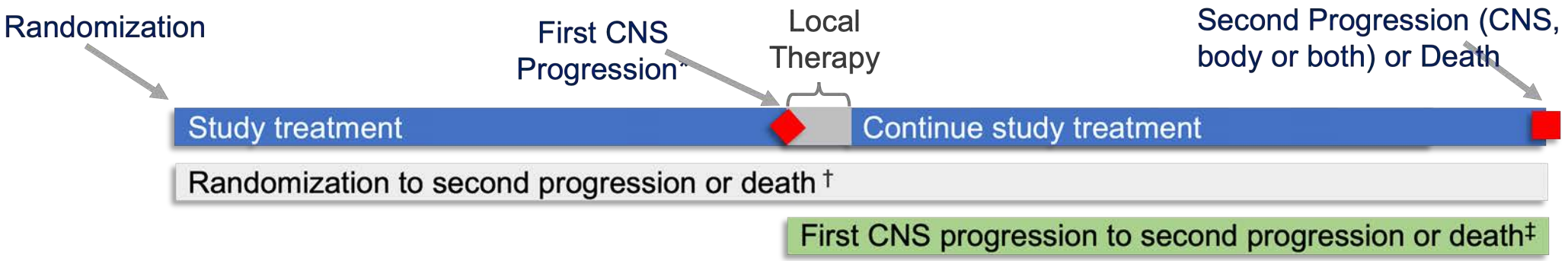
-Continuation of HP

-1st CNS progression-free interval

Collet et al, Breast Ca 2022

SRS for OligoPD in the CNS

Concept of Local-Therapy Augmented PFS



	Median time from randomization to second progression or death	HR	Median time from first CNS progression to second progression or death	HR
TUC+Tras+Cap N=21	15.9 months (11.7, 28.2)	0.292 (0.11, 0.77) P=0.009	7.6 months (3.9, 11.3)	0.332 (0.13, 0.85) P=0.02
Pbo+Tras+Cap N=9	9.7 months (4.9, 12.0)		3.1 months (1.2, 4.1)	

*Note: First CNS progression was captured as a PFS event in the primary analysis.

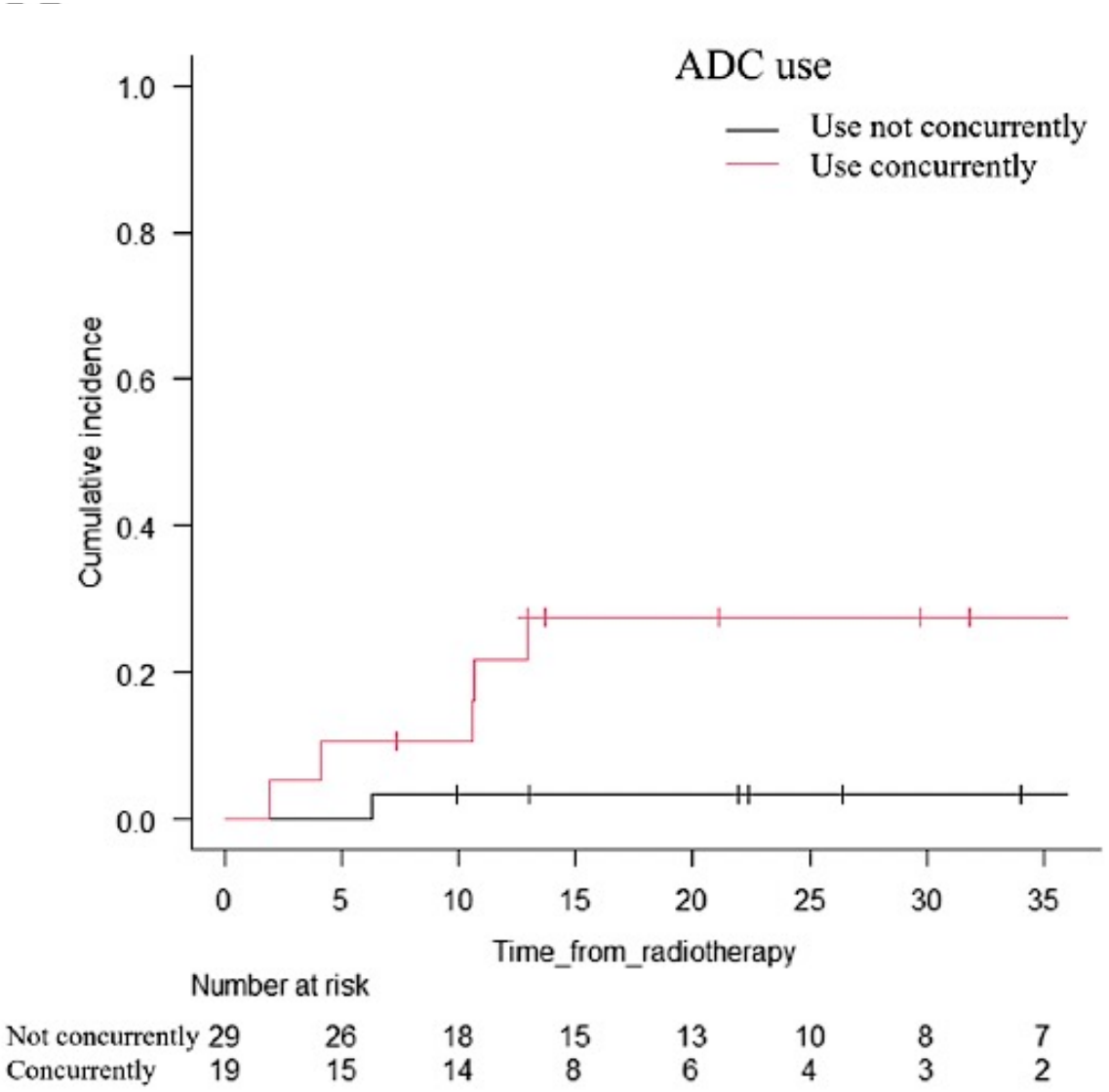
† Time from randomization to second progression or death among patients who received local therapy and continued study treatment after isolated CNS progression.

‡Time from first isolated CNS progression to second progression or death among patients who received local therapy and continued study treatment after isolated CNS progression.

Lin et al, J Clin Oncol 2020

Radionecrosis with concurrent ADC - SRS

Spacing of ADC and SRS affects risk of radionecrosis



Concurrent: Defined as SRS within 4 wks of TDM1 or T-DXd (median 9 days)

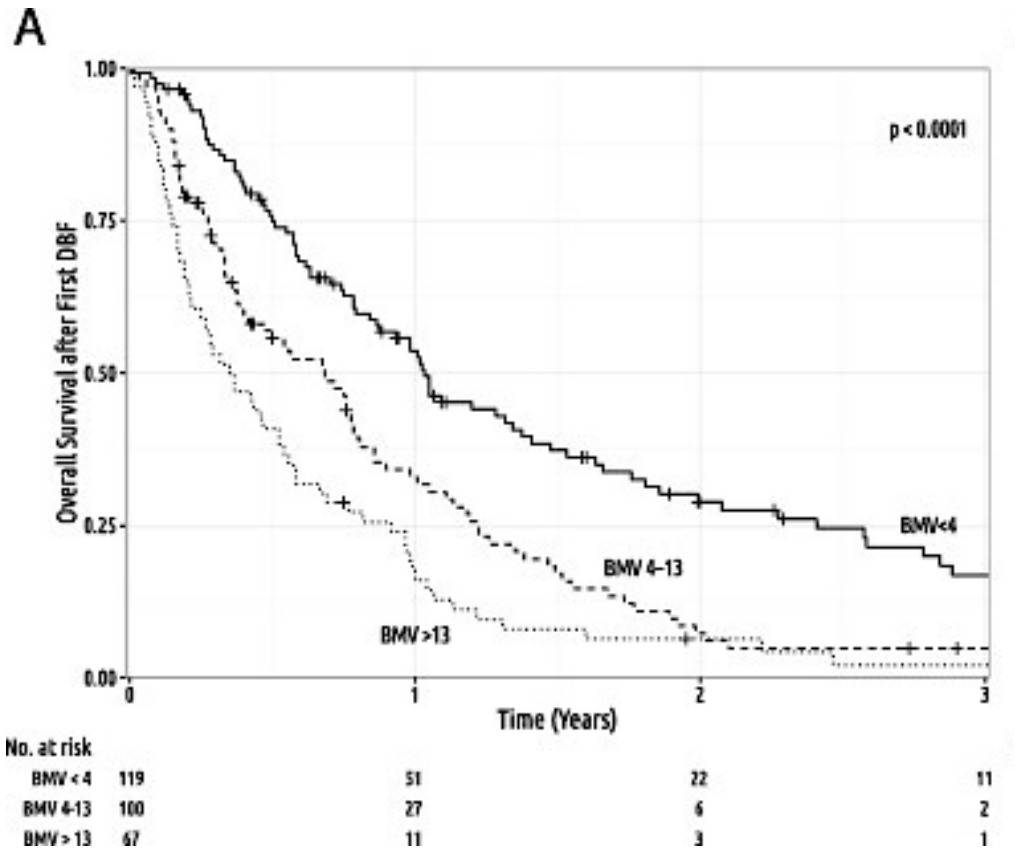
Non-concurrent: SRS > 4 wks from ADC (median 250 days)

Koide et al, J Neuro Oncol 2024

Factors associated with greater SRS efficacy and durability of intracranial control

<u>Smaller lesions</u>
- -Better lesion-specific control
- -Lower risk of radiation necrosis

<u>Lower brain metastasis velocity</u>
- -Better distant intracranial PFS
- -Less need for salvage WBRT



High Brain Met Velocity → shorter time to WBRT and worse OS

Higher brain metastasis velocity → *<u>May</u>* be more advantageous to switch systemic therapy

Rashid et al, J Neuro Oncol 2025
McTyre, Radiotherapy and Oncol 2020

NCCN 2025 Guidelines

CNS Tumors Guidelines – Breast Cancer

- **HER2 positive**
  - **Preferred regimens**
    - Tucatinib + trastuzumab + capecitabine (category 1)
    - Fam-trastuzumab deruxtecan-nxki
  - **Other Recommended Regimens**
    - Ado-trastuzumab emtansine (T-DM1)
    - Neratinib and T-DM1
    - Capecitabine + lapatinib
    - Capecitabine + neratinib
    - Pertuzumab and high-dose trastuzumab
    - Paclitaxel + neratinib (category 2B)

Summary and Conclusions

Multiple active regimens for patients with HER2+ brain metastases

Important role of multi-D collaboration

Consider evidence for CNS benefit, need for extracranial disease control, brain metastasis velocity, QoL, and short- and long-term toxicities in selecting between options

Need to develop preventive regimens, and effective options for refractory patients

Case Presentation: 60-year-old woman with ER-positive, HER2-positive BC develops a cerebellar metastasis while receiving adjuvant anastrozole after prior anti-HER2 therapy

Dr Justin Favaro (Charlotte, North Carolina)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

What treatment would you recommend next for this patient?

How do you currently sequence available therapies for patients with HER2-positive mBC and brain metastases?

Case Presentation: 41-year-old woman with ER-negative, HER2-positive mBC develops a headache shortly after neoadjuvant TCHP, surgery and postneoadjuvant T-DM1 and is found to have an isolated 4-cm brain lesion that on surgical resection is found to be metastatic disease

Dr Laila Agrawal (Louisville, Kentucky)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

What is your experience with treating radiation necrosis of the brain? How is this managed in your institutions? What has been your experience in terms of outcomes?

How has the availability of effective HER2-targeted systemic therapies affected your use of local therapies for patients with HER2-positive CNS metastases? Do you believe SRS or WBRT can be delayed or omitted in some situations with the initial use of systemic therapy?

Agenda

Module 1: Considerations in the Care of Patients with Localized HER2-Positive Breast Cancer — Prof Harbeck

Module 2: Previously Untreated HER2-Positive Metastatic Breast Cancer (mBC) — Prof Curigliano

Module 3: Optimal Management of Brain Metastases in Patients with HER2-Positive Breast Cancer — Dr Lin

Module 4: Selection and Sequencing of Therapy for Relapsed/Refractory (R/R) HER2-Positive mBC in the Absence of CNS Involvement — Dr Krop

Module 5: Tolerability Considerations with HER2-Targeted Therapies — Dr O'Shaughnessy

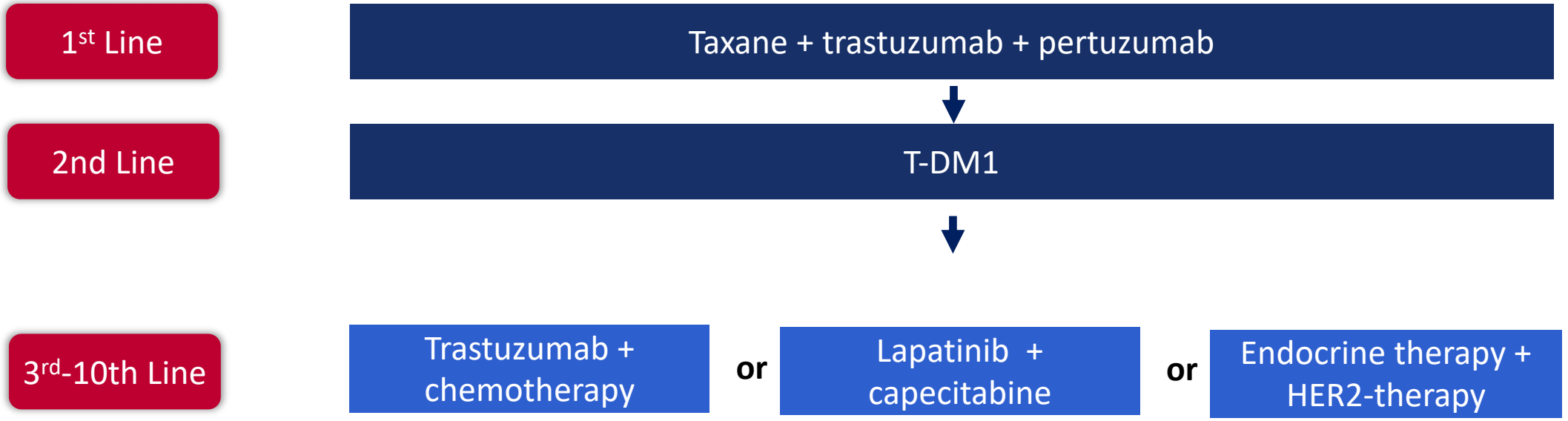
RTP RESEARCH TO PRACTICE

Optimizing Management of HER2-Positive Advanced Breast Cancer After Initial Therapy

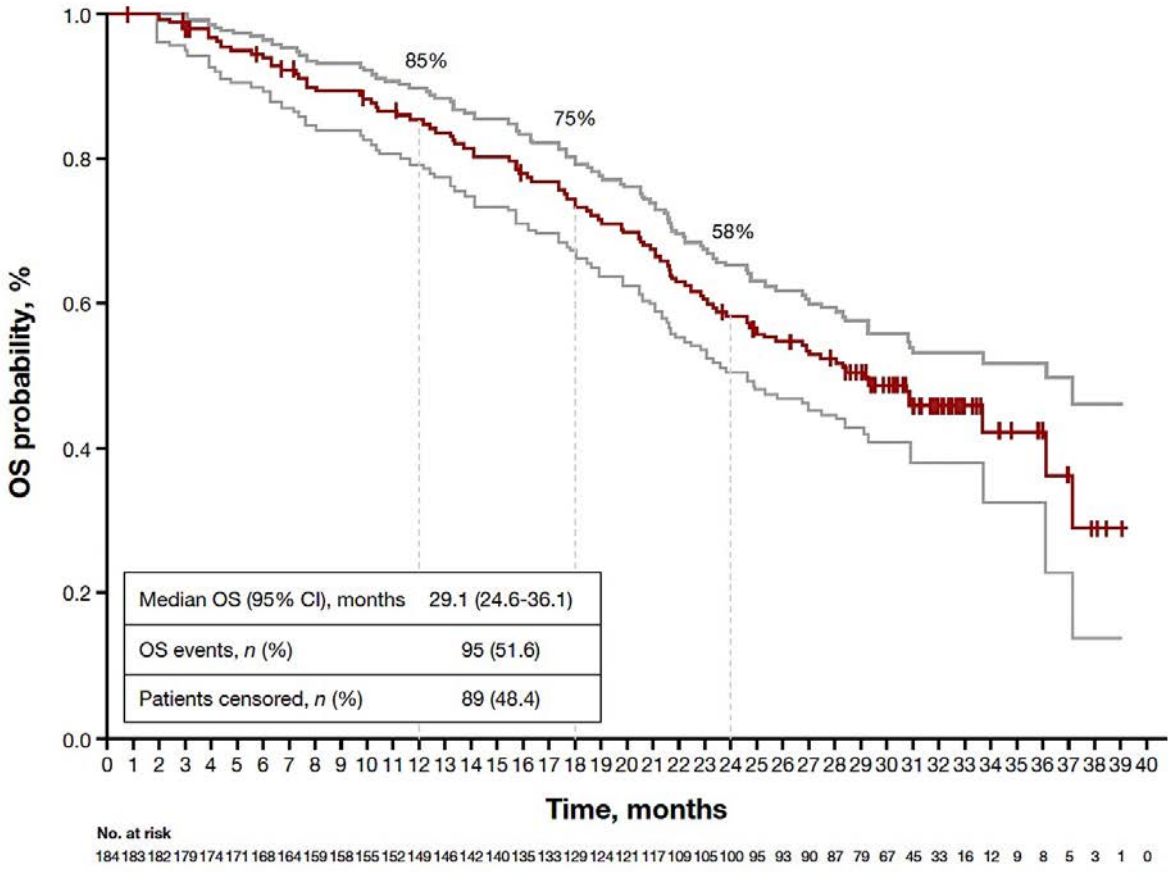
Ian Krop MD PhD

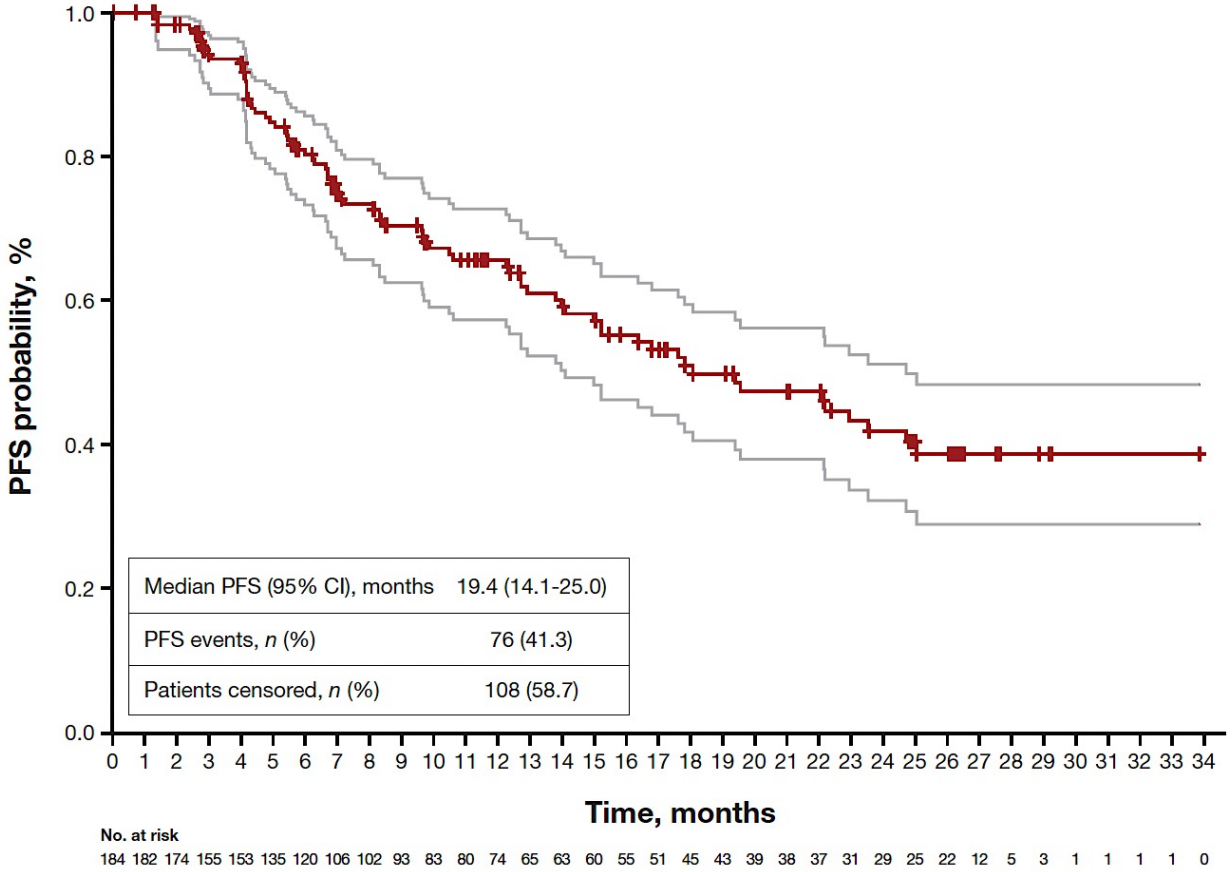
December 2025

Treatment Paradigm for Metastatic HER2+ Breast Cancer (Circa 2022)



