What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of HER2-Positive Breast Cancer

Part 1 of a 2-Part CME Satellite Symposium Series Held in Conjunction with the 2022 San Antonio Breast Cancer Symposium®

Wednesday, December 7, 2022

7:15 PM – 9:15 PM CT

Faculty

Erika Hamilton, MD

Sara A Hurvitz, MD

Ian E Krop, MD, PhD

Shanu Modi, MD

Sara M Tolaney, MD, MPH

Moderator

Neil Love, MD

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Faculty

Erika Hamilton, MD
Director, Breast and Gynecologic
Research Program
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Tennessee Oncology
Nashville, Tennessee

Shanu Modi, MD
Member and Attending
Breast Medicine Service
Memorial Sloan Kettering Cancer Center
Professor of Medicine
Weill Cornell Medical College
New York, New York

Sara A Hurvitz, MD
Professor of Medicine
Director, Breast Cancer Clinical Trials Program
Division of Hematology-Oncology
David Geffen School of Medicine at UCLA
Medical Director
Clinical Research Unit
Jonsson Comprehensive Cancer Center
Santa Monica, California

Sara M Tolaney, MD, MPH
Chief, Division of Breast Oncology
Associate Director, Susan F Smith Center for
Women's Cancers
Senior Physician
Dana-Farber Cancer Institute
Associate Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Ian E Krop, MD, PhD
Associate Director, Clinical Research
Director, Clinical Trials Office
Chief Clinical Research Officer
Yale Cancer Center
New Haven, Connecticut

Moderator

Neil Love, MD
Research To Practice

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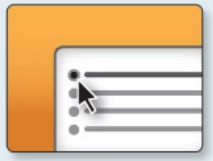
Clinicians in the Meeting Room

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. Survey results will be presented and discussed throughout the meeting.

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.

Complete Your Evaluation: Tap the CME Evaluation button to complete your evaluation electronically to receive credit for your participation.

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

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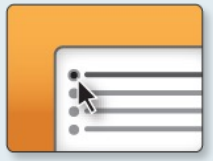
Clinicians Attending via Zoom

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. Survey results will be presented and discussed throughout the meeting.

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

Get CME Credit: A CME 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 video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

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What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of ER-Positive Breast Cancer

Part 2 of a 2-Part CME Satellite Symposium Series Held in Conjunction with the 2022 San Antonio Breast Cancer Symposium®

Thursday, December 8, 2022

7:15 PM – 9:15 PM CT (8:15 PM – 10:15 PM ET)

Faculty

Aditya Bardia, MD, MPH

Matthew P Goetz, MD

Virginia Kaklamani, MD, DSc

Kevin Kalinsky, MD, MS

Hope S Rugo, MD

Moderator

Neil Love, MD

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Addressing Current Questions and Controversies in the Management of Chronic Lymphocytic Leukemia — What Clinicians Want to Know

Part 1 of a 3-Part CME Friday Satellite Symposium and Virtual Event Series
Preceding the 64th ASH Annual Meeting

Friday, December 9, 2022
11:30 AM – 1:30 PM CT (12:30 PM – 2:30 PM ET)

Faculty

Alexey V Danilov, MD, PhD
Matthew S Davids, MD, MMSc
Professor Dr Arnon P Kater, MD, PhD
Lindsey Roeker, MD
Philip A Thompson, MB, BS

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Addressing Current Questions and Controversies in the Management of Hodgkin and Non-Hodgkin Lymphoma — What Clinicians Want to Know

Part 2 of a 3-Part CME Friday Satellite Symposium and Virtual Event Series
Preceding the 64th ASH Annual Meeting

Friday, December 9, 2022
3:15 PM – 5:15 PM CT (4:15 PM – 6:15 PM ET)

Faculty

Jonathan W Friedberg, MD, MMSc
Brad S Kahl, MD
David G Maloney, MD, PhD
Loretta J Nastoupil, MD
Sonali M Smith, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Addressing Current Questions and Controversies in the Management of Multiple Myeloma — What Clinicians Want to Know

Part 3 of a 3-Part CME Friday Satellite Symposium and Virtual Event Series
Preceding the 64th ASH Annual Meeting

Friday, December 9, 2022
7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Jesús G Berdeja, MD
Rafael Fonseca, MD
Sagar Lonial, MD
Robert Z Orlowski, MD, PhD
Noopur Raje, MD

Moderator

Neil Love, MD

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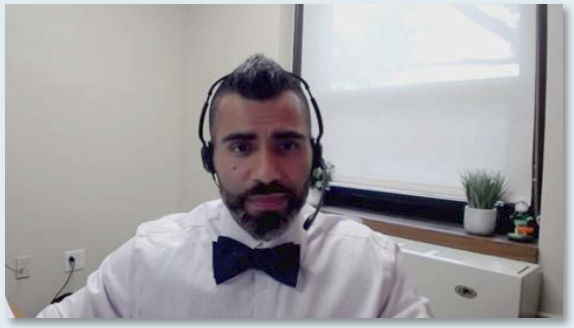
Laila Agrawal, MD
Norton Cancer Institute
Louisville, Kentucky



Rohit Gosain, MD
UPMC Hillman Cancer Center
Jamestown, New York

Susmitha Apuri, MD
Florida Cancer Specialists
Lutz, Florida

Ranju Gupta, MD
Lehigh Valley Topper Cancer Institute
Bethlehem, Pennsylvania

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

Dhatri Kodali, MD
Texas Oncology
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Kimberly Ku, MD
Bloomington, Illinois

Joanna Metzner-Sadurski, MD
University of South Carolina
Greenwood, South Carolina

Zanetta S Lamar, MD
Florida Cancer Specialists
Naples, Florida

Kelly Yap, MD
City of Hope
Arcadia, California

Henna Malik, MD
Texas Oncology
North Houston, Willowbrook/Cypress
Houston, Texas

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Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Puma Biotechnology Inc, and Seagen Inc.

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Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

Dr Love — Disclosures

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Contracted Research (Paid to Institution)	AbbVie Inc, Acerta Pharma — A member of the AstraZeneca Group, ADC Therapeutics, Akesobio Australia Pty Ltd, Amgen Inc, ArQule Inc, Arvinas, AstraZeneca Pharmaceuticals LP, Black Diamond Therapeutics Inc, Boehringer Ingelheim Pharmaceuticals Inc, Clovis Oncology, Compugen, Curis Inc, CytomX Therapeutics, Daiichi Sankyo Inc, Dana-Farber Cancer Institute, Deciphera Pharmaceuticals Inc, eFFECTOR Therapeutics Inc, Ellipses Pharma, EMD Serono Inc, Fochon Pharmaceuticals Ltd, FUJIFILM Pharmaceuticals USA Inc, G1 Therapeutics Inc, Genentech, a member of the Roche Group, H3 Biomedicine, Harpoon Therapeutics, Hutchison MediPharma, ImmunoGen Inc, Immunomedics Inc, Incyte Corporation, InventisBio, Jacobio Pharmaceuticals Group Co Ltd, Karyopharm Therapeutics, Leap Therapeutics Inc, Lilly, Lycera, MacroGenics Inc, Marker Therapeutics Inc, Merck, Mersana Therapeutics Inc, Merus BV, Molecular Templates, Myriad Genetic Laboratories Inc, Novartis, NuCana, Olema Oncology, OncoMed Pharmaceuticals Inc, Onconova Therapeutics Inc, ORIC Pharmaceuticals Inc, Orinove Inc, Pfizer Inc, PharmaMar, Pieris Pharmaceuticals Inc, Pionyr Immunotherapeutics, Plexxikon Inc, Puma Biotechnology Inc, Radius Health Inc, Regeneron Pharmaceuticals Inc, Repertoire Immune Medicines, Rgenix, Seagen Inc, Sermonix Pharmaceuticals, Shattuck Labs, Silverback Therapeutics, Stemcentrx, Sutro Biopharma, Syndax Pharmaceuticals Inc, Syros Pharmaceuticals Inc, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, Tesaro, A GSK Company, Transcenta Holding Ltd, Treadwell Therapeutics, Verastem Inc, Vincerx Pharma, Zenith Epigenetics, Zymeworks Inc

Dr Hurvitz — Disclosures

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One-Time Talk	Daiichi Sankyo Inc
Nonrelevant Financial Relationship	Ideal Implant (spouse)

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Dr Krop — Disclosures

Consulting Agreements	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, MacroGenics Inc, Seagen Inc
Contracted Research	Genentech, a member of the Roche Group, MacroGenics Inc, Pfizer Inc
Data and Safety Monitoring Board/Committee	Merck, Novartis

Dr Modi — Disclosures

Advisory Committee and Consulting Agreements	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, MacroGenics Inc, Seagen Inc
Contracted Research (To My Institution)	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Seagen Inc.

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Dr Tolaney — Disclosures

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Contracted Research	AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Cyclacel Pharmaceuticals Inc, Eisai Inc, Exelixis Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Lilly, Merck, NanoString Technologies, Nektar, Novartis, Pfizer Inc, Sanofi, Seagen Inc

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Moderator

Neil Love, MD

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Agenda

Module 1 – Optimizing the Management of Localized HER2-Positive Breast Cancer — Dr Tolaney

Module 2 – Current Considerations in the Treatment of HER2-Positive Metastatic Breast Cancer (mBC) — Dr Krop

Module 3 – Management of HER2-Positive Breast Cancer with CNS Metastases — Dr Hamilton

Module 4 – Recent Appreciation of HER2 Low as a Unique Disease Subset; Future Directions in the Management of HER2-Positive and HER2-Low Breast Cancer — Dr Modi

Module 5 – Incidence and Management of Adverse Events Associated with HER2-Targeted Therapy — Dr Hurvitz

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Agenda

Module 1 – Optimizing the Management of Localized HER2-Positive Breast Cancer — Dr Tolaney

▸ ***Real World Cases and Questions***

Module 2 – Current Considerations in the Treatment of HER2-Positive Metastatic Breast Cancer (mBC) — Dr Krop

▸ ***Real World Cases and Questions***

Module 3 – Management of HER2-Positive Breast Cancer with CNS Metastases — Dr Hamilton

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▸ ***Real World Cases and Questions***

Module 5 – Incidence and Management of Adverse Events Associated with HER2-Targeted Therapy — Dr Hurvitz

▸ ***Real World Cases and Questions***

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MODULE 1: Optimizing the Management of Localized HER2-Positive Breast Cancer — Dr Tolaney

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Case Presentation: 66-year-old woman with pulmonary hypertension and triple-positive, node-positive IDC, s/p neoadjuvant TCHP and clinical CR

Dr Susmitha Apuri (Lutz, Florida)

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Case Presentation: 62-year-old woman with a 1.7-cm, triple-positive, clinically node-negative IDC

Dr Ranju Gupta (Bethlehem, Pennsylvania)

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SUSAN F. SMITH CENTER FOR WOMEN'S CANCERS

Dana-Farber Cancer Institute

HARVARD MEDICAL SCHOOL

OPTIMIZING THE MANAGEMENT OF LOCALIZED HER2-POSITIVE BREAST CANCER

Sara M. Tolaney

Dana-Farber Cancer Institute

CAN ANTHRACYCLINES BE SUBSTITUTED BY TAXANES?

IS ANTHRACYCLINE-BASED CHEMOTHERAPY NECESSARY?

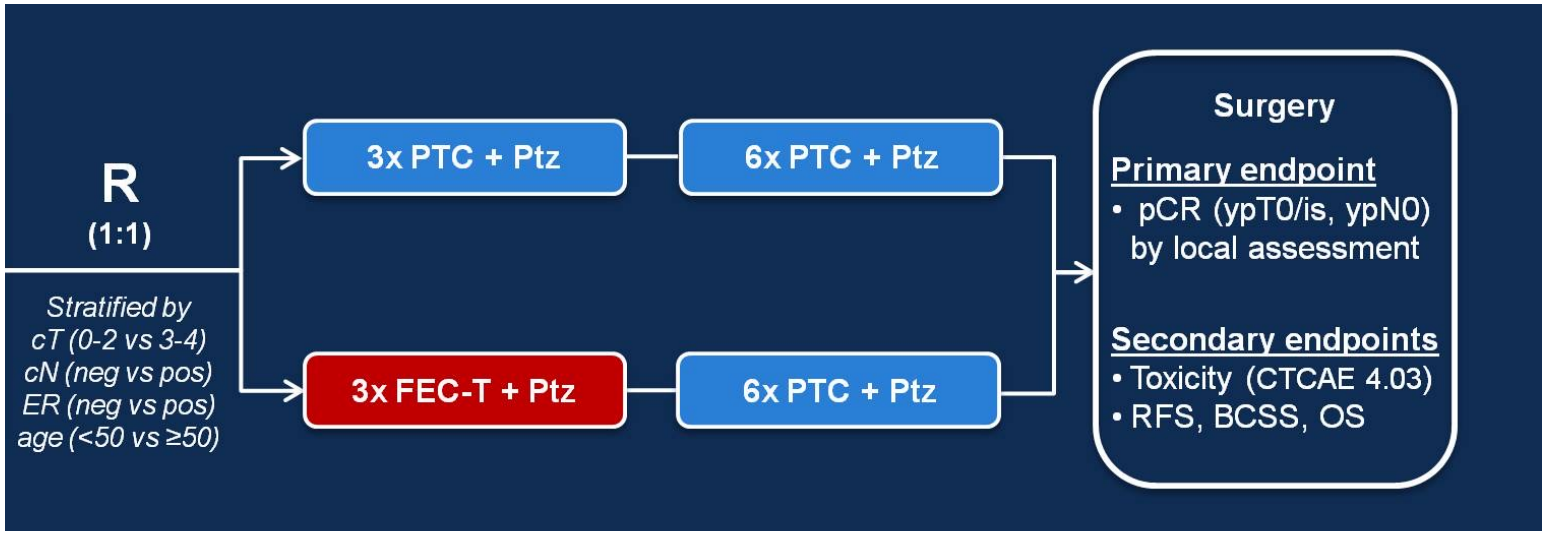
BCIRG006: 10.3 YRS FOLLOW-UP

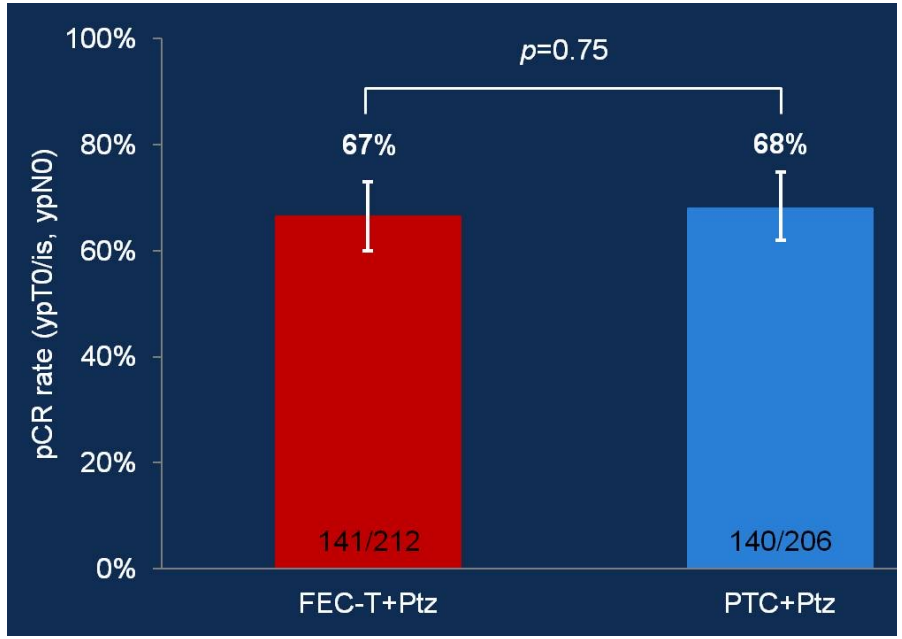
Outcome	AC → T (n = 1073)	AC → TH (n = 1074)	TCH (n = 1075)
DFS, % (n/N) HR (95% CI)	67.9 (328/1073) 1	74.6 (269/1074) 0.72 (0.61-0.85); *P* < .0001	73.0 (279/1075) 0.77 (0.65-0.90); *P* = .0011
OS, % (n/N) HR (95% CI)	78.7 (203/1073) 1	85.9 (141/1074) 0.63 (0.51-0.79); *P* < .0001	83.3 (167/1075) 0.76 (0.62-0.93); *P* = .0075
DFS in LN+ pts, % (n/N) HR (95% CI)	62.2 (265/764) 1	69.6 (217/764) 0.72 (0.61-0.87); *P* < .001	68.4 (224/766) 0.75 (0.63-0.90); *P* = .0018

TCH ASSOCIATED WITH LESS CARDIAC TOXICITY AND NUMERICALLY FEWER CASES OF SECONDARY LEUKEMIA

Slamon D et al. SABCS 2015. Abstract S5-05.

SUBSTITUTING ANTHRACYCLINE WITH TAXANE: TRAIN-2

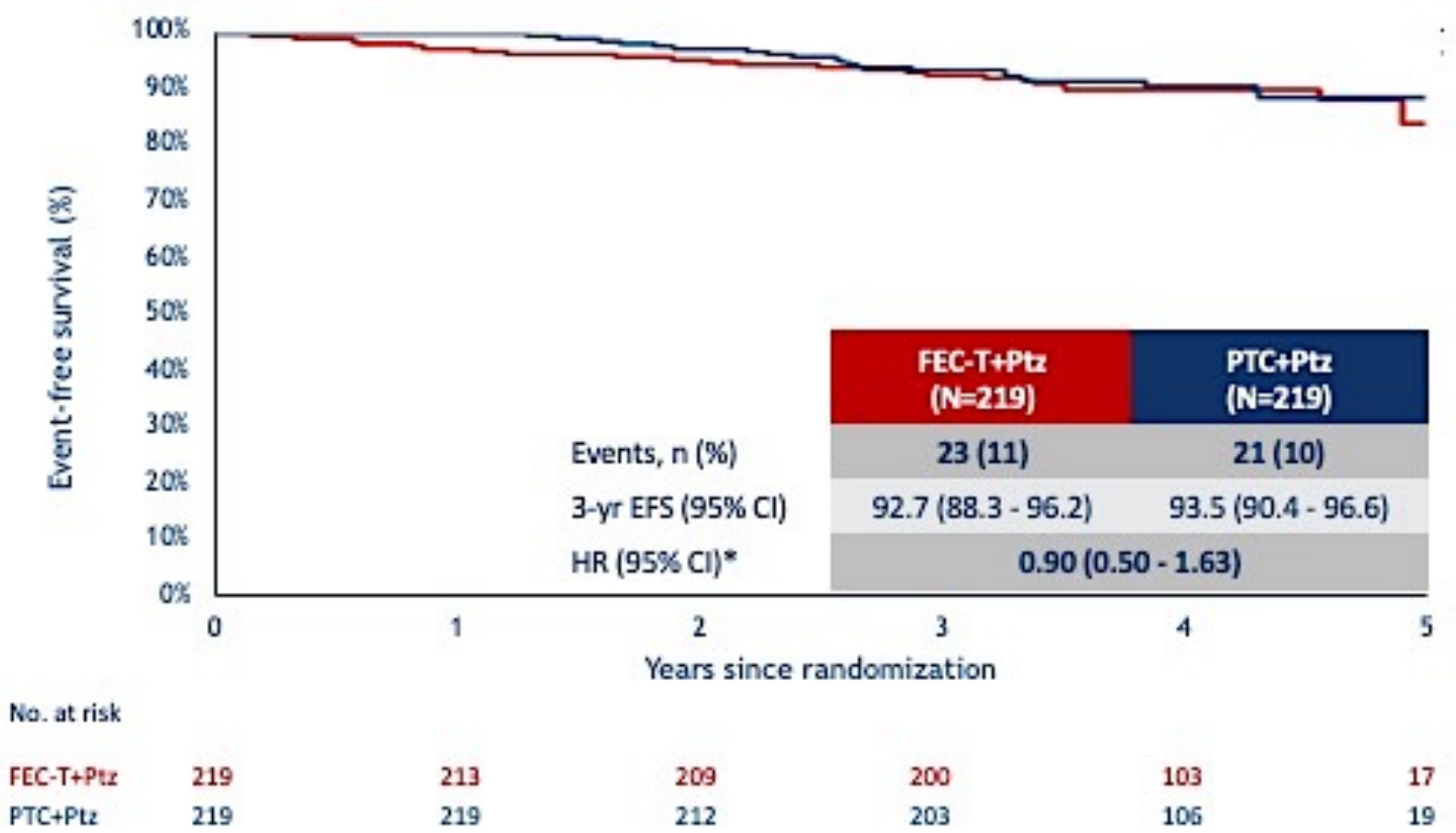




- 64% node positive, 42% HR negative
- pCR was consistent across all subgroups
- More pts completed 1 year trastuzumab in PTC/Ptz arm (97% vs 89%)
- Significantly more grade 3/4 febrile neutropenia (10% vs 1%) in anthracycline arm

Van Ramshorst MS, et al. ASCO 2017. Abstract 507.
Van Ramshorst MS, et al. *Lancet Oncol*. 2018;19(12):1630-1640.

TRAIN-2: EFS



- Significantly less cardiac toxicity PTCPtz
- 2 leukemia in FEC-arm

Van der Voort A et al. ASCO 2020. Abstract 501.

ANTHRACYCLINE CAN BE SUBSTITUTED WITH TAXANE-BASED HER2 DIRECTED THERAPY

- BCIRG006 and TRAIN-2 demonstrate similar long term outcomes with taxane-based therapy as with anthracycline-based therapy, even in high risk node-positive patients
- Less cardiac toxicity and numerically less leukemia
- Standard approach is TCH(P) for stage 2/3 HER2+ disease
- Hard to justify use of anthracyclines in era of HER2-directed therapies

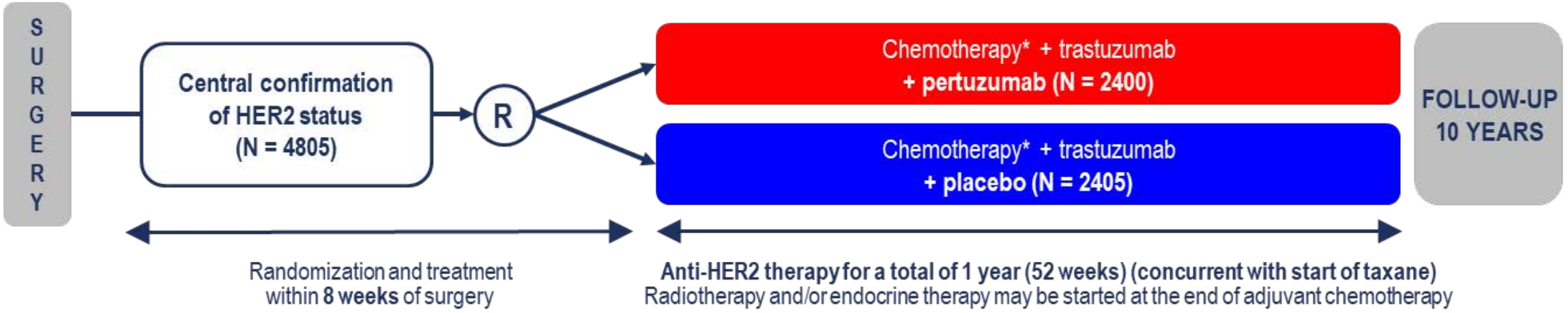
CAN WE ADD THERAPY TO IMPROVE OUTCOMES?

NEOADJUVANT PERTUZUMAB/TRASTUZUMAB (3 REGIMENS FDA APPROVED 9/2013)

	NEOSPHERE[1]	TRYPHAENA[2]	TRYPHAENA[2]
Treatment	Pertuzumab, Trastuzumab, Docetaxel THP x 4 FEC x 3 post-op)	Docetaxel/Carbo/ Trastuzumab/ Pertuzumab TCHP x 6	 FEC x 3 → THP x 3
N	107	77	75
ypT0/is ypN0 (%)	39.3	63.6	54.6

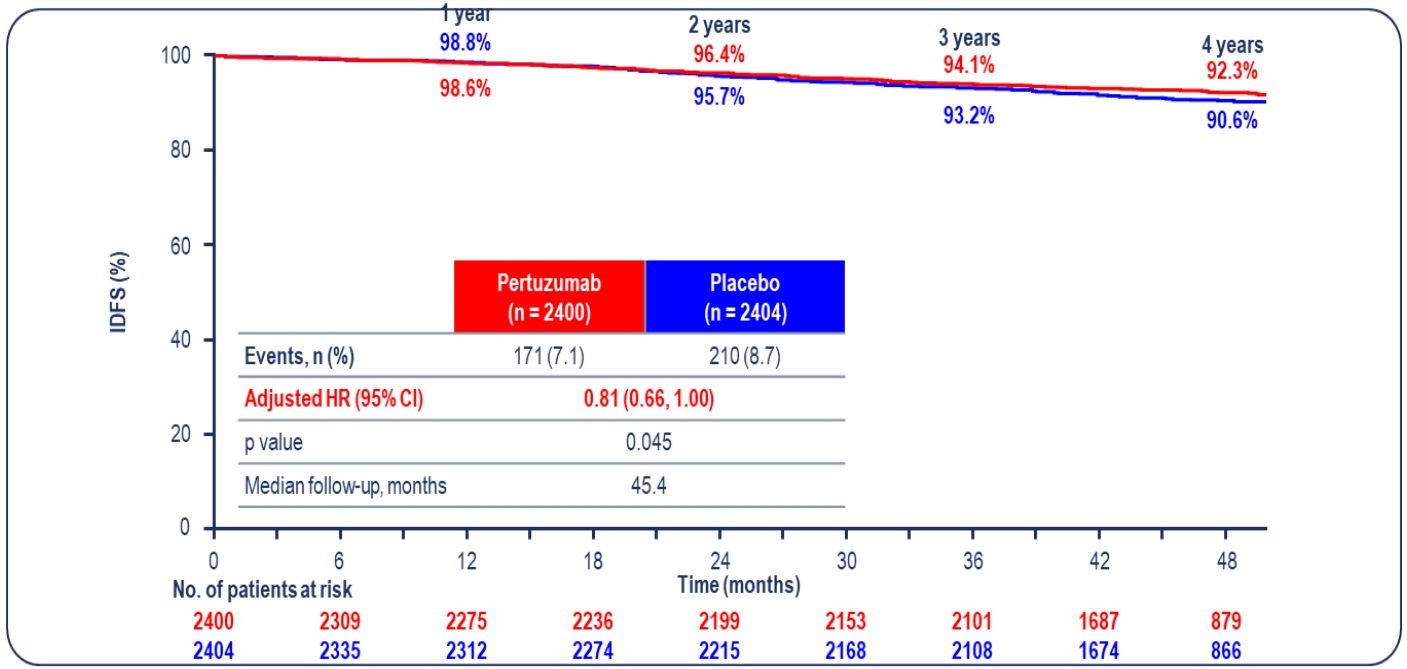
1. Gianni L, et al. *Lancet Oncol*. 2012;13(1):25-32.
2. Schneeweiss A, et al. *Ann Oncol*. 2013;24(9):2278-84.

Can we increase the efficacy of adjuvant trastuzumab? APHINITY Trial



- **Primary endpoint:** IDFS (APHINITY definition differs from STEEP definition)
- **Secondary endpoints:** IDFS with 2nd primary non-breast primary cancers included, DFS, OS, RFI, DRFI, safety, and HRQoL

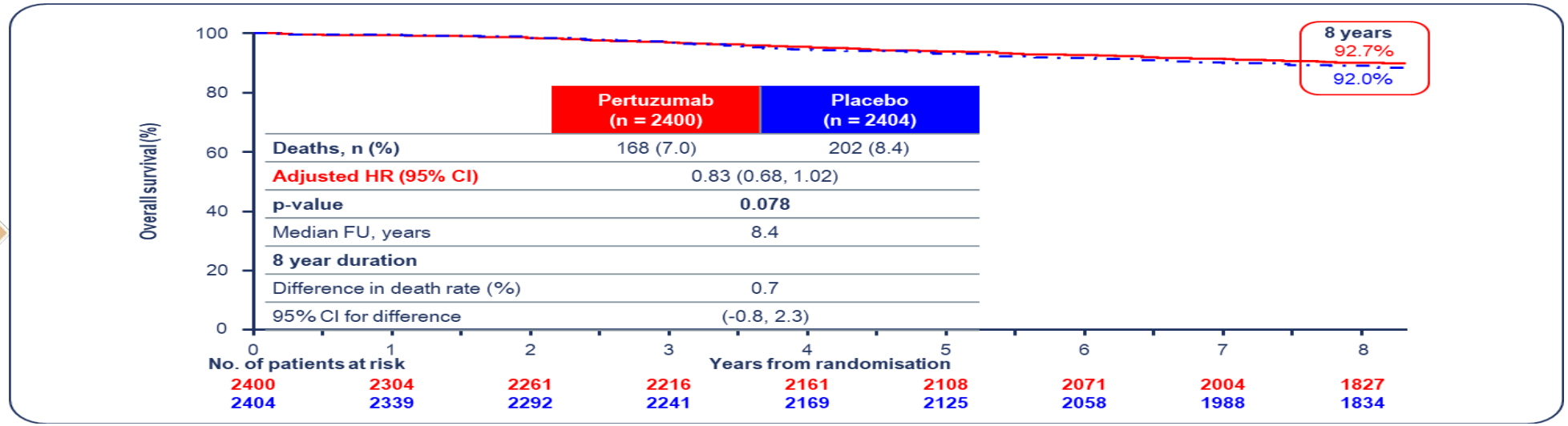
Node involvement	
Node negative	38%
1-3 nodes	37%
≥4 nodes	25%



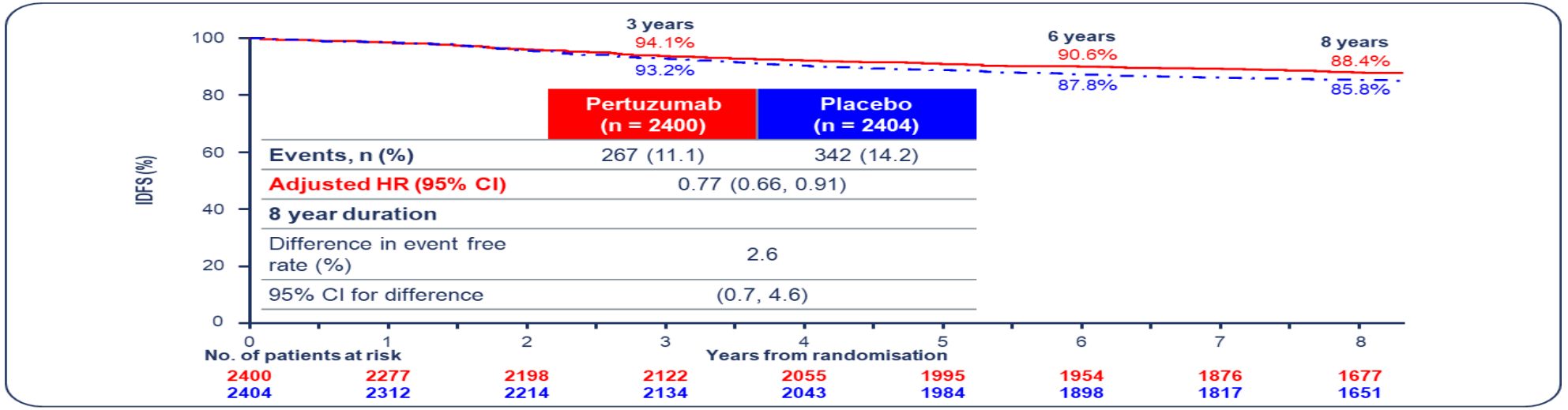
Adapted from von Minckwitz G, et al. *N Engl J Med*. 2017;377(2):122-131.
Slide courtesy of Javier Cortes

Updated results of APHINITY at 8.4 years median follow up

3rd interim OS analysis CCOD: Jan 10 2022



Updated Descriptive IDFS Analysis by Treatment Regimen



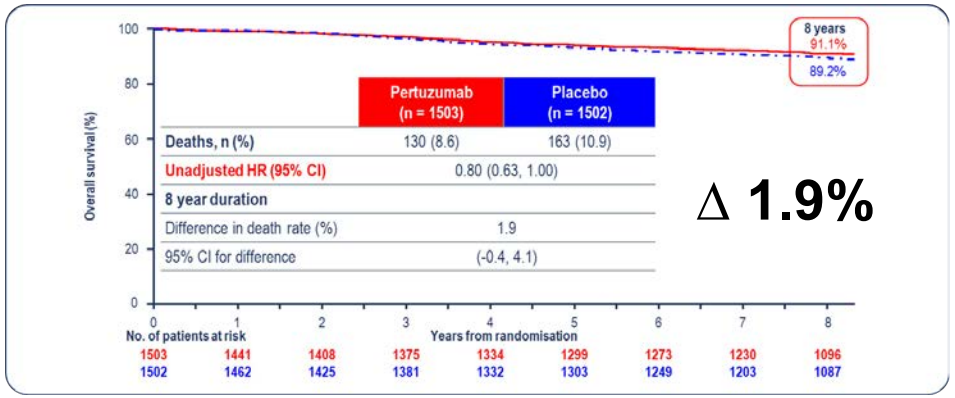
Loibl S, et al. ESMO Virtual Plenary 2022.

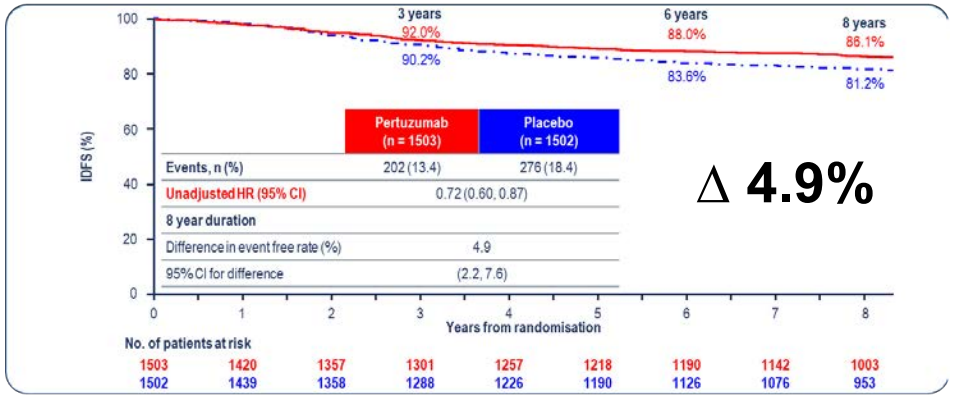
Updated results of APHINITY at 8.4 years median follow up

3rd interim OS analysis CCOD: Jan 10 2022

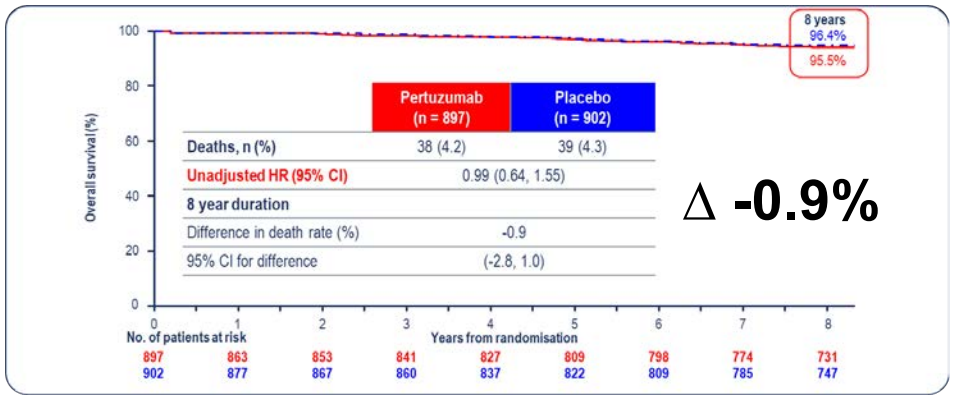
Updated Descriptive IDFS Analysis by Treatment Regimen

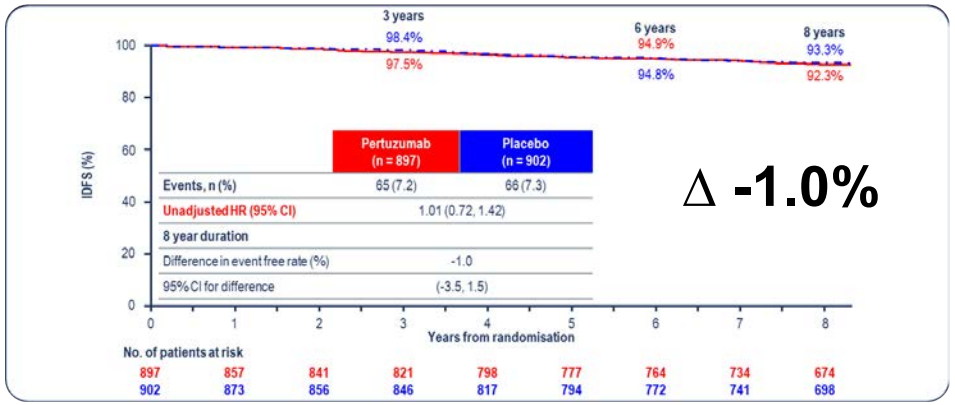
Node positive





Node negative





Loibl S, et al. ESMO Virtual Plenary 2022.

Updated results of APHINITY at 8.4 years compared with at 4 and 6 years median follow up

	4 yr IDFS (TP vs T)	4 yr IDFS Δ	6 yr IDFS (TP vs T)	6 yr IDFS Δ	8 yr IDFS (TP vs T)	8 yr IDFS Δ
ITT	92.3 vs 90.6%	1.7%	90.6 vs 87.8%	2.8%	88.4 vs 84.8%	2.6%
N0	96.7 vs 96.2%	0.5%	95.0 vs 94.9%	0.1%	92.3 vs 93.3	-1%
N+	**89.9 vs 86.7%**	**3.2%**	**87.9 vs 83.4%**	**4.5%**	**86.1 vs 81.2%**	**4.9%**
ER/PR+	93.0 vs 91.6%	1.4%	91.2 vs 88.2%	3%	88.9 vs 86.1%	2.8%
ER/PR-	91.0 vs 88.7%	2.3%	89.5 vs 87.0%	2.5%	87.5 vs 85.2%	2.3%

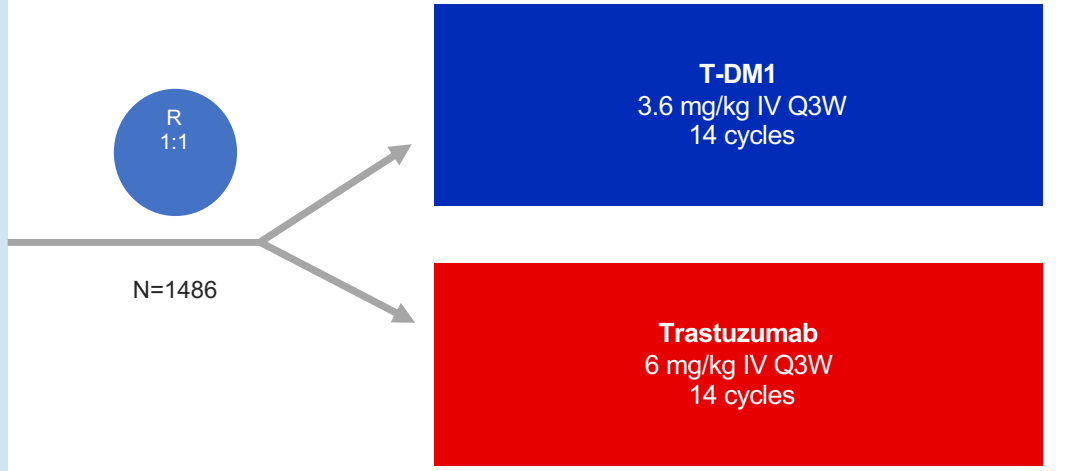
Von Minckwitz G, et al. *N Engl J Med*. 2017;377(2):122-131; Piccart M, et al. *J Clin Oncol*. 2021;39(13):1448-1457; Loibl S, et al. ESMO Virtual Plenary 2022.

WHEN DO WE THEN GIVE PERTUZUMAB?

- Most patients with HER2+ tumors >2cm or clinically node positive disease receive preoperative therapy
- The addition of pertuzumab improves pCR, but will not improve DFS in *all* patients (ie. not node negative patients)
- Administration of preoperative pertuzumab to all patients may result in some overtreatment, but challenging to discern which patients need pertuzumab upfront
- Adjuvant HP is reasonable for pts achieving pCR given APHINITY administered one year of HP therapy, given uncertainty of upfront nodal status in pts receiving preop therapy

KATHERINE: STUDY DESIGN

- cT1-4/N0-3/M0 at presentation (cT1a-b/N0 excluded)
- Centrally confirmed HER2-positive breast cancer
- Neoadjuvant therapy must have consisted of
  - Minimum of 6 cycles of chemotherapy
    - Minimum of 9 weeks of taxane
    - Anthracyclines and alkylating agents allowed
    - All chemotherapy prior to surgery
  - Minimum of 9 weeks of trastuzumab
    - Second HER2-targeted agent allowed
- Residual invasive tumor in breast or axillary nodes
- Randomization within 12 weeks of surgery

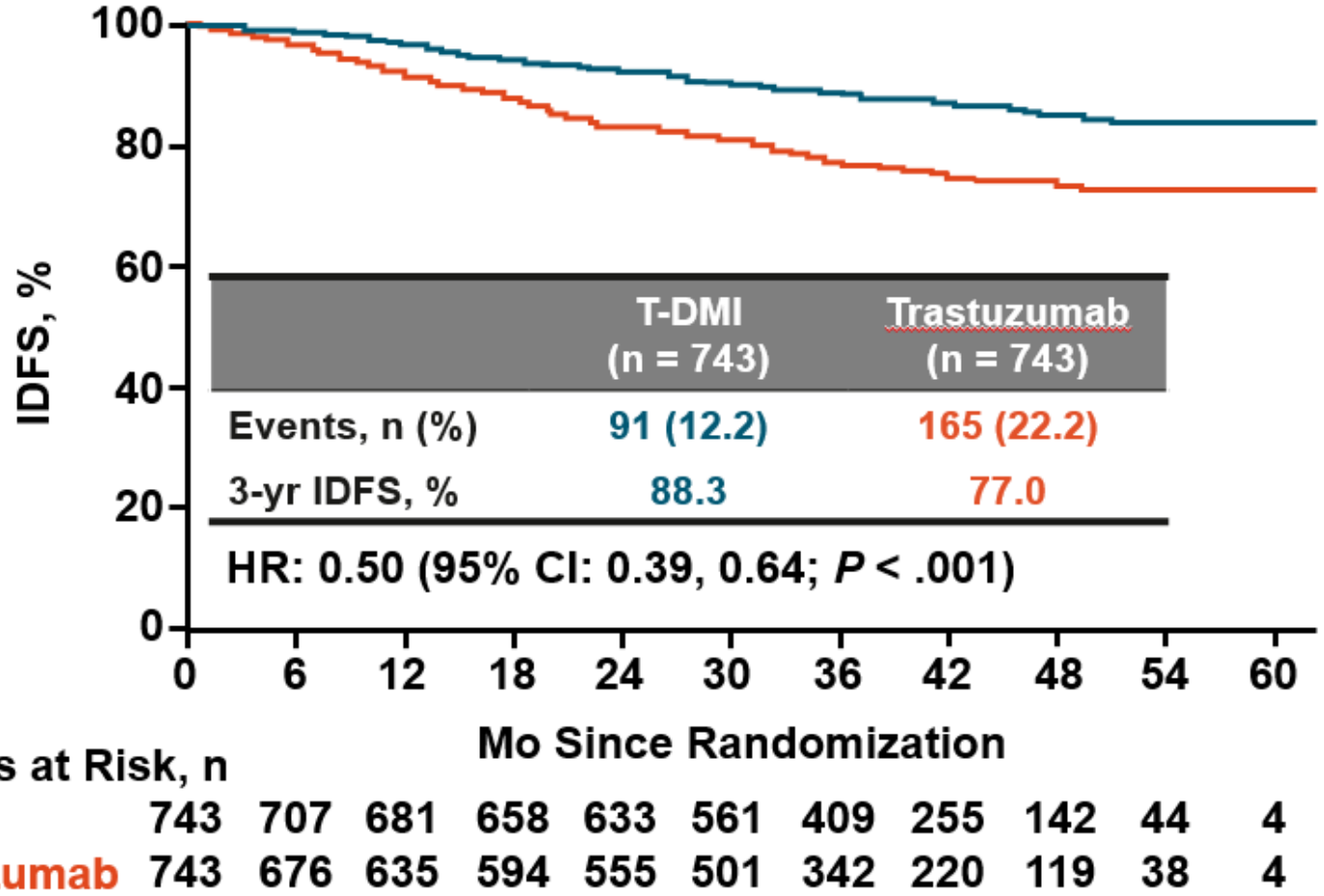


Radiation and endocrine therapy per protocol and local guidelines

Stratification factors:
- Clinical presentation: Inoperable (stage cT4 or cN2–3) vs operable (stages cT1-3N0-1)
- Hormone receptor: ER or PR positive vs ER negative and PR negative/unknown
- Preoperative therapy: Trastuzumab vs trastuzumab plus other HER2-targeted therapy
- Pathological nodal status after neoadjuvant therapy: Positive vs negative/not done

Geyer C, et al. SABCS 2018. Abstract GS1-10.
von Minckwitz G, et al. *N Engl J Med.* 2019;380(7) 617-628.

RESPONSE TO NEOADJUVANT TREATMENT CLEARLY IDENTIFIES HIGH RISK PATIENTS FOR TREATMENT WITH T-DM1 (KATHERINE)

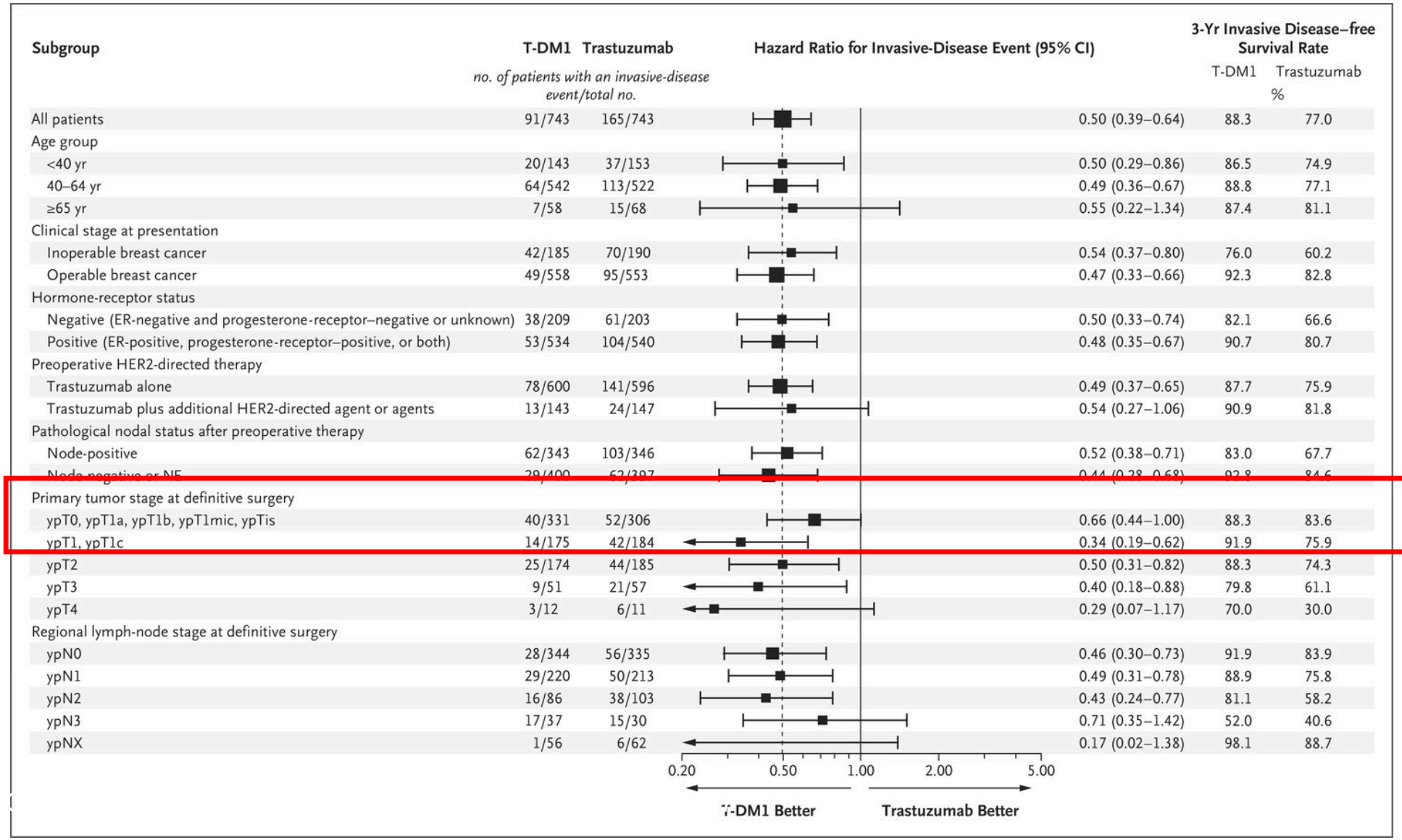


First IDFS Event, %	T-DM1	T
Any	12.2	22.2
Distant recurrence	10.5*	15.9†
Locoregional recurrence	1.1	4.6
Contralateral breast cancer	0.4	1.3
Death without prior event	0.3	0.4

CNS events: *5.9% vs †4.3%.

Geyer C, et al. SABCS 2018. Abstract GS1-10.
von Minckwitz G, et al. *N Engl J Med.* 2019;380(7) 617-628.

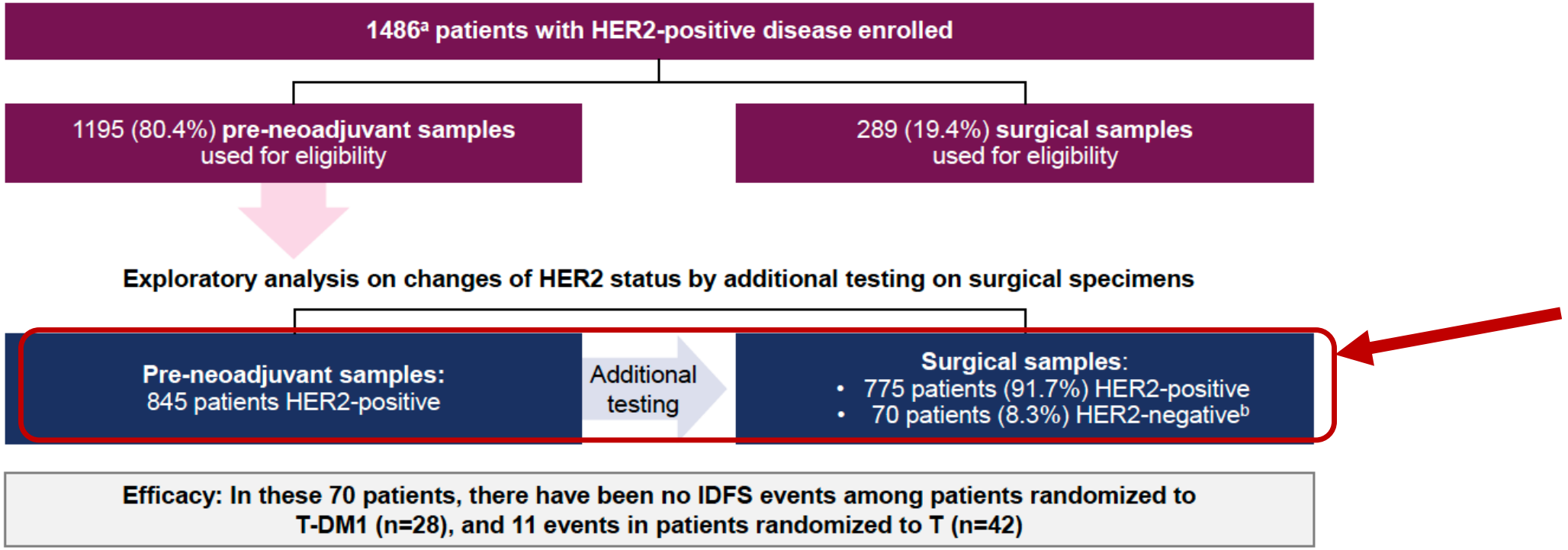
KATHERINE:
All benefit even those with small amounts of residual tumor



Subgroup	T-DM1 (no. of patients with an invasive-disease event/total no.)	Trastuzumab (no. of patients with an invasive-disease event/total no.)	Hazard Ratio for Invasive-Disease Event (95% CI)	3-Yr Invasive Disease–free Survival Rate: T-DM1 (%)	3-Yr Invasive Disease–free Survival Rate: Trastuzumab (%)
All patients	91/743	165/743	0.50 (0.39–0.64)	88.3	77.0
Age group					
<40 yr	20/143	37/153	0.50 (0.29–0.86)	86.5	74.9
40–64 yr	64/542	113/522	0.49 (0.36–0.67)	88.8	77.1
≥65 yr	7/58	15/68	0.55 (0.22–1.34)	87.4	81.1
Clinical stage at presentation					
Inoperable breast cancer	42/185	70/190	0.54 (0.37–0.80)	76.0	60.2
Operable breast cancer	49/558	95/553	0.47 (0.33–0.66)	92.3	82.8
Hormone-receptor status					
Negative (ER-negative and progesterone-receptor–negative or unknown)	38/209	61/203	0.50 (0.33–0.74)	82.1	66.6
Positive (ER-positive, progesterone-receptor–positive, or both)	53/534	104/540	0.48 (0.35–0.67)	90.7	80.7
Preoperative HER2-directed therapy					
Trastuzumab alone	78/600	141/596	0.49 (0.37–0.65)	87.7	75.9
Trastuzumab plus additional HER2-directed agent or agents	13/143	24/147	0.54 (0.27–1.06)	90.9	81.8
Pathological nodal status after preoperative therapy					
Node-positive	62/343	103/346	0.52 (0.38–0.71)	83.0	67.7
Node-negative or NE	29/400	62/397	0.44 (0.28–0.68)	92.8	84.6
Primary tumor stage at definitive surgery					
ypT0, ypT1a, ypT1b, ypT1mic, ypTis	40/331	52/306	0.66 (0.44–1.00)	88.3	83.6
ypT1, ypT1c	14/175	42/184	0.34 (0.19–0.62)	91.9	75.9
ypT2	25/174	44/185	0.50 (0.31–0.82)	88.3	74.3
ypT3	9/51	21/57	0.40 (0.18–0.88)	79.8	61.1
ypT4	3/12	6/11	0.29 (0.07–1.17)	70.0	30.0
Regional lymph-node stage at definitive surgery					
ypN0	28/344	56/335	0.46 (0.30–0.73)	91.9	83.9
ypN1	29/220	50/213	0.49 (0.31–0.78)	88.9	75.8
ypN2	16/86	38/103	0.43 (0.24–0.77)	81.1	58.2
ypN3	17/37	15/30	0.71 (0.35–1.42)	52.0	40.6
ypNX	1/56	6/62	0.17 (0.02–1.38)	98.1	88.7

KATHERINE:
What about those with HER2- residual disease?

PATIENTS WITH HER2-NEGATIVE DISEASE AT SURGERY



TREAT PATIENTS WITH HER2+ PRIMARY TUMORS WITH ADJUVANT T-DM1

EVEN IF RESIDUAL DISEASE IS HER2-NEGATIVE

Loibl S, et al. ESMO Breast 2020.