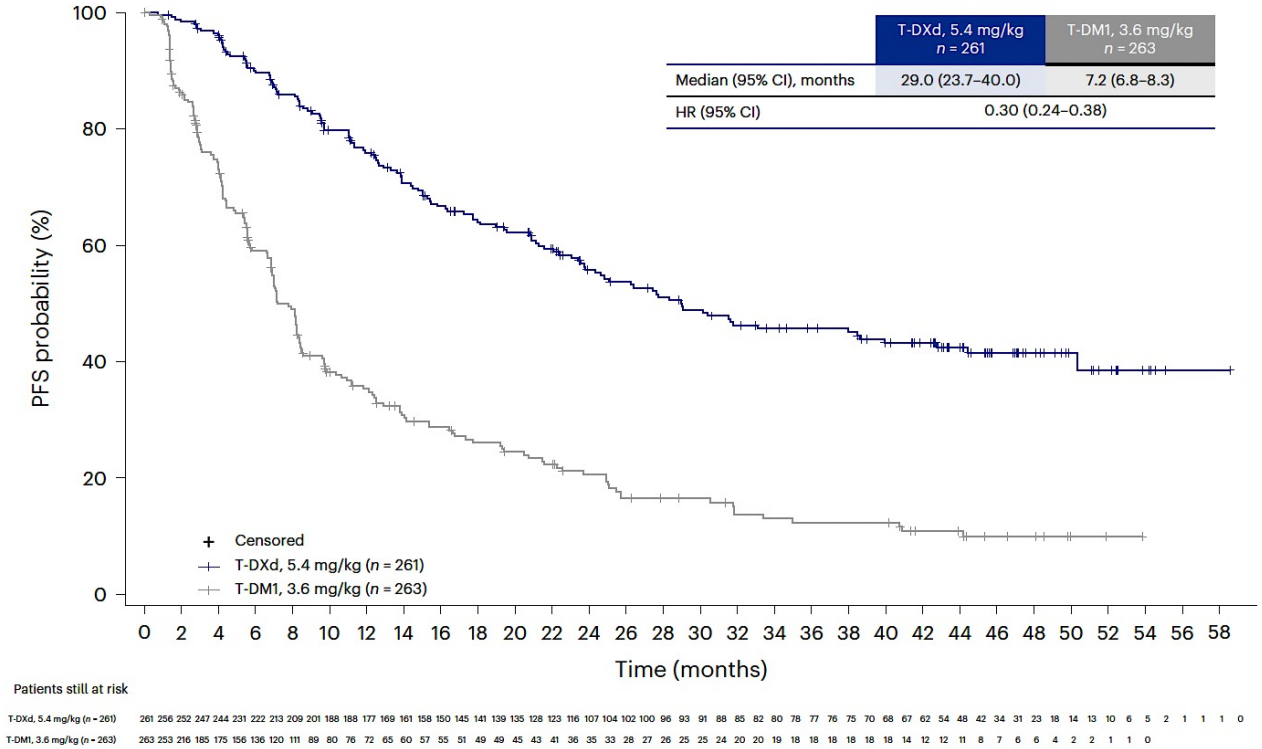
DESTINY-Breast01: Updated Survival Analysis of T-DXd in HER2-Positive mBC Previously Treated with T-DM1

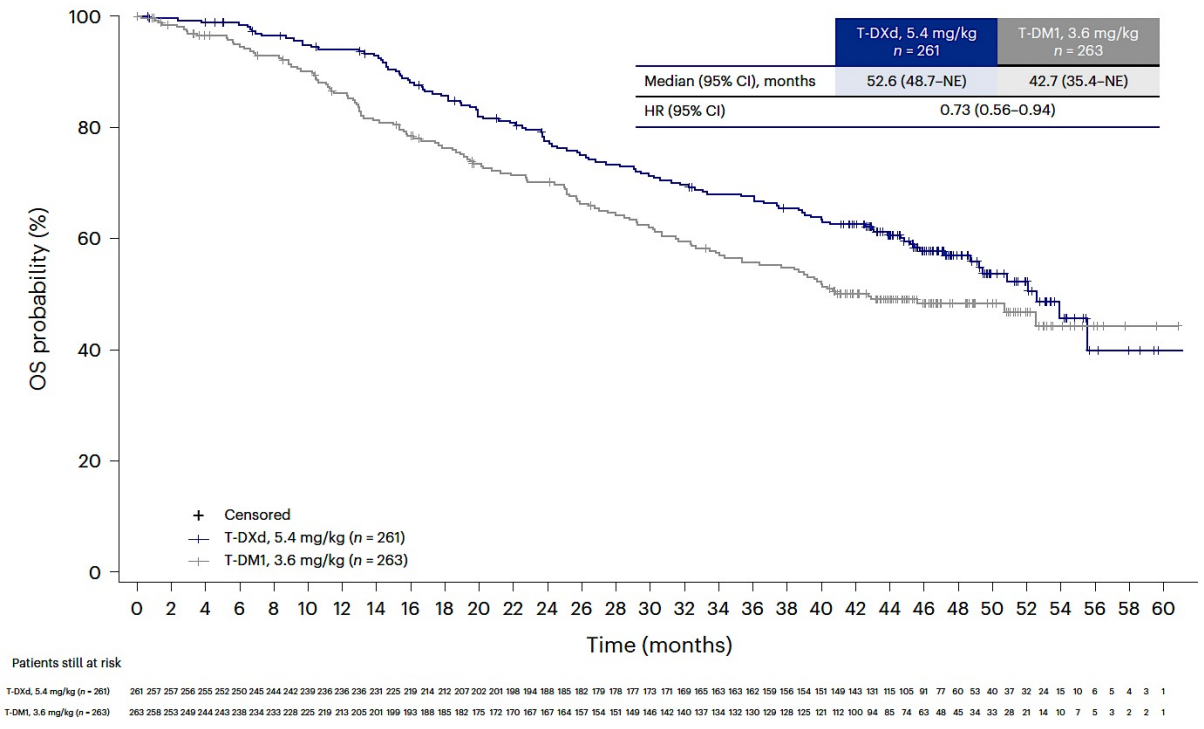




Saura C et al. *Ann Oncol* 2024;35(3):302-7.

DESTINY-Breast03: Long-Term Survival Analysis of T-DXd Versus T-DM1 in HER2-Positive mBC Previously Treated with Trastuzumab and a Taxane





Cortés J et al. *Nature Med* 2024;30:2208-15.

DESTINY-Breast03: Safety Summary

Table 3 | Overall safety summary

n (%)	T-DXd, 5.4 mg/kg Q3W, *n*=257	T-DM1, 3.6 mg/kg Q3W, *n*=261
Any-grade TEAEs	256 (99.6)	249 (95.4)
Drug-related	252 (98.1)	228 (87.4)
Grade ≥3 TEAEs	149 (58.0)	136 (52.1)
Drug-related	125 (48.6)	111 (42.5)
Serious TEAEs	71 (27.6)	59 (22.6)
Drug-related	35 (13.6)	20 (7.7)
TEAEs leading to drug discontinuation	63 (24.5)	27 (10.3)
Drug-related	58 (22.6)	19 (7.3)
TEAEs leading to dose reduction	73 (28.4)	40 (15.3)
Drug-related	72 (28.0)	40 (15.3)
TEAEs leading to drug interruption	146 (56.8)	78 (29.9)
Drug-related	113 (44.0)	48 (18.4)
TEAEs associated with death	9 (3.5)	7 (2.7)
Drug-related	0	0

Table 4 | Adjudicated drug-related ILD and pneumonitis[a,b]

n (%)	T-DXd, 5.4 mg/kg Q3W, *n*=257	T-DM1, 3.6 mg/kg Q3W, *n*=261
Any grade	43 (16.7)	9 (3.4)
Grade 1	11 (4.3)	5 (1.9)
Grade 2	30 (11.7)	3 (1.1)
Grade 3	2 (0.8)	1 (0.4)
Grade 4	0	0
Grade 5	0	0
Grade ≥3	2 (0.8)	1 (0.4)

[a]The grade is based on the worst Common Terminology Criteria for Adverse Events (CTCAE) grade within the same adverse or ILD event. [b]There were four new events (all grade 2) reported since the previous data cutoff (25 July 2022) with a time to onset of 832 d (not recovered or resolved), 851 d (recovered or resolved with sequelae), 910 d (recovered or resolved with sequelae) and 961 d (recovered or resolved).

Cortés J et al. *Nature Med* 2024;30:2208-15.

Treatment Paradigm for Metastatic HER2+ Breast Cancer

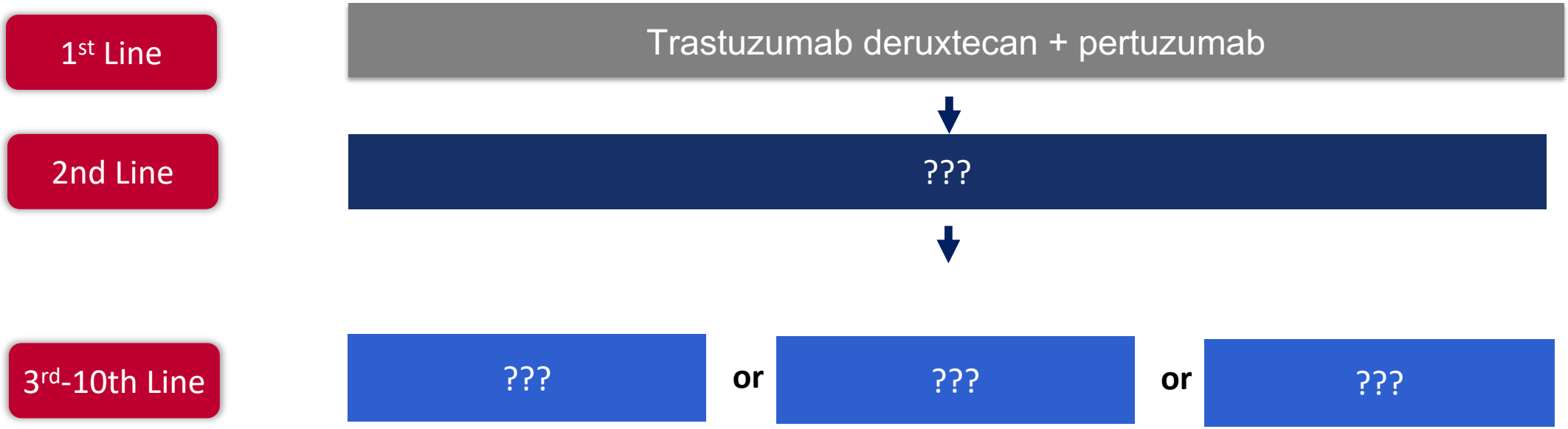
1st Line

Trastuzumab deruxtecan + pertuzumab

2nd Line

3rd-10th Line

Treatment Paradigm for Metastatic HER2+ Breast Cancer



- Important to include HER2 targeted therapy in each regimen
- No benefit to >1 chemotherapy agent in combination with HER2 therapy
- Useful to incorporate newer generation HER2 therapies

HER2CLIMB Trial Design

Key Eligibility Criteria

- HER2+ metastatic breast cancer
- Prior treatment with trastuzumab, pertuzumab, and T-DM1
- ECOG performance status 0 or 1
- Brain MRI at baseline
  - Previously treated stable brain metastases
  - Untreated brain metastases not needing immediate local therapy
  - Previously treated progressing brain metastases not needing immediate local therapy
  - No evidence of brain metastases

R* (2:1)

N=410

Tucatinib + Trastuzumab + Capecitabine
(21-day cycle)

Tucatinib 300 mg PO BID
+
Trastuzumab 6 mg/kg Q3W (loading dose 8 mg/kg C1D1)
+
Capecitabine 1000 mg/m^2 PO BID (Days 1-14)

N=202

Placebo + Trastuzumab + Capecitabine
(21-day cycle)

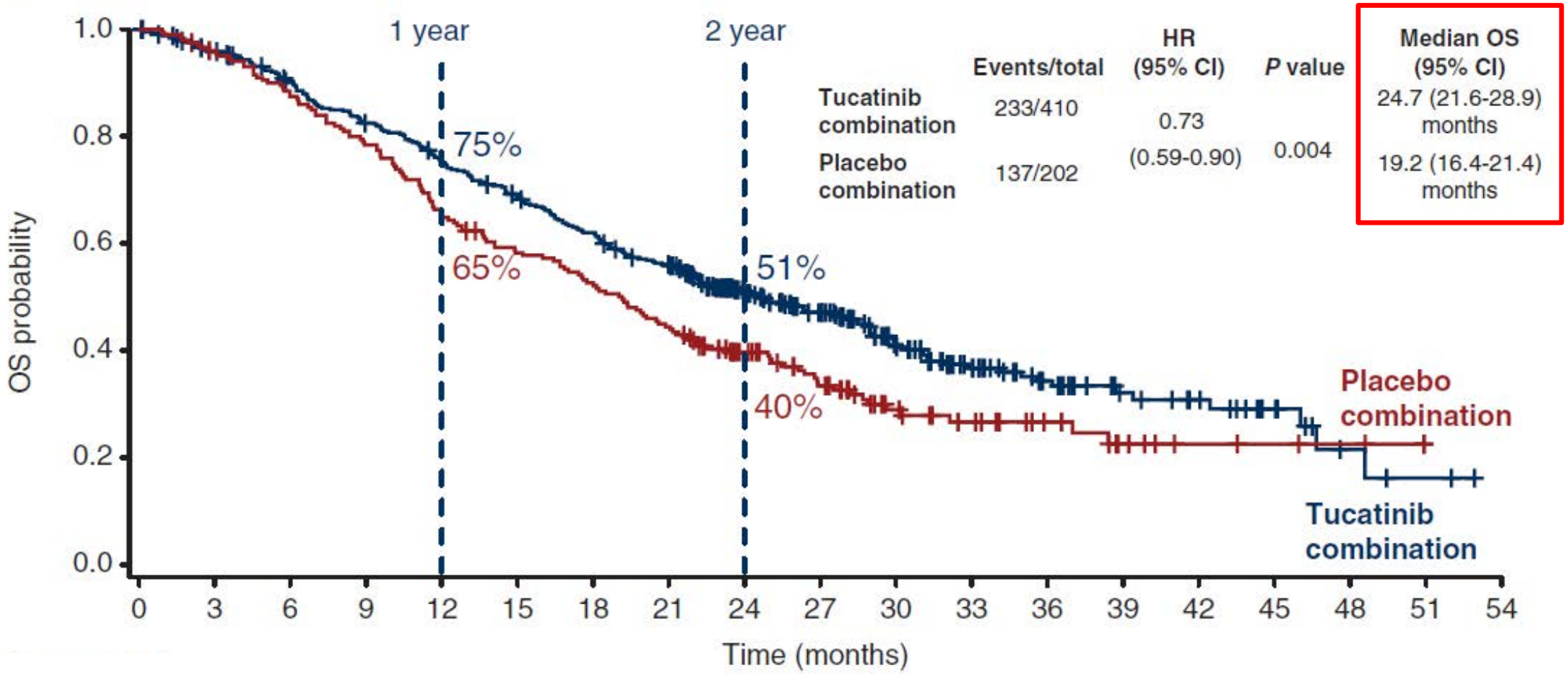
Placebo
+
Trastuzumab 6 mg/kg Q3W (loading dose 8 mg/kg C1D1)
+
Capecitabine 1000 mg/m^2 PO BID (Days 1-14)

*Stratification factors: presence of brain metastases (yes/no), ECOG status (0 or 1), and region (US or Canada or rest of world)

https://clinicaltrials.gov/ct2/show/NCT02614794

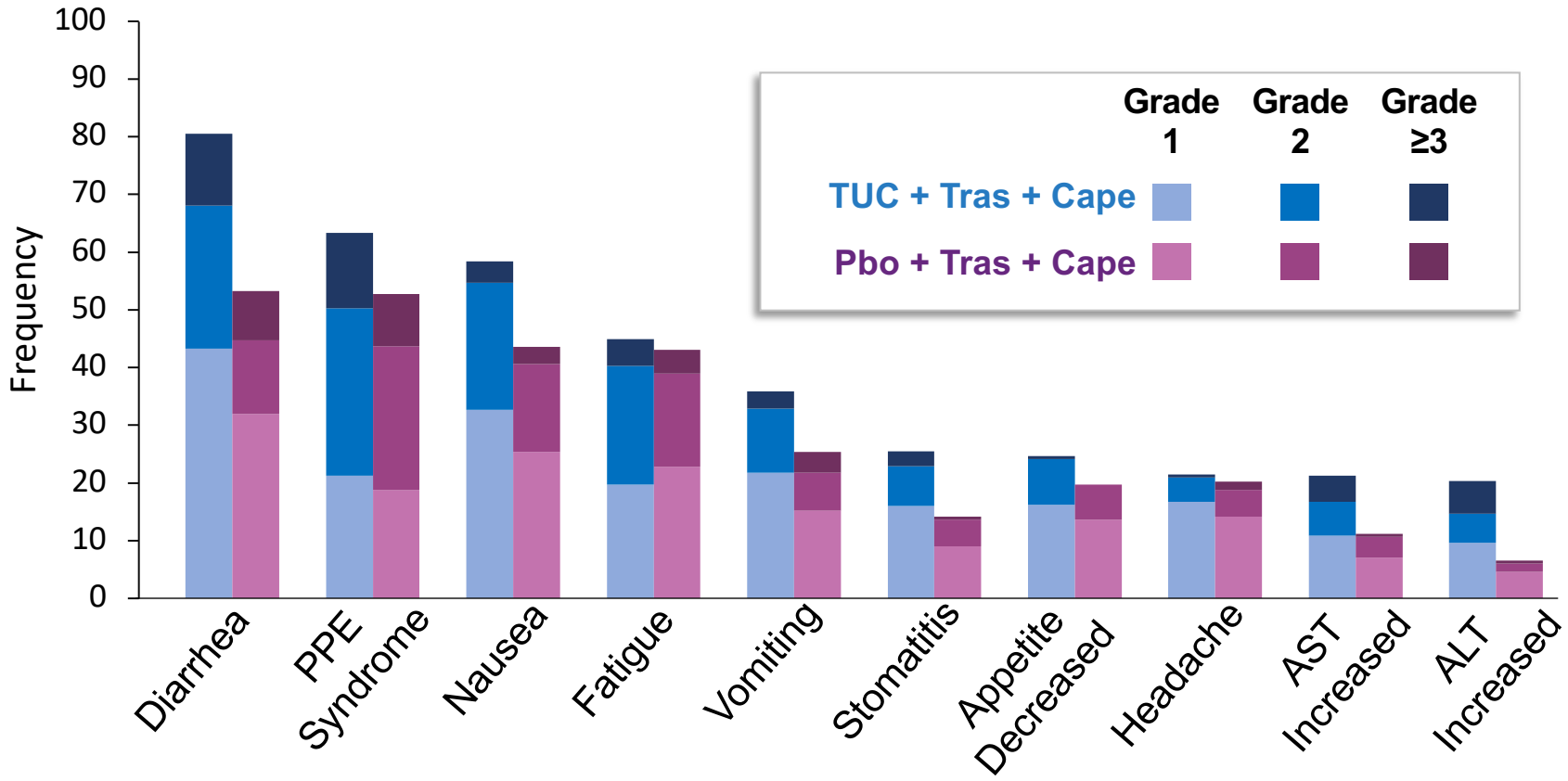
Murthy RK et al. SABCS 2019;Abstract GS1-01; Murthy RK et al. N Engl J Med 2020;382:597-609.