COMPASSHER2 TRIALS

Eligibility:
Stage II or IIIA HER2+ BC (T2-3, N0-2)

- cN0 eligible if ≥ 2.0 cm
- cN1-2 eligible ≥ 1.5cm
- ER+ and ER- eligible

REGISTRATION

Preoperative Phase: all patients

THP x 4 Cycles
Paclitaxel qwk x12
OR
Docetaxel q3 wk x4
with
Trastuzumab (H)
& Pertuzumab (P) q3 wk x4

* nab-pacl allowed

SURGERY

pCR (ypT0/Tis ypN0) *40%*

No pCR *60%*

Arm A: pCR (no invasive disease)

EA1181
CompassHER2-pCR

- Complete 1 yr HP
- Radiation and endocrine Rx (if appropriate)

ECOG-ACRIN cancer research group
Reshaping the future of patient care

A011801
CompassHER2-RD

Alliance for Clinical Trials in Oncology

Grp 1: pre-op THP-> AC, Cb/HP x 4
Grp 2: pre-op TCHP, *AC-THP* -> no further chemo

Eligibility
HER2+ RD
ER- & ER+
(ER+ must be N+)
(~30% of A011801 expected to come from EA1181)

Registration

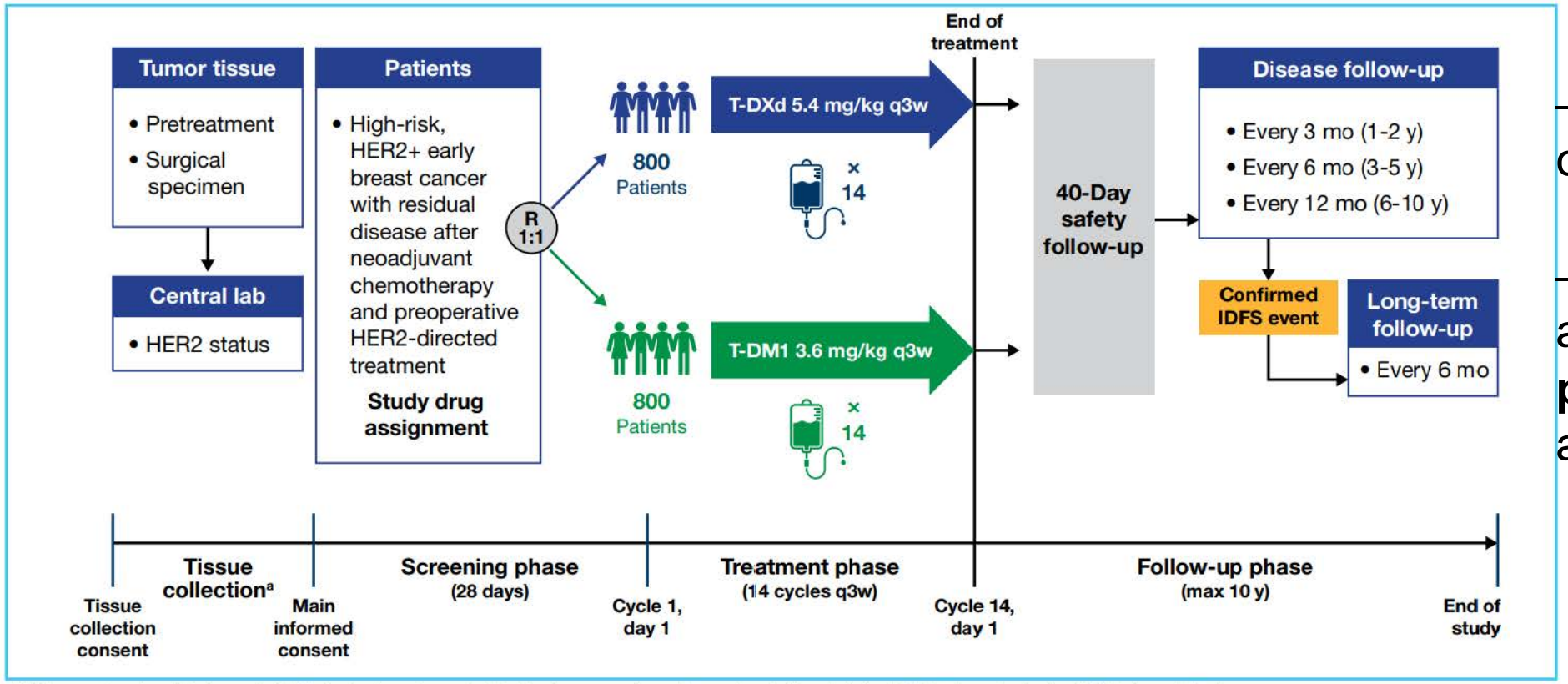
R

T-DM1 x 14 doses

T-DM1/tucatinib x 14 doses

DESTINY-Breast05 phase 3 trial

DESTINY-Breast05: A Multicenter, Open-Label, Randomized Phase 3 Trial Comparing the Efficacy and Safety of T-DXd vs T-DM1 in High-Risk Patients With HER2-Positive, Residual, Invasive Breast Cancer After Neoadjuvant Therapy (N≈1600)



HER2, human epidermal growth factor receptor 2; IDFS, invasive disease–free survival; lab, laboratory; max, maximum; q3w, every 3 weeks; R, randomization; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a] Patients may move into the main screening phase before HER2 status results are available from the central laboratory.

– **Inoperable** breast cancer at presentation

– Operable breast cancer at presentation with **node–positive (ypN1-3) disease** after neoadjuvant therapy

Geyer et al. SABCS 2020. Abstract OT-03-01.

Escalation based on clinical risk: DESTINY-Breast11 Trial

Population

HER2+ EBC

HR+ or HR-

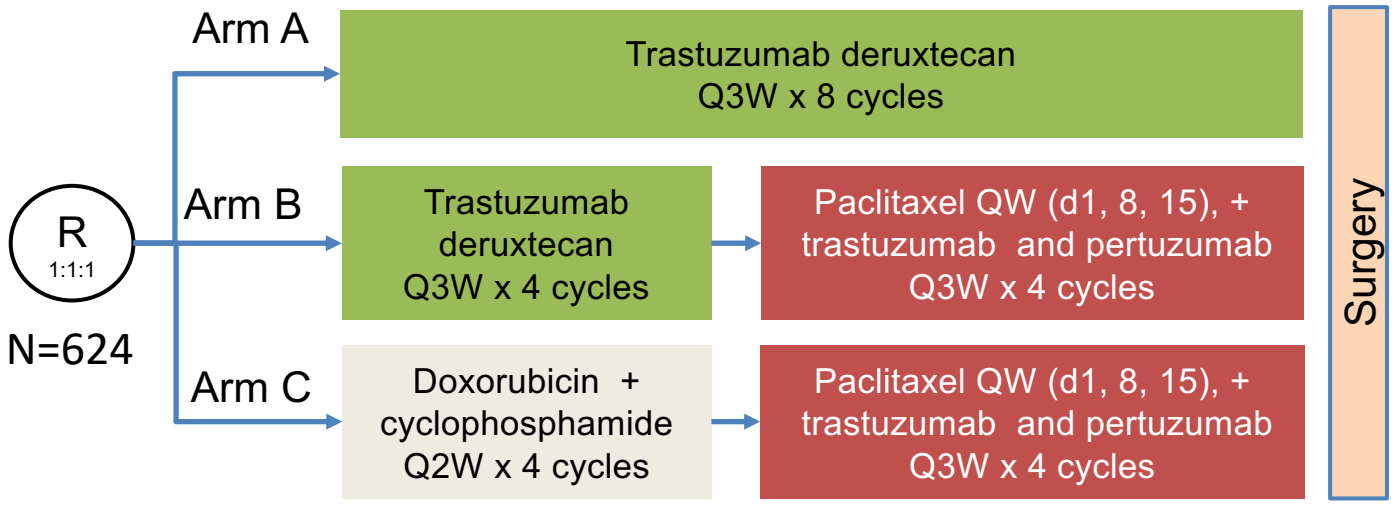
High-risk defined as one of the following:

- $T_xN_{1-3}M_0$
- $T_{3-4}N_xM_0$
- Inflammatory BC

Stratification factors:

- HR Status
  - HR+ vs HR-
- HER2 IHC
  - IHC3+ vs Other

Study Design



Endpoints

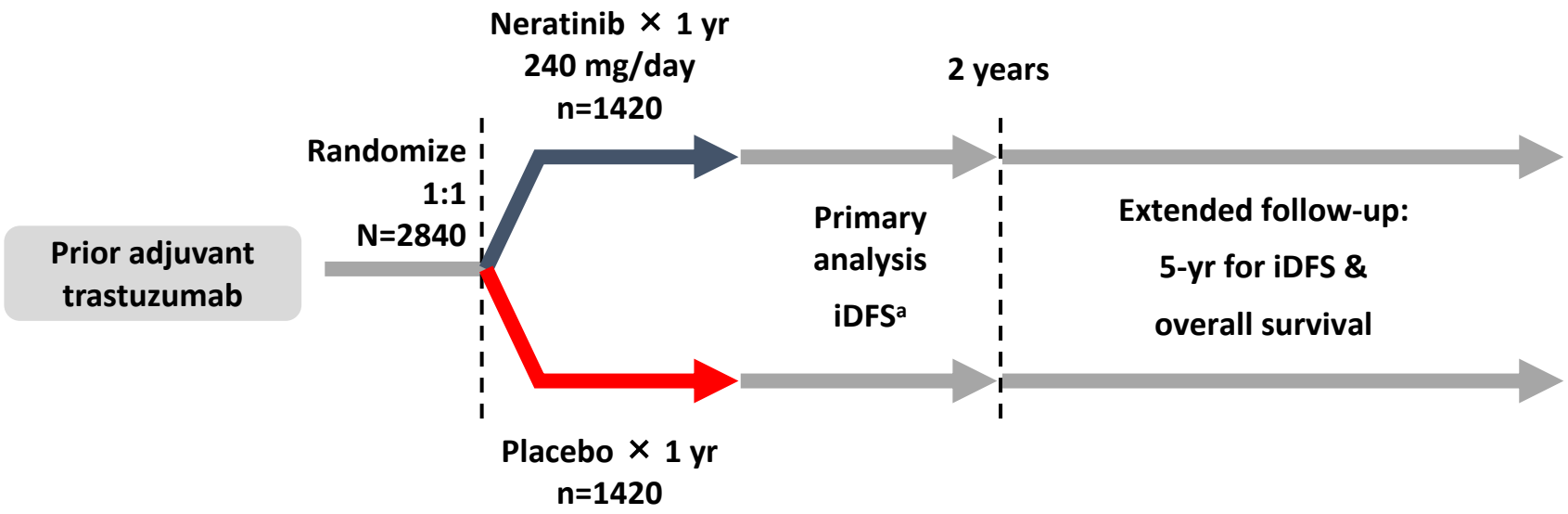
Primary Endpoint:

- pCR (ypT0/Tis ypN0)

Secondary Endpoints:

- pCR (ypT0 ypN0)
- EFS
- IDFS
- OS
- HRQoL
- Safety
- PK and immunogenicity

ADDING NERATINIB: EXTENET STUDY



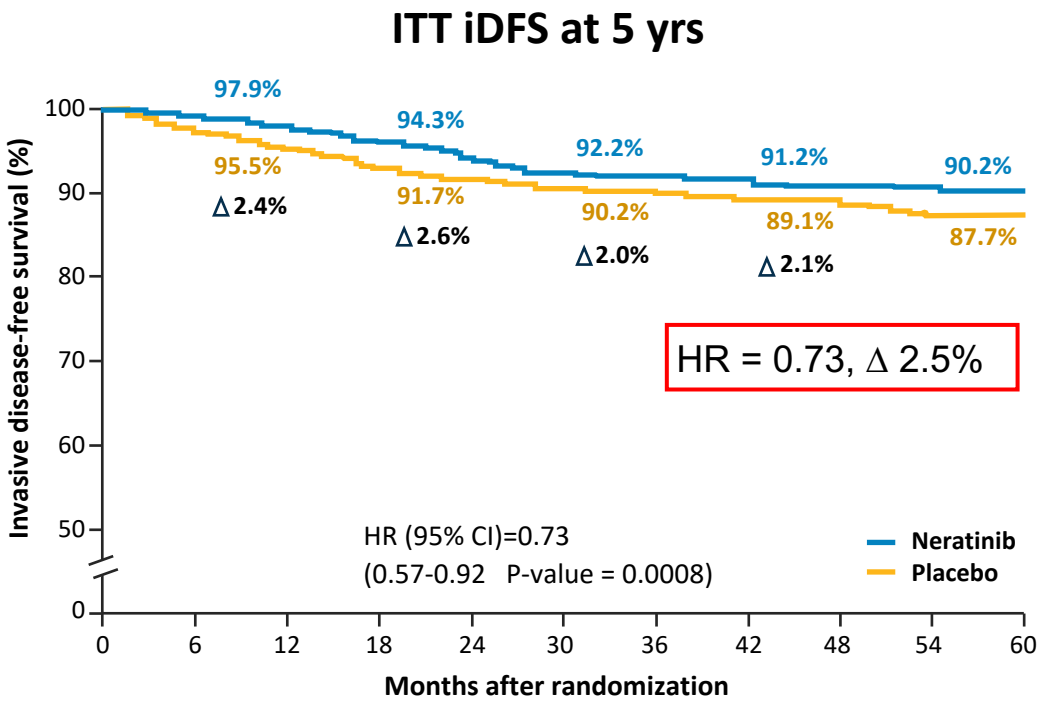
Primary endpoint: invasive disease-free survival (iDFS)[a]

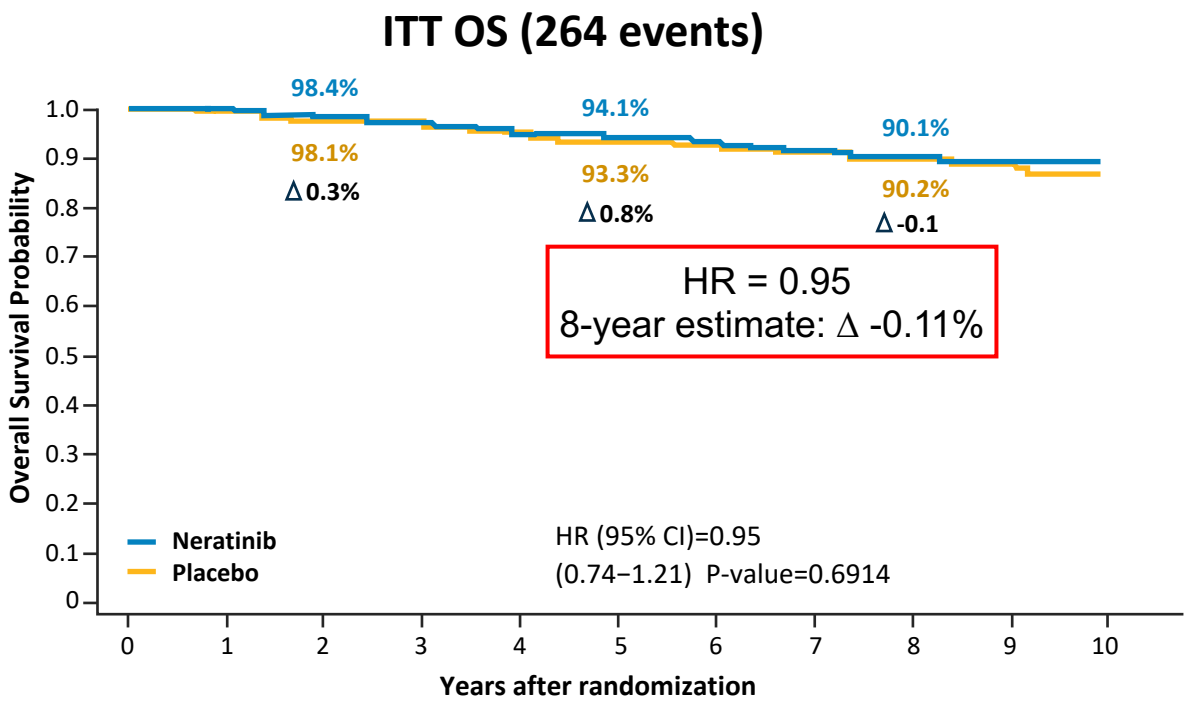
Secondary endpoints: overall survival, DFS-DCIS, distant DFS, time to distant recurrence, CNS metastases, safety,

Stratification: nodes 0, 1-3 vs 4+, ER/PR status, concurrent vs sequential trastuzumab

Study blinded: Until primary analysis; OS remains blinded

ExteNET iDFS and OS Intent-To-Treat Population (N=2,840)





No. at risk

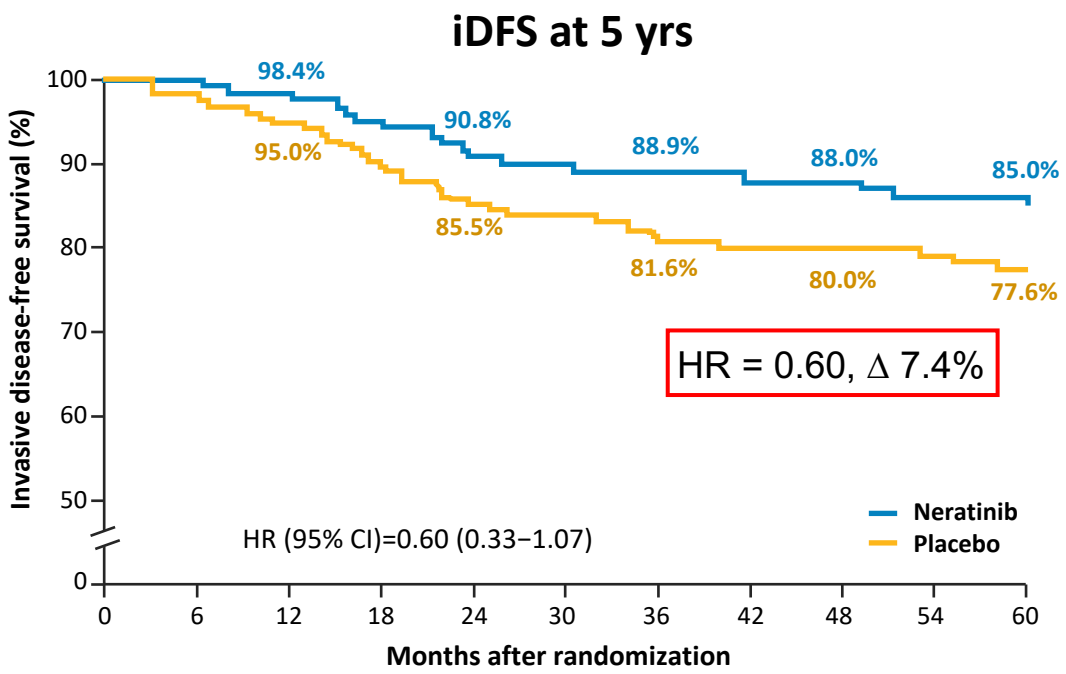
Neratinib	1420	1316	1272	1225	1106	978	965	949	938	920	885
Placebo	1420	1354	1298	1248	1142	1029	1011	991	978	958	927

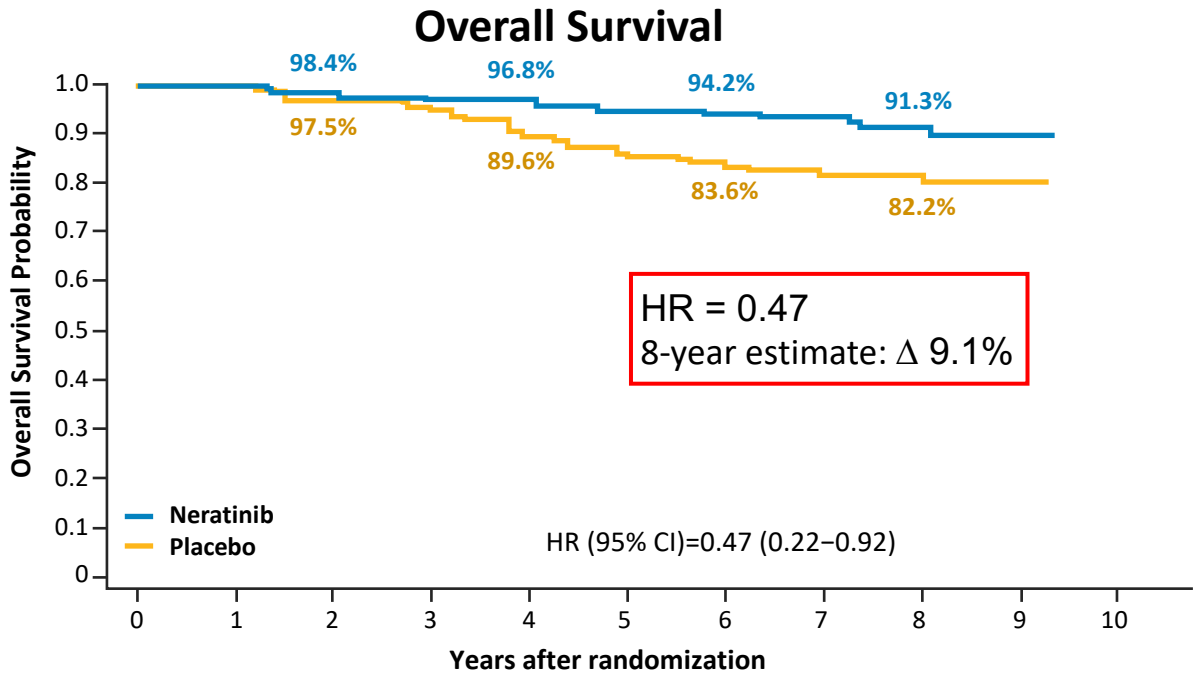
No. at risk

Neratinib	1420	1364	1309	1213	1118	1168	1123	1041	746	218	0
Placebo	1420	1384	1341	1249	1223	1199	1166	1086	796	221	0

Martin et al. *Lancet Oncol*. 2017;18(12):1688-1700.

ExteNET: No pCR Post Neoadjuvant Therapy HR+, ≤1 Year from Trastuzumab (N=295)





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.

WHEN SHOULD WE GIVE NERATINIB?

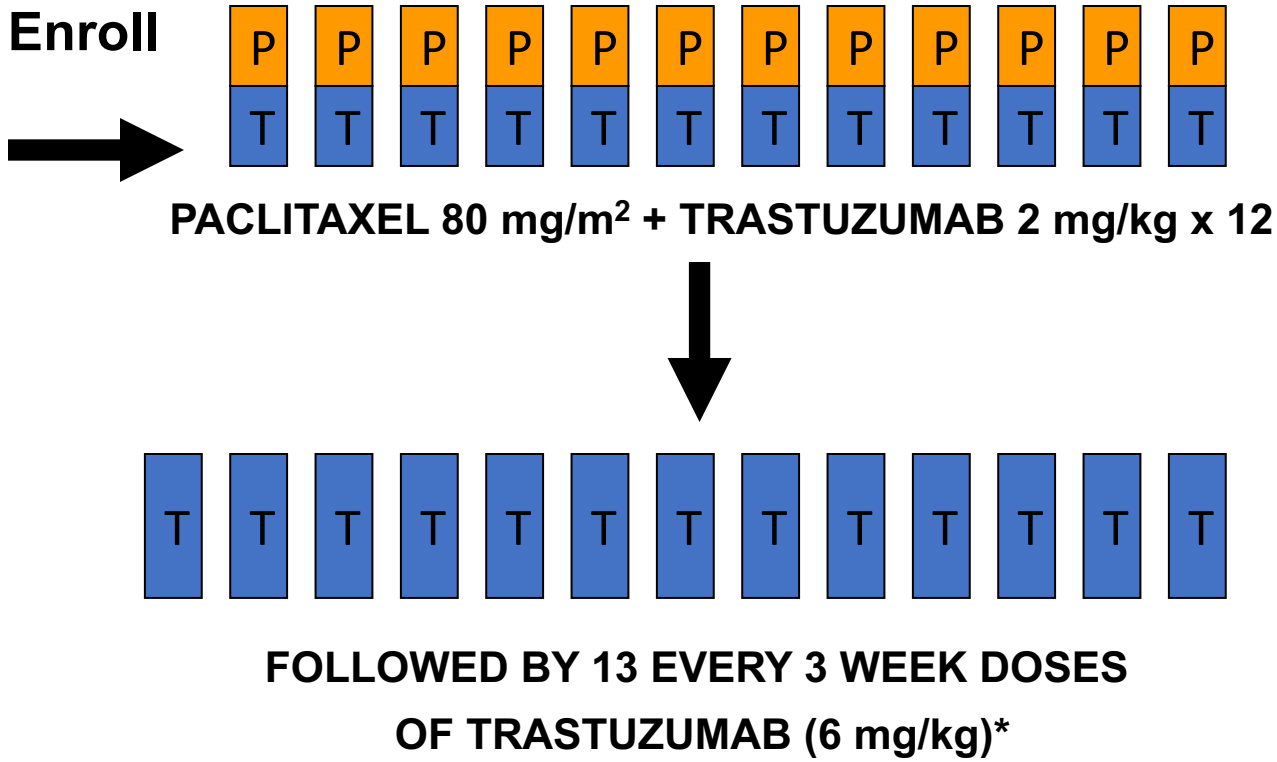
- Benefit seen in patients with high risk HR+ HER+ disease (larger benefit in patients with residual disease after preoperative therapy)
- Challenge is lack of data in patients who have previously received pertuzumab and/or T-DM1
- Must also weigh potential benefit with toxicity (~40% grade 3/4 diarrhea)
    - All patients should receive prophylactic anti-diarrheals (OR can consider a dose escalation approach)

CONSIDER NERATINIB IN HIGH RISK MULTI-NODE POSITIVE HR+ HER2+ PATIENTS AFTER COMPLETION OF HP or T-DM1

APT TRIAL: STUDY DESIGN

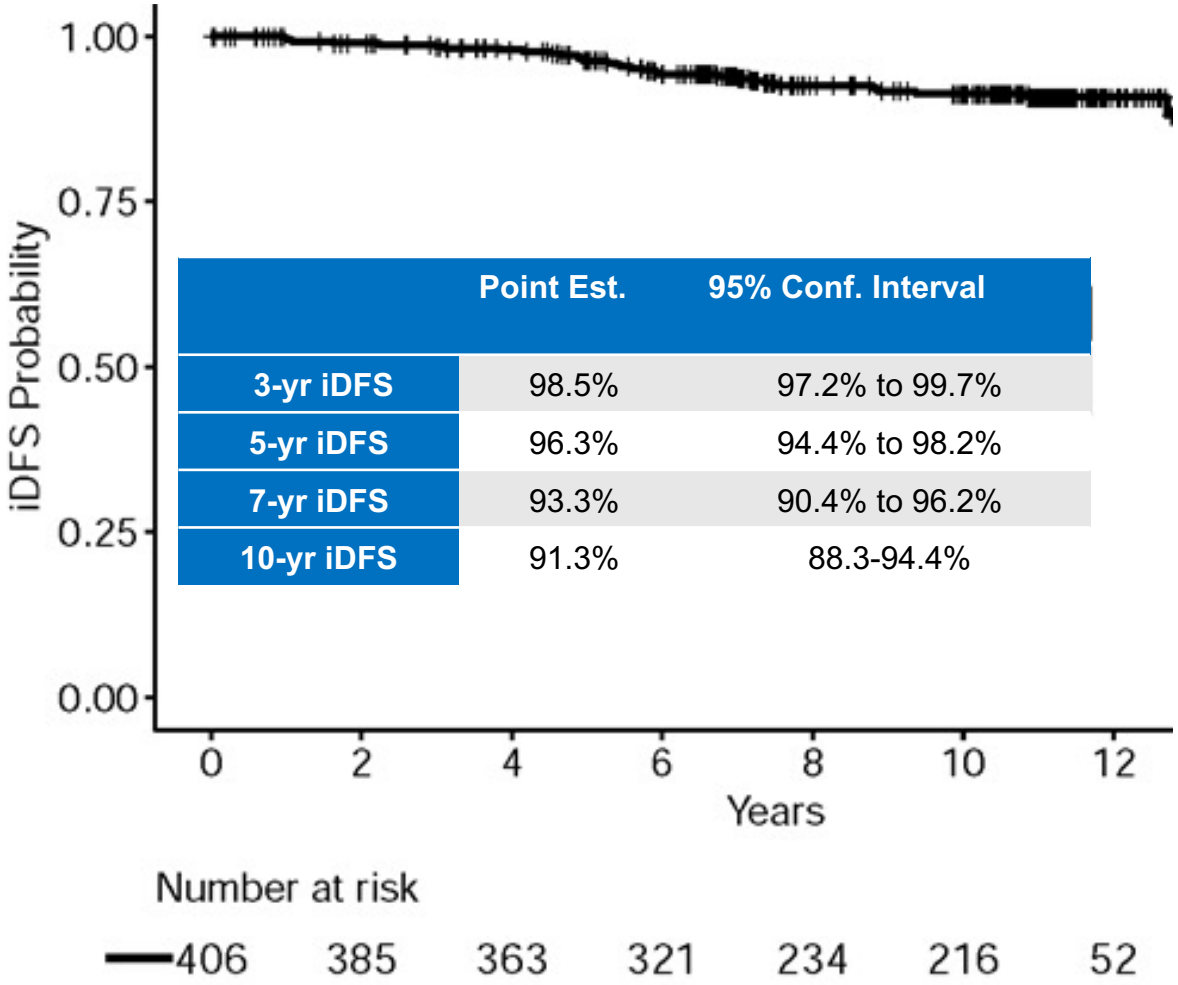
HER2+
ER+ or ER-
Node Negative
≤ 3 cm

Planned N=400



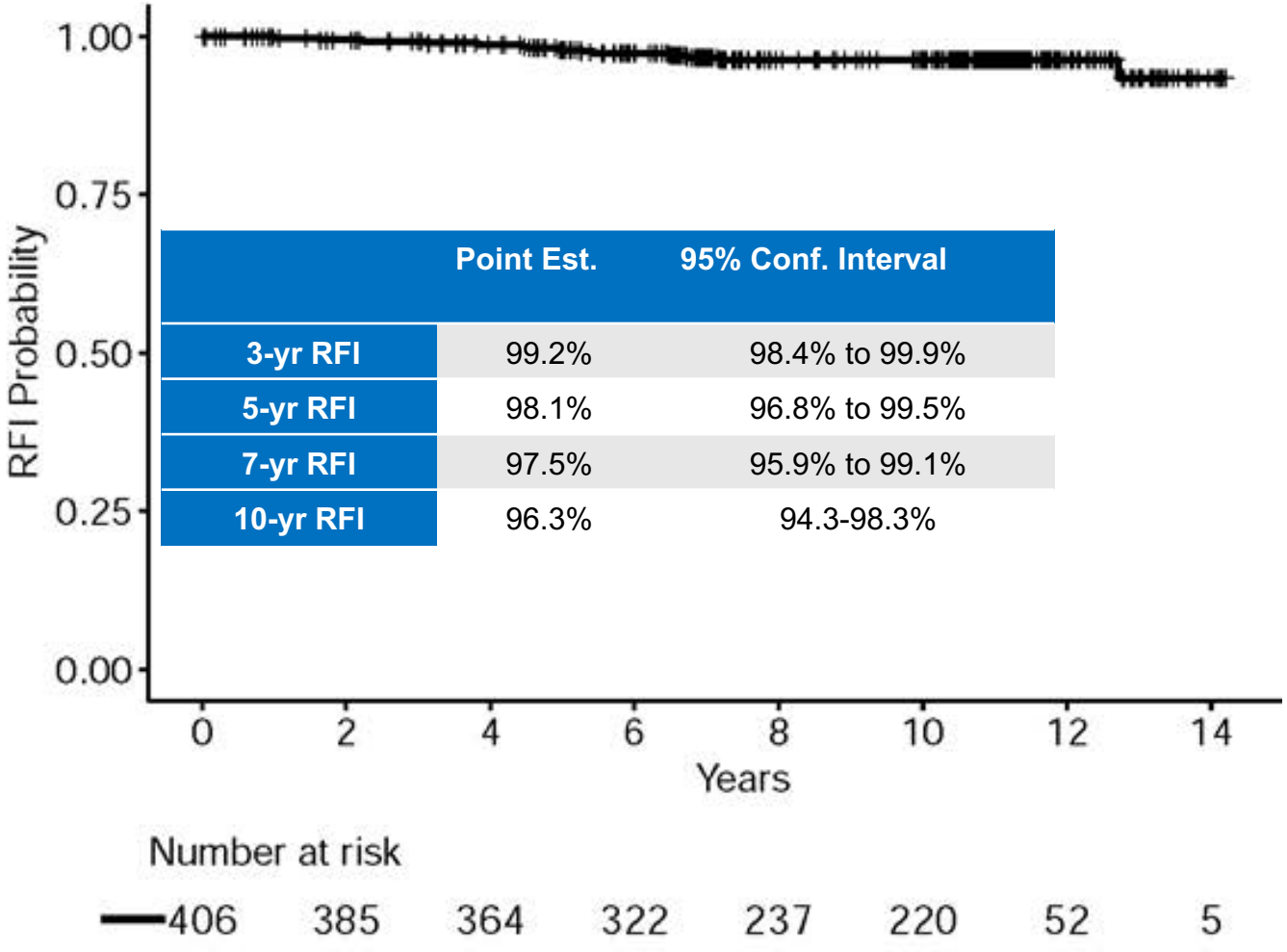
Tolaney SM et al. *N Engl J Med*. 2015;372(2):134-41.
Tolaney SM et al. *J Clin Oncol*. 2019;37(22):1868-1875.