HER2CLIMB Updated OS results



Curigliano et al, Annals Oncology 2022 33:321

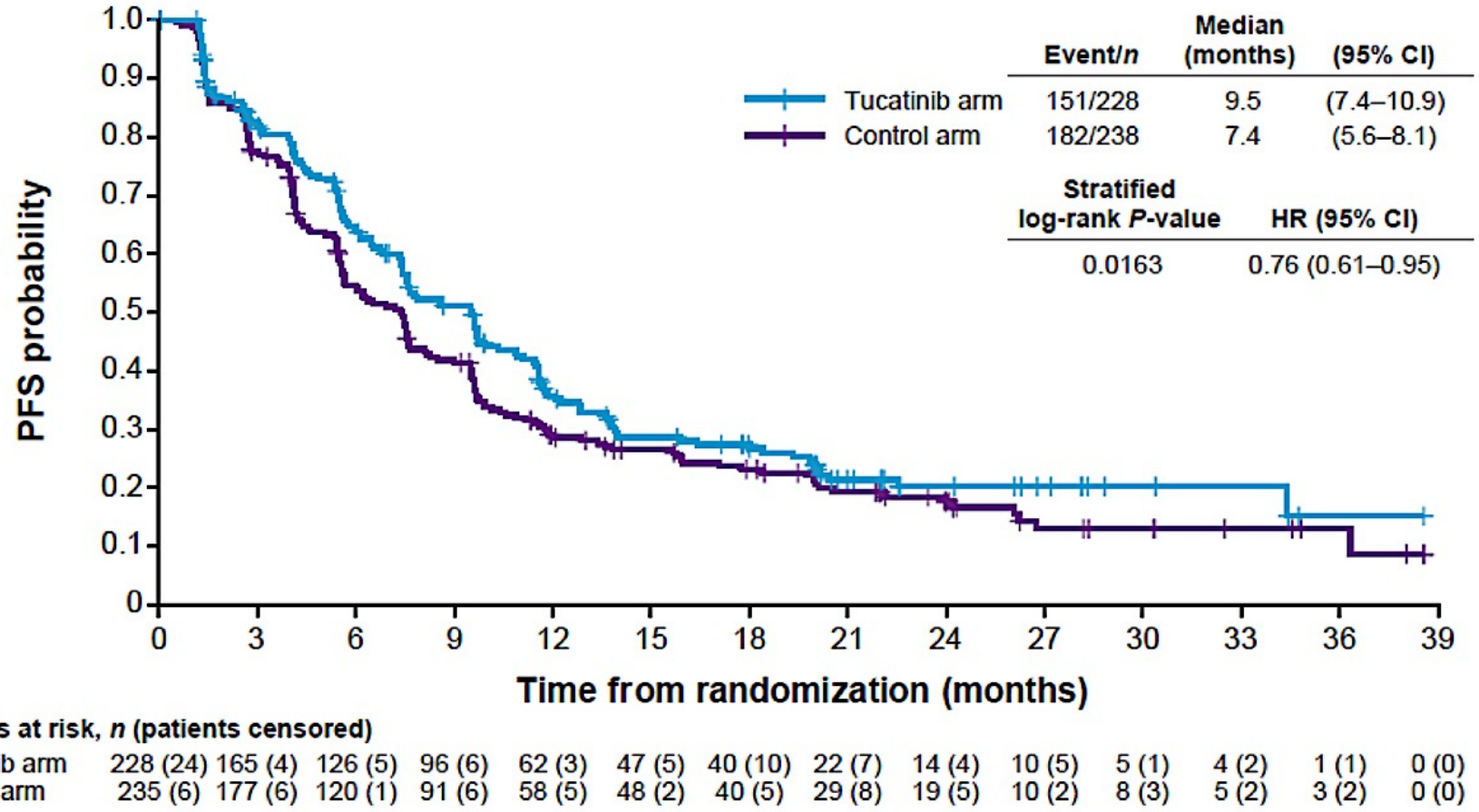
Most Common Adverse Events (≥20% in the Tucatinib Arm)



PPE: palmar-plantar erythrodysesthesia, AST: aspartate transaminase, ALT: alanine transaminase

Murthy RK et al. SABCS 2019;Abstract GS1-01; Murthy RK et al. N Engl J Med 2020;382:597-609.

HER2CLIMB-02: Tucatinib plus T-DM1 Compared to T-DM1 Alone for Previously Treated Locally Advanced and Metastatic HER2-Positive BC

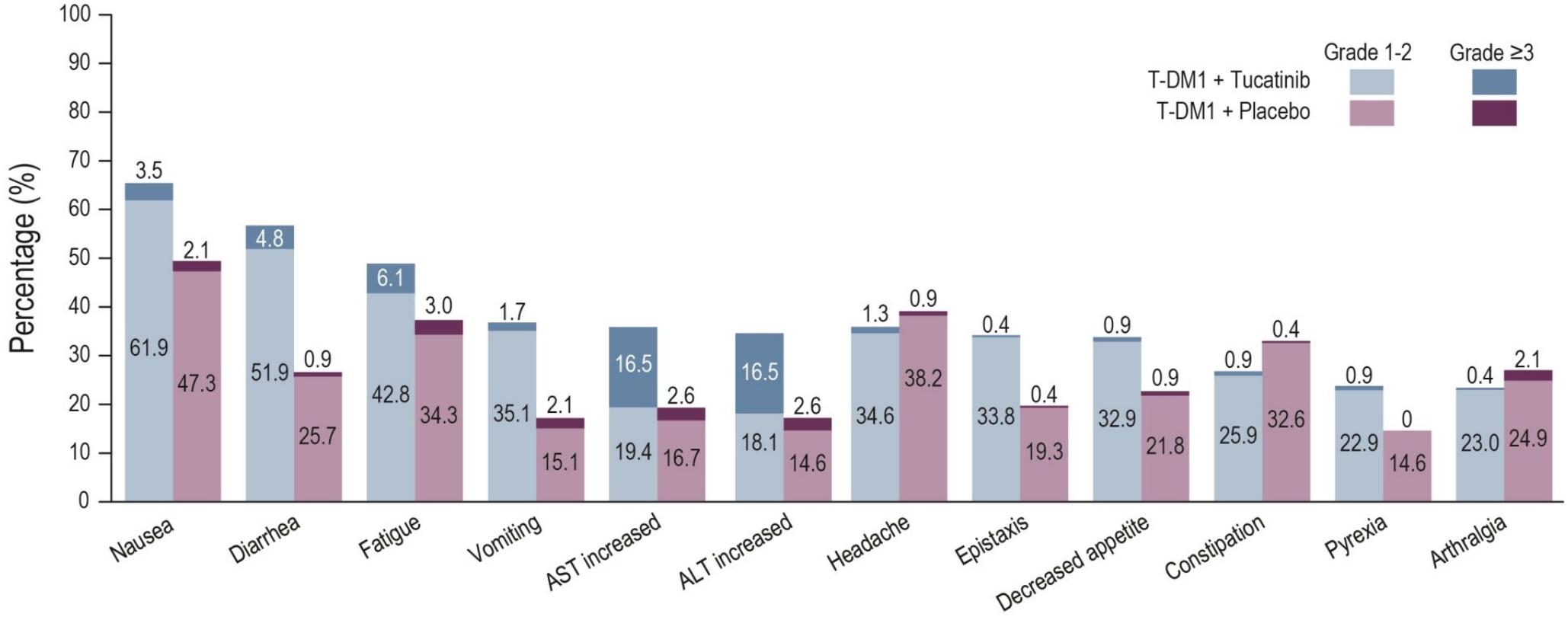


Interim overall survival analysis results were immature.

- Median OS tucatinib/T-DM1 vs T-DM1 arm: Not reached vs 38.0 months (HR=1.23; 95% CI, 0.87–1.74).

Hurvitz SA et al. *Ann Oncol* 2025; Nov 17[Article in Press].

HER2CLIMB-02 Most Common TEAEs (≥20%)



Most common (≥5%) grade ≥3 TEAEs (T-DM1 + Tucatinib vs T-DM1 + Placebo): ALT increased (16.5% vs 2.6%), AST increased (16.5% vs 2.6%), anemia (8.2% vs 4.7%), thrombocytopenia (7.4% vs 2.1%), and fatigue (6.1% vs 3.0%)

TEAEs occurring in ≥20% of patients in T-DM1 + Tucatinib arm are shown.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; T-DM1, trastuzumab emtansine; TEAEs, treatment-emergent adverse events.
Date of data cutoff: Jun 29, 2023.

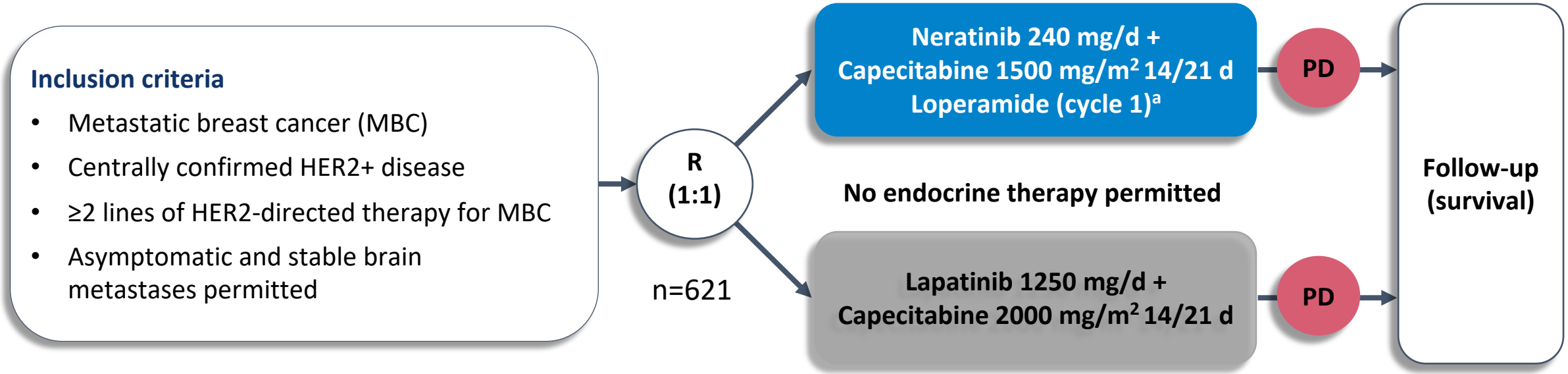
Sara Hurvitz et al, SABCS 2023

HER2CLIMB-02 Summary

- Addition of tucatinib to T-DM1 modestly improves PFS
  - Substanial increase in toxicity with ≈20% drug discontinuation

- Does not support use of tucatinib with T-DM1 in MBC setting

NALA study design



Stratification variables

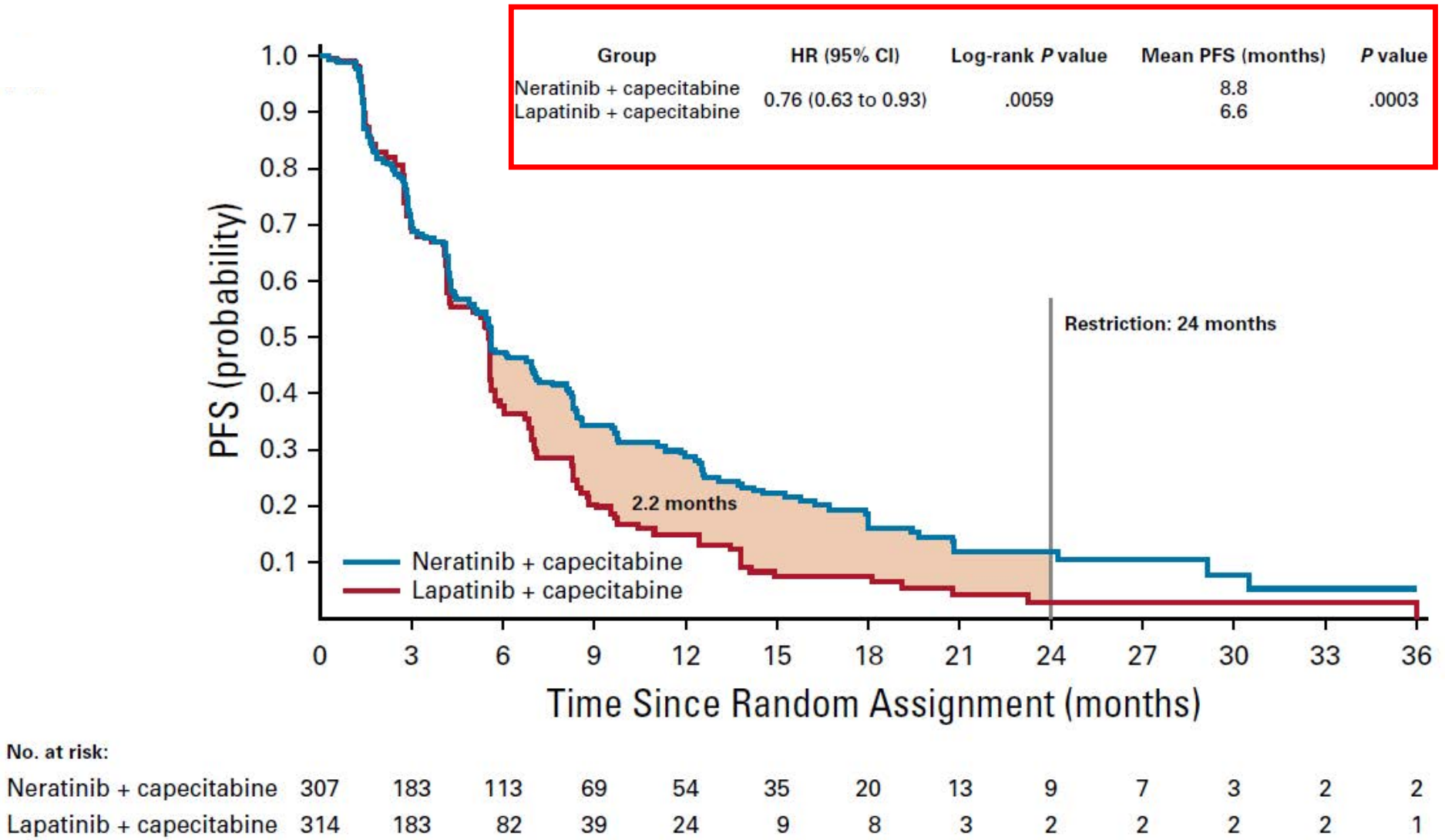
- Number of prior HER2 therapies for MBC
- Disease location
- HR status
- Geographic location

Endpoints

- Co-primary: PFS (centrally confirmed) and OS
- Secondary: PFS (local), ORR, DoR, CBR, intervention for CNS metastases, safety, health outcomes

Loperamide 4 mg with first dose of neratinib, followed by 2 mg every 4 h for first 3 d, then loperamide 2 mg every 6–8 h until end of Cycle 1. Thereafter as needed

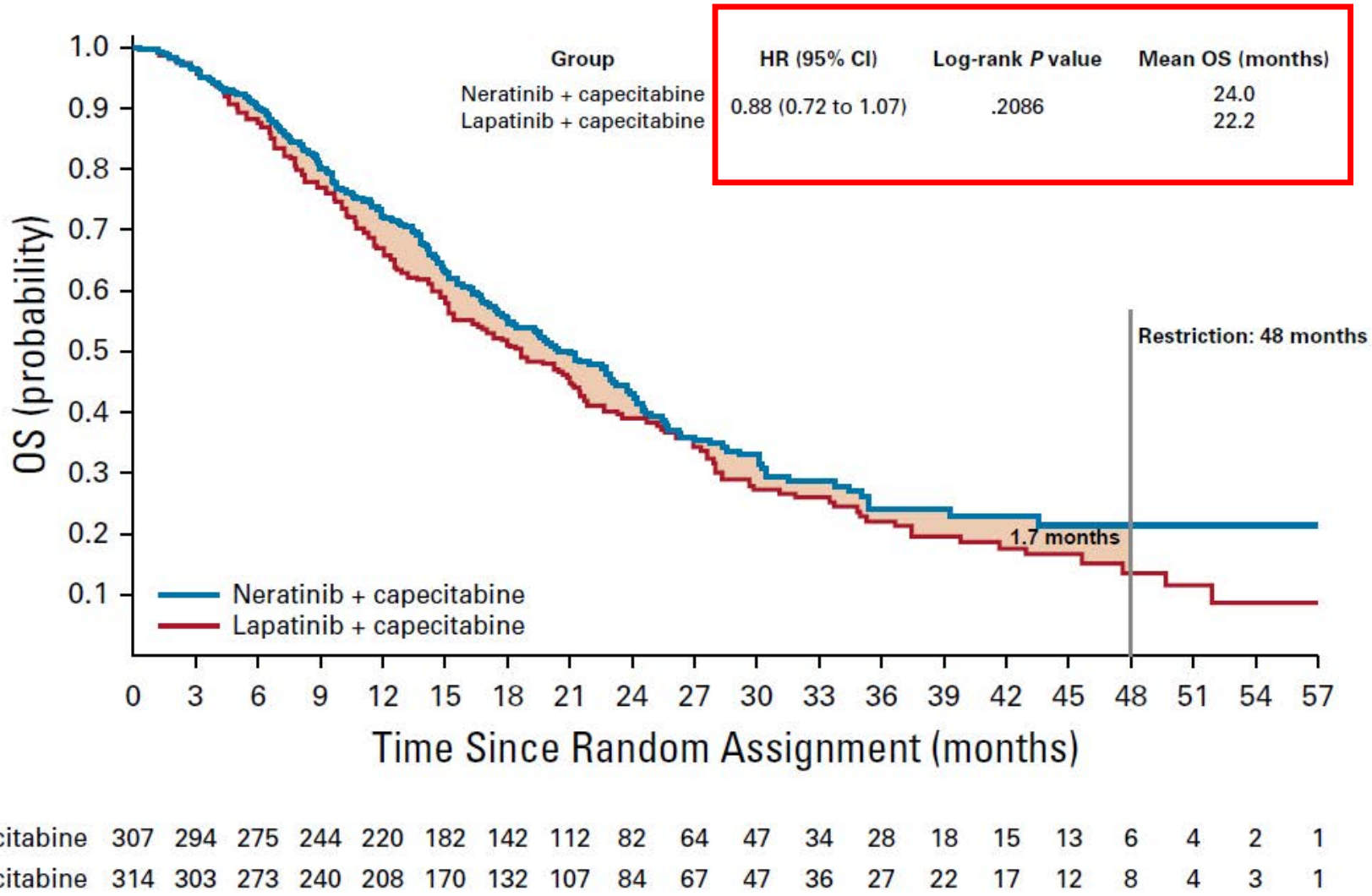
NALA Centrally Confirmed PFS



Saura et al, JCO 2020 38:3138

NALA Overall Survival Analysis

24% Gr3 Diarrhea



No. at risk:

Neratinib + capecitabine	307	294	275	244	220	182	142	112	82	64	47	34	28	18	15	13	6	4	2	1
Lapatinib + capecitabine	314	303	273	240	208	170	132	107	84	67	47	36	27	22	17	12	8	4	3	1

Saura et al, JCO 2020 38:3138

Margetuximab: HER2-Targeted Antibody With Modified Fc to Increase Immune Response

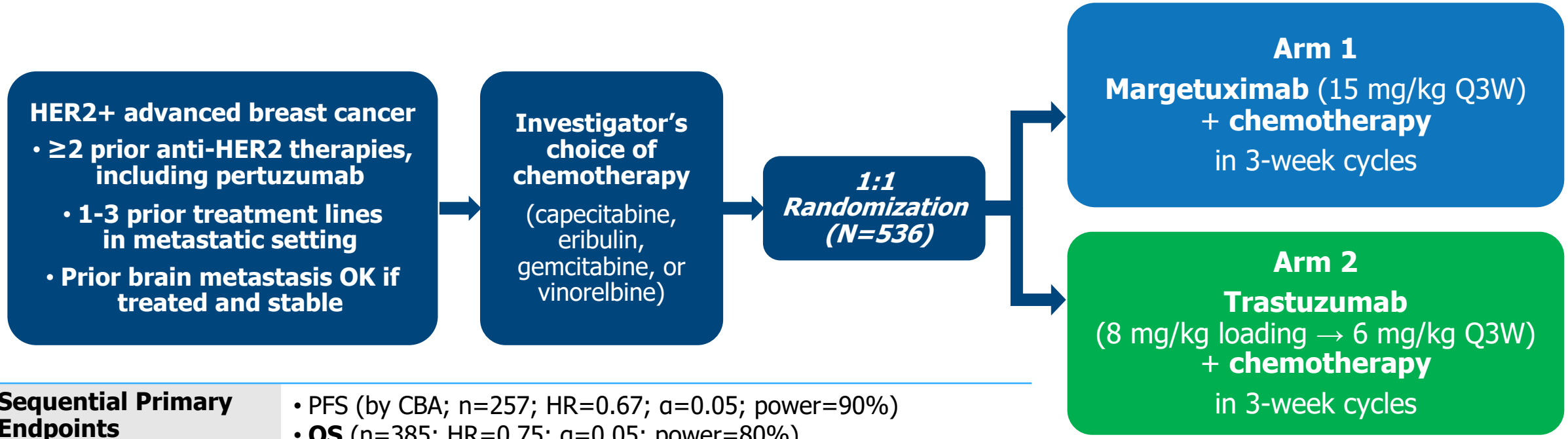
- Margetuximab has same affinity for HER2 as trastuzumab
- Modified Fc (constant) domain with change in 5 amino acids
  - ↑ binding to **activating CD16A** (FcγRIIIA) → ↑ NK, monocyte ADCC
  - ↓ binding to **inhibitory CD32B** (FcγRIIB) → ↑ monocyte ADCC
- Largest impact in cells with low affinity Fc receptor (FF or FV)

		Affinity (nM)		
CD16A (activating) aa158		~ Trastuzumab (IgG1)	Margetuximab	Margetuximab **Affinity Fold Change**
F (Phe) allele	Low Affinity	1059	161	↑ **6.6 x**
V (Val) allele	High Affinity	415	89	↑ **4.6 x**
CD32B (inhibitory)		52	437	↓ **8.4x**

- *Hypothesis: Margetuximab superiority over trastuzumab will be greatest in patients with low affinity Fc receptor (FF or FV)*

Nordstrom JL et al. *Breast Cancer Res*. 2011;13(6):R123.

Study CP-MGAH22-04 (SOPHIA) Design[1,2]



Sequential Primary Endpoints	• PFS (by CBA; n=257; HR=0.67; α=0.05; power=90%) • **OS** (n=385; HR=0.75; α=0.05; power=80%)
Secondary Endpoints	• **PFS** (Investigator assessed) • Objective response rate (ORR) by CBA
Tertiary/Exploratory Endpoints	• **ORR** (Investigator assessed) • **Clinical benefit rate** (CBR), **duration of response** (DoR) • **Safety** profile, antidrug antibody • **Effect of CD16A**, CD32A, and CD32B on margetuximab efficacy

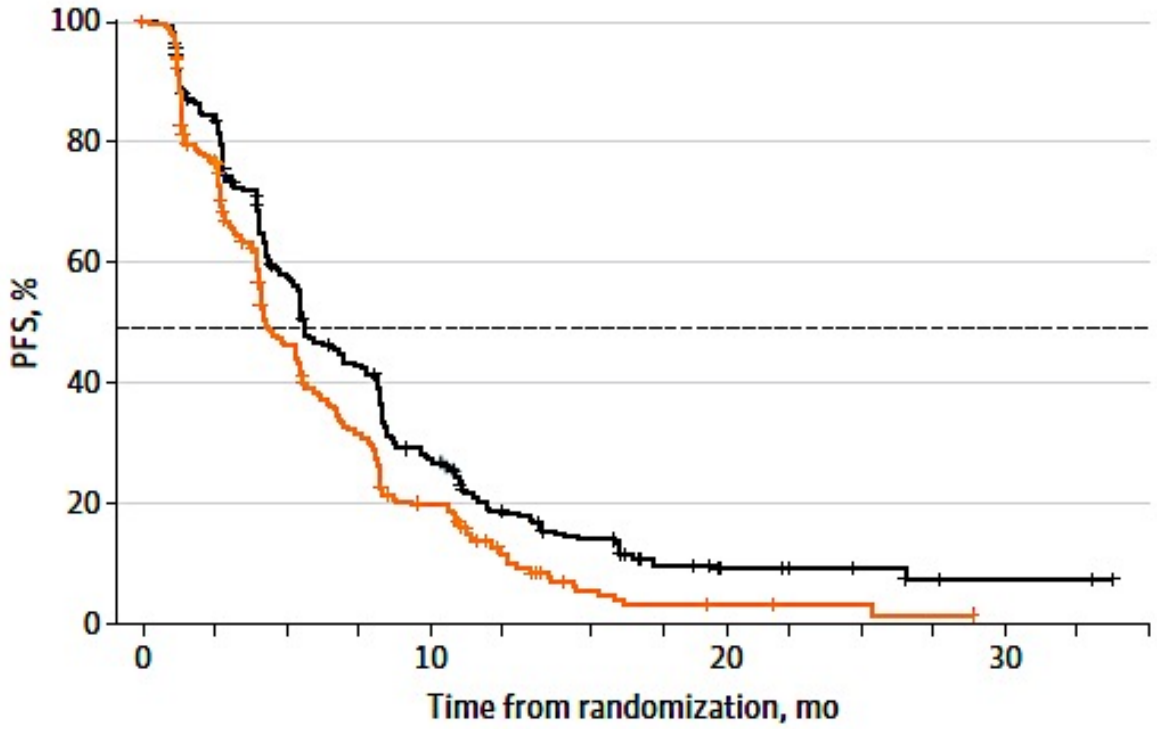
Stratification:
- Chemotherapy choice
- Prior therapies (≤2 *vs* >2)
- Metastatic sites (≤2 *vs* >2)

CBA=central blinded analysis; HR=hazard ratio; OS=overall survival; PFS=progression-free survival; Q3W=every 3 weeks.

1. Rugo HS, et al. *J Clin Oncol*. 2016;34(suppl 15):TPS630. 2. Clinicaltrials.gov. NCT02492711. https://clinicaltrials.gov/ct2/show/NCT02492711. Accessed September 30, 2019.

SOPHIA: PFS

C PFS by investigator, September 2019 cutoff



No. at risk

Margetuximab	266	210	137	100	62	36	25	14	11	6	5	3	2	2	0
Trastuzumab	270	192	108	72	42	20	8	4	3	2	2	1	0		

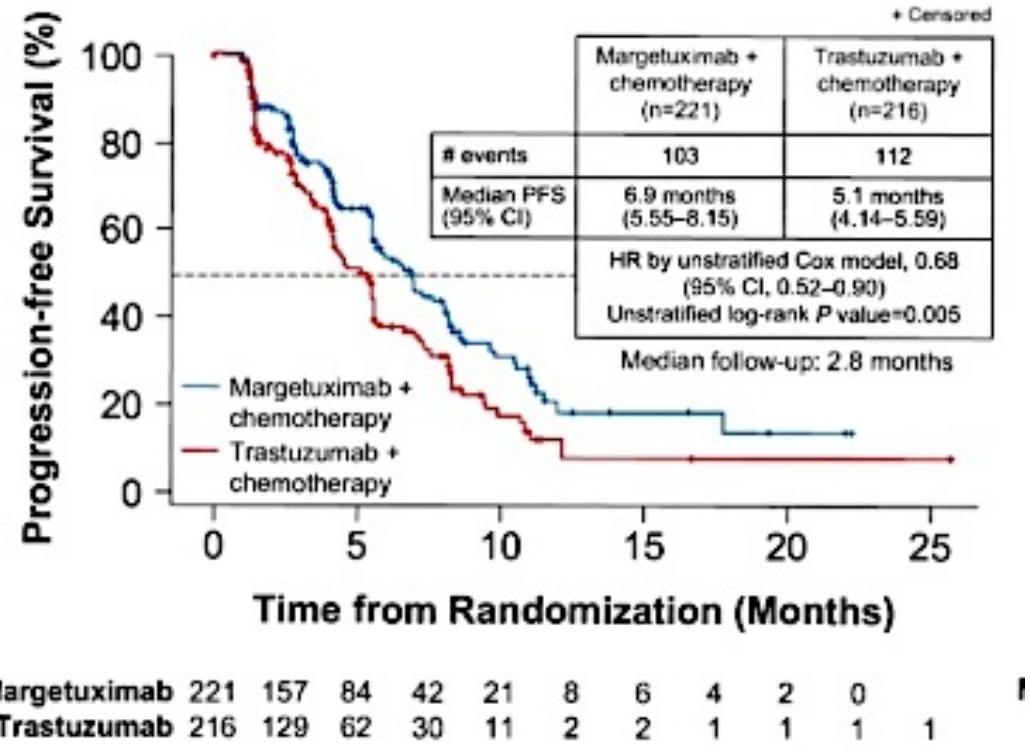
	Margetuximab + chemotherapy (n = 266)	Trastuzumab + chemotherapy (n = 270)
No. of events	208	222
Median PFS (95% CI)	5.7 mo (5.22-6.97)	4.4 mo (4.14-5.45)
3-mo PFS rate	74% (68%-79%)	67% (61%-72%)
6-mo PFS rate	47% (41%-53%)	38% (32%-45%)
9-mo PFS rate	29% (24%-35%)	20% (16%-26%)

HR by stratified Cox model, 0.71 (95% CI, 0.58-0.86)
Stratified log-rank $P<.001$
29% Risk reduction of disease progression[b]

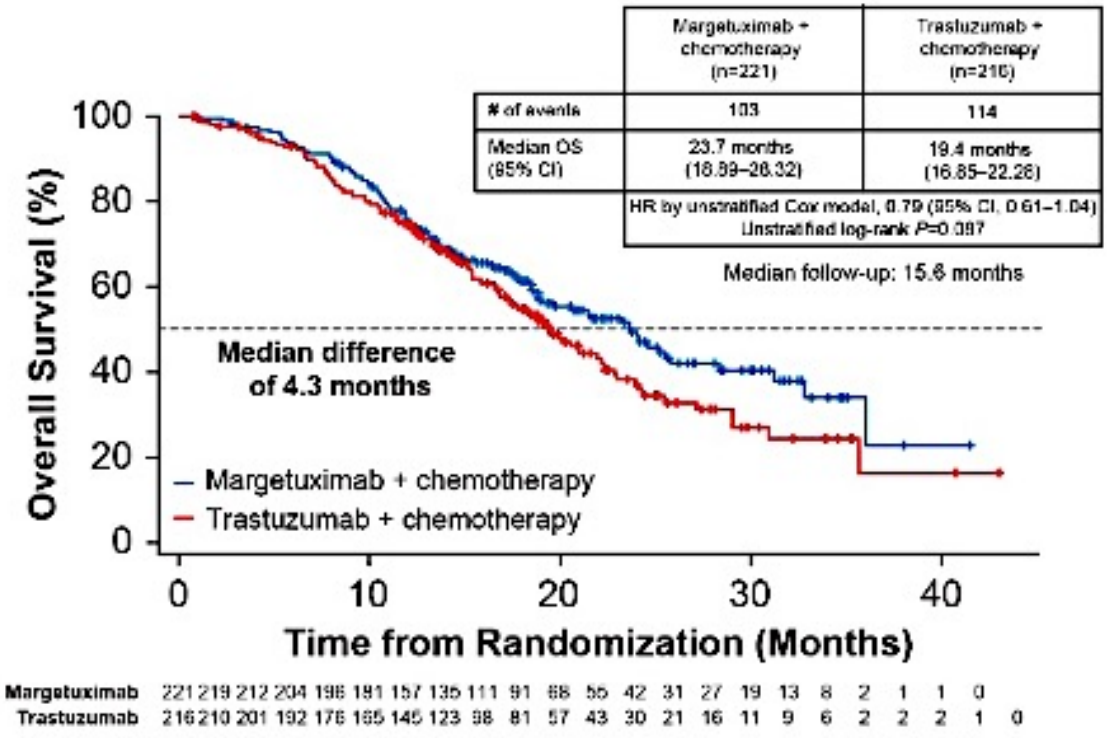
Rugo HS, et al. *JAMA Oncol*. 7:573. 2021

SOPHIA: PFS and OS in CD16-158F Carriers (86% of patients)

PFS

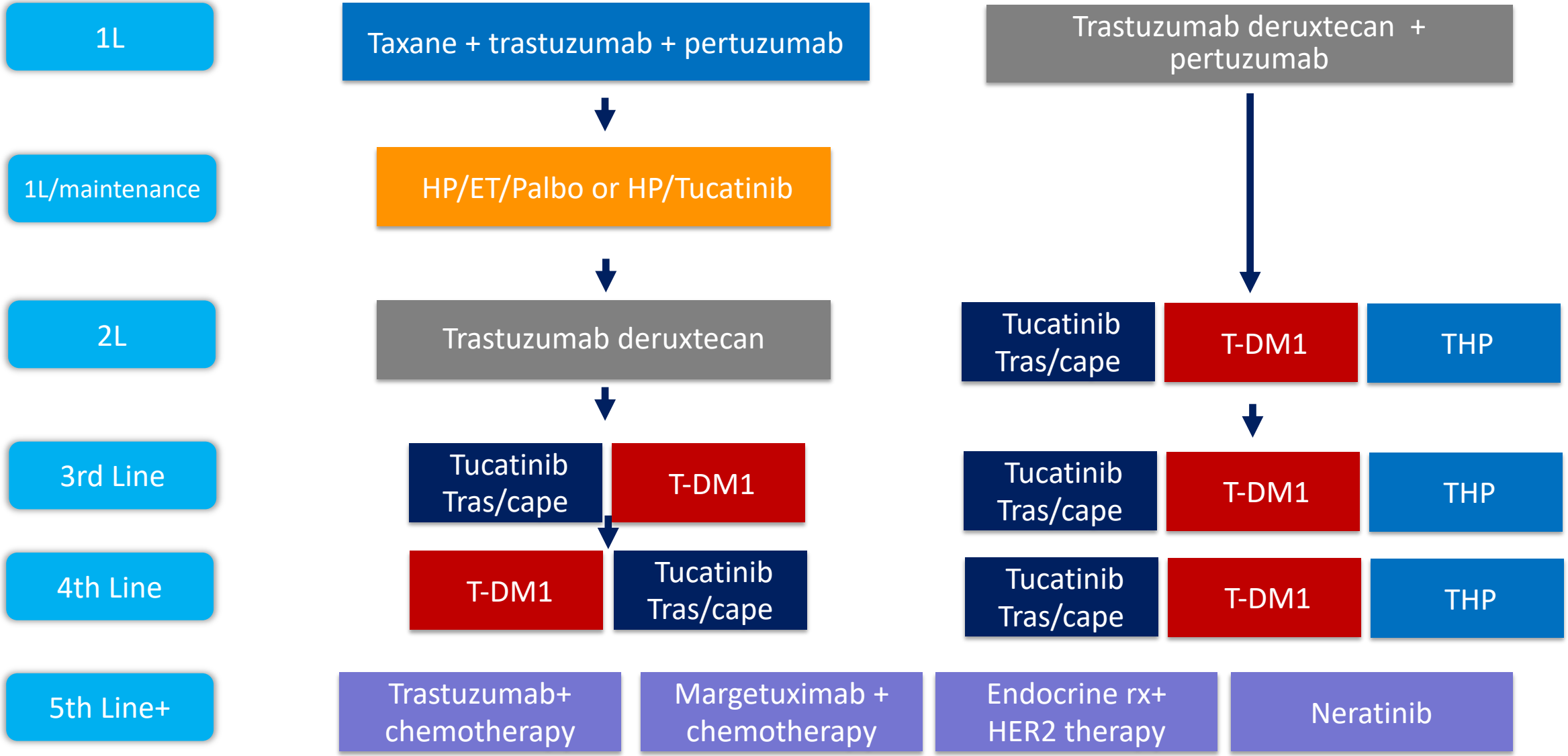


OS



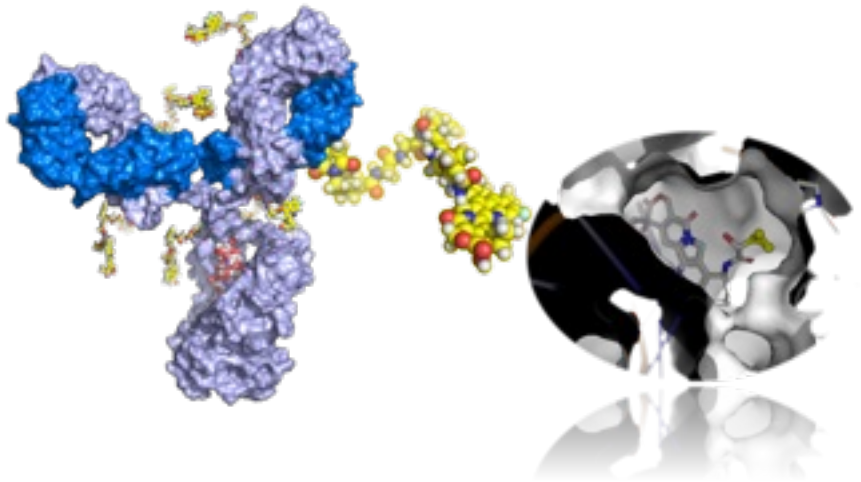
Rugo HS, et al. *JAMA Oncol*. 7:573. 2021

Approach to Therapy for Metastatic HER2+ disease



Background: SHR-A1811

- **SHR-A1811** is a novel HER2-targeted new-generation ADC composed of trastuzumab, a cleavable linker, and the topoisomerase I inhibitor payload SHR169265:[1]
  - Payload **SHR169265**: high membrane permeability and potent cell-killing effect;
  - **Protease-cleavable GGFG linker**: high stability;
  - Moderate **drug-antibody ratio of 6** and minimal amount of early-released toxin contribute to a favorable safety profile



References: 1. 2023 AACR LB031. 2. J Clin Oncol. 2024;42(29):3453-65.

HORIZON-Breast01 study design

Randomized, open-label, multicenter, active-controlled, phase 3 trial (NCT05424835)

HER2+ advanced breast cancer

Eligibility criteria

- HER2-positive unresectable or metastatic breast cancer
- Prior treatment with taxane and trastuzumab at the advanced stage
- or DFI ≤ 12 months

R 1:1

SHR-A1811 (4.8 mg/kg, IV) on day 1 of each 21-day cycle

Stratification factors:
- ✓ Prior lines of chemotherapy for metastatic disease (1 vs 2)
- ✓ Hormone receptor status (ER- and/or PR-positive vs ER- and PR-negative)

Pyrotinib (400 mg once daily, oral) on days 1-21 of each 21-day cycle **+**
capecitabine (1000 mg/m^2 twice daily, oral) on days 1-14 of each 21-day cycle

Primary endpoint:
- PFS (per BICR)

Secondary endpoints:
- PFS (per INV)
- OS
- ORR
- DoR
- Safety

Treatment until disease progression, unacceptable toxicity, patient withdrawal, or investigator decision.
Tumor assessments by RECIST v1.1.