APT: 10 year RESULTS



	Point Est.	95% Conf. Interval
3-yr iDFS	98.5%	97.2% to 99.7%
5-yr iDFS	96.3%	94.4% to 98.2%
7-yr iDFS	93.3%	90.4% to 96.2%
10-yr iDFS	91.3%	88.3-94.4%

6 Distant Events



	Point Est.	95% Conf. Interval
3-yr RFI	99.2%	98.4% to 99.9%
5-yr RFI	98.1%	96.8% to 99.5%
7-yr RFI	97.5%	95.9% to 99.1%
10-yr RFI	96.3%	94.3-98.3%

RFI Events=
- **Invasive Local/Regional Recurrence**
- **Distant Recurrence**
- **Death from Breast Cancer**

Tolaney SM et al SABCS 2022

Does T-DM1 have a role for Stage I HER2+ Disease? ATEMPT Trial

Key Eligibility Criteria

- Stage 1 HER2+ breast cancer
  - HER2 centrally tested (ASCO CAP 2013 guidelines)
- N0 or N1mic
- Left Ventricular EF ≥ 50%
- No prior invasive breast cancer
- ≤90 days from last surgery

N = 497

R 3:1

3

1

N = 383

T-DM1

3.6 mg/kg IV q3 wks x 17

N = 114

TH

Paclitaxel 80 mg/m^2 IV + Trastuzumab 2 mg/kg IV wkly x12 → Trastuzumab 6 mg/kg every 3 wks x13

Stratification factors:

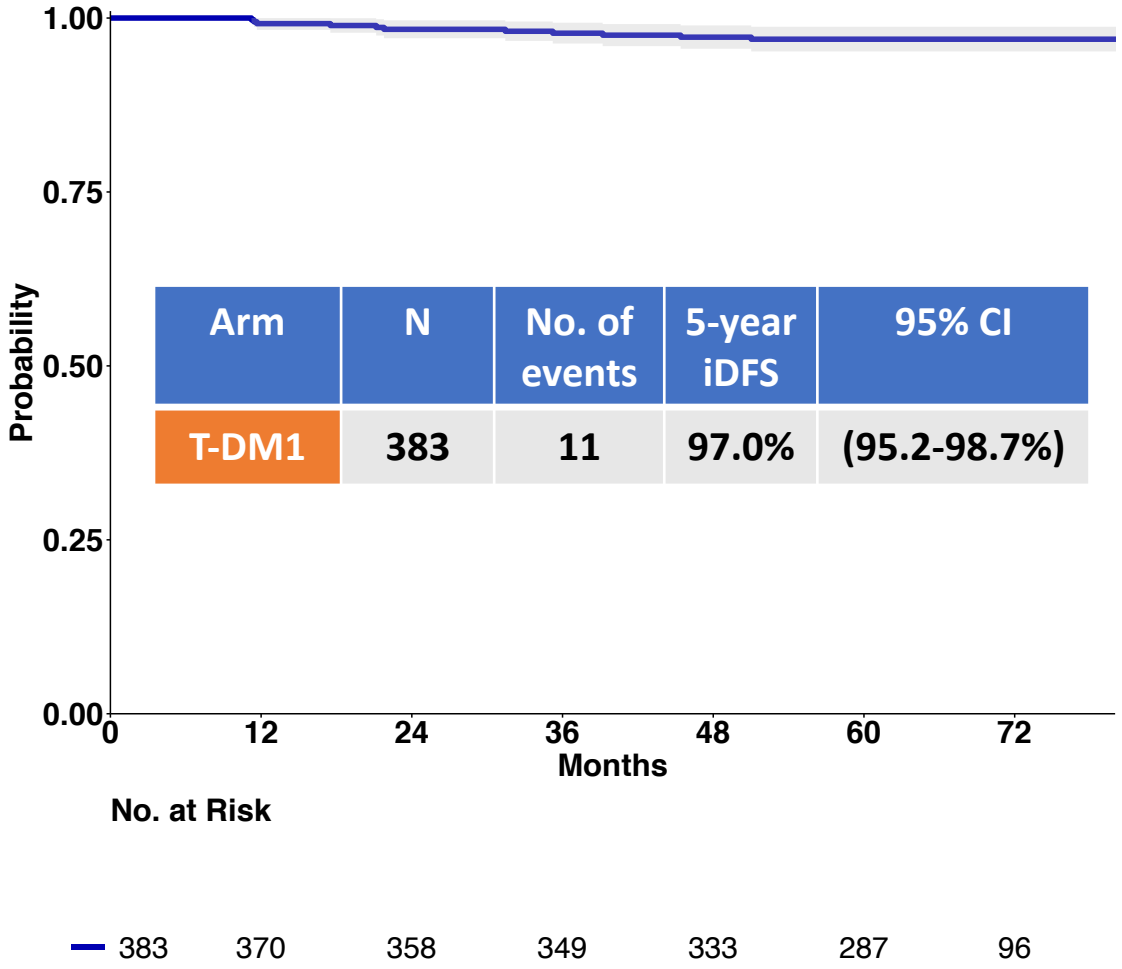
- Age (<55, ≥55)
- Planned radiation (Yes/No)
- Planned hormonal therapy (Yes/No)

*Radiation and endocrine therapy could be initiated after 12 weeks on study therapy

Tolaney S et al. SABCS 2019. GS1-05.

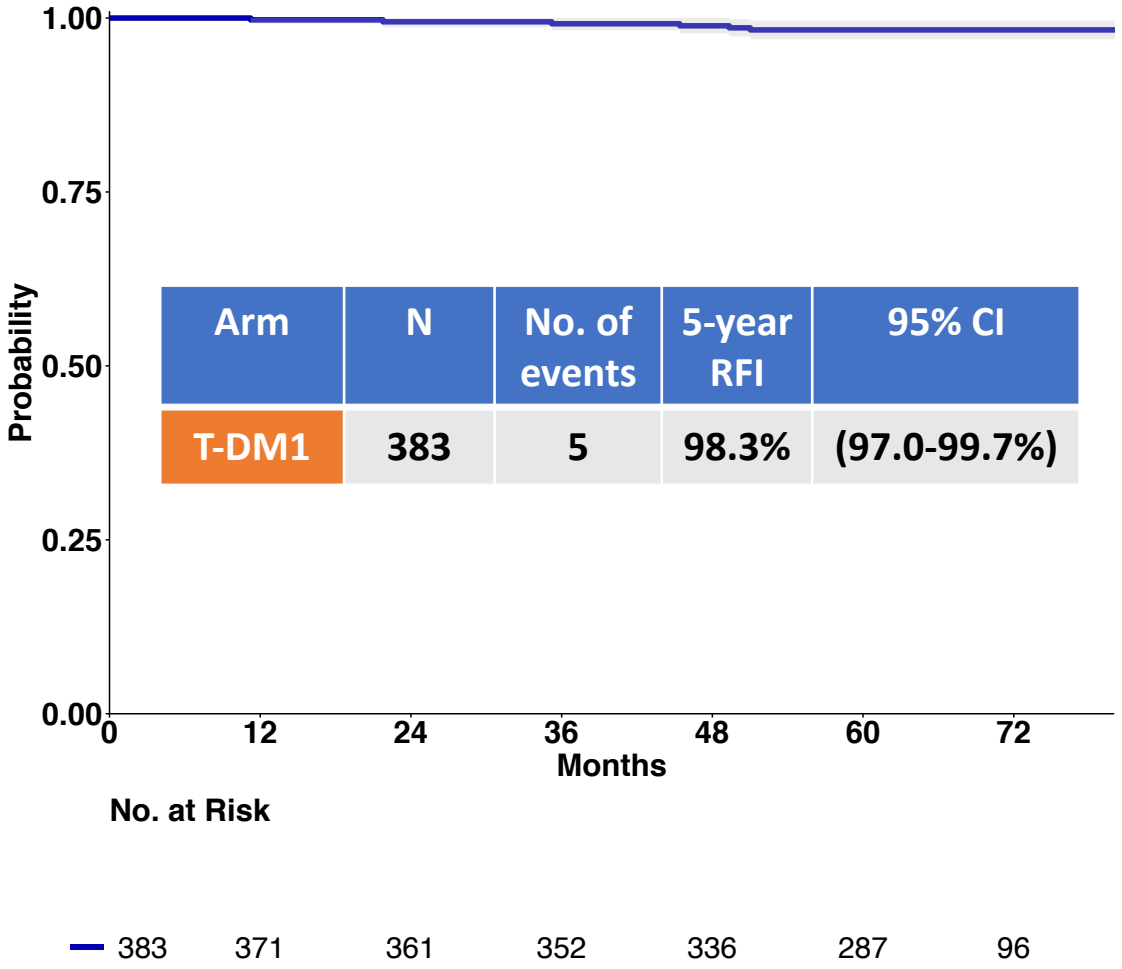
5-year outcomes with T-DM1: iDFS and RFI

5-year iDFS



Arm	N	No. of events	5-year iDFS	95% CI
T-DM1	383	11	97.0%	(95.2-98.7%)

5-year RFI



Arm	N	No. of events	5-year RFI	95% CI
T-DM1	383	5	98.3%	(97.0-99.7%)

3 Distant Events

ATEMPT: CLINICALLY RELEVANT TOXICITY

Clinically Relevant Toxicity	T-DM1 (n = 383) N (%)	TH (n = 114) N (%)
Grade ≥3 non-hematologic toxicity	37 (10%)	13 (11%)
Grade ≥ 2 neurotoxicity	42 (11%)	26 (23%)
Grade ≥4 hematologic toxicity	4 (1%)	0 (0%)
Febrile neutropenia	0 (0%)	2 (2%)
Any toxicity requiring dose delay	106 (28%)	30 (26%)
Any toxicity requiring early discontinuation	67 (17%)	7 (6%)
Total	176 (46%)	53 (46%)

p=0.91

Tolaney S et al. SABCS 2019. GS1-05.

WHICH PATIENTS WITH STAGE I HER2+ DISEASE SHOULD GET T-DM1?

- **T-DM1 for 1 year was associated with very few recurrences in patients with Stage I HER2+ disease**
  - **3 year DFS 97.7% (95% CI: 96.2-99.3), RFI 99.1% (95% CI: 98.1-100)**
- **T-DM1 was not associated with significantly fewer clinically relevant toxicities than TH**
- **Not all toxicities are captured in the CRT endpoint, including alopecia, and patient reported outcomes (PROs) should be considered when assessing tolerability (generally favored T-DM1)**
- **Given the low event rate seen in this trial, T-DM1 may be an alternative to TH**

Which stage I HER2+ breast cancer patients should get systemic therapy (TH or T-DM1)?

Hormone Receptor Status	<0.5 cm	0.5-1.0cm	>1.0-2.0cm
HR+	NO	YES	YES
HR-	Sometimes*	YES	YES

*if high risk features (high grade with LVI), and relatively larger size

Should small HER2+ tumors get preop therapy?

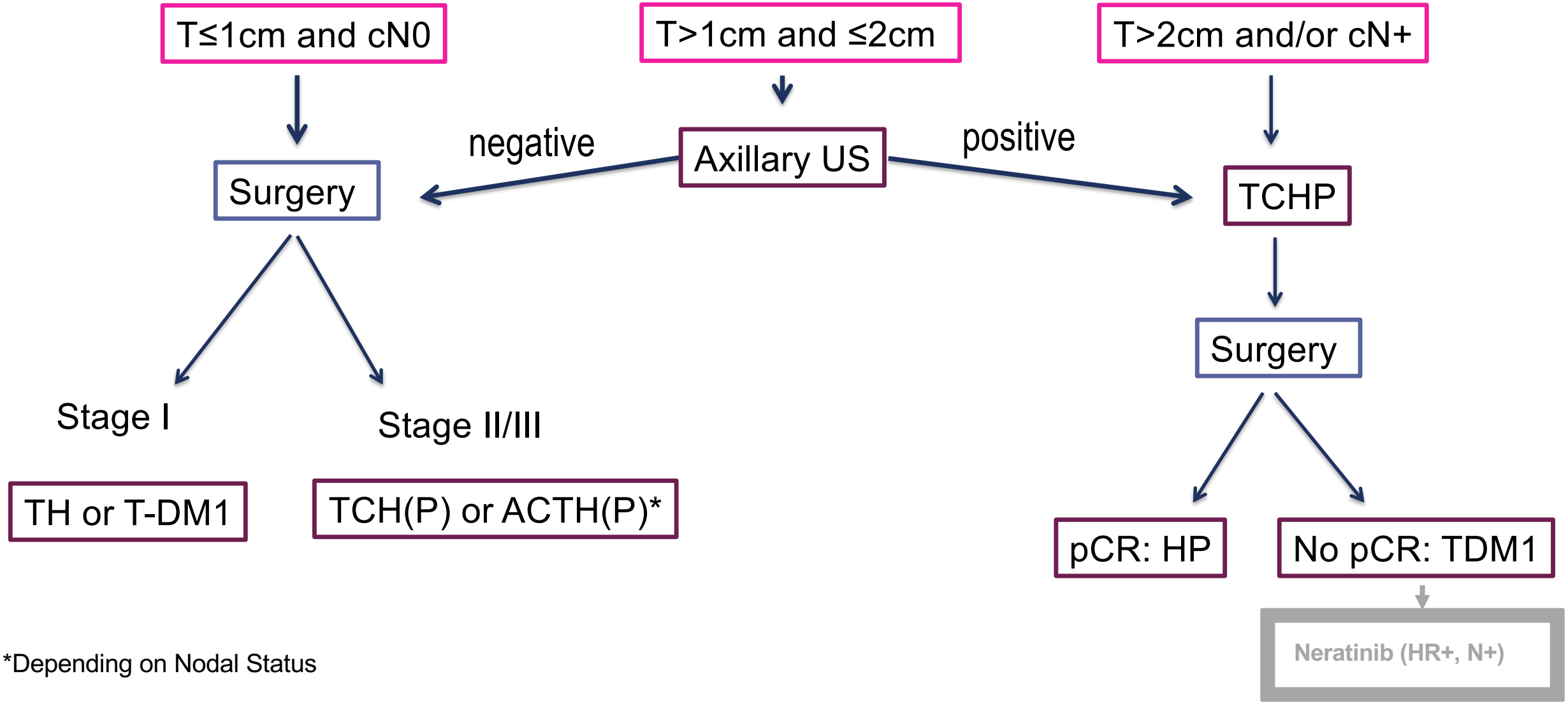
DFCI SERIES: Pathologic nodal status with upfront surgery in HER2+ cancers

	pN+ N= 73	pN0 N= 295	P value*
Clinical T category			**< 0.001**
1mic	6 (10.4%)	42 (89.6%)	
1a	3 (11.5%)	23 (88.5%)	
1b	7 (8.0%)	80 (92.0%)	
1c	**38 (24.7%)**	116 (75.3%)	
2	**19 (35.8%)**	34 (64.2%)	

- Up to 25% of T1c tumors will be node positive, and therefore should be getting preoperative therapy
- Should we do axillary US upfront on all clinically node-negative patients and if negative, then take to surgery, and give adjuvant TH, or give preop TH for these pts?
  - RFI 97.5% suggests may not need more than TH for almost all pts, so could lead to overtreatment

Axillary Ultrasound for clinically node-negative stage I patients is critical for decision-making

HER2+ Early Breast Cancer Algorithm



*Depending on Nodal Status

MODULE 2: Current Considerations in the Treatment of HER2-Positive Metastatic Breast Cancer — Dr Krop

RTP
RESEARCH
TO PRACTICE

Case Presentation: 60-year-old woman with an 8-cm, ER-negative, PR-positive, HER2-positive IDC and positive nodes bilaterally, s/p neoadjuvant TCHP and bilateral mastectomies with no residual disease

Dr Henna Malik (Houston, Texas)

RTP
RESEARCH
TO PRACTICE

Case Presentation: 58-year-old woman with Stage IIIA, ER/PR-negative, HER2-positive, node-positive IDC with residual disease s/p neoadjuvant TCHP and mastectomy

Dr Laila Agrawal (Louisville, Kentucky)

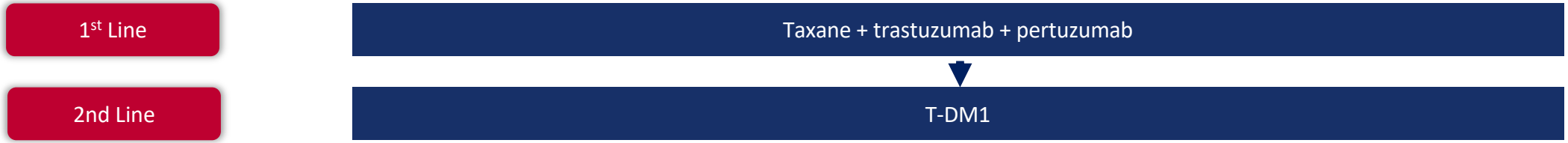
RTP
RESEARCH
TO PRACTICE

Optimizing Management of HER2-Positive Advanced Breast Cancer

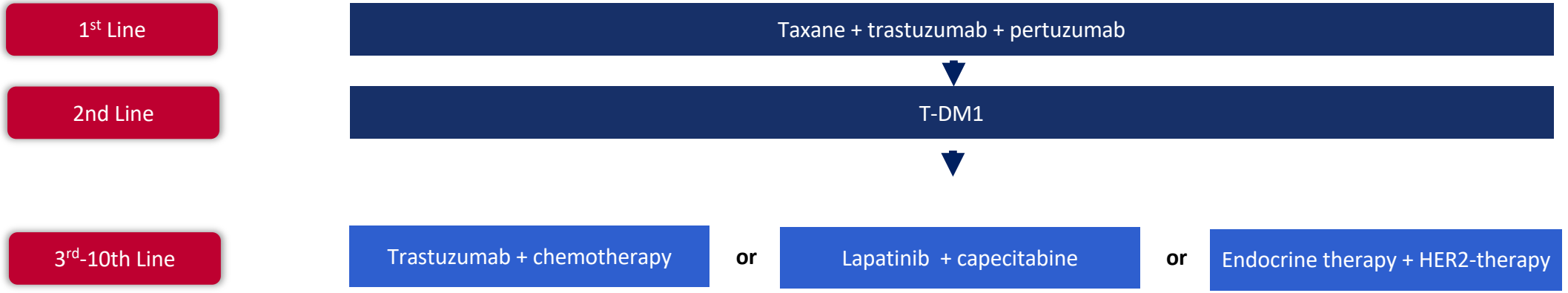
Ian Krop MD PhD

December 2022

Treatment Paradigm for Metastatic HER2+ Breast Cancer (Circa 2019)



Treatment Paradigm for Metastatic HER2+ Breast Cancer (Circa 2019)



Efficacy of Chemotherapy + Trastuzumab is limited in ≥3rd line*

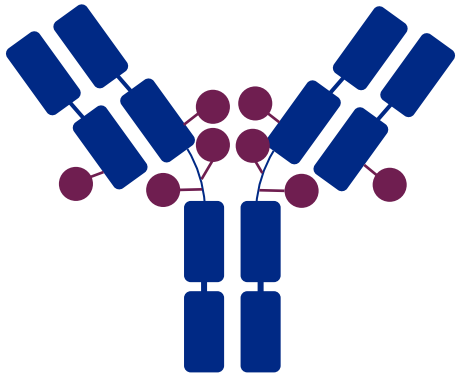
– PFS ≈ 5 months

– ORR ≈ 20%

* Ie control arms of SOPHIA and HER2CLIMB

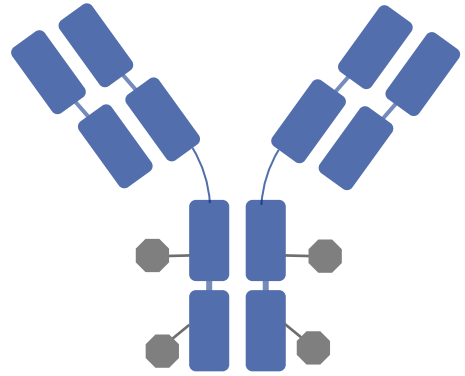
Trastuzumab deruxtecan: a 2nd generation HER2-targeted ADC

Trastuzumab deruxtecan (T-DXd)[1]



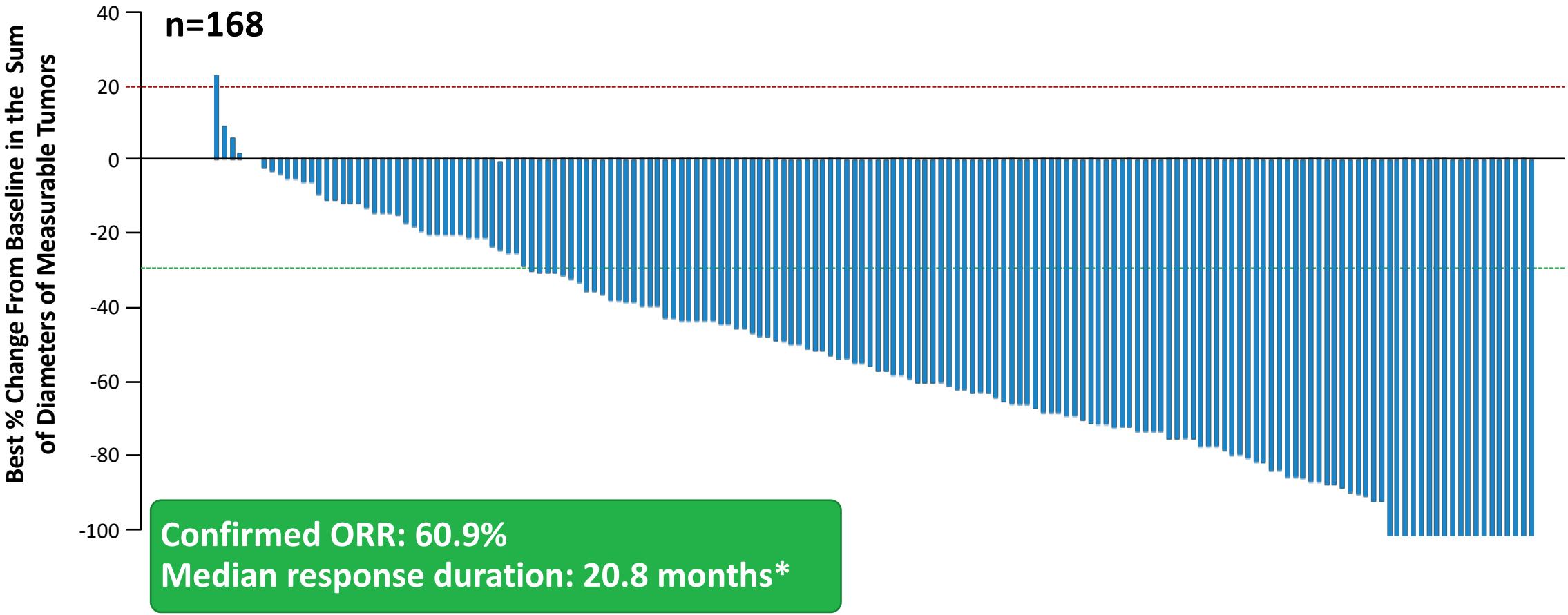
T-DXd[1-4,a]	ADC Attributes	T-DM1[3-5]
Topoisomerase I inhibitor	**Payload MoA**	Anti-microtubule
~8:1	**Drug-to-antibody ratio**	~3.5:1
Yes	**Tumor-selective cleavable linker?**	No
Yes	**Evidence of bystander anti-tumor effect?**	No

Trastuzumab emtansine (T-DM1)[5]



Adapted from J Cortes et al, ESMO 2021

Destiny Breast-01: Phase 2 Efficacy of Trastuzumab Deruxtecan in heavily pretreated HER2+ metastatic breast cancer



By independent central review.
The line at 20% indicates progressive disease; the line at −30% indicates partial response.
[a] Includes all patients who received T-DXd 5.4 mg/kg (intent-to-treat analysis; N=184).

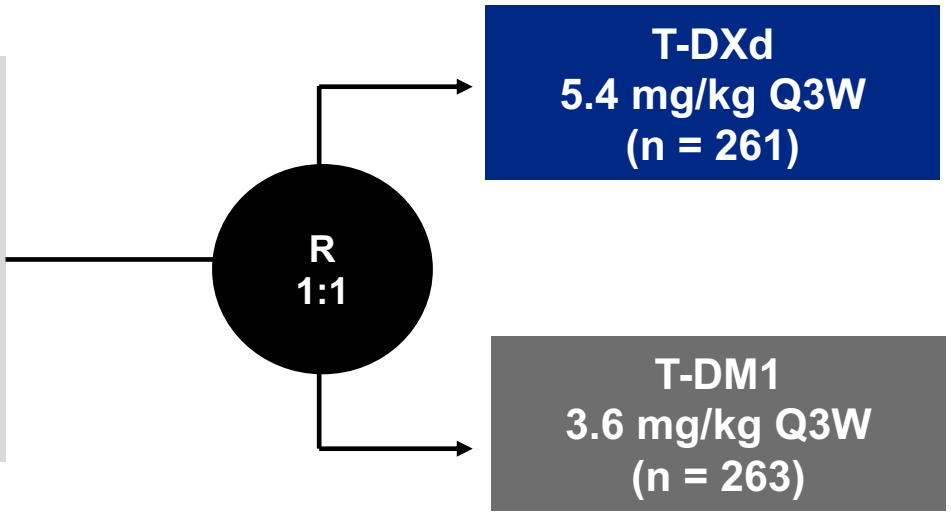
Adapted from Krop et al, SABCS 2019; *Modi S et al, SABCS 2020

Updated OS Analysis of DESTINY-Breast03

Randomized, open-label, multicenter study (NCT03529110)

Patients (N = 524)

- Unresectable or metastatic HER2-positive[a] breast cancer
- Previously treated with trastuzumab and a taxane in metastatic or (neo)adjuvant setting with recurrence within 6 months of therapy[b]



Primary endpoint

- PFS (BICR)

Key secondary endpoint

- OS[c]

Secondary endpoints

- ORR (BICR and investigator)
- DoR (BICR)
- Safety

Stratification factors

- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease

The prespecified OS interim analysis was planned with 153 events.[d] At the time of data cutoff (July 25, 2022), 169 OS events were observed and the *P* value to achieve statistical significance was 0.013

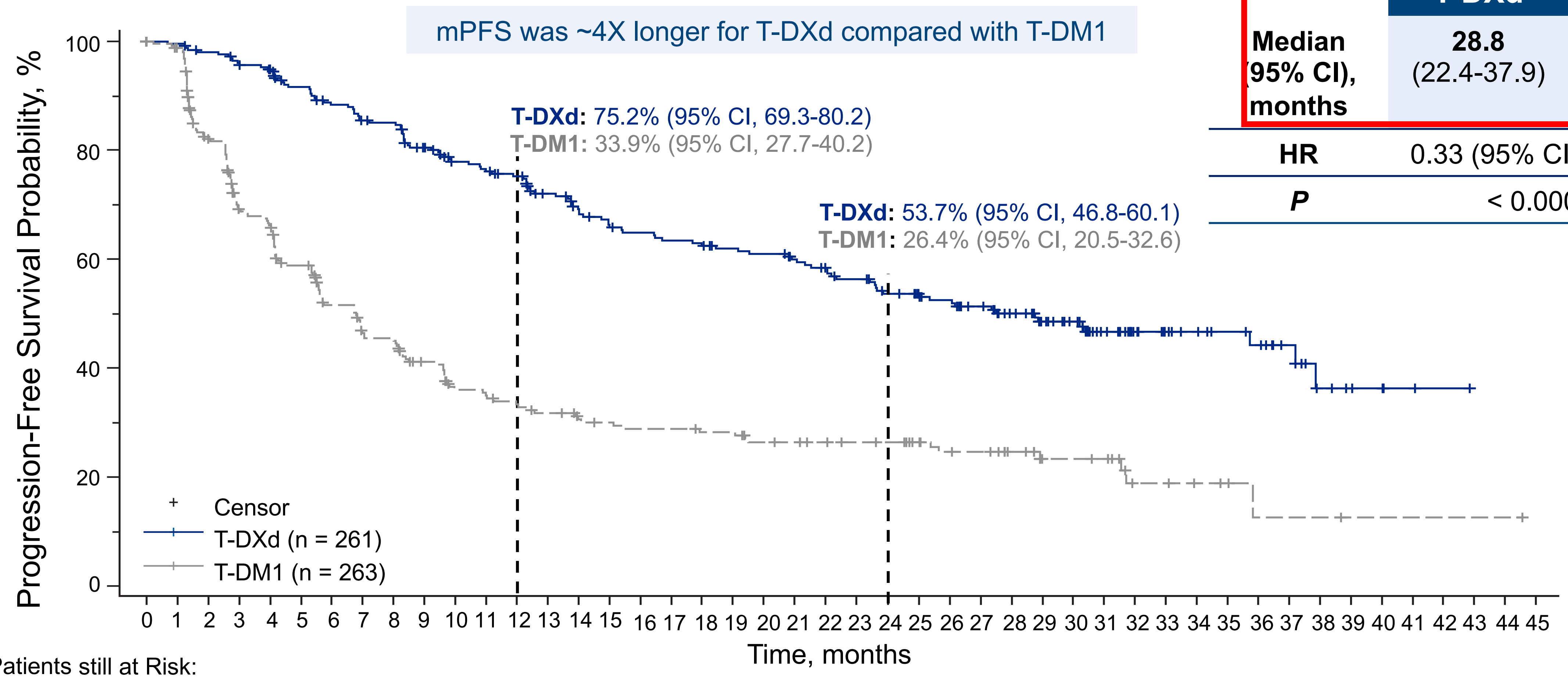
BICR, blinded independent central review; DoR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

[a]HER2 IHC 3+ or IHC 2+/ISH+ based on central confirmation. [b]Progression during or within 6 months after completing adjuvant therapy involving trastuzumab and a taxane. [c]80% powered at 2-sided significance level of 5%. [d]Information fraction of 61%, with a *P* value boundary to reach statistical significance of 0.008. The *P* value was recalculated based on the actual OS events at the data cutoff.