Presenter: Erwei Song, MD

HER2, human epidermal growth factor receptor 2; DFI, disease-free interval; ER, estrogen receptor; PR, progesterone receptor; PFS, progression-free survival; BICR, blinded independent central review; INV, investigator; OS, overall survival; ORR, objective response rate; DoR, duration of response.; R, randomization

Baseline characteristics

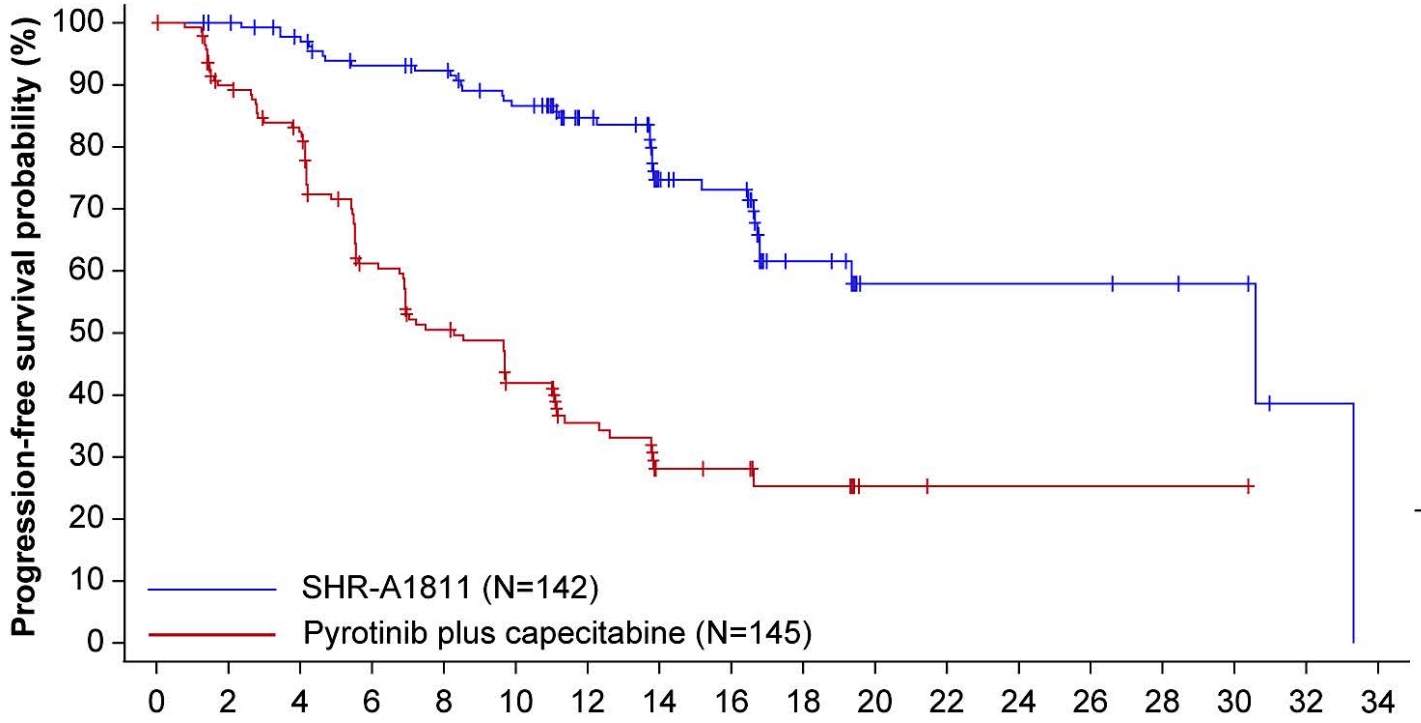
	SHR-A1811 4.8 mg/kg (N=142)	Pyrotinib plus capecitabine (N=145)
Median age (range), years	56.0 (27–74)	55.0 (31–74)
≥65 years, n (%)	24 (16.9)	14 (9.7)
ECOG performance status, n (%)		
0	71 (50.0)	84 (57.9)
1	71 (50.0)	61 (42.1)
HER2 status, n (%)		
IHC 3+	108 (76.1)	104 (71.7)
IHC 2+ and ISH+	34 (23.9)	41 (28.3)
Hormone receptor status, n (%)		
Negative	74 (52.1)	76 (52.4)
Positive	68 (47.9)	69 (47.6)
Visceral metastases, n (%)	108 (76.1)	103 (71.0)
Liver metastases, n (%)	55 (38.7)	44 (30.3)
Lung metastases, n (%)	64 (45.1)	63 (43.4)
Brain metastases, n (%)	7 (4.9)	4 (2.8)
Number of organs involved by tumor metastases		
<3	76 (53.5)	77 (53.1)
≥3	66 (46.5)	68 (46.9)

	SHR-A1811 4.8 mg/kg (N=142)	Pyrotinib plus capecitabine (N=145)
Lines of previous therapy		
Median number of lines (range)	1 (1–4)	1 (1–3)
Number of lines, n (%)		
1	119 (83.8)	111 (76.6)
≥2	23 (16.2)	34 (23.4)
Primary resistance to trastuzumab, n (%)		
Yes	56 (39.4)	65 (44.8)
No	84 (59.2)	75 (51.7)
Unknown	2 (1.4)	5 (3.4)
Previous anti-cancer therapy, n (%)		
Taxane	142 (100.0)	145 (100.0)
Trastuzumab	142 (100.0)	142 (97.9)
Pertuzumab	102 (71.8)	105 (72.4)
Trastuzumab emtansine	7 (4.9)	10 (6.9)
Endocrine therapy	42 (29.6)	41 (28.3)

Presenter: Erwei Song, MD

Human epidermal growth factor receptor 2 (HER2) status was evaluated by immunohistochemical analysis at the pathology department of the participating study site. HER2 ISH-positive refers to positive results on in situ hybridization.
Patients who had progression that had occurred within 12 months after receipt of neoadjuvant or adjuvant therapy were considered to have had one line of previous therapy. Lines of previous therapy did not include endocrine therapy.
Primary resistance to trastuzumab is defined as disease recurrence during or within 12 months after completing (neo)adjuvant trastuzumab therapy, or disease progression within 6 months of trastuzumab treatment in the advanced-stage setting.
ECOG, Eastern Cooperative Oncology Group;

Primary endpoint: PFS (per BICR)



No. at Risk

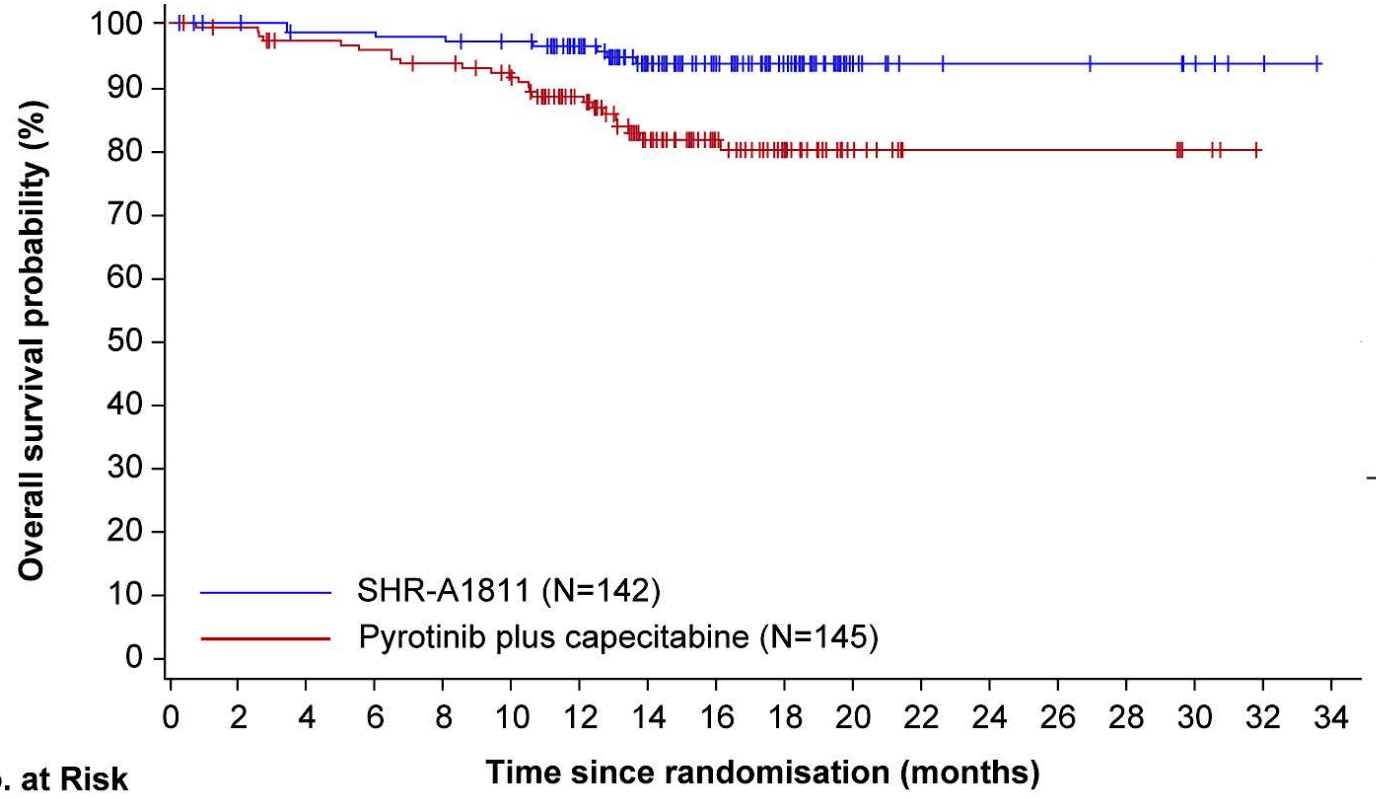
SHR-A1811	142	135	128	119	116	106	76	51	45	19	6	6	6	6	5	4	1	0
Pyrotinib plus capecitabine	145	121	108	75	60	46	30	17	16	9	2	1	1	1	1	1	0	

	SHR-A1811	Pyrotinib plus capecitabine
12-month PFS rate % (95% CI)	84.7 (77.0-90.0)	35.5 (26.8-44.2)
mPFS (95% CI), months	30.6 (16.8-NR)	8.3 (6.9-11.0)
HR (95% CI)	0.22 (95% CI, 0.15-0.34) P<0.0001	

Presenter: Erwei Song, MD

BICR, blinded independent central review; mPFS, median progression-free survival.

OS



No. at Risk

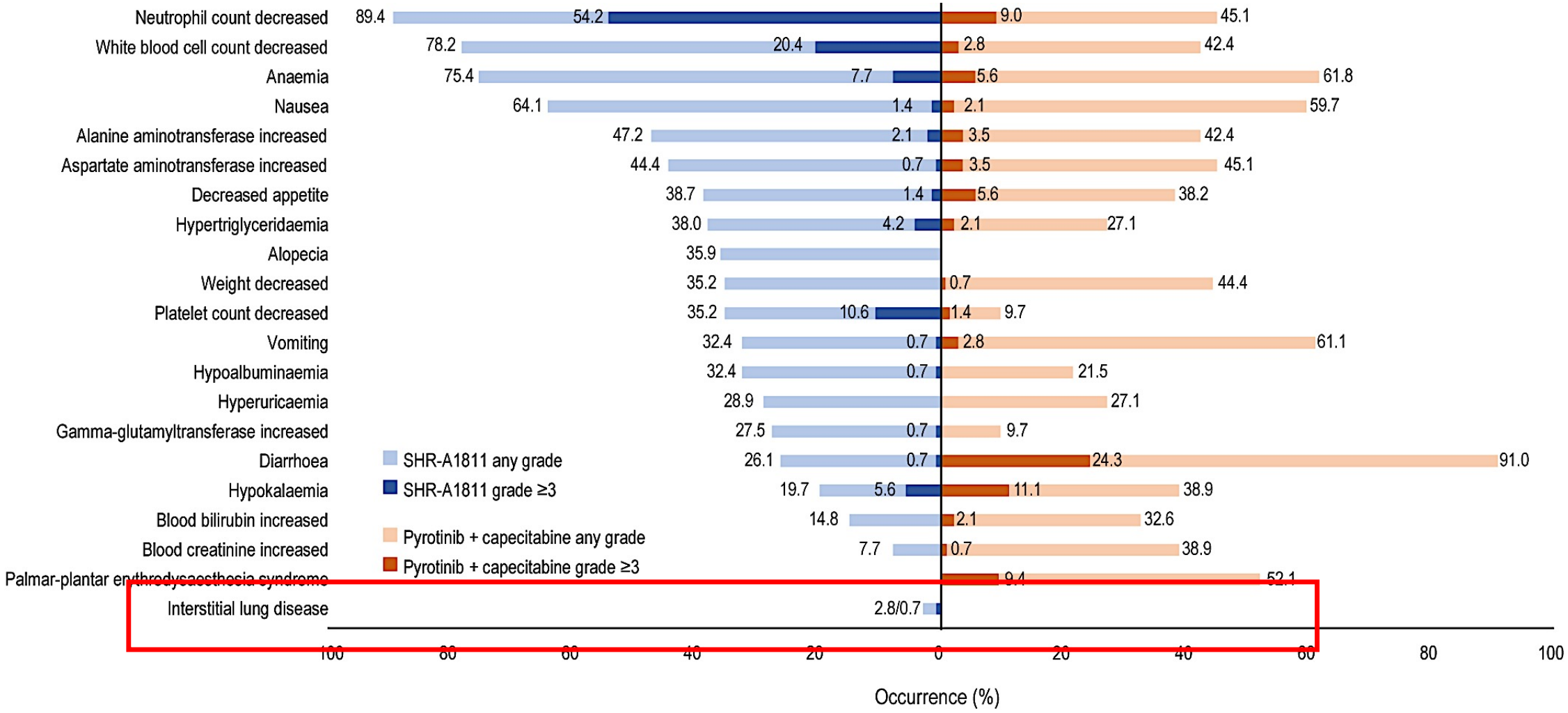
SHR-A1811	142	139	135	135	134	131	117	85	65	43	16	9	8	8	7	5	2	0
Pyrotinib plus capecitabine	145	142	136	134	130	123	102	72	52	34	15	7	7	7	7	3	0	

	SHR-A1811	Pyrotinib plus capecitabine
12-month OS rate % (95% CI)	96.3 (91.4-98.5)	88.4 (81.8-92.7)
mOS (95% CI), months	NR (NR-NR)	NR (NR-NR)
HR (95% CI)	0.31 (95% CI, 0.14-0.69)	

Presenter: Erwei Song, MD

mOS, median overall survival, NR, not reached.

TRAEs occurring in >25% of patients (either group) and ILD

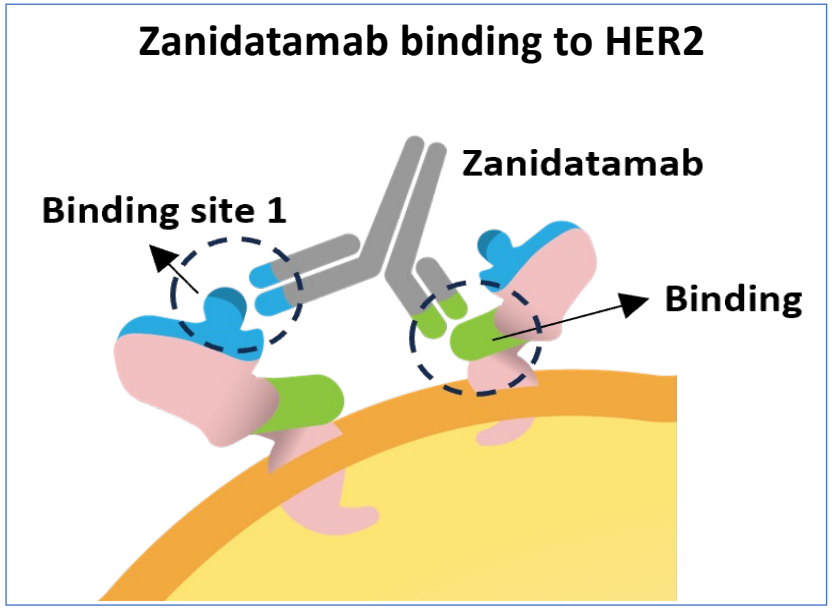


Presenter: Erwei Song, MD

TRAE, treatment-related adverse event; ILD, interstitial lung disease.

Zanidatamab (ZW25)

- Humanized IgG1-like **biparatopic** HER2 antibody
- Binds the two HER2 domains targeted by trastuzumab (ECD4) and pertuzumab (ECD2)
  - Crosslinks multiple HER2 receptors
  - Improves HER2 internalization and degradation
- Preclinical studies showed growth inhibition of cancer cell lines with wide range of HER2 expression



Weisser et al Nat Commun. 2023; 14: 1394

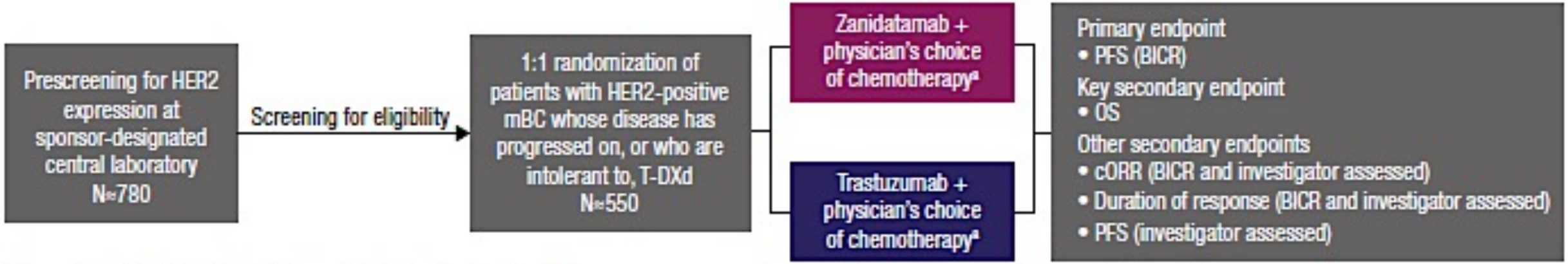
Zanidatamab combinations in HER2+ MBC

	Zani + Docetaxel[1] N=37	Zani + several CT[2a] N=24	Zani + CDK4/6i + Fulv[3] N=45	Zani + Evorpacept N=21
Population	1L mBC	3L+ mBC	3L+ mBC	3L+ mBC
Brain metastasis	5.4%	38.0%	16.0%	42.9%
Prior anti-HER2				
Trastuzumab	21.6%	96.0%	100%	100%
Pertuzumab	2.7%	96.0%	98.0%	95.2%
T-DXd	0	0	24.0%	100%
T-DM1	0	96%	100%	66.7%
ORR	90.9%	36.4%	33.0%	33.3%
DCR	97.0%	86.4%	92.0%	71.4%
PFS, median	PFS@12m 73.3%	7.3 months	12 months	3.6 months
Incidence of G3 AEs	67.6%	54.0%	60.0%	13.5%
Neutropenia	49.6%	38.0%	56.0%	0
Diarrhea	8.1%	8.0%	9.0%	13.5%

[1]Wang X et al. ASCO 2023 | [2]Bedard P et al. SABCS 2021 | 3Escrivá-de-Romani S et al. SACBS 2022

[a]Vinorelbine (n=12), capecitabine (n=8), or paclitaxel (n=4)

EmpowHER-303: A Phase 3 Study of Zanidatamab vs Trastuzumab with Chemotherapy in Patients with Metastatic HER2+ Breast Cancer Whose Disease Has Progressed on Trastuzumab Deruxtecan



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.

BICR, blinded independent central review; cORR, confirmed objective response rate; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan.

NCT06435429

SUMMIT: Does neratinib have activity in breast cancers with somatic HER2 mutations?

- Somatic HER2 mutations seen in 3-5% of HR+ HER2 non-amplified cancers
  - More common in lobular cancers (5-8%)
  - May be acquired with endocrine resistance
- SUMMIT trial is basket study evaluating neratinib alone and in combination in patients with HER2 mutant breast cancer
  - Initial results showed single agent activity: 17% ORR in HR+ HER2 mutant MBC
  - Combination of neratinib and fulvestrant: 30% ORR
- Data led to cohort of neratinib + fulvestrant + trastuzumab (NFT) performed (in pts previously treated with CDK4/6 inhibitor

Jhaveri et al, Annals of Oncology 34:885 2023

SUMMIT: Does neratinib have activity in breast cancers with somatic HER2 mutations?

Parameter	Non-randomized + randomized HR+, prior CDK4/6i (N+F+T, *N*=57)	Randomized HR+, prior CDK4/6i (F+T, *n*=7)	After crossover from F+T to N+F+T (*n*=4)	Randomized HR+, prior CDK4/6i (F, *n*=7)	After crossover from F to N+F+T (*n*=6)
Objective response (confirmed CR or PR)[b], *n* (%)	22 (39)	0	1 (25)	0	2 (33)
CR	1 (2)	0	0	0	0
PR	21 (39)	0	1 (25)	0	2 (33)
Best overall response (confirmed or unconfirmed PR or CR), *n* (%)	29 (51)	0	1 (25)	0	3 (50)
Median DOR[c], months (95% CI)	14.4 (6.4–21.7)	No response	6.2 (NE–NE)	No response	6.3 (6.2–6.4)
Clinical benefit[d], *n* (%)	31 (54)	0	1 (25)	0	5 (83)
Median PFS[c], months (95% CI)	8.3 (6.0–15.1)	3.9 (1.9–4.1)	5.8 (3.3–8.3)	4.1 (1.6–4.1)	9.5 (3.9–NE)

- ORR: 63% V777L
  24% L755S
  80% dual mutation
- HER2 expression level or FISH amplification were not assoc with ORR
- Grade 3 diarrhea was 53% with triplet despite loperamide prophylaxis

Jhaveri et al, Annals of Oncology 34:885 2023

SUMMIT: Does neratinib have activity in breast cancers with somatic HER2 mutations?

- Neratinib + fulvestrant has clinically meaningful activity in patients with ER+HER2 mutant MBC
  - Addition of trastuzumab may further increase benefit
  - Substantial Gr3 diarrhea – consider neratinib dose escalation

- Neratinib based therapy can be considered an effective treatment option for ER+HER2 mutant MBC
  - Included in NCCN guidelines

- These data provide additional support for obtaining somatic tumor sequencing (tissue or ctDNA) in the MBC setting

Case Presentation: 40-year-old woman with ER-positive, HER2-positive mBC receives THP and maintenance tucatinib + HP on trial and now has disease progression

Dr Yanjun Ma (Murfreesboro, Tennessee)

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

What treatment would you recommend for this patient who is concerned about hair loss?

Is rechallenging with tucatinib and trastuzumab, with added capecitabine, a reasonable option for this patient?

Are cold caps effective against hair loss with antibody-drug conjugates, including T-DXd?

Agenda

Module 1: Considerations in the Care of Patients with Localized HER2-Positive Breast Cancer — Prof Harbeck

Module 2: Previously Untreated HER2-Positive Metastatic Breast Cancer (mBC) — Prof Curigliano

Module 3: Optimal Management of Brain Metastases in Patients with HER2-Positive Breast Cancer — Dr Lin

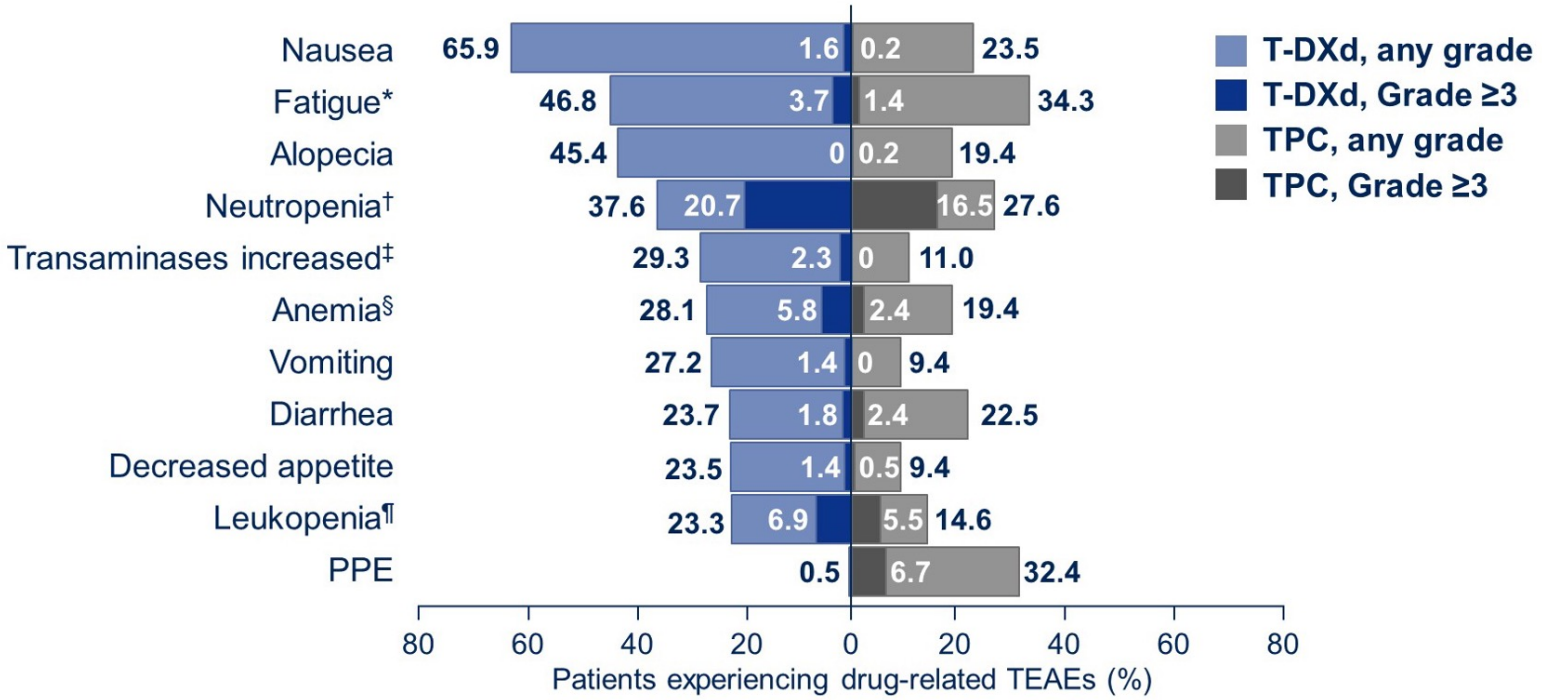
Module 4: Selection and Sequencing of Therapy for Relapsed/Refractory (R/R) HER2-Positive mBC in the Absence of CNS Involvement — Dr Krop

Module 5: Tolerability Considerations with HER2-Targeted Therapies — Dr O'Shaughnessy

Tolerablity Consideratons with the Use of HER2-Targeted Agents

Joyce O'Shaughnessy, MD
Baylor University Medical Center
Texas Oncology
Sarah Cannon Research Institute
Dallas TX

Trastuzumab Deruxtecan (T-DXd): Destiny-Breast 06 Safety



TEAEs leading to death

- 11 (2.4%) vs 6 (1.4%)
- Treatment related: 5 (1.2%) vs 0

Most common TEAE associated with treatment discontinuation

- T-DXd: 5.3%, pneumonitis
- TPC: 1.4%, peripheral neuropathy

Left ventricular dysfunction

- 8.1% any grade
- 0.7% grade 3

General tips:

- For nausea, olanzapine 2.5mg D1-7 at night
- Dose reductions if needed for fatigue
- Monitor baseline TTE and q3-4mo
- ILD management: Patient counseling, more frequent CT scans (q9 to 12w), steroid if needed, ILD rechallenge for G1

Adjudicated as drug-related interstitial lung disease / pneumonitis*

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd (n=434)	7 (1.6)	36 (8.3)	3 (0.7)	0	3 (0.7)	49 (11.3)
TPC (n=417)	0	1 (0.2)	0	0	0	1 (0.2)

Bardia et. al. *NEJM* 2024
Curigliano et al. ASCO 2024

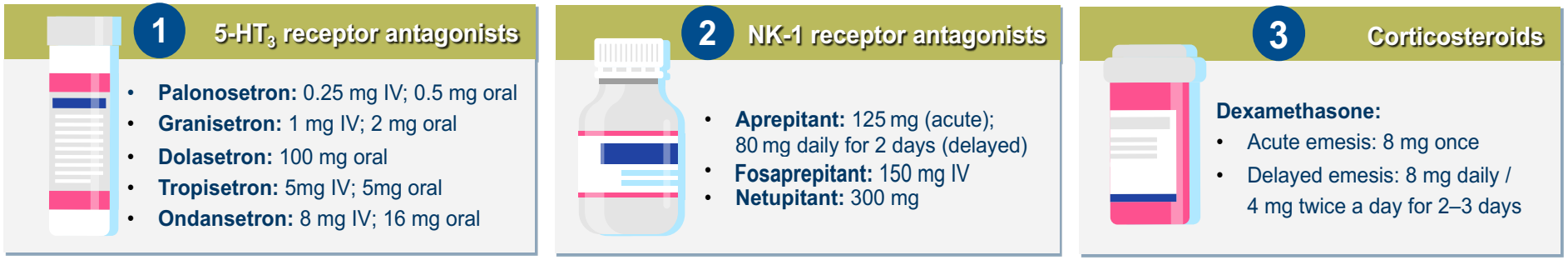
DB04: Nausea and Vomiting

- 189/371 patients (50.9%) in the T-DXd arm and 64/172 patients (37.2%) in the TPC arm received antiemetic prophylaxis[a]
- Prophylaxis was not mandatory per study protocol, but was recommended

	Nausea		Vomiting	
n (%)	T-DXd n = 371	TPC n = 172	T-DXd n = 371	TPC n = 172
Dose reduction associated with N/V	17 (4.6)	4 (2.3)	3 (0.8)	1 (0.6)
Drug interruption associated with N/V	5 (1.3)	4 (2.3)	0	0
Drug discontinuation associated with N/V	1 (0.3)	0	1 (0.3)	0

Three Classes of Anti-Emetic Premedication are Recommended

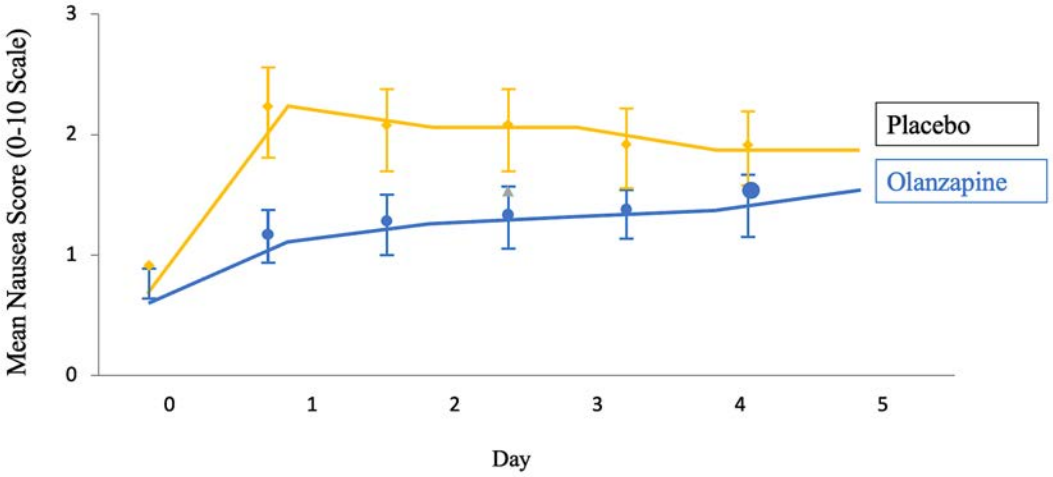
These can be individualized to patient symptoms

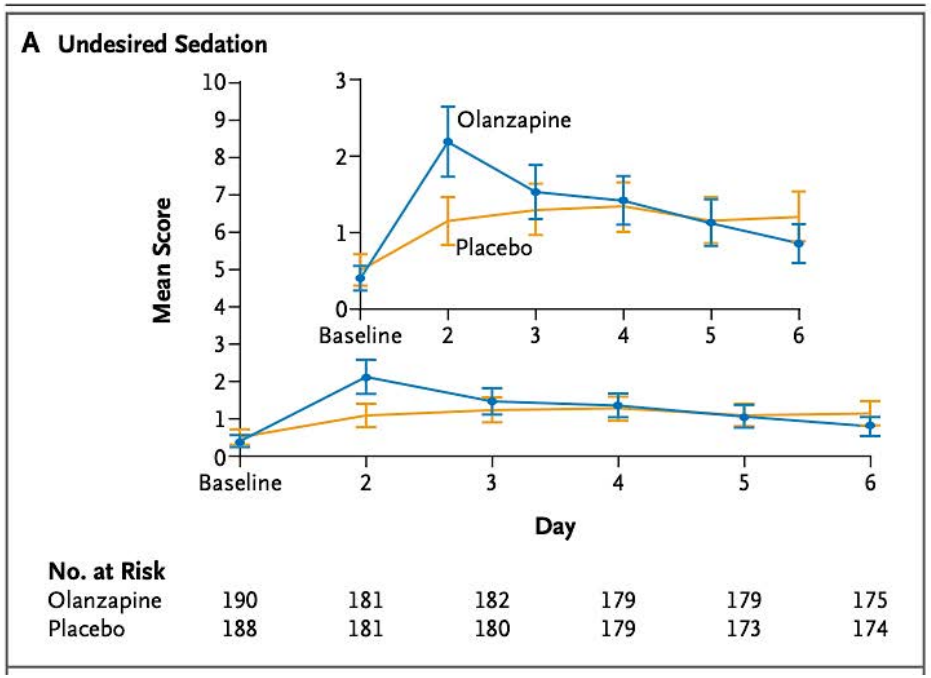


N/V, nausea or vomiting; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Prophylaxis included antiemetics and antinauseants, corticosteroids for systemic use, drugs for functional gastrointestinal disorders, or other.

Rugo et al, ESMO Breast 2023; NCCN 2023

Chemo-Induced Nausea and Vomiting (CINV): Olanzapine





- **Study design:**
  - Randomized, double-blind, placebo controlled trial that enrolled 380 patients (majority breast cancer, also lung cancer, other)
- **Results:**
  - Olanzapine significantly improved nausea vs. placebo
    - Initial 24 hr: 74% vs. 45%, P=0.002
    - 25-120 hr: 42% vs. 25%, P=0.002
    - Overall 120-hour period:37% vs. 22%, P=0.002
  - Some increase in undesired sedation
- **Practical tips:**
  - 2.5mg olanzapine at night often sufficient
    - Can decrease further to 1.25 if too drowsy
    - Can increase to 5 or 10mg if needed and tolerated
    - Can extend to 10-14+ days for pts with prolonged nausea

Navari RM, et al. *N Engl J Med.* 2016

Chemo-Induced Nausea and Vomiting (CINV): Treatment

- **Prevention of CINV is the goal**

- **High emetogenicity**
  - NK 1 antagonist + dexamethasone + 5HT3
  - Olanzapine + dexamethasone + palonosetron
  - Olanzapine + NK1 RA + 5HT3 + dexamethasone

- **Moderate emetogenicity**
  - Dexamethasone + 5HT3 ± NK 1 antagonist
  - Olanzapine + dexamethasone + 5HT3
  - NK 1 antagonist + dexamethasone + 5HT3

- **Low emetogenicity**
  - Dexamethasone or metoclopramide or prochlorperazine or 5HT3

- **Breakthrough CINV**
  - Add agents from different drug classes and schedule doses

Adapted from NCCN Guidelines, Antiemesis 2025

DB04: Adverse Events of Special Interest

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
ILD/pneumonitis (adjudicated, drug-related), n (%)						
T-DXd (n = 371)	13 (3.5)	24 (6.5)	4 (1.1)[a]	0	4 (1.1)[a]	45 (12.1)
TPC (n = 172)	1 (0.6)	0	0	0	0	1 (0.6)
Left ventricular dysfunction						
Ejection fraction decreased, n (%)						
T-DXd (n = 371)	2 (0.5)	15 (4.0)	1 (0.3)	0	0	18 (4.9)
TPC (n = 172)	0	0	0	0	0	0
Cardiac failure, n (%)						
T-DXd (n = 371)	0	1 (0.3)	1 (0.3)	0	0	2 (0.5)
TPC (n = 172)	0	0	0	0	0	0

Assess LVEF at baseline then every 3-4 mos, holding T-DXd as needed per standard trastuzumab guidelines

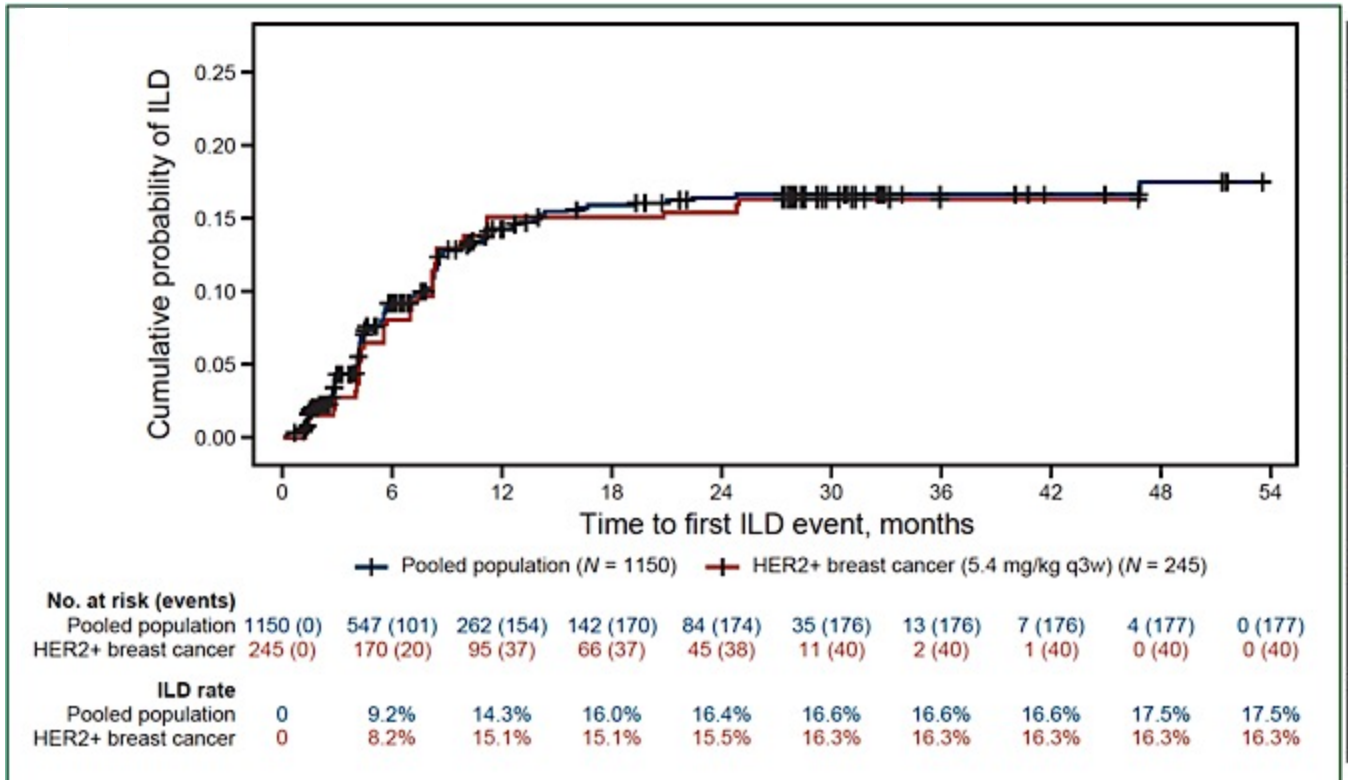
ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

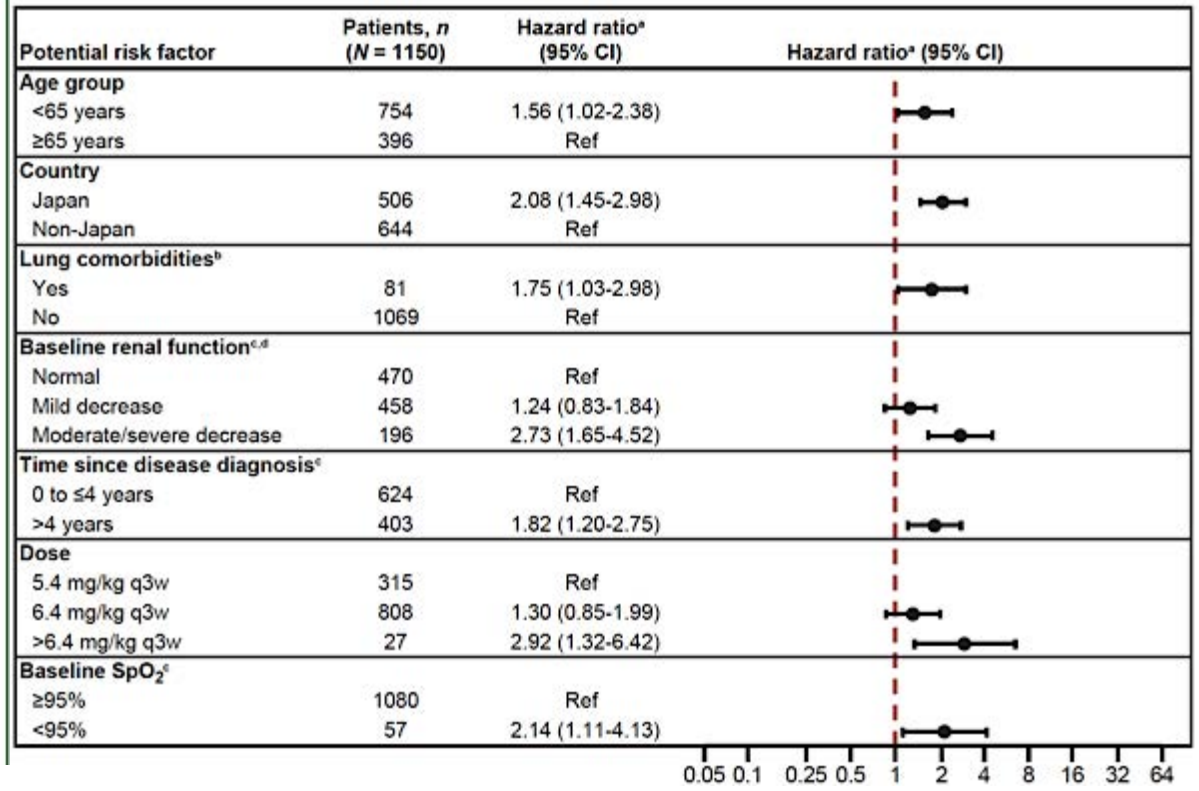
[a]At the primary analysis (data cutoff, January 11, 2022), grade 3 adjudicated drug-related ILD was reported in 5 patients (1.3%). At the current data cutoff, grade 3 adjudicated drug-related ILD is reported in 4 patients (1.1%) as 1 grade 3 ILD case worsened to grade 5 ILD. Consequently, there is an increase in the rate of grade 5 ILD (from 0.8% to 1.1%) without impact on the overall rate of adjudicated drug-related ILD. No ILD cases were pending adjudication at the updated data cutoff.