Thi

Updated Primary Endpoint: PFS by BICR

	T-DXd	T-DM1
Median (95% CI), months	**28.8** (22.4-37.9)	**6.8** (5.6-8.2)
HR	0.33 (95% CI, 0.26-0.43)	
P	< 0.000001[a,b]	



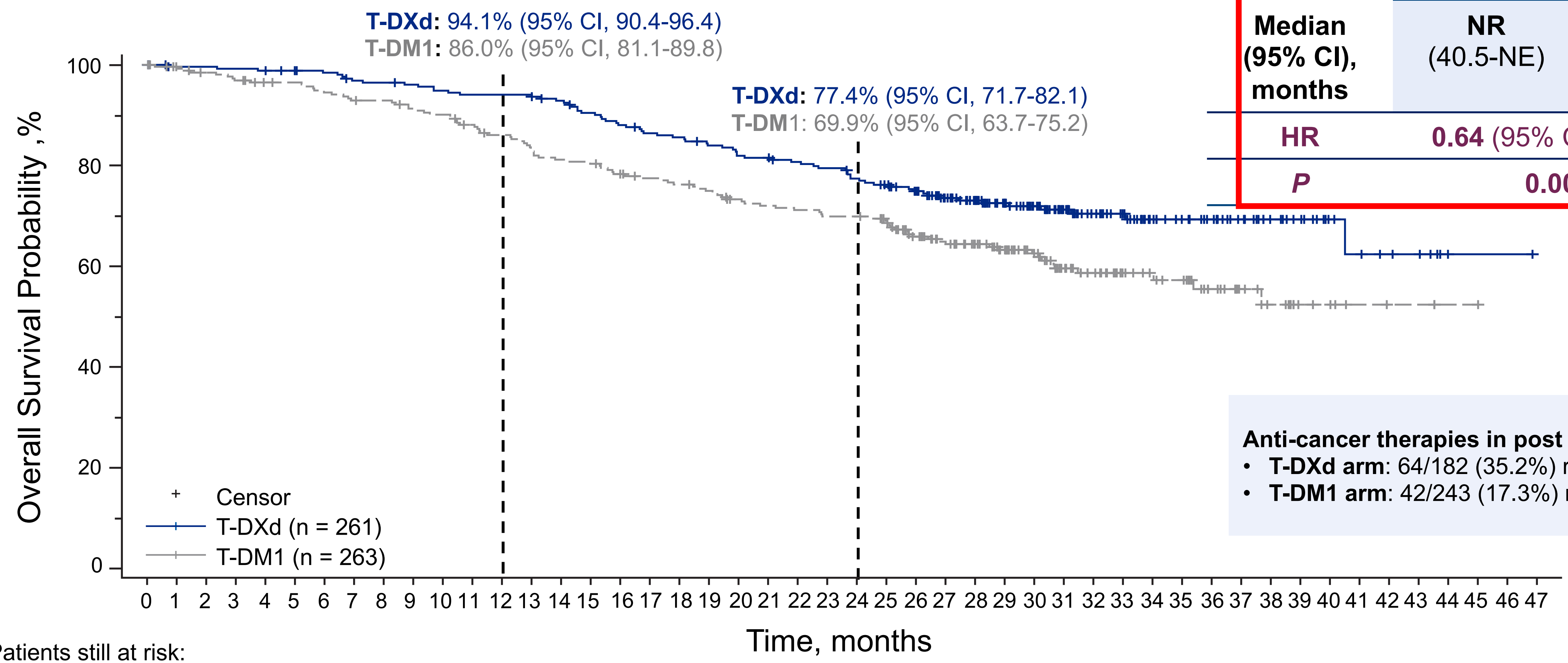
Patients still at Risk:

T-DXd	261	256	250	244	240	225	216	207	205	191	176	173	167	154	146	140	134	131	130	125	123	117	113	107	99	96	90	82	73	64	55	41	32	28	23	20	18	13	7	5	4	2	1	0	
T-DM1	263	253	201	164	156	134	111	99	96	81	69	67	63	58	54	51	49	49	47	47	42	41	39	37	36	32	28	27	22	19	15	14	8	7	6	4	2	2	2	1	1	1	1	1	1	0

BICR, blinded independent central review; HR, hazard ratio; mo, month; mPFS, median progression-free survival; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]Two-sided, from stratified log rank test. [b]Nominal *P* value.

Thi

Key Secondary Endpoint: Overall Survival



	T-DXd	T-DM1
Median (95% CI), months	**NR** (40.5-NE)	**NR** (34.0-NE)
HR	**0.64** (95% CI, 0.47-0.87)	
P	**0.0037**[a,b]	

Anti-cancer therapies in post trial setting:
- **T-DXd arm**: 64/182 (35.2%) received T-DM1
- **T-DM1 arm**: 42/243 (17.3%) received T-DXd

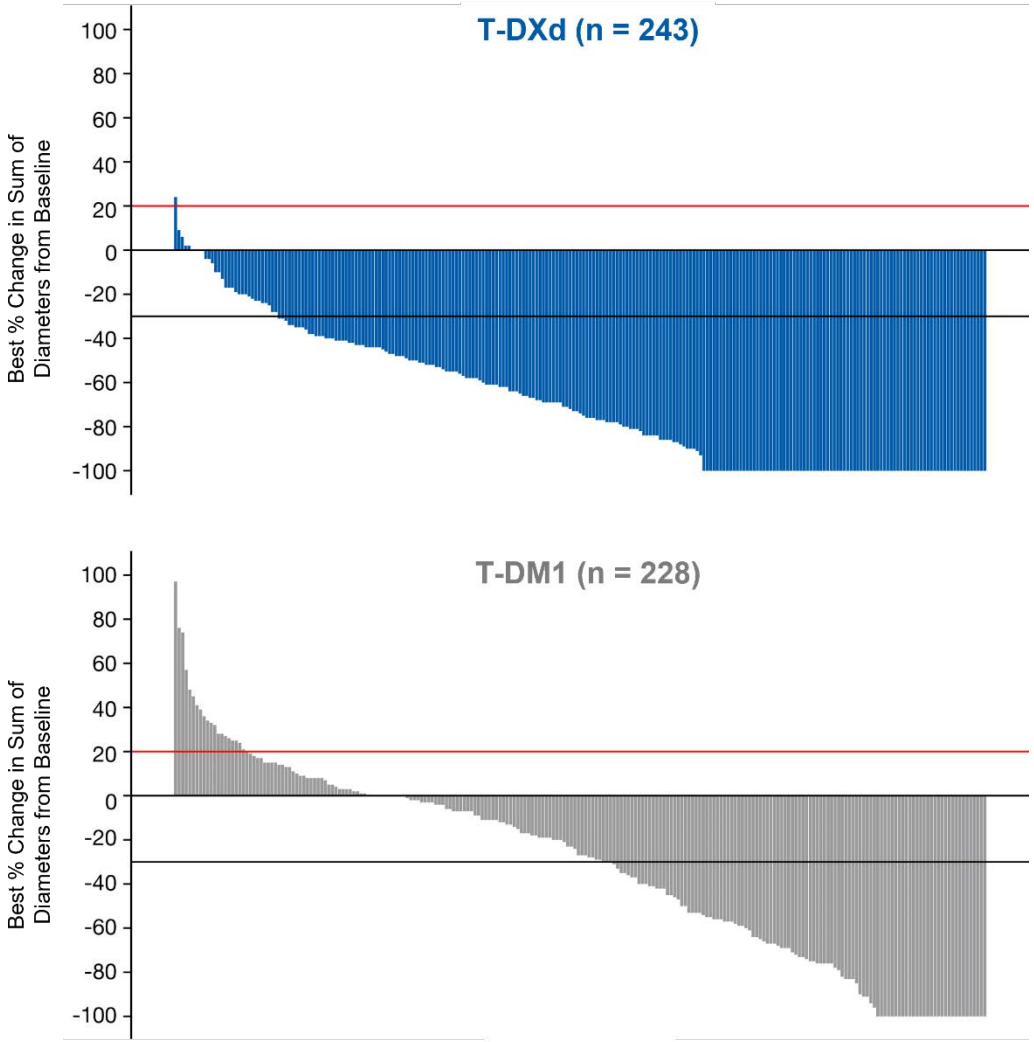
Patients still at risk:

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47
T-DXd	261	256	256	255	254	251	249	244	243	241	238	236	236	236	231	224	218	213	211	206	201	200	196	193	187	182	173	156	142	124	109	91	73	64	51	44	38	30	22	18	11	9	7	6	1	1	1	0
T-DM1	263	257	252	248	243	242	237	233	232	227	224	217	211	203	199	197	191	186	183	179	172	169	167	164	164	158	140	129	117	106	90	70	59	45	41	38	27	20	15	8	7	4	3	3	1	1	0	

HR, hazard ratio; mOS, median overall survival; NE, not estimable; NR, not reached; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
There were 19 patients (7.3%) treated with T-DXd and 28 patients (10.6%) treated with T-DM1 who were lost to follow-up.
[a]The *P* value for overall survival crossed the prespecified boundary (*P* = 0.013) and was statistically significant. [b]Two-sided from stratified log-rank test.

Thi

Confirmed ORR and Other Efficacy Endpoints



	T-DXd n = 261[a]	T-DM1 n = 263[a]
Confirmed ORR by BICR		
n (%)	205 (**78.5**)	92 (**35.0**)
[95% CI]	[73.1-83.4]	[29.2-41.1]
Nominal *P* value	< 0.0001	
CR, n (%)	55 (**21.1**)	25 (**9.5**)
PR, n (%)	150 (57.5)	67 (25.5)
SD, n (%)	47 (18.0)	110 (41.8)
PD, n (%)	3 (1.1)	47 (17.9)
NE, n (%)	6 (2.3)	14 (5.3)
CBR, n (%) [95% CI]	233 (89.3) [84.9-92.8]	122 (46.4) [40.2-52.6]
Nominal *P* value	< 0.0001	
mDoR by BICR, months (95% CI)	**36.6** (22.4-NE)	**23.8** (12.6-34.7)

BICR, blinded independent central review; CBR, clinical benefit rate; CR, complete response; mDoR, median duration of response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Red line at 20% indicates progressive disease; black line at −30% indicates partial response.

[a]Only patients with measurable disease at baseline and at least 1 postbaseline target lesion assessment were included.

Thi

Most Common TEAEs in ≥20% of Patients

System Organ Class Preferred Term, n (%)	T-DXd n = 257		T-DM1 n = 261	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Blood and lymphatic system disorders				
Anemia	95 (37.0)	24 (9.3)	51 (19.5)	17 (6.5)
Platelet count decreased	64 (24.9)	20 (7.8)	114 (43.7)	52 (19.9)
White blood cell count decreased	60 (23.3)	16 (6.2)	16 (6.1)	2 (0.8)
Gastrointestinal disorders				
Nausea	198 (77.0)	18 (7.0)	79 (30.3)	1 (0.4)
Vomiting	133 (51.8)	4 (1.6)	28 (10.7)	2 (0.8)
Constipation	96 (37.4)	0	51 (19.5)	0
Diarrhea	83 (32.3)	3 (1.2)	21 (8.0)	2 (0.8)
General disorders				
Fatigue	79 (30.7)	15 (5.8)	53 (20.3)	2 (0.8)
Headache	61 (23.7)	1 (0.4)	40 (15.3)	0
Investigations				
Neutrophil count decreased	79 (30.7)	41 (16.0)	30 (11.5)	8 (3.1)
Aspartate aminotransferase increased	72 (28.0)	2 (0.8)	108 (41.4)	14 (5.4)
Alanine aminotransferase increased	59 (23.0)	4 (1.6)	83 (31.8)	12 (4.6)
Metabolism and nutrition disorders				
Decreased appetite	78 (30.4)	4 (1.6)	46 (17.6)	1 (0.4)
Weight decreased	58 (22.6)	6 (2.3)	23 (8.8)	2 (0.8)
Skin and subcutaneous tissue disorders				
Alopecia	102 (39.7)	1 (0.4)[a]	9 (3.4)	0

T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
Adverse events were managed according to the protocol. [a]Cases of alopecia reported during the study were graded based on the clinical judgement of the investigator. 1 case of alopecia was categorized as grade 3 by the investigator despite grade 3 alopecia not being recognized by the NCI Common Terminology criteria. The event outcome was reported as recovered by the investigator.

Thi

Adjudicated Drug-Related Interstitial Lung Disease/Pneumonitis

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd (n = 257)	11 (4.3)	26 (10.1)	2 (0.8)	0	0	39 (15.2)
T-DM1 (n = 261)	4 (1.5)	3 (1.1)	1 (0.4)	0	0	8 (3.1)

- Adjudicated drug-related ILD/pneumonitis rates were similar to other mBC trials with T-DXd[1,2]
- With longer treatment exposure and follow-up, the ILD/pneumonitis rate increased from 10.5% in the PFS interim analysis[3] to 15.2%
  - There were 4 additional grade 1, 8 additional grade 2, and no additional grade 3 events
- The overall incidence of grade 3 events (0.8%) was the same as in the PFS interim analysis[3]
- There were no adjudicated drug-related grade 4 or 5 events

ILD, interstitial lung disease; mBC, metastatic breast cancer; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

1. Modi S et al. *N Engl J Med* 2020; 382(7): 610-21. 2. Powell CA et al. *ESMO Open* 2022; 7(4): 100554. 3. Cortes J et al. *N Engl J Med.* 2022;386:1143-1154.

Thi

DESTINY-Breast02

Randomized phase 3, open-label, multicenter study (NCT03523585)

Key eligibility criteria[a]

- Centrally confirmed HER2-positive (IHC 3+ or IHC 2+/ISH+) unresectable or metastatic breast cancer
- Documented radiographic progression after most recent treatment
- Previously treated with T-DM1

Stratification factors

- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 406)

TPC
Per label (n = 202)
- Trastuzumab / Capecitabine
or
- Lapatinib / Capecitabine

Primary endpoint
- PFS (BICR[b])

Key secondary endpoint
- OS

Secondary endpoints
- ORR (BICR[b])
- DoR (BICR[b])
- PFS (investigator)
- Safety

Exploratory endpoints
- CBR (BICR[b])
- PFS2[c] (investigator)

At data cutoff (June 30, 2022), the median duration of follow-up[d] was:
- **21.5 months** (range, 0.1-45.6 months) in the T-DXd arm
- **18.6 months** (range, 0-45.7 months) in the TPC arm

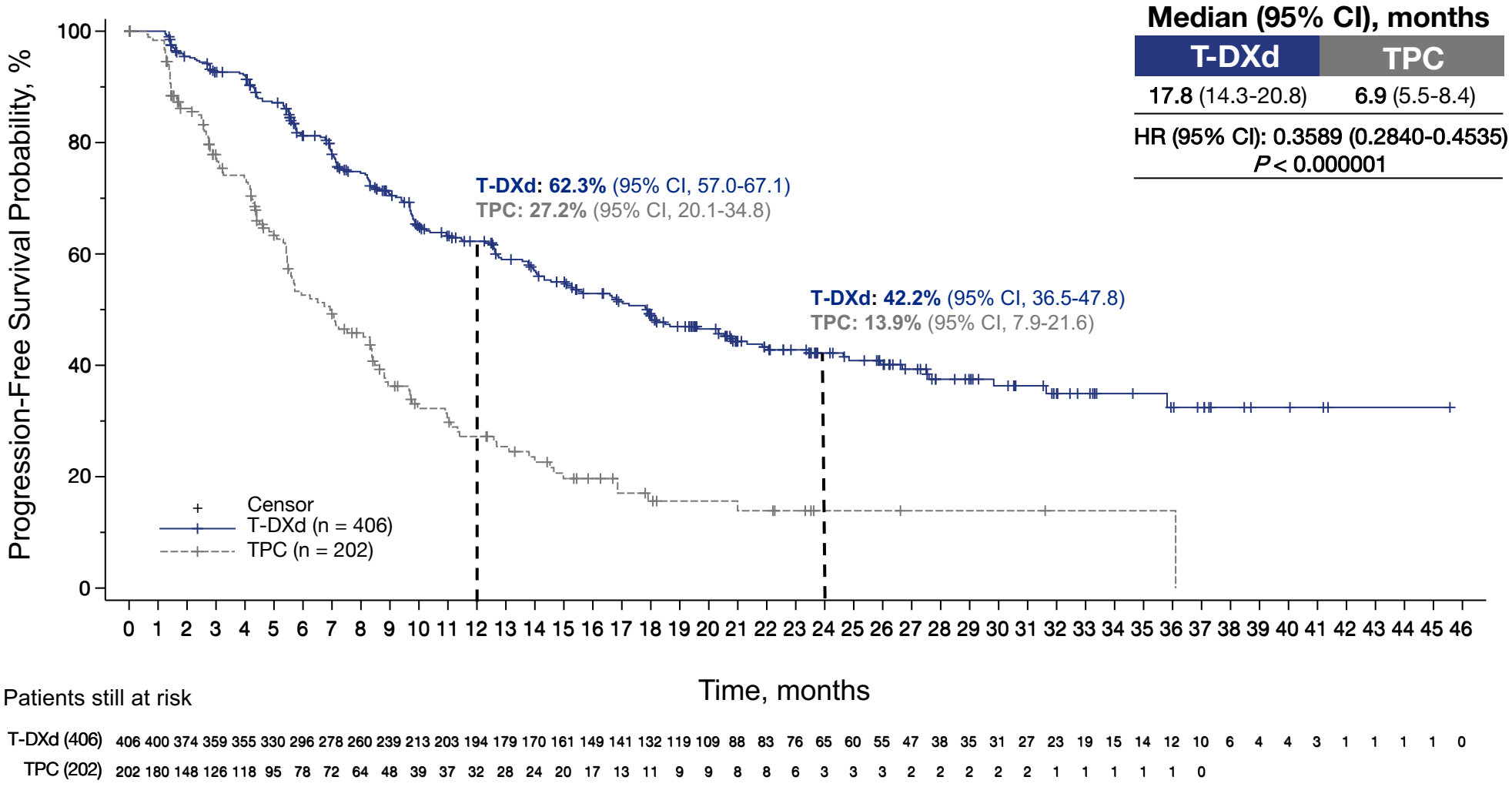
Protocol-prespecified statistical analysis plan

- Primary analysis planned for ~372 BICR PFS events observed or 18 months from the last patient randomized, whichever came first
- Group sequential testing was used to compare OS between treatment groups hierarchically, provided PFS was significant

BICR, blinded independent central review; CBR, clinical benefit rate; DoR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; mRECIST, modified Response Evaluation Criteria in Solid Tumors version 1.1; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2; progression-free survival on the next line of therapy; Q3W, every 3 weeks; R, randomization, T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

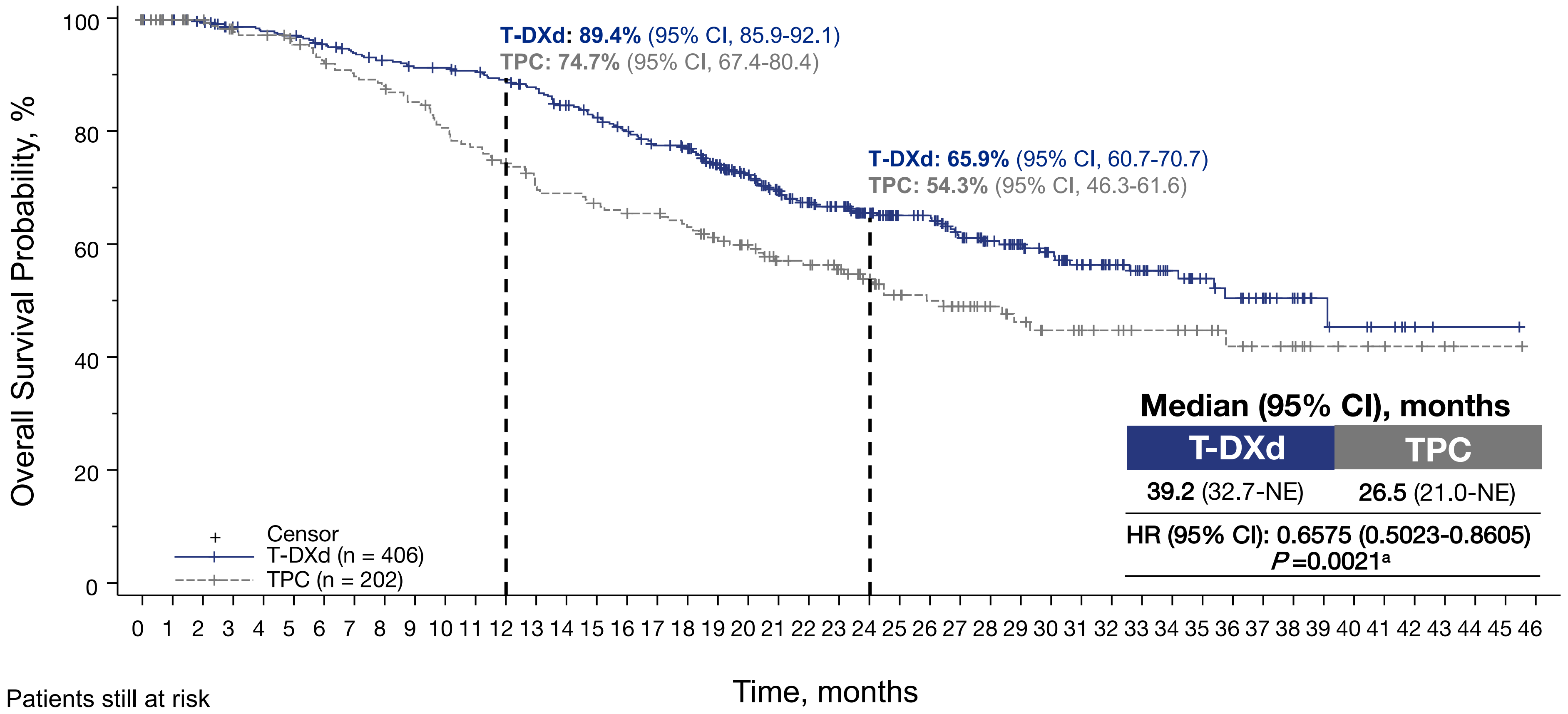
[a]Patients with clinically inactive brain metastases and patients with treated brain metastases that were no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants could be included. [b]BICR assessed per mRECIST 1.1. [c]PFS2 was defined as the time from date of randomization to the first documented progression on the next line of therapy or death due to any cause, whichever came first. [d]Duration of follow up is defined as study duration = the date last known alive minus date of randomization plus 1.

Primary Endpoint: PFS by BICR



BICR, blinded independent central review; HR, hazard ratio; mo, month; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Key Secondary Endpoint: OS



Patients still at risk

T-DXd (406)	406	404	400	390	385	382	374	366	357	352	350	346	339	331	317	306	295	282	277	257	234	215	196	183	160	144	139	122	104	93	82	72	63	51	40	34	29	25	19	10	8	6	3	1	1	1	0
TPC (202)	202	192	187	182	178	173	167	161	157	151	142	136	130	124	118	114	111	110	106	95	89	79	76	72	61	53	50	46	38	33	29	28	25	22	22	18	15	13	12	7	6	5	4	3	1	1	0

In the TPC arm
- **69.3% (140/202) of patients who discontinued therapy received a new systemic anticancer**
- **25.7% (52/202) of patients received T-DXd in the post-trial setting**

[a]The boundary for statistical significance is 0.0040. HR, hazard ratio; mo, month; NE, not estimable; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Adverse Events of Special Interest: ILD and LV Dysfunction

Adjudicated as Drug-related ILD[a]						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 404)	11 (2.7)	26 (6.4)	3 (0.7)	0	2 (0.5)	42 (10.4)
TPC (n = 195)	0	0	1 (0.5)	0	0	1 (0.5)

- Median time to onset of adjudicated drug-related ILD was 209.5 days (range, 41-638 days) with T-DXd

LV dysfunction[b]

- In the T-DXd arm, 18 (4.5%) patients experienced an LV dysfunction event[c]
  - 2 (0.5%) patients had a grade ≥3 event
- In the TPC arm, 3 (1.5%) patients experienced an LV dysfunction[d]
  - 1 (0.5%) patient had a grade ≥3 event

ILD, interstitial lung disease; LV, left ventricular; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]The safety analysis set includes all randomly assigned patients who received at least 1 dose of study treatment. [b]Left ventricular dysfunction included preferred terms of acute left ventricular failure, acute right ventricular failure, cardiac failure, cardiac failure acute, cardiac failure chronic, cardiac failure congestive, chronic left ventricular failure, chronic right ventricular failure, ejection fraction decreased, left ventricular failure, right ventricular failure, ventricular failure, and left ventricular dysfunction. [c]17 ejection fraction decreased (2 grade ≥3), 1 LV dysfunction (grade 1). [d]1 ejection fraction decreased (grade 1), 2 cardiac failure (1 grade ≥3).