1. Modi S et al. *N Engl J Med*. 2022;387:9-20.

Modi et al, ESMO 2023

Pooled Analysis of ILD/Pneumonitis in 9 Trastuzumab deruxtecan Monotherapy Studies





- 1150 pts (44.3% breast cancer) with a median treatment duration 5.8 mo (0.7-56.3)
- Overall incidence: 15.4% (grade 5: 2.2%); grade 1-2: 77.4%
- 87% had their first event within 12 months of their first dose

Powell et al, ESMO Open 2022

It is recommended that patients treated with T-DXd should have HRCT scans at least every 12 weeks and every 6–9 weeks for those with respiratory history or symptoms[1]

Pre-T-DXd treatment

- Complete history and physical
- HRCT
- Baseline SpO_2
- Consider pulmonary consult for patients with significant lung comorbidities
- Provide patient education on risk and symptom identification

On T-DXd treatment

- **HRCT at least every 12 weeks, or every 6–9 weeks with baseline respiratory symptoms**
- Vital signs including SpO_2 and symptom assessment with treatment visits

If ILD suspected

T-DXd-related ILD/pneumonitis should be suspected when:
- Radiographic changes potentially consistent with ILD/pneumonitis are seen
- Patient experiences acute onset of new or worsening pulmonary signs/symptoms, such as dyspnoea, cough or fever

- Immediately hold T-DXd therapy and proceed with diagnostic workup

- Vitals and SpO_2, HRCT, blood tests
- If clinically indicated, consider PFTs, ABG, and bronchoscopy/BAL

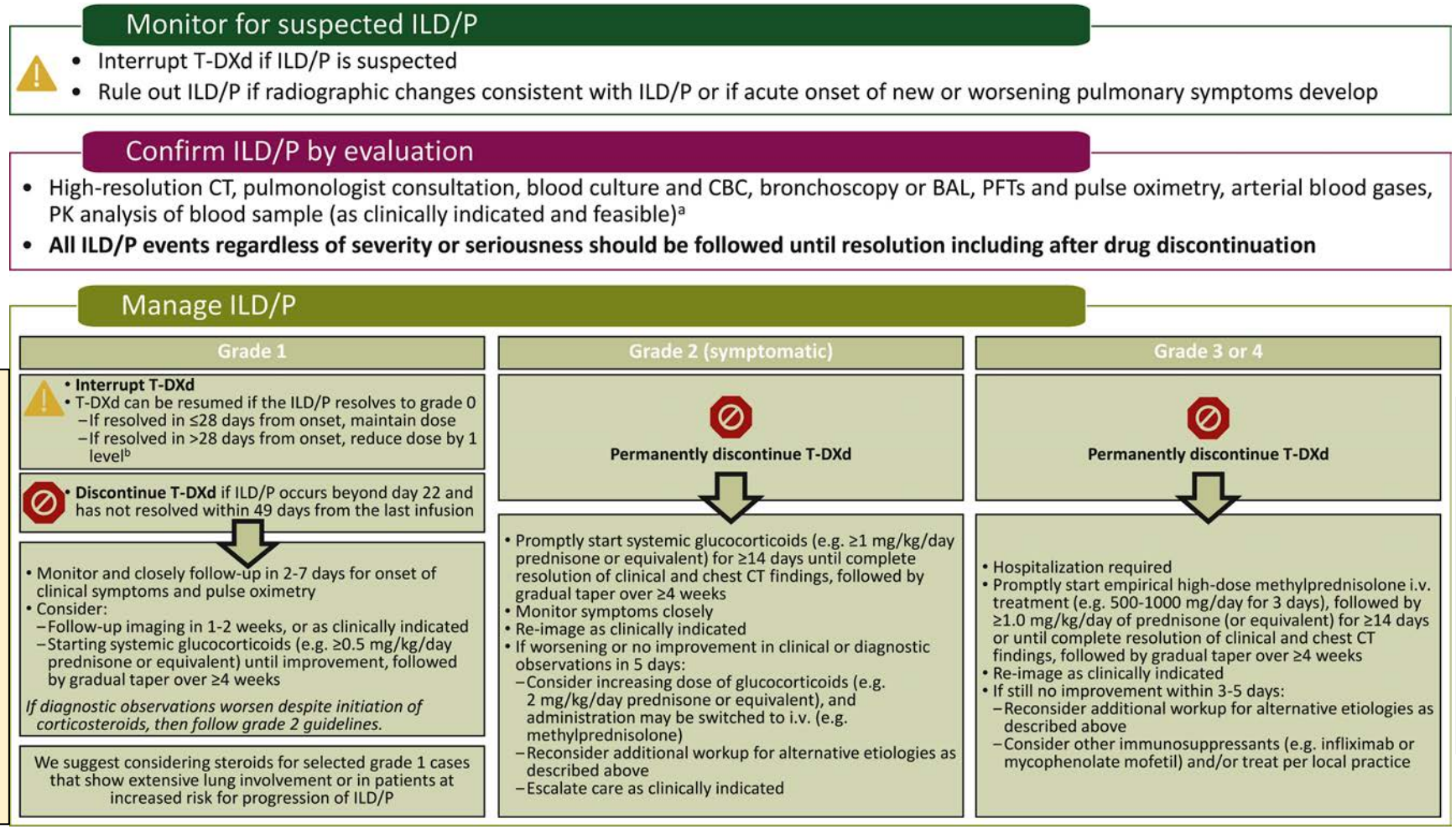
Consider:
- Consultation of a pulmonologist
- Treatment with corticosteroids as clinically indicated

ABG=arterial blood gas; BAL=bronchoalveolar lavage; HRCT=high-resolution computerised tomography; ILD=interstitial lung disease; PFT=pulmonary function test; SpO2=peripheral oxygen saturation; T-DXd=trastuzumab deruxtecan.

1. Rugo HS, et al. *JCO Oncol Pract*. 2023;1–8.

Trastuzumab Deruxtecan (T-DXd): ILD Management

Grade 1 ILD = Asymptomatic
- Hold T-DXd
- Consider steroids
- Consider re-challenge if CT findings resolve



Grade 2+ ILD = Symptomatic
- Permanently discontinue T-DXd
- Recommend steroids

Rugo et al., *ESMO Open* 2022

Management of LVEF Changes Associated with T-DXd

Routine Monitoring

1. LVEF assessment at baseline
2. Repeat LFEV every 3 months

	LVEF >45%	LVEF 40-45%	LVEF <40%
Decrease from BL <10%	Continue	Continue. Repeat LVEF after 3 weeks	• Hold T-DXd. • Repeat LVEF after 3 weeks. • If confirmed, discontinue
Decrease from BL 10-20%	Continue	• Hold T-DXd. • Repeat LVEF after 3 weeks. • If not recovered to within 10% from BL, discontinue. • If recovered, resume at same dose	
Decrease from BL >20%	• Hold T-DXd. • Repeat LVEF after 3 weeks. • If confirmed, discontinue		

Discontinue if symptomatic congestive heart failure

Schmid P. ESMO Breast 2024.

Management of Neutropenia/Thrombocytopenia

Routine Monitoring

1. Prior to D1 of each cycle ANC≥1 and Plt ≥75
2. Nadir control not required
3. Primary G-CSF prophylaxis only in risk groups
4. Secondary G-CSF as indicated

Neutropenia	Grade 1	Grade 2	Grade 3	Grade 4	Febrile Neutropenia
Description	ANC 1.5 - <2	ANC 1 - <1.5	ANC 0.5 - <1	ANC <0.5	ANC <1 & T>38.3
ADC	Continue	Continue	Hold until ≥1	Hold until ≥1	Hold until resolved
Dose reduction	N/A	N/A	N/A	Reduce by 1 level	Reduce by 1 level
G-CSF	No primary prophylaxis (unless risk group)		Consider G-CSF	Consider G-CSF	Consider G-CSF

Thrombocytopenia:

1. **Hold if Platelets <50, until ≥75**
2. **Reduce by 1 level if Platelet nadir <25**

Schmid P. ESMO Breast 2024.

Trastuzumab Deruxtecan (T-DXd): T-DXd Rechallenge for G1 ILD

Pooled data from DESTINY-Breast trials[1] (n=2145)

- 9.0% rate of any grade ILD (n=193)
- 45 patients retreated; 50% received steroids
- 33% rate of recurrent ILD, all grade 1-2
- Median time to recurrent ILD 64 days (range 22-391)

	T-DXd retreatment (N = 45)
Dose level of T-DXd retreatment	
Same dose, n (%)	31 (68.9)
Reduced dose, n (%)	14 (31.1)
Median time to retreatment after ILD1 onset (range), days	28 (8-48)
Median retreatment cycles (range)	5.0 (1-37)
Patients with ILD2 (n = 15)	5.0 (2-23)
Patients without ILD2 (n = 30)	4.5 (1-37)
Median retreatment duration (range), days	85.0 (1-848)
Patients with ILD2 (n = 15)	85.0 (22-648)
Patients without ILD2 (n = 30)	82.5 (1-848)

Similar findings in real-world studies

French retrospective cohort study[2]

- Median re-treatment duration not reported
- 33% rate of recurrent ILD (grades not reported)

UCSF retrospective cohort study[3]

- 44 pts rechallenged G1 / 19 pts G2 rechallenged; 16-27% rate of recurrent ILD, mostly G1-2, no G5
- Median re-treatment duration 215 days (!)

- Re-treatment with T-DXd after grade 1 ILD is safe with low rates of recurrent ILD
- Patients can have ongoing clinical benefit after re-treatment.

1. Rugo et al., ESMO Breast 2024
2. Canellas et al. ESMO 2024
3. Natsuhara et al., ASCO 2025

T-DXd Retreatment Characteristics

	T-DXd retreatment (N = 45)
Dose level of T-DXd retreatment	
Same dose, n (%)	31 (68.9)
Reduced dose, n (%)	14 (31.1)
Median time to retreatment after ILD1 onset (range), days	28 (8-48)
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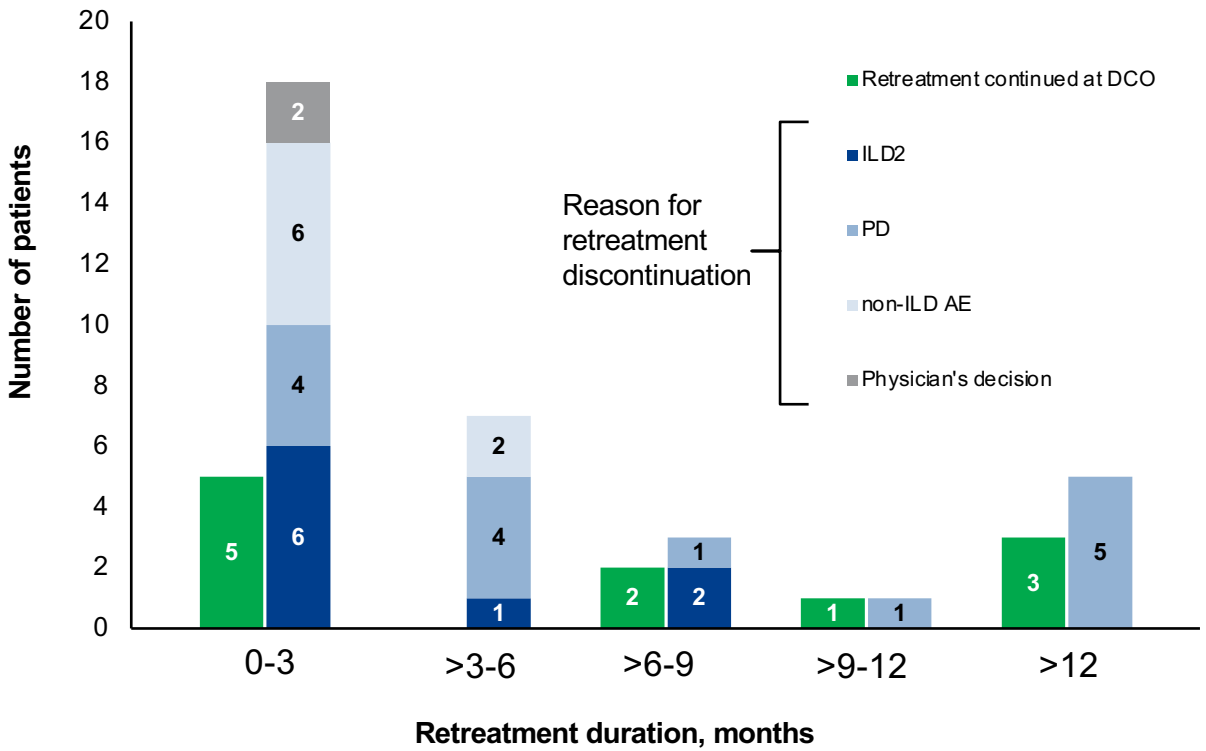


- 68.9% (31/45) of patients were retreated without any dose reductions
- 24.4% (11/45) of patients were still receiving T-DXd retreatment at the DCOs of each respective study
- Progressive disease was the main reason for T-DXd retreatment discontinuation (33.3% [15/45] of patients)
  - 20.0% (9/45) of patients discontinued retreatment due to recurrent ILD (ILD2)
- **33.3% (15/45) of patients were retreated for >6 months and 17.8% (8/45) of patients were retreated for >12 months**

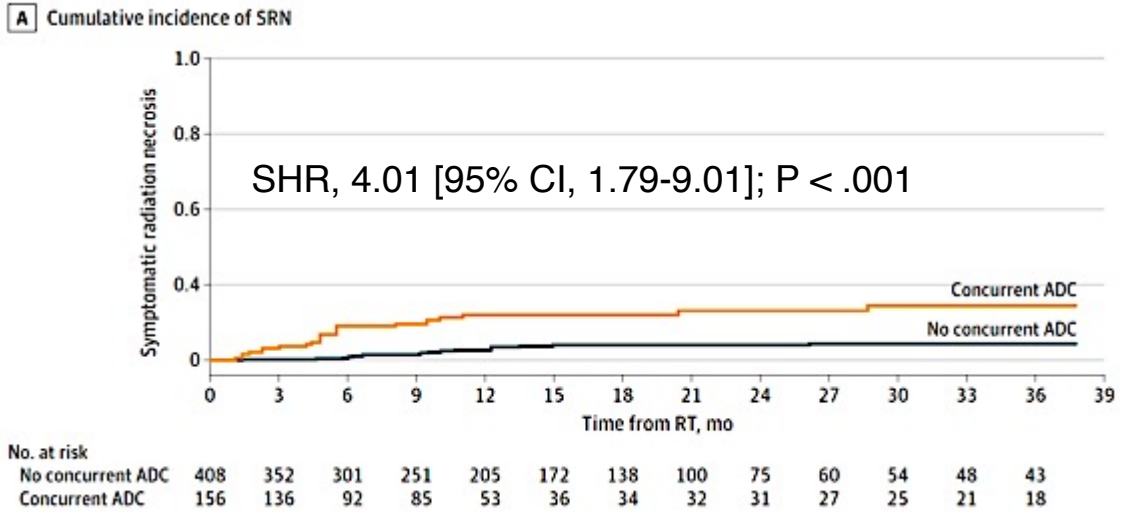
AE, adverse event; DCO, data cutoff; ILD, interstitial lung disease/pneumonitis; ILD1; first Gr 1 ILD event; ILD2, any-grade recurrent ILD event; PD, progressive disease; T-DXd, trastuzumab deruxtecan.

Rugo et al, ESMO Breast 2024

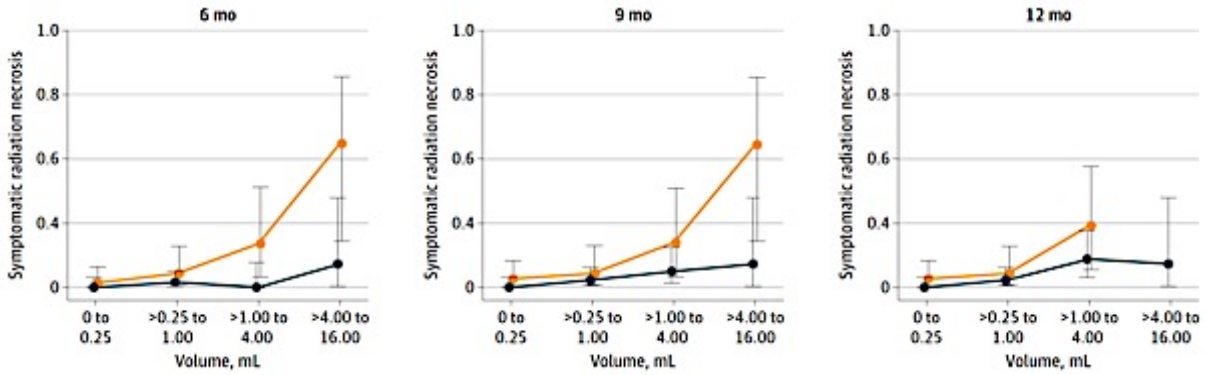
Symptomatic Radiation Necrosis with Concurrent ADC and Stereotactic Brain Radiation?