Tucatinib – A Potent & Selective HER2 Inhibitor

- Selective small molecular tyrosine kinase inhibitor with nanomolar potency
- HER2 selectivity leads to decreased potential for EGFR-related toxicities compared to dual inhibitors
  - Phase 1 single agent data had no treatment-related g3 diarrhea in heavily pretreated patients
- Penetrates CNS very well

Compound	Cellular Selectivity Data	
	HER2 IC_{50} (nM)	EGFR IC_{50} (nM)
Lapatinib	49	31
Neratinib	7	8
Tucatinib	**8**	**>10,000**

Moulder et al. AACR-NCI-EORTC 2011; Koch et al. AACR 2011

Slide adapted from S Tolaney ASCO 2018

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

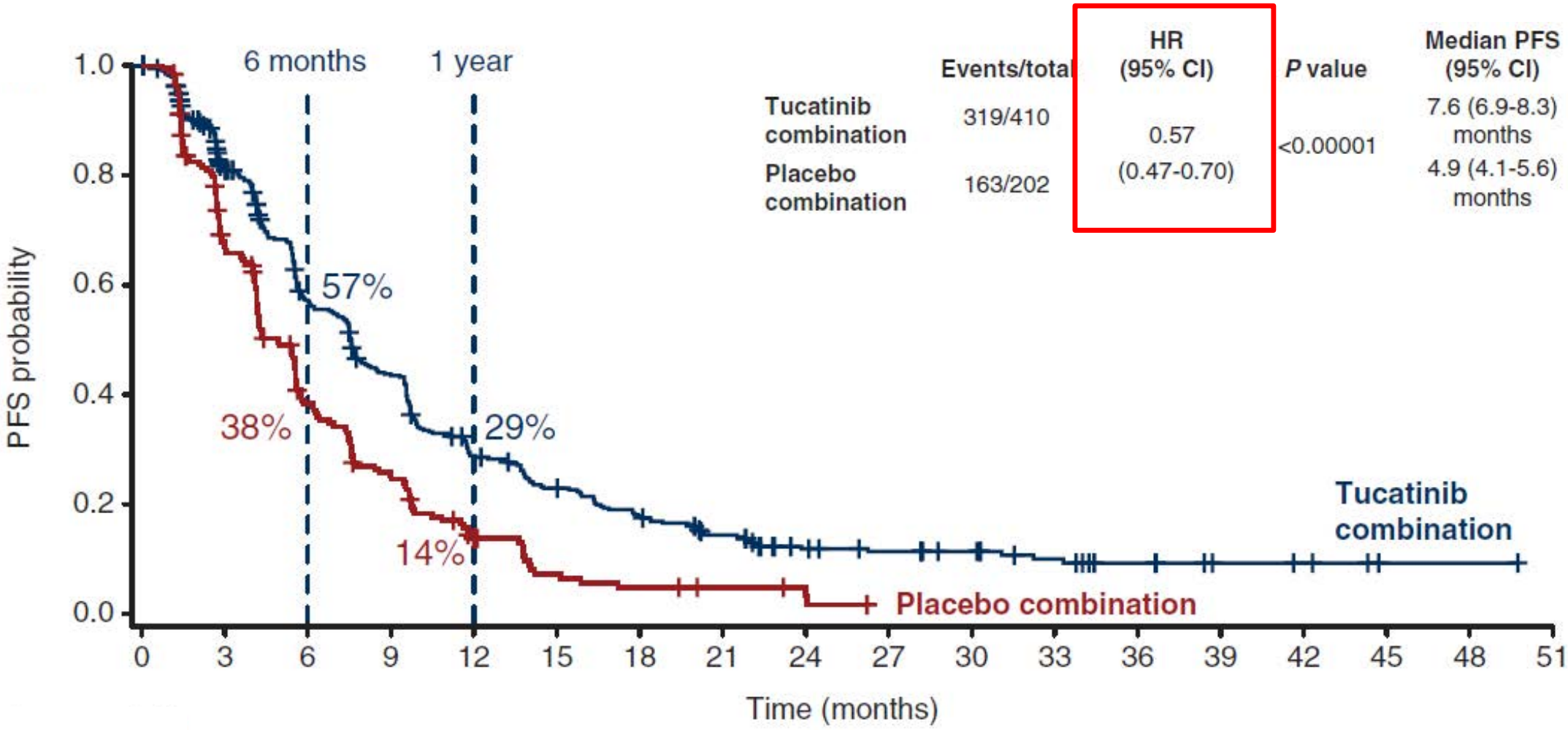
Placebo + Trastuzumab + Capecitabine
(21-day cycle)

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

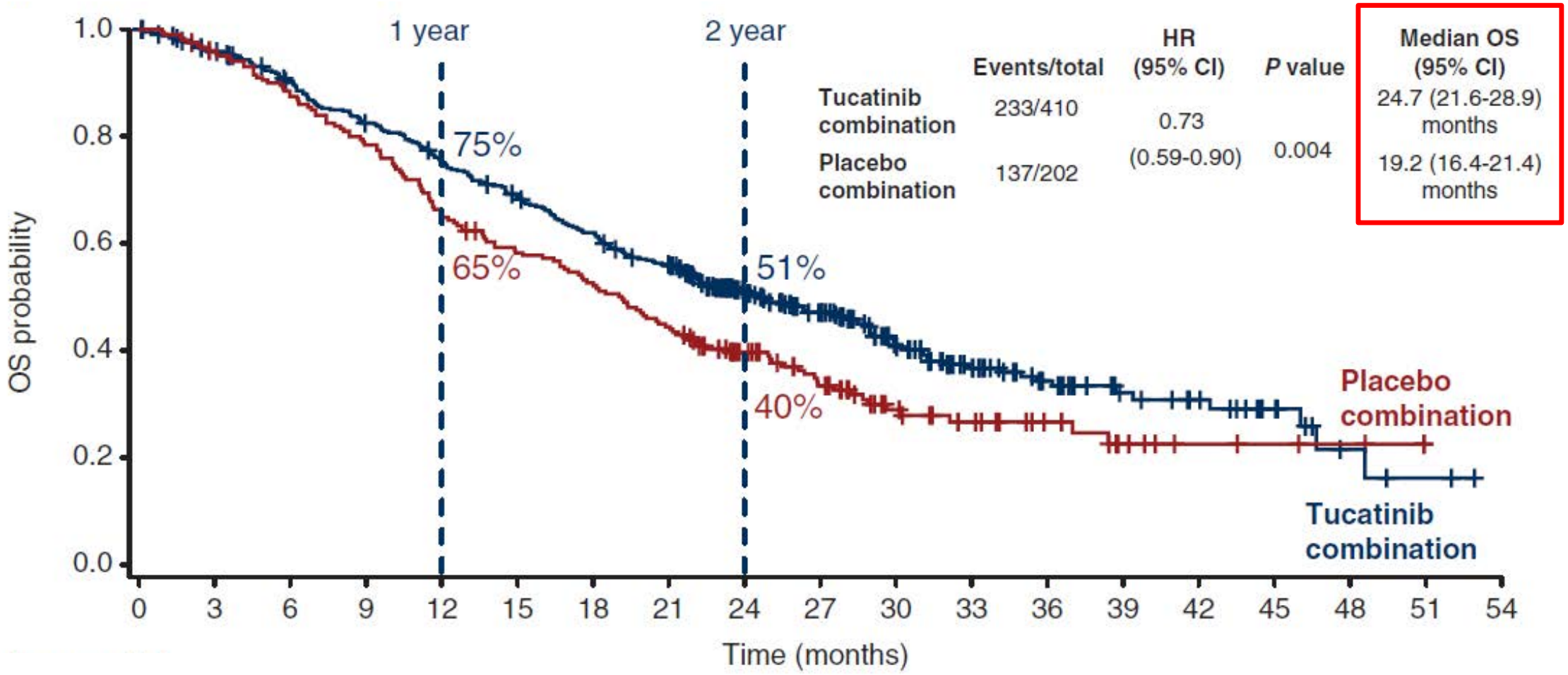
HER2CLIMB Updated PFS results



	Events/total	HR (95% CI)	*P* value	Median PFS (95% CI)
Tucatinib combination	319/410	0.57 (0.47-0.70)	<0.00001	7.6 (6.9-8.3) months
Placebo combination	163/202			4.9 (4.1-5.6) months

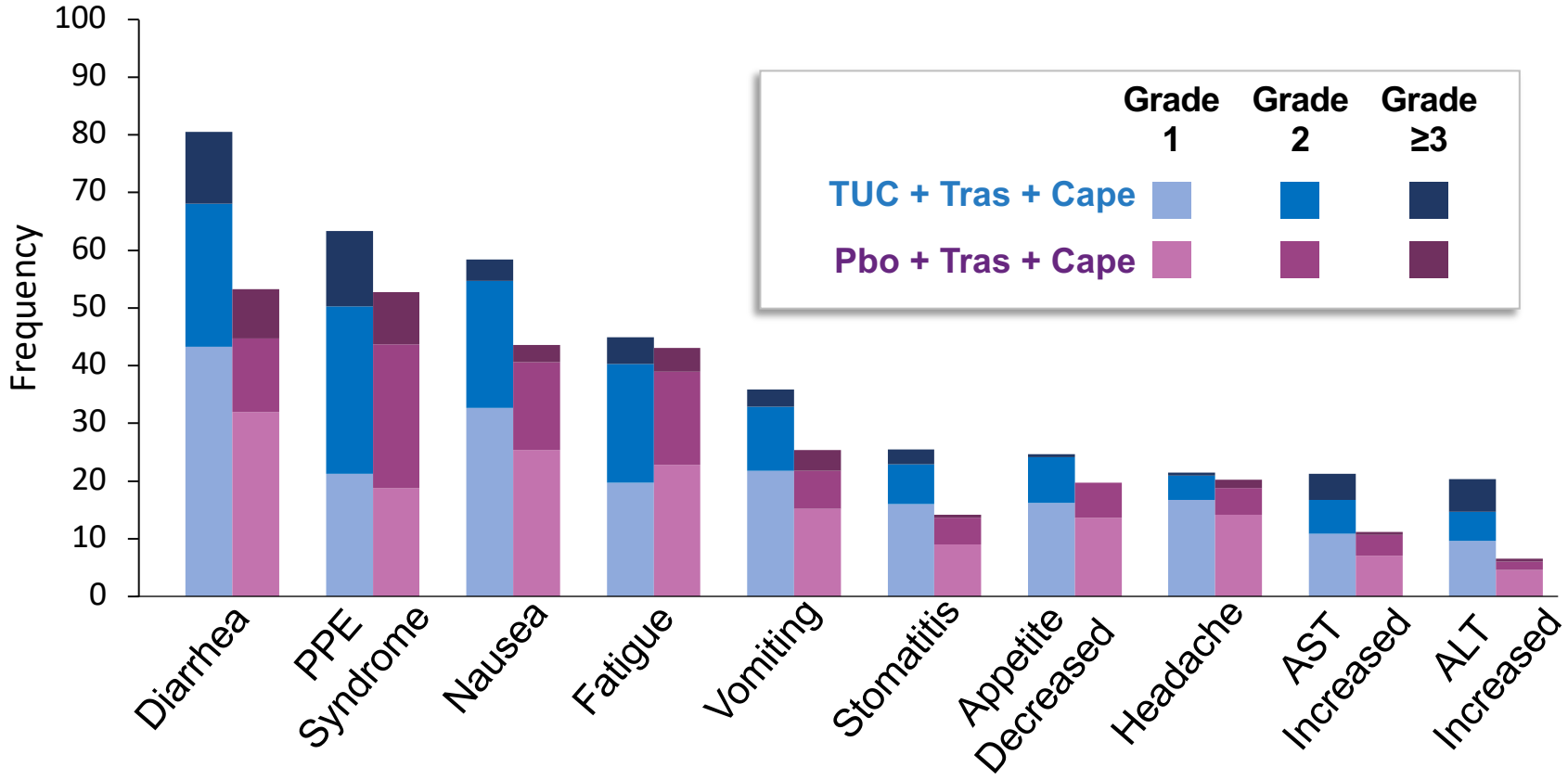
Curigliano et al, Annals Oncology 2022 33:321

HER2CLIMB Updated OS results



Curigliano et al, Annals Oncology 2022 33:321

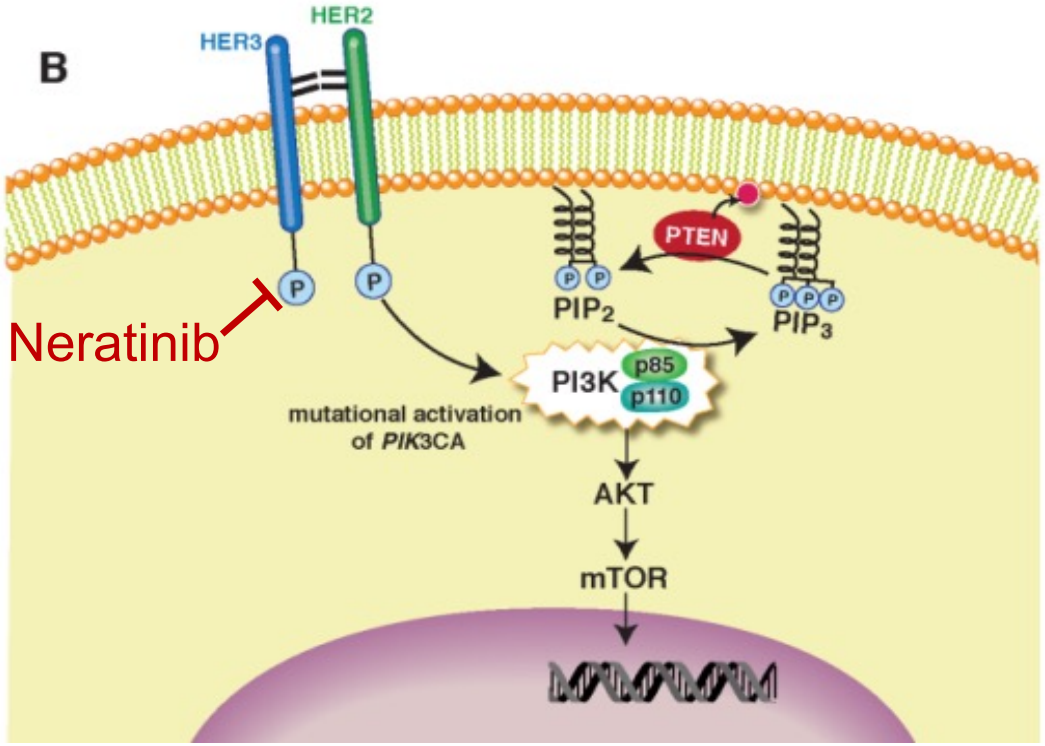
Most Common Adverse Events (≥20% in the Tucatinib Arm)



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

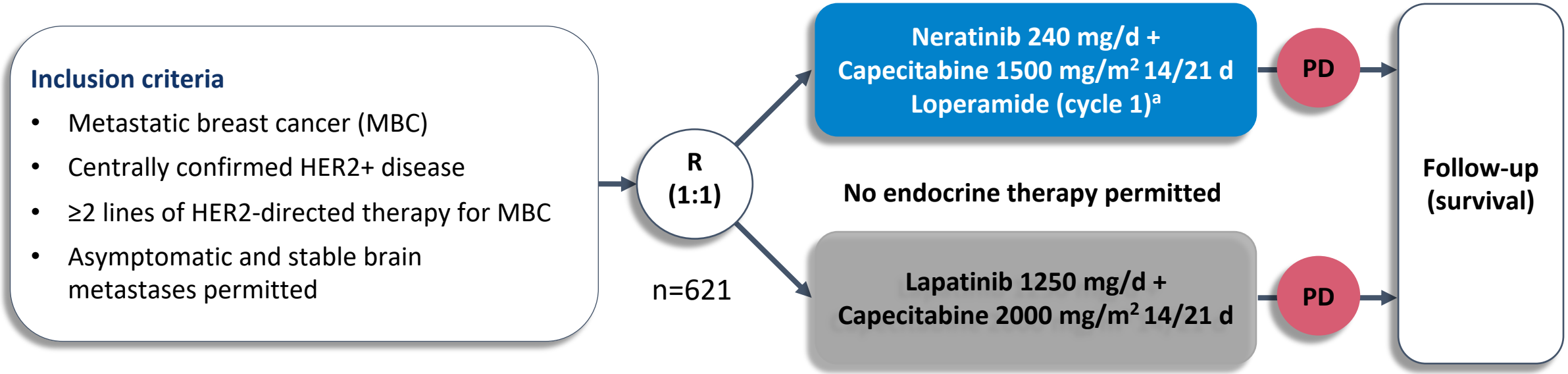
NERATINIB

- Low-molecular-weight, irreversible, pan-HER inhibitor (ErbB1,2,4)
- Significant toxicity: 21% Grade 3-4 diarrhea



Burstein et al
JCO. 2010. 28:1301

NALA study design



Stratification variables

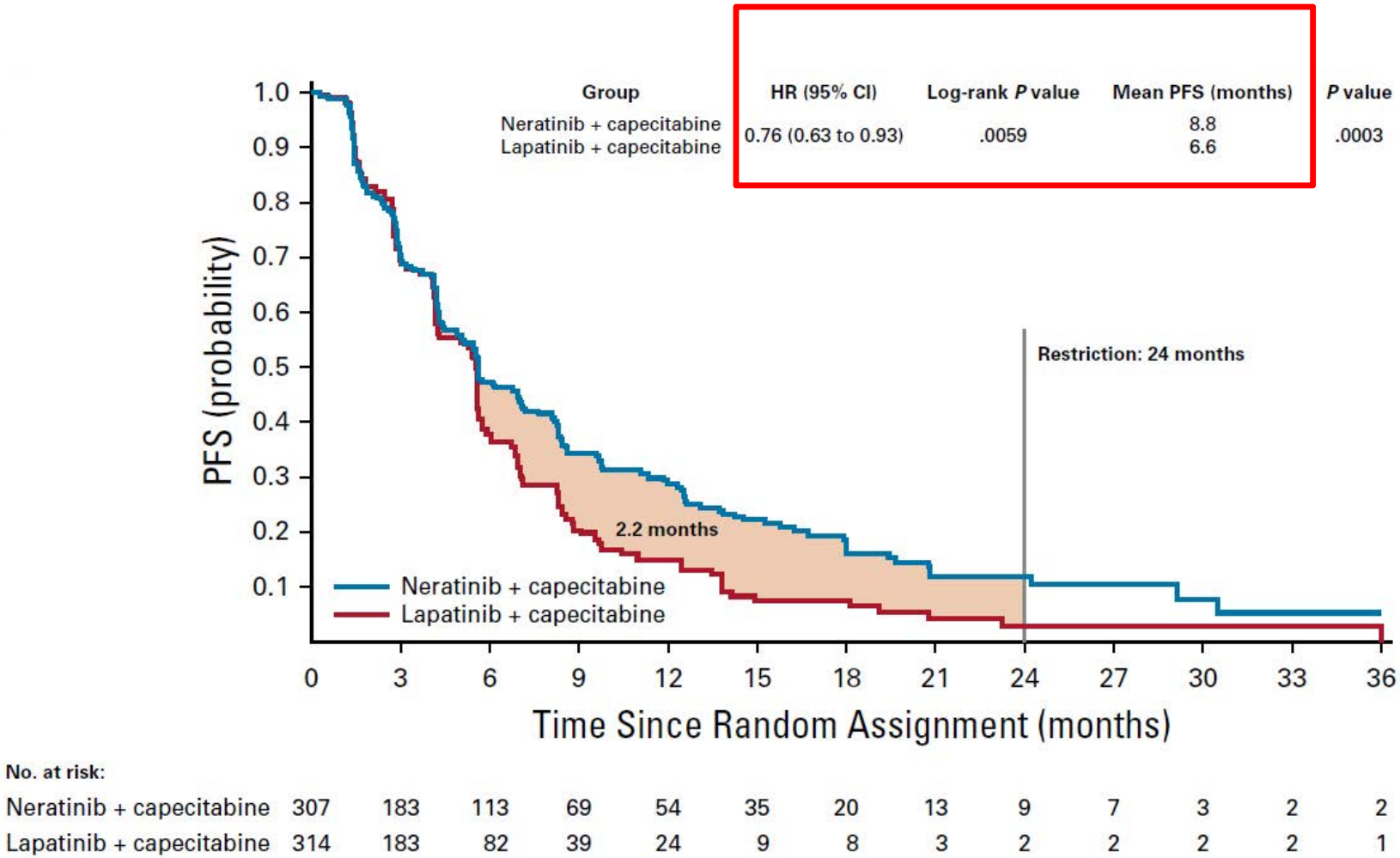
- Number of prior HER2 therapies for MBC
- Disease location
- HR status
- Geographic location

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

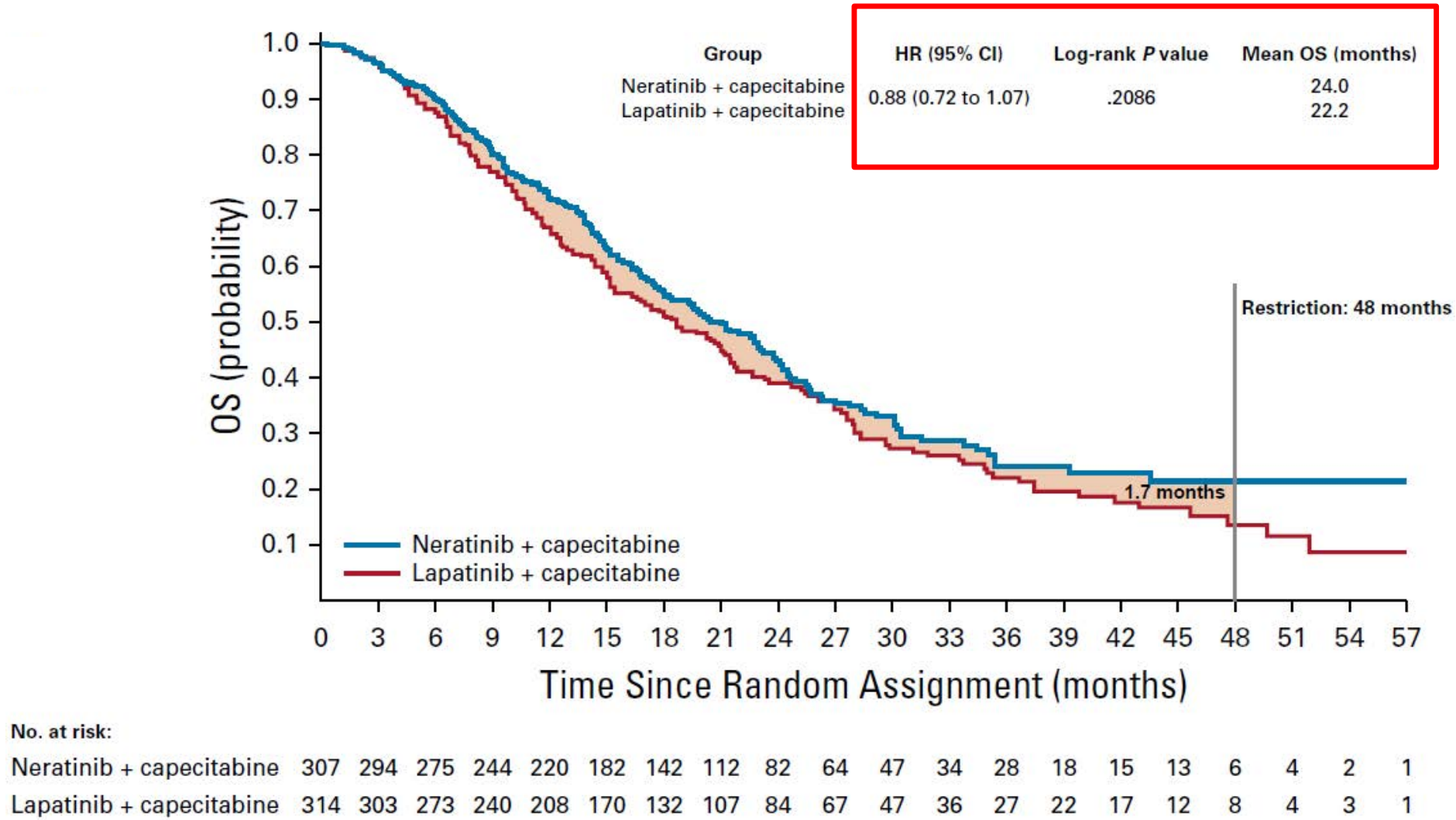


No. at risk:

Neratinib + capecitabine	307	183	113	69	54	35	20	13	9	7	3	2	2
Lapatinib + capecitabine	314	183	82	39	24	9	8	3	2	2	2	2	1

Saura et al, JCO 2020 38:3138

NALA Overall Survival Analysis



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

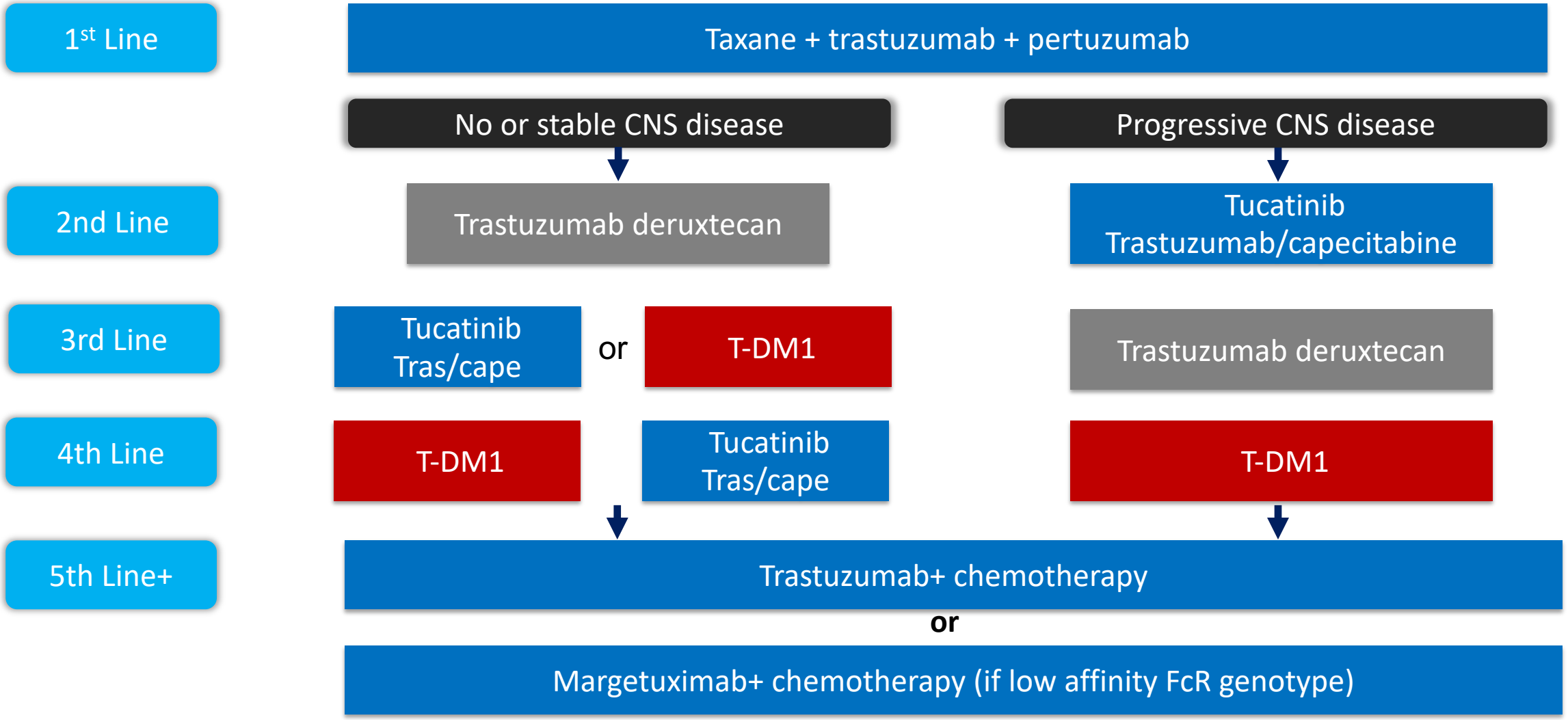
Most frequent grade 3/4 adverse events

	Neratinib + Capecitabine (n=303)		Lapatinib + Capecitabine (n=311)	
	All grade	Grade 3/4	All grade	Grade 3/4
Treatment-emergent AE, %	100	61	99	60
Diarrhea	83	24*	66	13*
Hand-foot syndrome	46	10	56	11
Hypokalemia	12	5	14	6
Nausea	53	4	42	3
Vomiting	46	4	31	2
Fatigue	34	3	31	3
Neutropenia	7	3	5	2
Asthenia	12	3	12	2
Decreased appetite	35	3	22	2
Dehydration	6	2	6	2

Treatment discontinuation due to treatment-emergent AEs: N+C: 10.9%; L+C: 14.5%

*No Grade 4 diarrhea

Approach to Therapy for Metastatic HER2+ disease



Adapted from Modi et al, ESMO 2021

Unanswered questions in HER2+ MBC

- What is the efficacy of T-DM1 after trastuzumab deruxtecan?
- Is there a role for neratinib or pyrotinib?
- What is comparative efficacy of T-DXd vs tucatinib in patients with active brain metastases?

MODULE 3: Management of HER2-Positive Breast Cancer with CNS Metastases — Dr Hamilton

RTP
RESEARCH
TO PRACTICE

Case Presentation: 91-year-old woman with “mild” dementia and ER/PR-negative, HER2 IHC 1+ IDC with symptomatic chest wall recurrence s/p neoadjuvant paclitaxel/trastuzumab and lumpectomy

Dr Alan Astrow (Brooklyn, New York)

RTP
RESEARCH
TO PRACTICE

Case Presentation: 49-year-old woman with a triple-positive, gBRCA2-mutant multifocal IDC with HER2-negative axillary nodes, s/p neoadjuvant TCHP and bilateral mastectomies with significant response in the breast but 49 positive nodes

Dr Zanetta Lamar (Naples, Florida)

RTP RESEARCH TO PRACTICE

Management of HER2-Positive BC with CNS Metastases

Erika Hamilton, M.D.

Director Breast Cancer Research

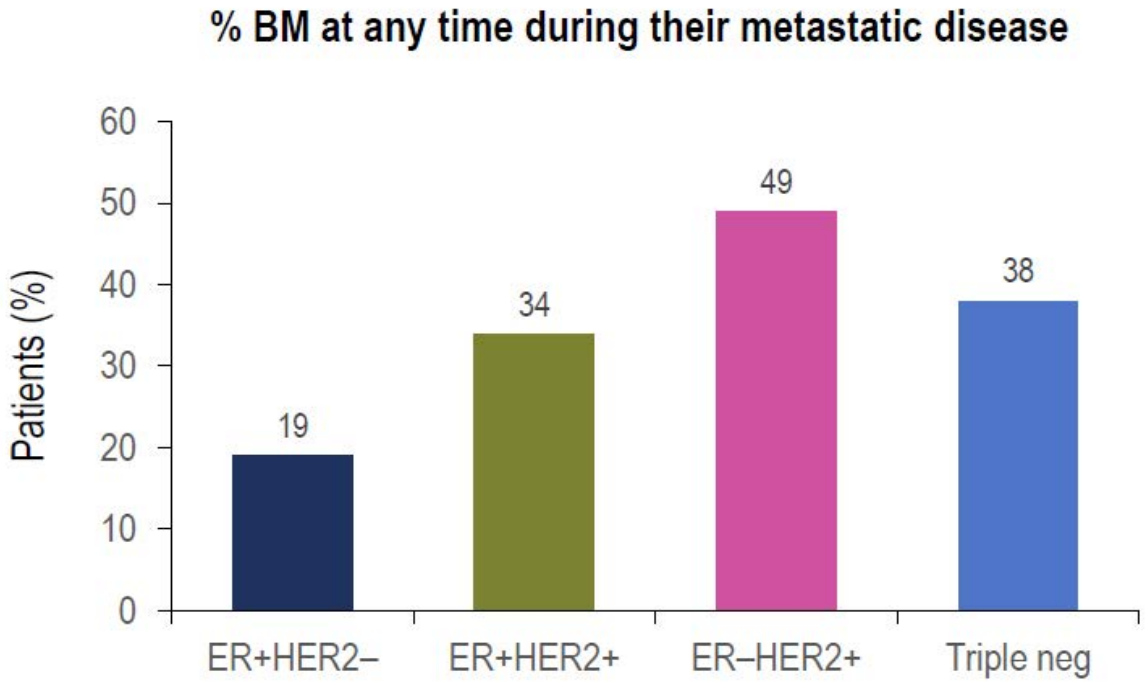
Sarah Cannon Research Institute/Tennessee Oncology

Nashville, TN

SARAH CANNON

Breast cancer and Brain Metastases

- Breast cancer has 2nd highest incidence of brain metastasis among all cancers
- Risk and incidence of brain mets varies depending on BC subtype



- The brain is frequently the 1st site of relapse in HER2+ BC patients treated with trastuzumab, whether administered in the adjuvant or metastatic setting

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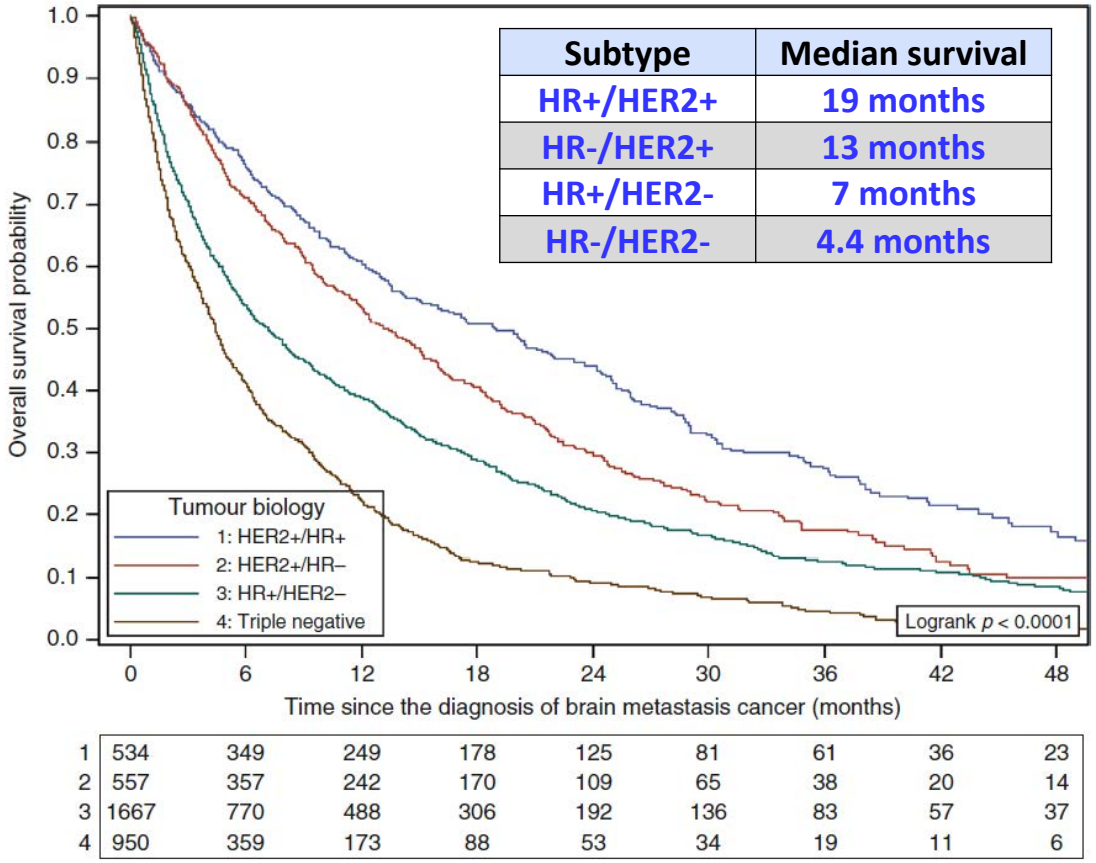
Darlix A, *et al*. Br J Cancer 2019;121:991-1000;
Pasquier D, *et al.* Eur J Cancer 2020;125:22e30.

Survival in BC brain mets patients based on subtype

ESME MBC database
CNS mets cohort (n=4118)



Subtype	Median survival
HR+/HER2+	19 months
HR-/HER2+	13 months
HR+/HER2-	7 months
HR-/HER2-	4.4 months

NCI SEER registry
BCBM cohort (n=1268)

5-year percent survival analysis

	BCBM	All BC
HR+/HER2-	9.8 (6.9-13.3)	86.3 (86.2-86.5)
HR+/HER2+	21.9 (16.0-28.4)	85.6 (85.1-86.0)
HR-/HER2+	14.3 (8.5-21.5)	79.7 (79.0-80.4)
HR-/HER2-	**3.6 (1.6-6.9)**	**71.9 (71.4-72.4)**
All subtypes	11.3 (9.2-13.6)	84.3 (84.1-84.4)

BCBM= breast cancer brain mets

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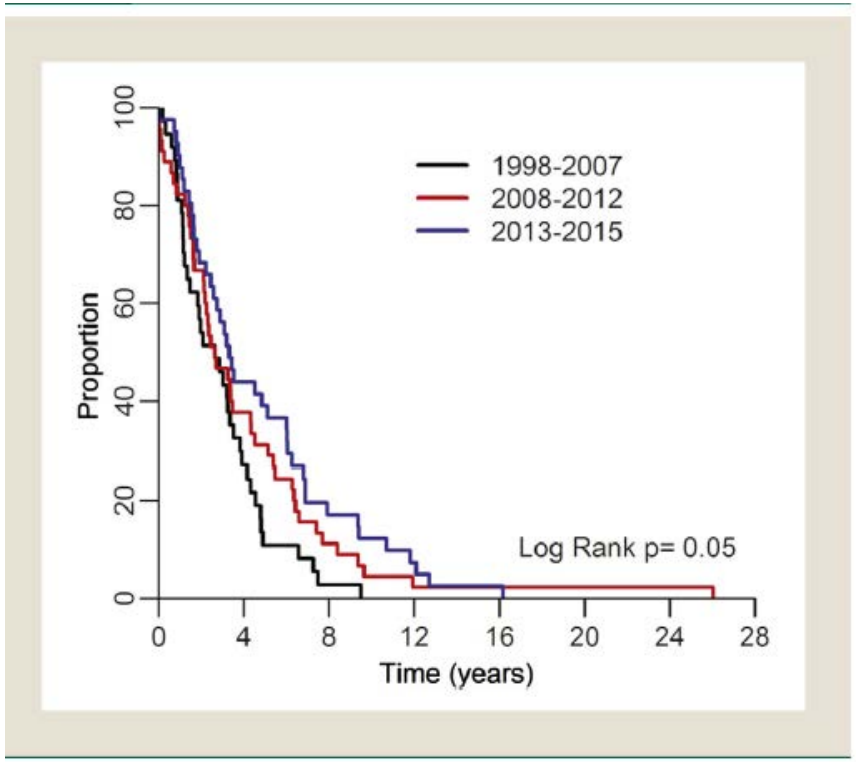
Darlix A, *et al*. Br J Cancer 2019;121:991-1000.
Devanaboyina M. et al. ASCO 2021 Abstract #1031

Brain mets and anti-HER2 therapy



- Time from initial diagnosis of BC→ brain mets: ↑ ~ 9 months from 1998-2007 cohort to 2013-2015 cohort
  - ↑ time from initial diagnosis to metastatic disease
  - ↑ time from 1st metastatic diagnosis to brain mets diagnosis

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Mounsey LA et al. Clinical Breast Cancer 2017; 18:29-37

CNS penetrance of approved agents for HER2+ MBC

Although CSF levels of **neratinib and trastuzumab** are low, there is evidence that it accumulates in the brain tissue

Ratio of trastuzumab levels in serum: CSF 420:1 pre- ***vs.*** 76:1 post-radiation[1]

Accumulation of trastuzumab was 17.5-fold higher in brain metastases than in normal brain tissue[2]

Neratinib levels were very low in CSF(<1.5ng/mL), although it was detected in plasma (34.3ng/mL)[3]

However neratinib has been shown to accumulate in the actual brain tissue, ~10X levels seen in plasma[3]

Tucatinib on the other hand does appear to have greater concentration in CSF

Tucatinib easily found in CSF 0.57- 25ng/mL (IC_{50} of tucatinib against HER2= 3.3ng/mL)[4]

Similar CSF: plasma ratios that are consistent over time[4]

1. Stemmler HJ et . 2007
2. Dijkers EC et al. 2010
3. Freedman RA et al. 2020
4. Stringer-Reasor EM et al. ASCO 2021

HER2- TKIs

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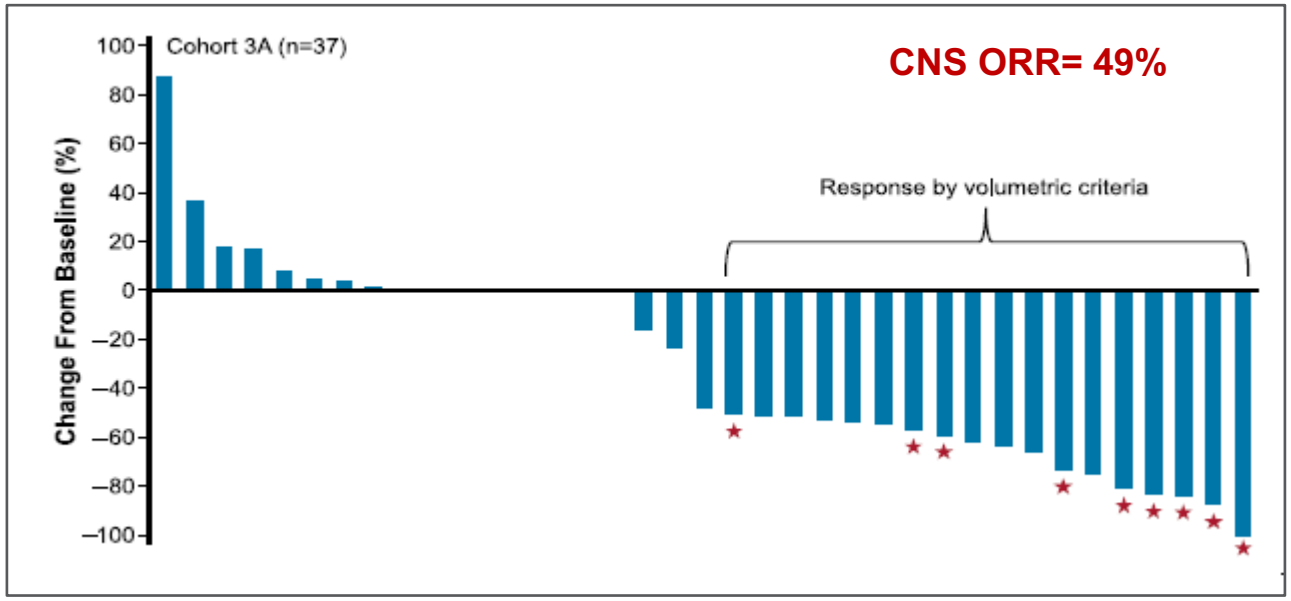
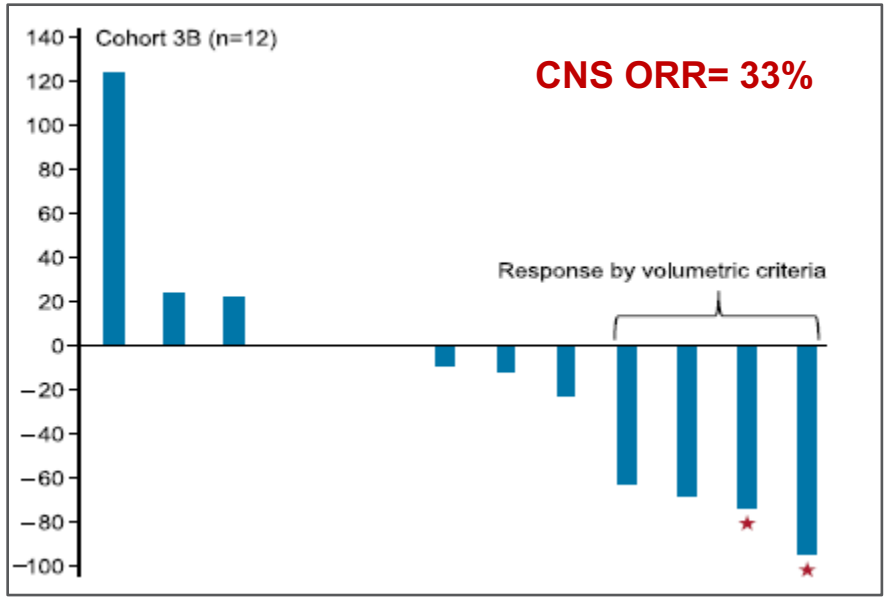
Neratinib+capecitabine for HER2+ BC pts with brain mets

TBCRC 022: Phase II study of Neratinib+capecitabine in HER2+ MBC pts with brain mets

No prior treatment with Lapatinib



Prior treatment with Lapatinib



★ Patients who also had a CNS response by RANO-brain mets criteria

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Freedman RA *et al*. JCO. 2019;37:1081

NALA: Outcomes in patients with CNS disease

NALA: Phase III study of Neratinib+capecitabine vs Lapatinib+capecitabine in HER2+ MBC

Table 1. Efficacy outcomes in patients with CNS disease at baseline

	CNS metastases at baseline (n=101)		
	N+C (n=51)		L+C (n=50)
Progression-free survival[a]			
Hazard ratio (95% CI)		0.66 (0.41–1.05)	
P-value		0.0741	
Restricted mean PFS[b], months	7.8		5.5
Difference, months		2.3	
Overall survival			
Hazard ratio (95% CI)		0.90 (0.59–1.38)	
P-value		0.6352	
Restricted mean OS[b], months	16.4		15.4
Difference, months		1.0	

CNS-specific outcomes	N+C (n=51)		L+C (n=50)
CNS progression-free survival			
Median, months	12.4		8.3
Hazard ratio (95% CI)		0.62 (0.32–1.18)	
P-value		0.143	

81 patients (80.2%) had received prior CNS-directed radiotherapy and/ or surgery

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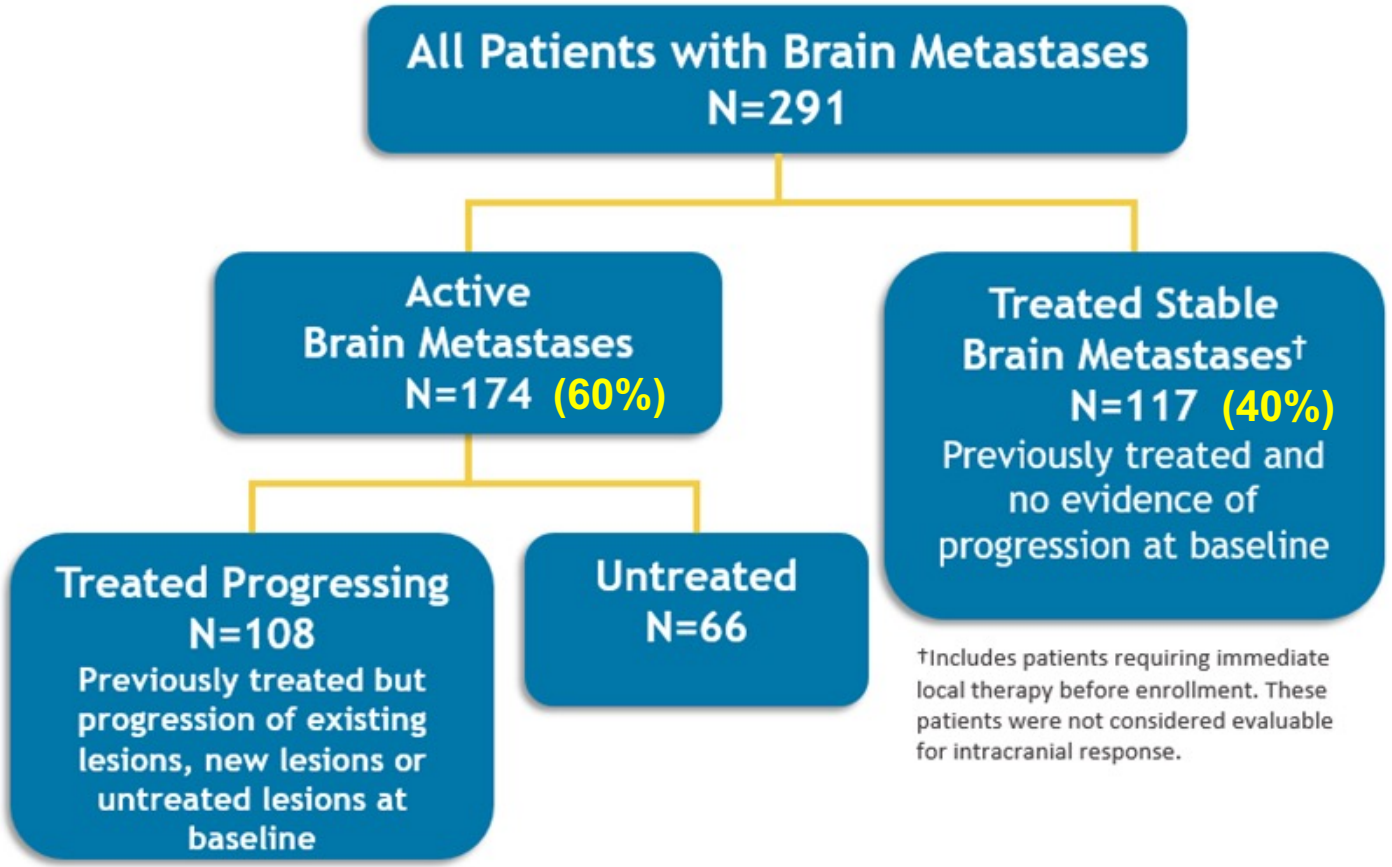
Saura C et al. SABCS 2020 Abstract PD13-09; Hurvitz *Oncologist*. 2021;26(8):e1327-e1338.

HER2CLIMB: CNS mets subset

48% of the patients enrolled on the trial had brain mets

- Brain MRI at baseline for all patients
- Brain MRI for brain metastases patients every 6 weeks in first 24 weeks, every 9 weeks thereafter
- Eligible brain metastases patients:
  - Not requiring immediate local therapy
  - Requiring local therapy during screening could be eligible after washout*



*These patients were included in the Treated Stable group for analysis.

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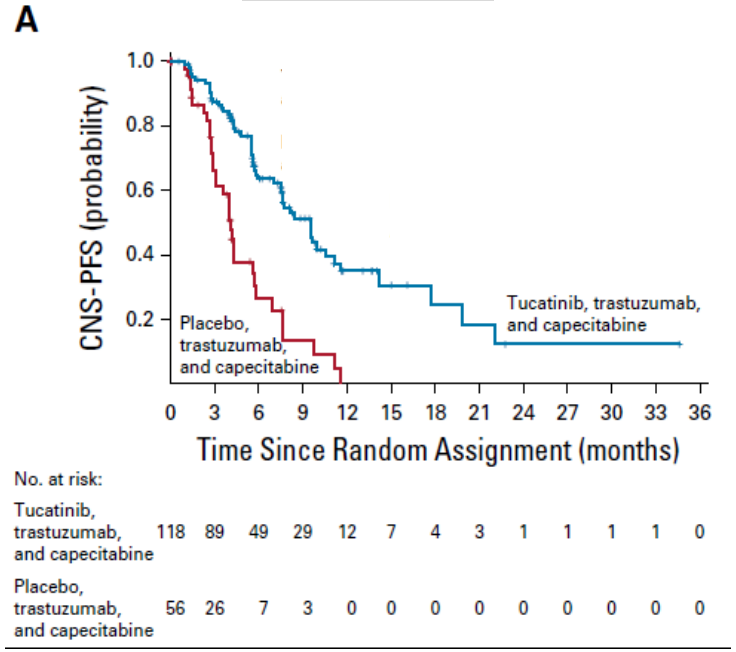
Lin NU et al ASCO 2020

HER2CLIMB: CNS - PFS & OS benefit in patients with brain mets

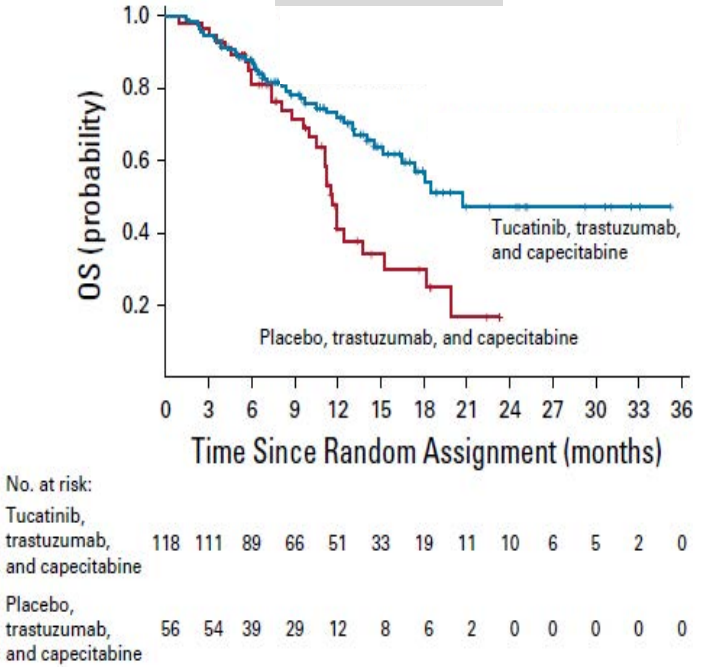
CNS-PFS



	Median PFS (months)
Tucatinib arm	9.5
Placebo arm	4.1
	HR 0.36 p <0.00001

Risk of progression or death in patients with active brain mets was reduced by 64%

CNS-OS



	Median OS (months)
Tucatinib arm	20.7
Placebo arm	11.6
	HR 0.49 p 0.004

Risk of death in patients with active brain mets was reduced by 51%

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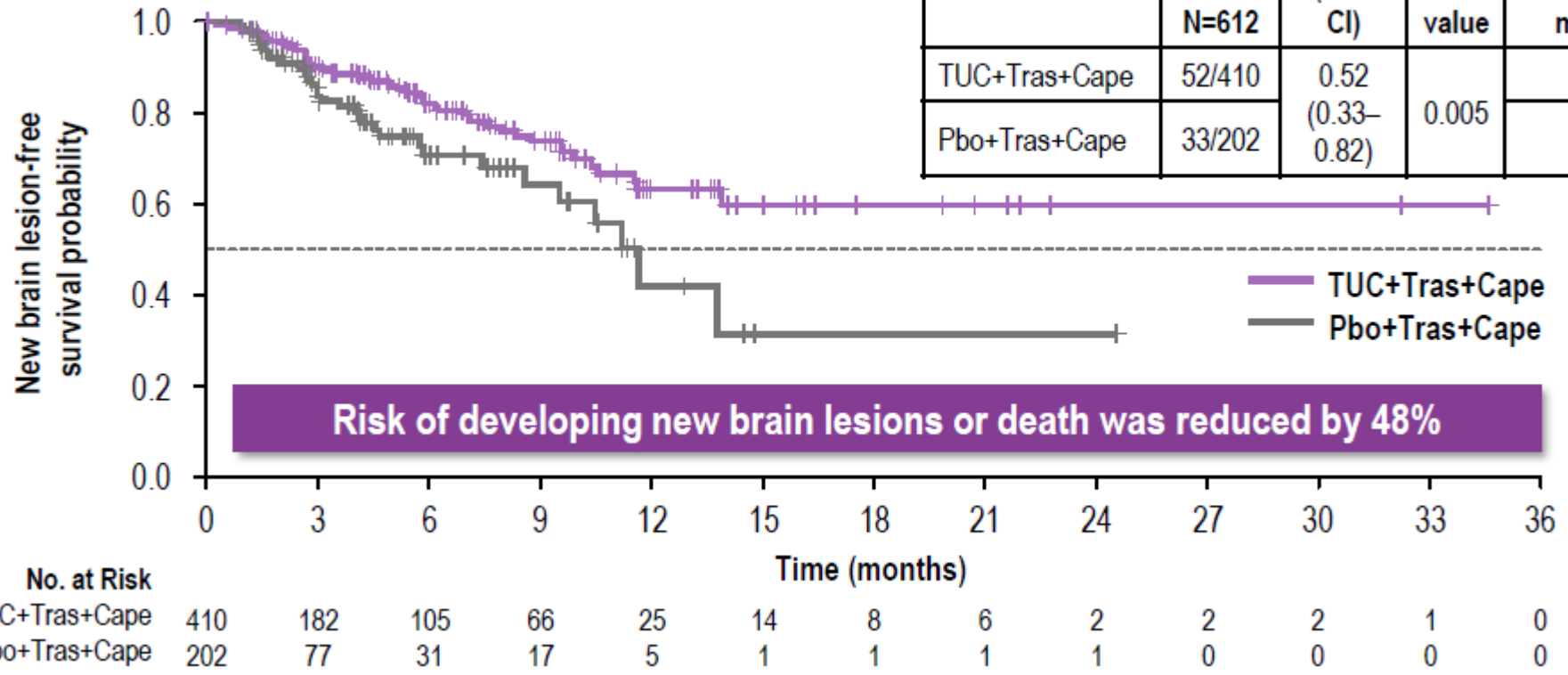
Lin NU et al. JCO 2020

HER2CLIMB: Time to new brain lesions or death (all patients)

	Events N=612	HR (95% CI)	P value	Median new brain lesion-free survival, months (95% CI)
TUC+Tras+Cape	52/410	0.52 (0.33–0.82)	0.005	NR (13.9–NR)
Pbo+Tras+Cape	33/202			11.7 (9.5–NR)



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Bachelot T et al ESMO 2020

HER2-ADCs

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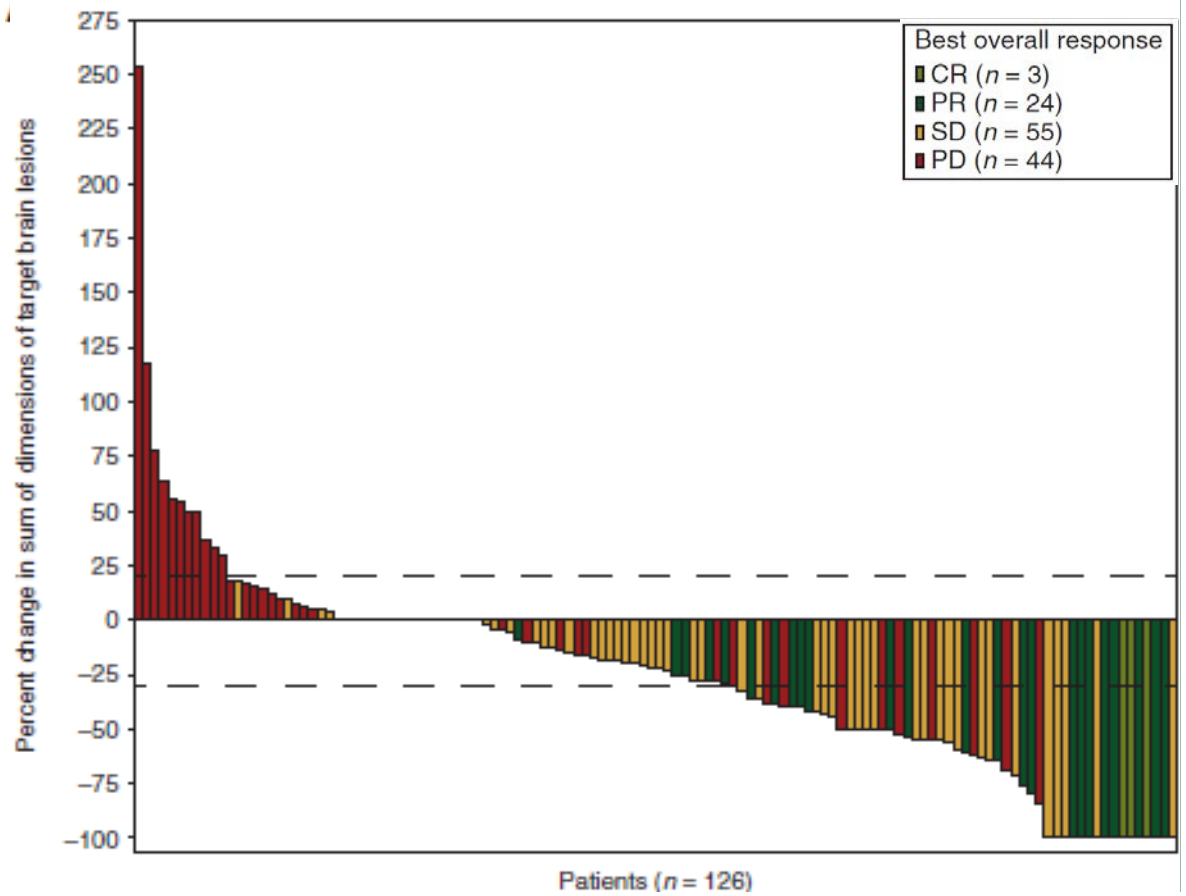
KAMILLA: T-DM1 in HER2+ brain mets subset