Characteristic	Patient group[a] Concurrent ADC	No concurrent ADC	All (N = 98)
Patients			
Age, median (range), y[b]	54 (27-77)	55 (34-77)	55 (27-77)
Sex			
Women	33/42 (78.6)	66/74 (89.2)	82/98 (83.7)
Men	9/42 (21.4)	8/74 (10.8)	16/98 (16.3)
Primary cancer diagnosis			
Breast	30/42 (71.4)	55/74 (74.3)	71/98 (72.4)
Non-small cell lung cancer, *ERBB2* variant	4/42 (9.5)	11/74 (14.9)	13/98 (13.3)
Esophageal and/or gastric cancer, *ERBB2* amplified	2/42 (4.8)	4/74 (5.4)	6/98 (6.1)
Salivary, *ERBB2* amplified	3/42 (7.1)	2/74 (2.7)	4/98 (4.1)
Other[c]	3/42 (7.1)	2/74 (2.7)	4/98 (4.1)
ADC received[d]			
Trastuzumab emtansine	21/42 (50.0)	43/74 (58.1)	52/98 (53.1)
Trastuzumab deruxtecan	14/42 (33.3)	42/74 (56.8)	50/98 (51.0)
Sacituzumab govitecan	7/42 (16.7)	23/74 (31.1)	26/98 (26.5)

Concurrent ADC + SRT defined as SRT given within 7 days before the ADC or within 21 days after the ADC



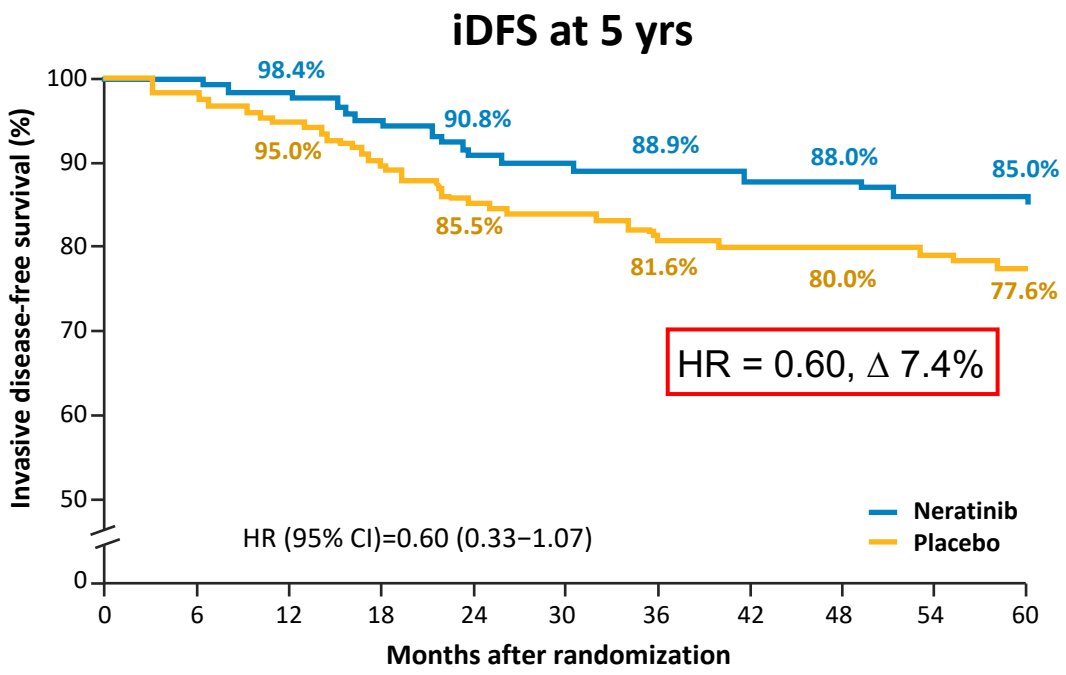
MV analysis: SHR, 4.31 [95%CI, 1.95-9.50];P <.001

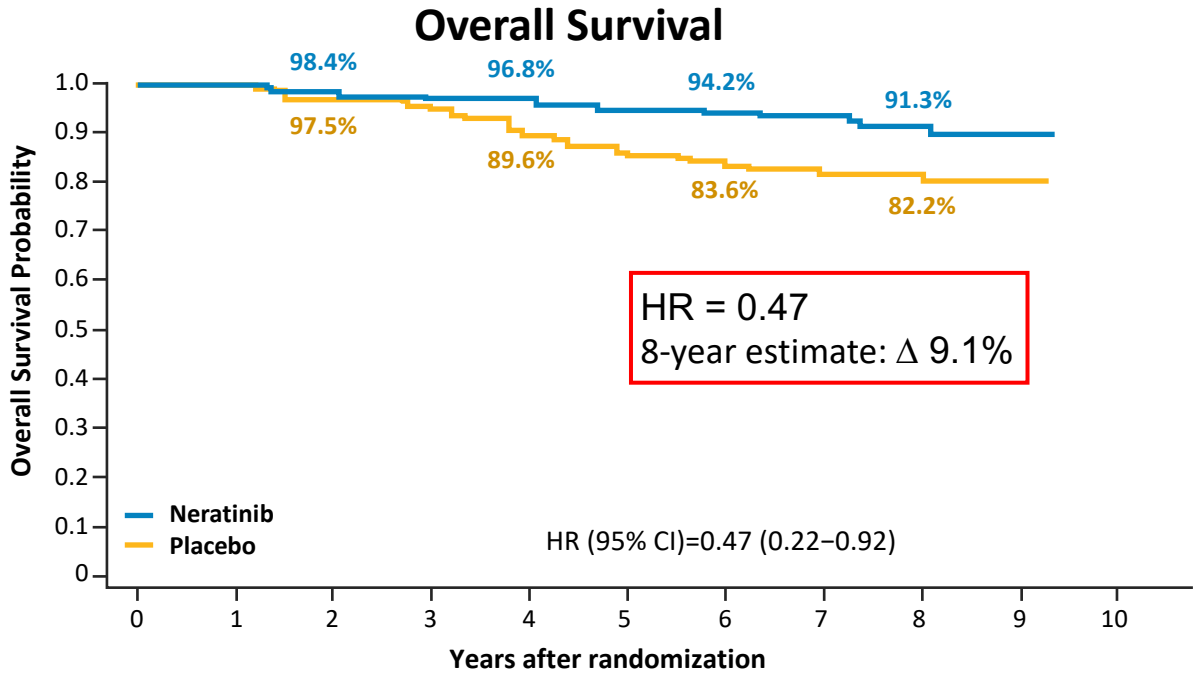


SHR: Subdistribution hazard ratios; MV: controlled for prior RT and volume

Lebow E et al. JAMA Onc 2023 (Letter)

ExteNET: Neratinib Post-Neoadjuvant Therapy for Residual Disease HR+, ≤1 Year from Trastuzumab





No. at risk

Neratinib	131	126	121	113	100	94	93	91	91	88	84
Placebo	164	159	151	143	125	107	103	99	99	98	94

No. at risk

Neratinib	131	126	121	116	113	110	106	100	60	14	0
Placebo	164	161	156	143	135	129	123	115	65	12	0

Chan A, et al. *Clin Breast Cancer*. 2021;21(1):80-91.e7.

Grade 3 diarrhea was the most frequent AE in both the ITT and HR+/≤1-year populations[1,a]

ExteNET: TEAEs occurring in ≥10% of patients in the neratinib arm (HR+/≤1-year population)

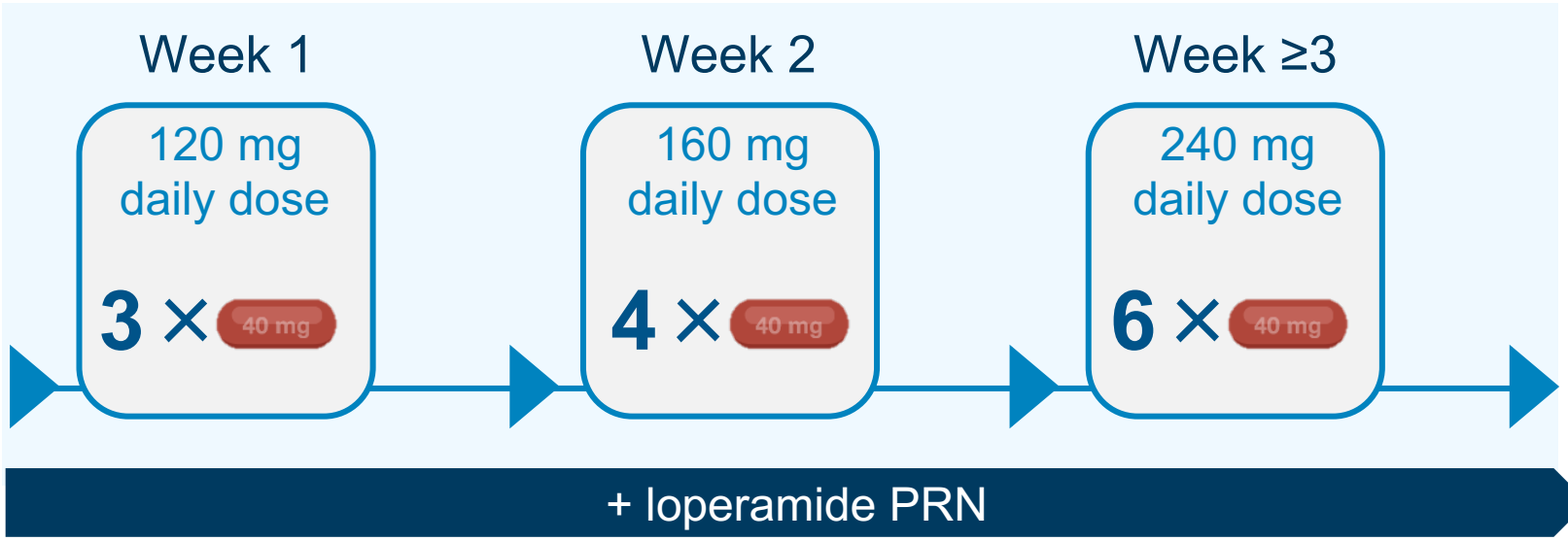
TEAE, n (%)	Neratinib (n=662)		Placebo (n=657)	
	Grade 1/2	Grade 3	Grade 1/2	Grade 3
Diarrhea	365 (55)	261 (39)	213 (32)	7 (1)
Nausea	280 (42)	9 (1)	135 (21)	2 (<1)
Fatigue	177 (27)	13 (2)	129 (20)	2 (<1)
Vomiting	150 (23)	24 (4)	41 (6)	2 (<1)
Abdominal pain	145 (22)	11 (2)	58 (9)	1 (<1)
Headache	119 (18)	6 (<1)	125 (19)	1 (<1)
Upper abdominal pain	90 (14)	6 (<1)	35 (5)	3 (<1)
Rash	90 (14)	3 (<1)	40 (6)	0 (0)
Decreased appetite	79 (12)	1 (<1)	13 (2)	0 (0)
Muscle spasms	81 (12)	0 (0)	21 (3)	1 (<1)

Primary anti-diarrhea prophylaxis was not protocol-specified in ExteNET

[a] A total of 1319 patients with HER2+/HR+ eBC who completed prior trastuzumab-based therapy ≤1 year from randomisation were included in the safety analysis.
TEAEs were monitored until 28 days after the last dose of study drug and graded according to National Cancer Institute Common Terminology Criteria, version 3.0.
AE, adverse event; eBC, early breast cancer; HER2+, human epidermal growth factor receptor 2-positive; HR+, hormone receptor-positive; TEAE, treatment-emergent adverse event.
1. Chan A, et al. *Clin Breast Cancer* 2021;21:80–91.e7.

Recommendations for minimizing diarrhea with neratinib

Neratinib dose escalation



93% of patients (56/60) in the DE1 cohort of the CONTROL study escalated to the full dose of neratinib at Week ≥3

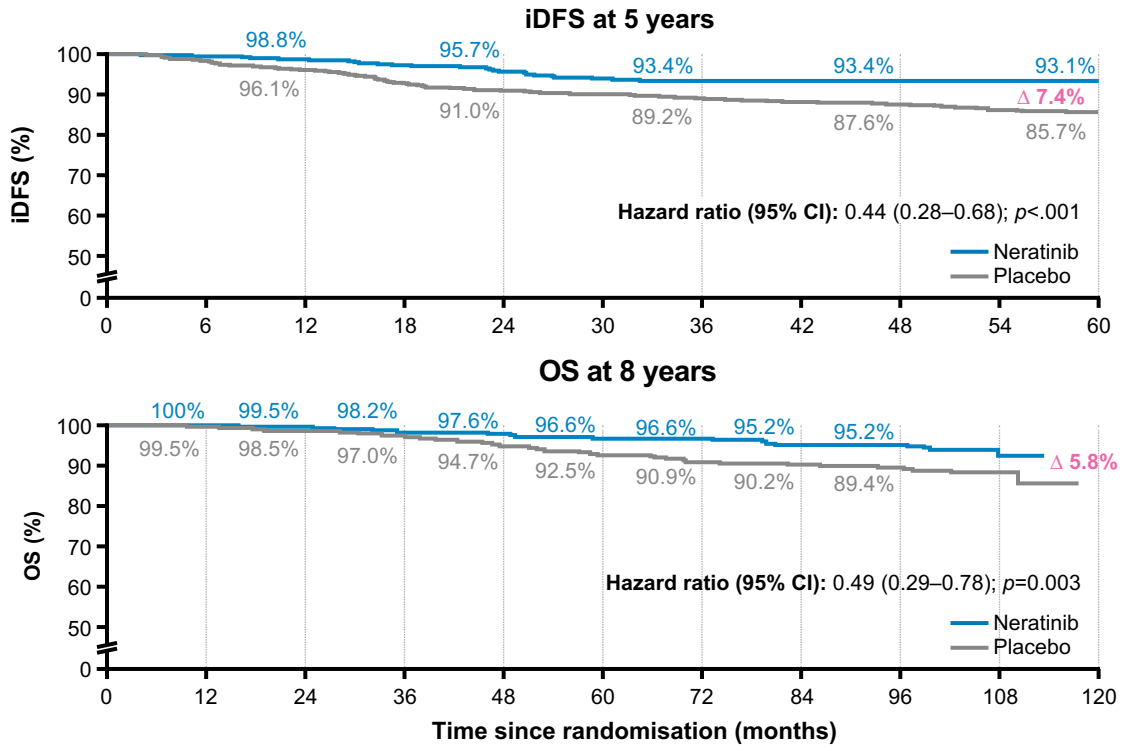
- In the CONTROL study, no patients in the neratinib DE1 cohort discontinued due to diarrhea after the first month

[a] Based on CONTROL data set published by Barcenas CH, et al. *Ann Oncol* 2020;31:1223–30.
DE, dose escalation; PRN, as needed.

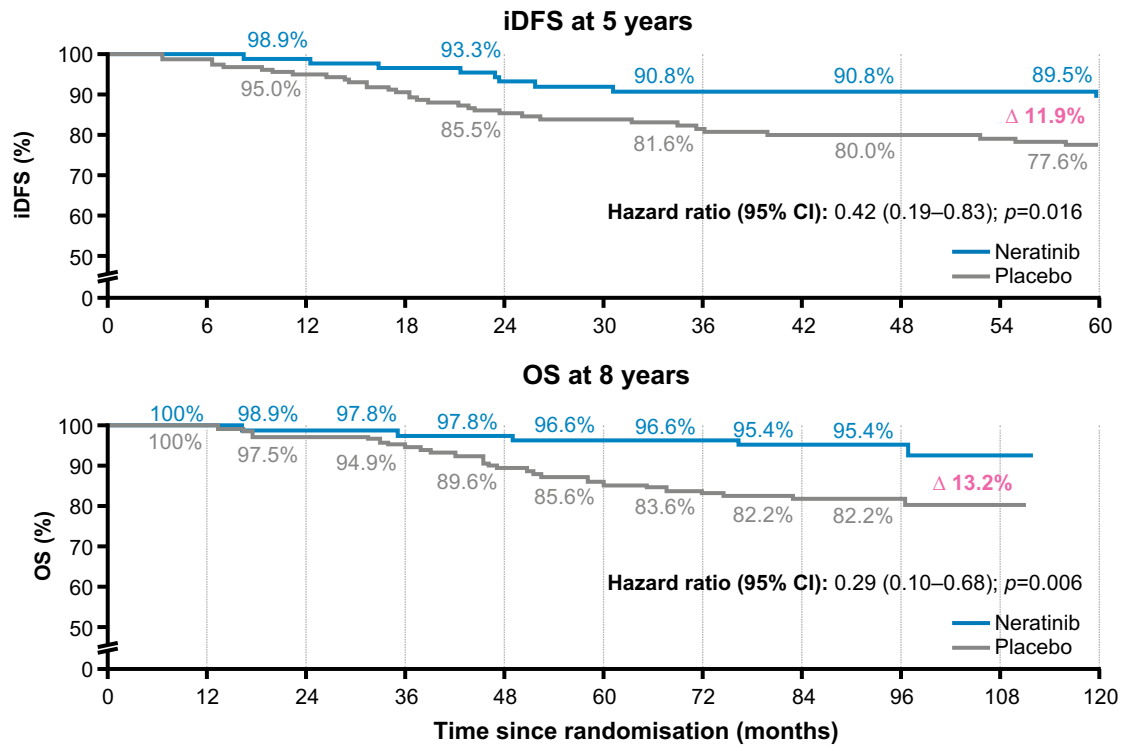
Impact of Persistance on Efficacy in the ExteNET Study With Extended Adjuvant Neratinib: iDFS and OS in Patients Who Received Neratinib Treatment for ≥ 11 Months

Patients who complete the recommended 1-year duration of extended adjuvant neratinib therapy* have an absolute benefit, with 5-year iDFS improved from 5.1%[1] (HR+ / ≤1 year population) to 7.4%[2] and from 7.4%[1] % (HR+ / ≤1 year no pCR population) to 11.9%[2]

ExteNET: HR+ / ≤1 year population (EMA label population)†
≥11 months of neratinib treatment[2]



ExteNET: HR+ / ≤1 year, no pCR population‡
≥11 months of neratinib treatment[2]



*Defined as ≥11 months of therapy or ended treatment due to disease recurrence in the neratinib group versus all randomised patients in the placebo group;
†HR+ and ≤1 year after prior trastuzumab; ‡HR+ and ≤1 year after prior trastuzumab with residual disease post-neoadjuvant therapy (no pCR).
EMA, European Medicines Agency; HR, hormone receptor; OS, overall survival; pCR, pathologic complete response.
1. Chan A. et. al. Clin Breast Cancer.2021;21:80-91; 2. Moy B, et al. ASCO Annual Meeting. 4–8 June 2021; Poster 540.

Take-Home Messages HER2-directed Therapy Toxicities

- Chest CT scans every 6-12 weeks for pts receiving T-DXd – monitor for ILD
- Hold for grade 1 – treat with steroids – resume T-DXd when ILD resolved
- Grade 2+ ILD discontinue T-DXd and treat with steroids and pulmonary consult

- T-DXd-related acute and chronic nausea – low dose olanzapine added to highly emetogenic 3-drug regimen – continue until no breakthrough nausea

- Monitor LVEF baseline and every 3-4 mos

- T-DXd dose reduction reduces risk of ILD and reduces treatment-limiting fatigue

- Neratinib-related diarrhea – start at 120 to 160 mg QD and increase as tolerated
- Aim for 11 mos adjuvant neratinib to obtain full benefit

- Avoid concurrent ADC + SRT to decrease risk of symptomatic radiation necrosis

Case Presentation: 64-year-old woman presents with localized ER-negative, HER2-positive IDC

Dr Erik Rupard (Reading, Pennsylvania)

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QUESTIONS FOR THE FACULTY

What is your threshold for treatment interruption/discontinuation for patients experiencing LVEF decline on adjuvant trastuzumab?

How does the potential for cardiotoxicity with other HER2-targeted strategies, such as T-DM1 and T-DXd, compare to that with trastuzumab?

How do you think through the use of T-DXd for patients with preexisting cardiac dysfunction? How often do you monitor LVEF in your patients receiving T-DXd?

Dr Kimberly Ku
(Bloomington, Illinois)

Case Presentation: 72-year-old woman with recurrent ER-positive, HER2-positive mBC receives T-DXd and has concerning pulmonary symptoms but without findings on diagnostic imaging

Dr Richard Zelkowitz
(Bridgeport, Connecticut)

Case Presentation: 46-year-old woman with ER-positive, HER2-positive mBC to brain and lung with multiple prior treatments responds to T-DXd but develops Grade 1 ILD

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QUESTIONS FOR THE FACULTY

What is your approach to screening for ILD with T-DXd? How would you approach a patient like Dr Ku's with nonspecific shortness of breath but no changes on imaging? How long would you continue corticosteroids for this patient?

How do you manage Grade 1 ILD with T-DXd? In what situations will you rechallenge? What about Grade 2 ILD?

CASES FROM THE COMMUNITY
Investigators Discuss the Optimal Role of Endocrine-Based and Other Strategies in the Management of HR-Positive Breast Cancer

Part 3 of a 3-Part CME Satellite Symposium Series

Thursday, December 11, 2025

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Angela DeMichele, MD, MSCE
Komal Jhaveri, MD, FACP, FASCO
Erica Mayer, MD, MPH, FASCO
Hope S Rugo, MD
Seth Wander, MD, PhD

Moderator

Neil Love, MD

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Contributing General Medical Oncologists

Laila Agrawal, MD
Norton Cancer Institute
Louisville, Kentucky

Kimberly Ku, MD
Illinois CancerCare
Bloomington, Illinois

Alan B Astrow, MD
Weill Cornell Medicine
Brooklyn, New York

Zanetta S Lamar, MD
Florida Oncology and Hematology
Naples, Florida

Justin Favaro, MD, PhD
Oncology Specialists of Charlotte
Charlotte, North Carolina

Yanjun Ma, MD, PhD
Tennessee Oncology
Murfreesboro, Tennessee

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Contributing General Medical Oncologists

Erik Rupard, MD
Penn State Cancer Institute
Reading, Pennsylvania

Richard Zelkowitz, MD
Hartford HealthCare Cancer Institute
Bridgeport, Connecticut

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