Phase IIIb single arm study of T-DM1 in HER2+ MBC pts treated with prior anti-HER2 therapy and chemotherapy (N=2002)

Response of target brain lesions to T-DM1



Exploratory analysis of T-DM1 in subset of patients with measurable brain lesions (n=126)

- ORR: 21.4%
- CBR: 42.9%

- Median PFS*: 5.5 months
- Median OS*: 18.9 months

*n= 398 pts with baseline brain mets

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Montemurro F *et al*. Annals of Onc. 2020;31:1350

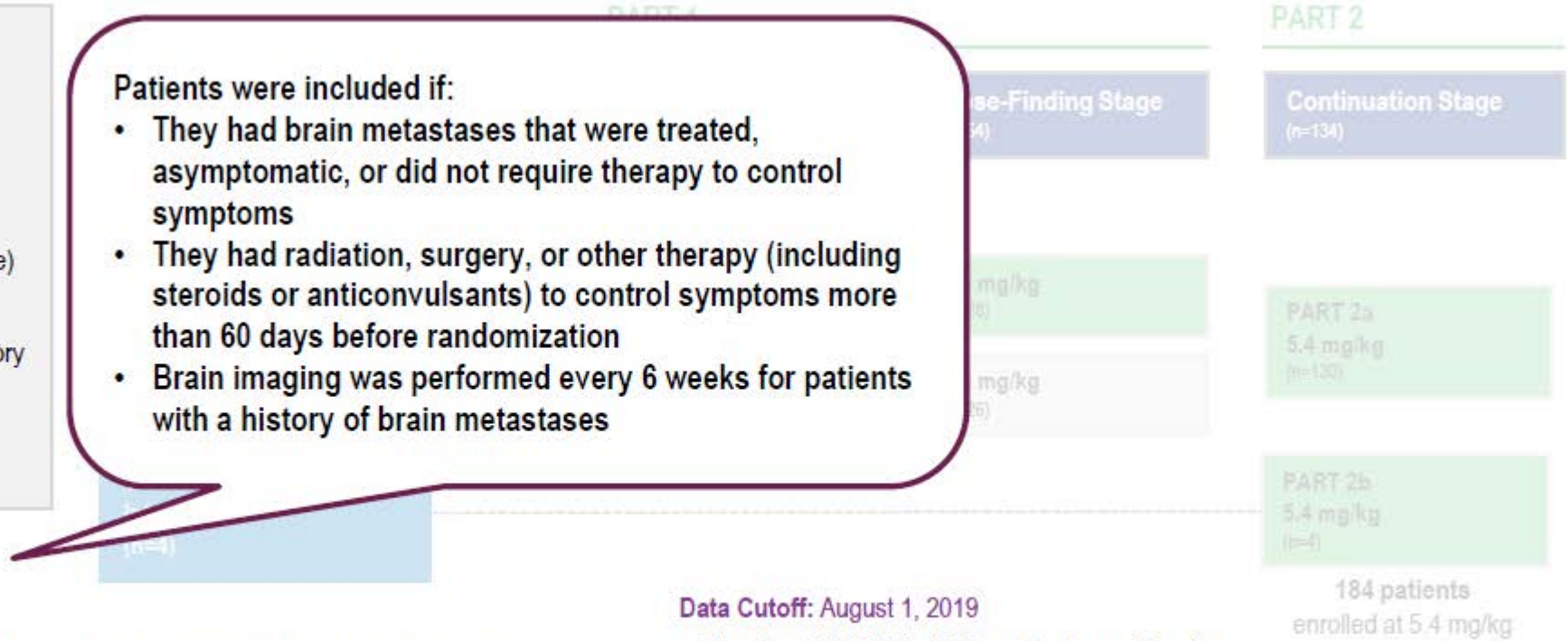
DESTINY Breast-01: CNS Subgroup

Population

- ≥18 years of age
- Unresectable and/or metastatic BC
- HER2 positive (centrally confirmed on archival tissue)
- **Prior T-DM1**
- Excluded patients with history of significant ILD
- Stable, treated brain metastases were allowed

Patients were included if:

- **They had brain metastases that were treated, asymptomatic, or did not require therapy to control symptoms**
- **They had radiation, surgery, or other therapy (including steroids or anticonvulsants) to control symptoms more than 60 days before randomization**
- **Brain imaging was performed every 6 weeks for patients with a history of brain metastases**



Endpoints

- **Primary:** confirmed ORR by independent central imaging facility review per RECIST v1.1
- **Secondary:** investigator-assessed ORR, DCR, DOR, CBR, PFS, OS, PK and safety

Data Cutoff: August 1, 2019

- **24 patients (13.0%) had CNS metastases at baseline**
  - 11 (45.8%) ongoing
  - 13 (54.2%) discontinued, primarily for progressive disease (6/24, 25.0%)

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Jerusalem G et al ESMO Breast 2020

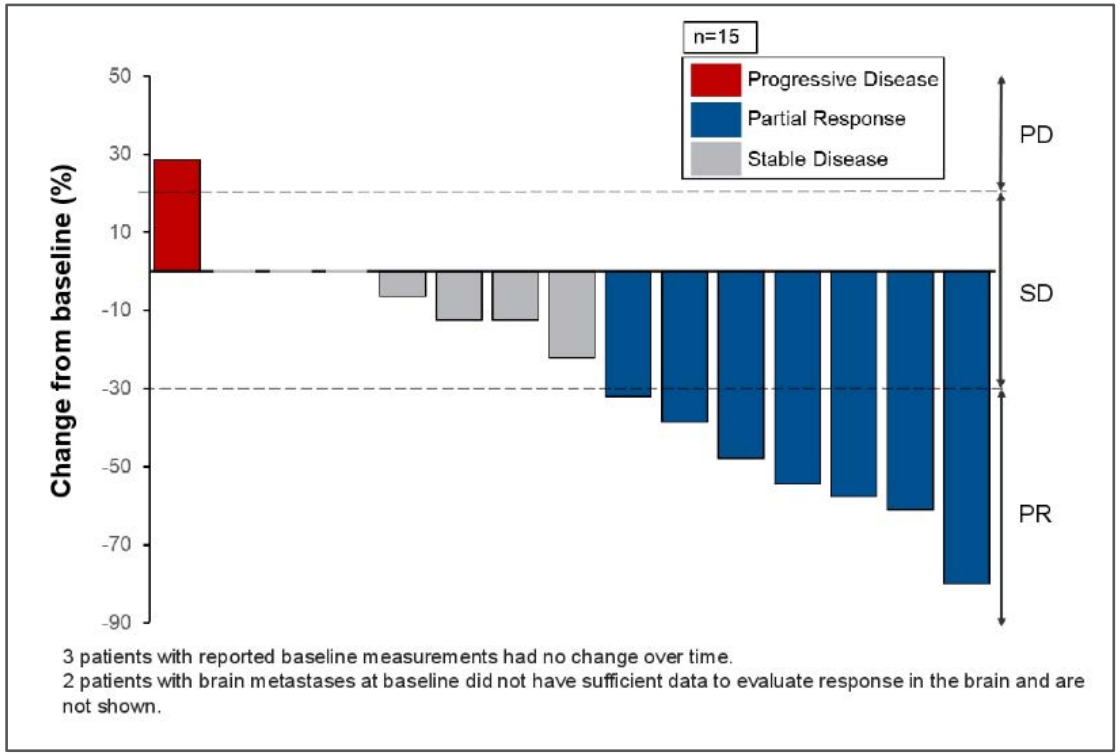
DESTINY Breast-01: Efficacy of T-DXd

Intent-to-treat analysis	CNS subgroup† (n=24)	All patients (N=184)
Confirmed ORR by ICR, % (n) [95% CI]	**58.3 (14)** [36.6–77.9]	**60.9 (112)** [53.4–68.0]
CR	4.2 (1)	6.0 (11)
PR	54.2 (13)	54.9 (101)
SD	33.3 (8)	36.4 (67)
PD	4.2 (1)	1.6 (3)
Not evaluable	4.2 (1)	1.1 (2)
DCR, % (95% CI)	91.7 (22)	97.3 (93.8–99.1)
Median duration of response, months (95% CI)	16.9 (5.7–16.9)	14.8 (13.8–16.9)
Median time to response, months (95% CI)	2.8 (1.3–4.1)	1.6 (1.4–2.6)
Median PFS, months (95% CI)	18.1 (6.7–18.1)	16.4 (12.7–NE)

Jerusalem G et al ESMO Breast 2020

DESTINY Breast-01: Efficacy with T-DXd

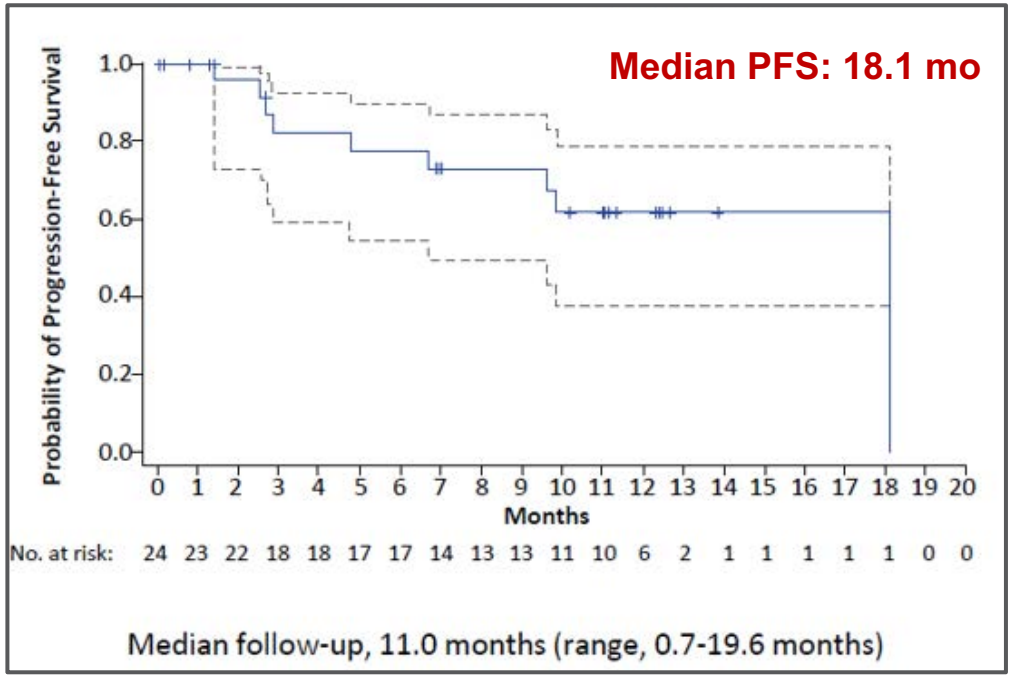
Best response in brain lesions in CNS subgroup[1]



CNS subgroup N=24
Brain lesions at BL n=17
Evaluable for response in brain n=15

❖ 7/17 pts with brain lesions at BL had a PR in CNS lesions (41.2%)

PFS in CNS subgroup[2] (n=24)



- Confirmed ORR in CNS subgroup: 58.3%
- Median DoR in CNS subgroup: 16.9 months

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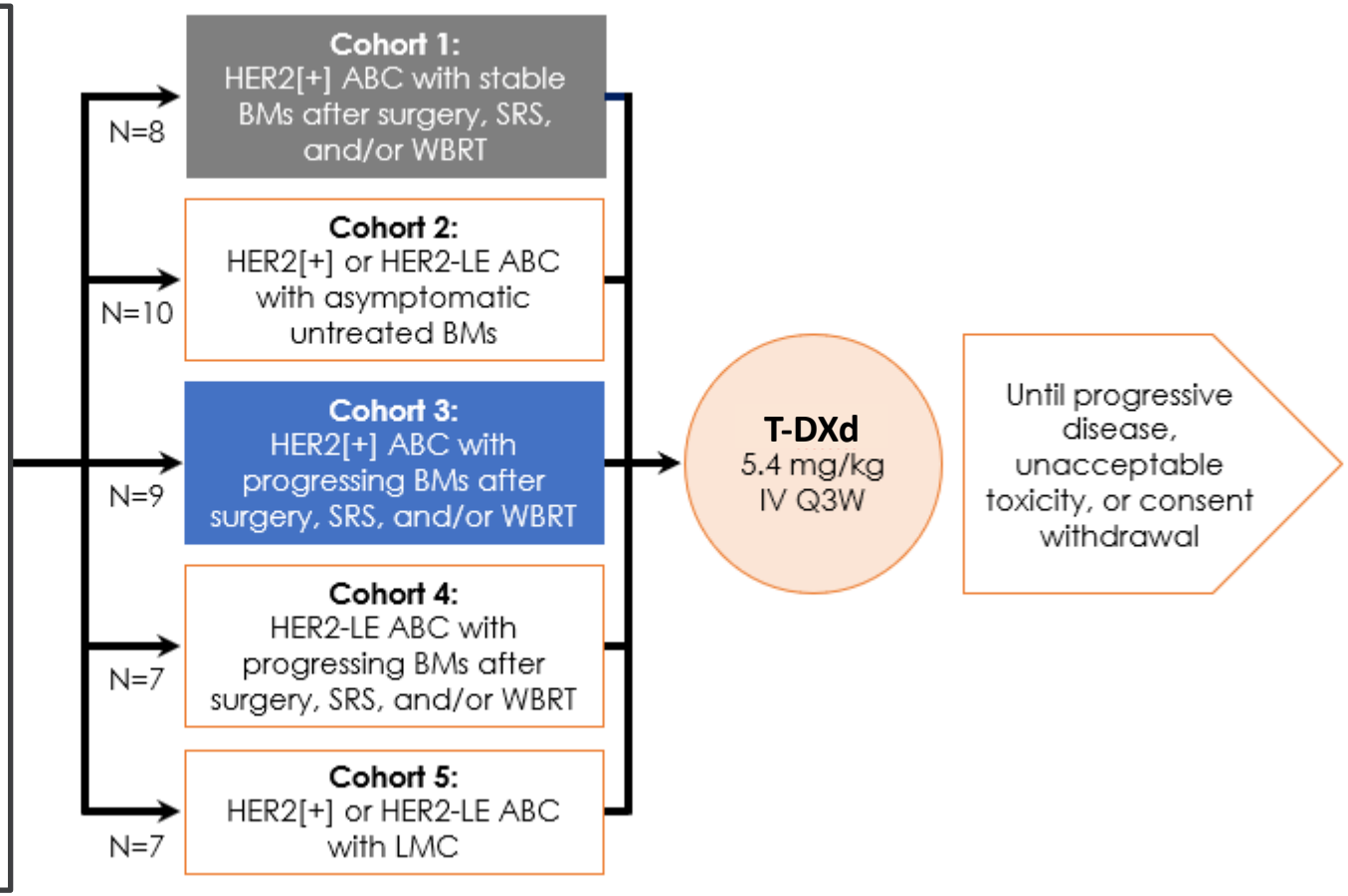
1. Jerusalem G et al ASCO 2021; Abstract 526
2. Jerusalem G et al ESMO Breast 2020

DEBBRAH: Ph 2 trial of T-DXd in pts with HER2+/ HER2-low MBC & history of brain mets

Cohorts 1 and 3 enrolled patients with **HER2+ MBC** and stable or progressing brain mets respectively

- HER2+ /HER2-low MBC with stable or active brain mets and/or leptomeningeal disease
- Pts with HER2+ MBC
  - Prior tx with a taxane and ≥1 prior line for MBC
- Pts with HER2-low MBC
  - ≥1 prior line of chemo for MBC
- Cohorts 2, 3, 4: Measurable brain lesions
- Cohort 5: LMC with CSF+ cytology



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Vaz Batista M et al. SABCS 2021

DEBBRAH: Outcomes & Safety

Efficacy in Cohort 1 (stable brain mets)

1. **7/8 pts (87.5%) alive without PD at 16 weeks**
   Trial met primary EP

2. **At data cut-off 5/8 pts had not experienced progression or death**

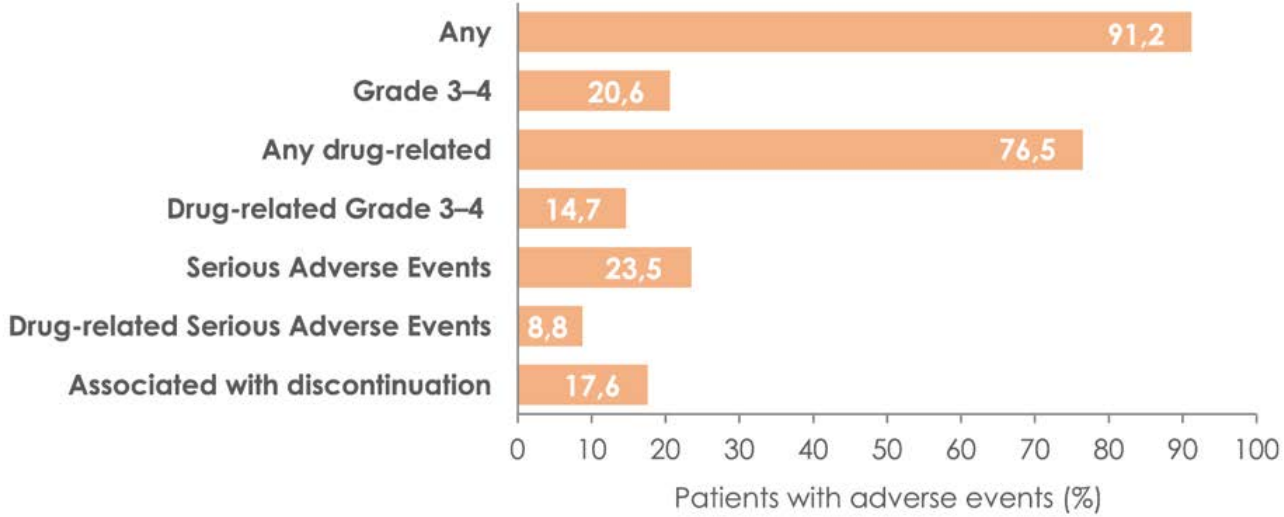
Efficacy in Cohort 3 (progressing brain mets)

1. **ORR-IC reported in 4/9 pts (44.4%)**
   Trial met primary EP

2. **CBR-IC: 55.6%**

3. **At data cut-off 4/9 pts had not experienced progression or death**

Safety (Cohorts 1-5)



T-DXd demonstrated preliminary efficacy with manageable toxicity in pts with HER2+ MBC with brain mets

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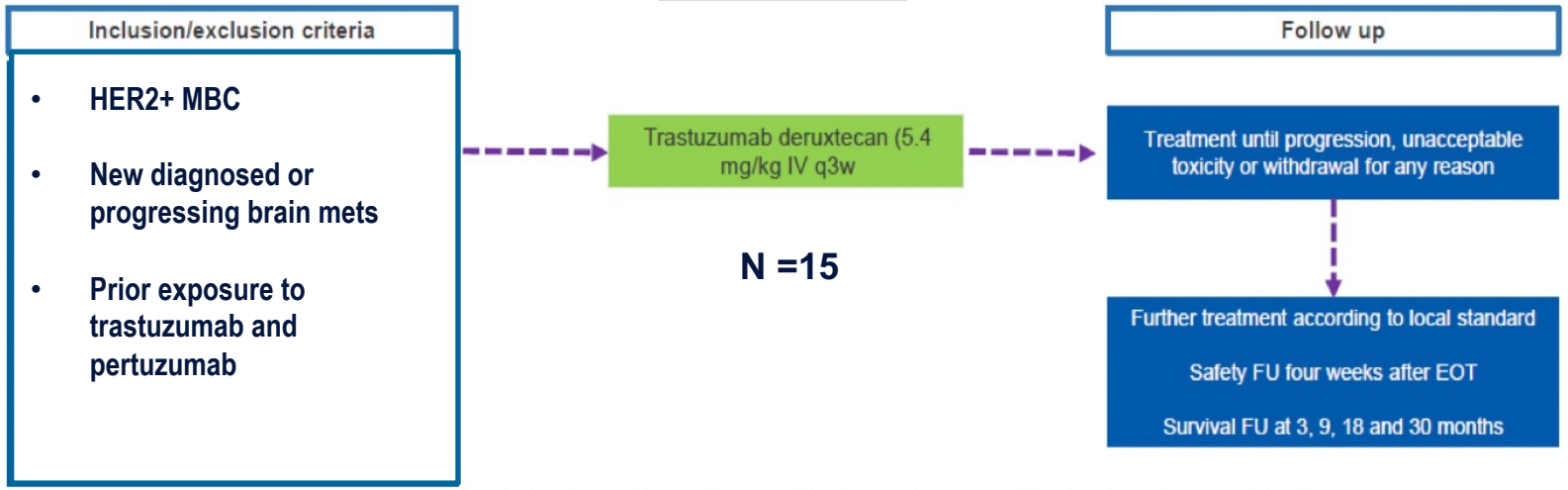
Vaz Batista M et al. SABCS 2021

TUXEDO-1: T-DXd in pts with HER2+ BC & active brain mets

Study schema



BM, brain metastasis; BW, body weight; CNS, central nervous system; D1, day 1; EOT, end of treatment; FU, follow up; IV, intravenous; KPS, Karnofsky performance; LVEF, left ventricular ejection fraction; q3w, once every 3 weeks; RANO, response assessment in neuro-oncology; T-DXd, trastuzumab deruxtecan.
EudraCT: 2020-000981-41.

Primary Endpoint: ORR (CNS) by RANO-BM criteria
Secondary Endpoints:
- Clinical Benefit Rate (CR+PR+SD ≥6 months)
- Extracranial Response rate
- PFS
- OS
- Safety
- Quality of Life

Patient population (n=15)

Visceral mets	**80%**
Progressive brain mets*	**60%**
Untreated brain mets	**40%**
Prior T-DM1	**60%**
Prior lapatinib	**26.7%**

* After local therapy

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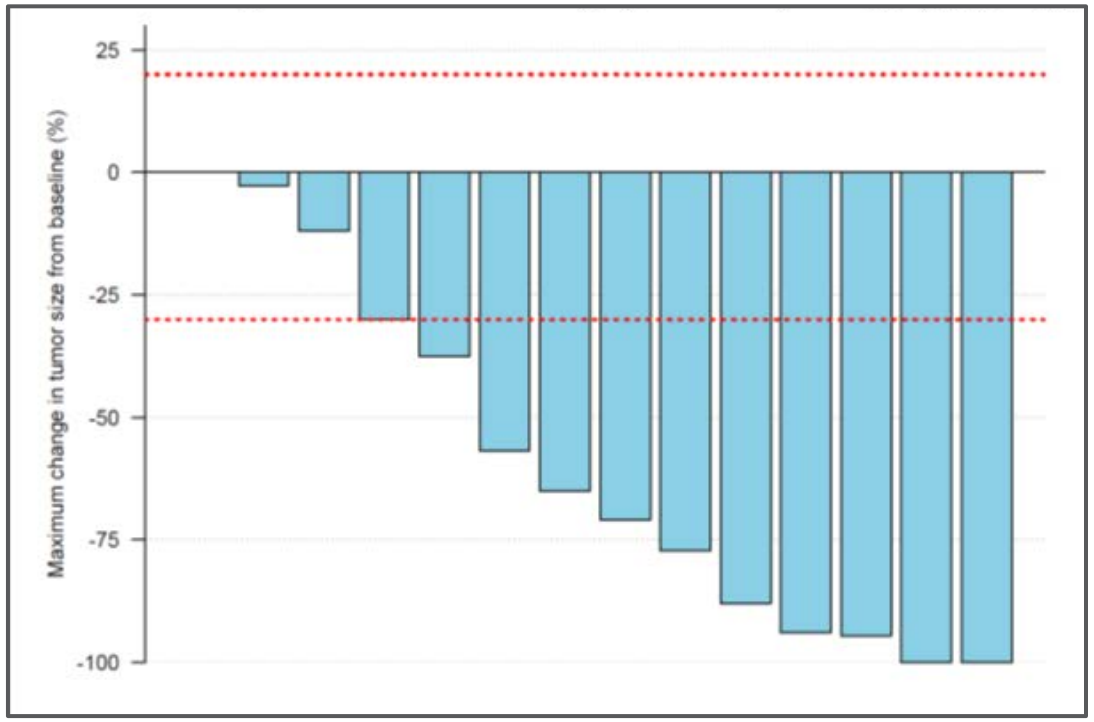
Bartsch R et al. ESMO Breast 2022

TUXEDO: Efficacy endpoints

ORR by RANO-BM criteria (Primary EP)



ORR (ITT population; *n*=15): 73.3% (95% CI 48.1-89.1)

Secondary Endpoints

Median follow-up: 11 months (range 3 – 17 months)

1. **PFS: 14 months (95% CI 11.0-n.r.)**

2. **CBR*: 86.7% (13/15) in ITT**
   CBR: 92.9% (13/14) in PP**

3. **Extracranial response rate:**
   Pts. with extracranial metastases at BL (*n*=13):
   PR 5/13 (27.8%)
   Pts with measurable extracranial disease at BL (*n*=8):
   PR 5/8 (62.5%)

4. **Median OS: Not reached**

- Study met primary EP
- No new safety signals reported (EF decrease G3 in 1 pt; ILD G2 in 1 pt)
- QoL maintained during treatment duration

* CR+PR+SD ≥6 months
** Per protocol population

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Bartsch R et al. ESMO Breast 2022

Select ongoing trials in HER2+ BC w/ brain mets

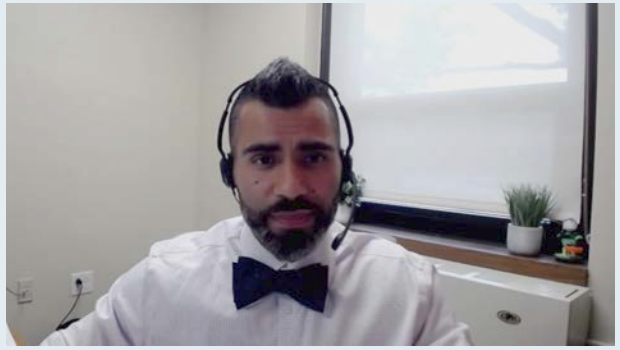
- DESTINY Breast 07: Evaluating T-DXd and T-DXd + Tucatinib in pts with active brain mets (NCT04538742)
- DESTINY Breast-12: T-DXd in pretreated HER2+ MBC patients w/ or w/o brain mets (NCT04739761)
- GDC-0084 (dual PI3K/mTOR inhibitor) +Trastuzumab for pts with HER2+ BC brain mets (NCT03765983)
- HER2-CAR T cells for pts with brain or leptomeningeal mets from HER2+ BC (NCT03696030)
- Dendritic cell vaccines against HER2/HER3 + pembrolizumab for pts with HER2+ BC & brain mets (NCT04348747)

MODULE 4: Recent Appreciation of HER2 Low as a Unique Disease Subset; Future Directions in the Management of HER2-Positive and HER2-Low Breast Cancer — Dr Modi

RTP
RESEARCH
TO PRACTICE

Dr Kelly Yap
(Arcadia, California)

Case Presentation: 39-year-old premenopausal woman with a triple-positive IDC who develops brain metastases while receiving THP



Dr Rohit Gosain
(Jamestown, New York)

Case Presentation: 67-year-old woman with an ER/PR-negative, HER2-positive IDC who develops brain metastases s/p first-line THP and second-line T-DM1

RTP
RESEARCH
TO PRACTICE

Case Presentation: 65-year-old woman with ER/PR-negative, HER2-positive mBC treated with paclitaxel/trastuzumab, then T-DXd on progression

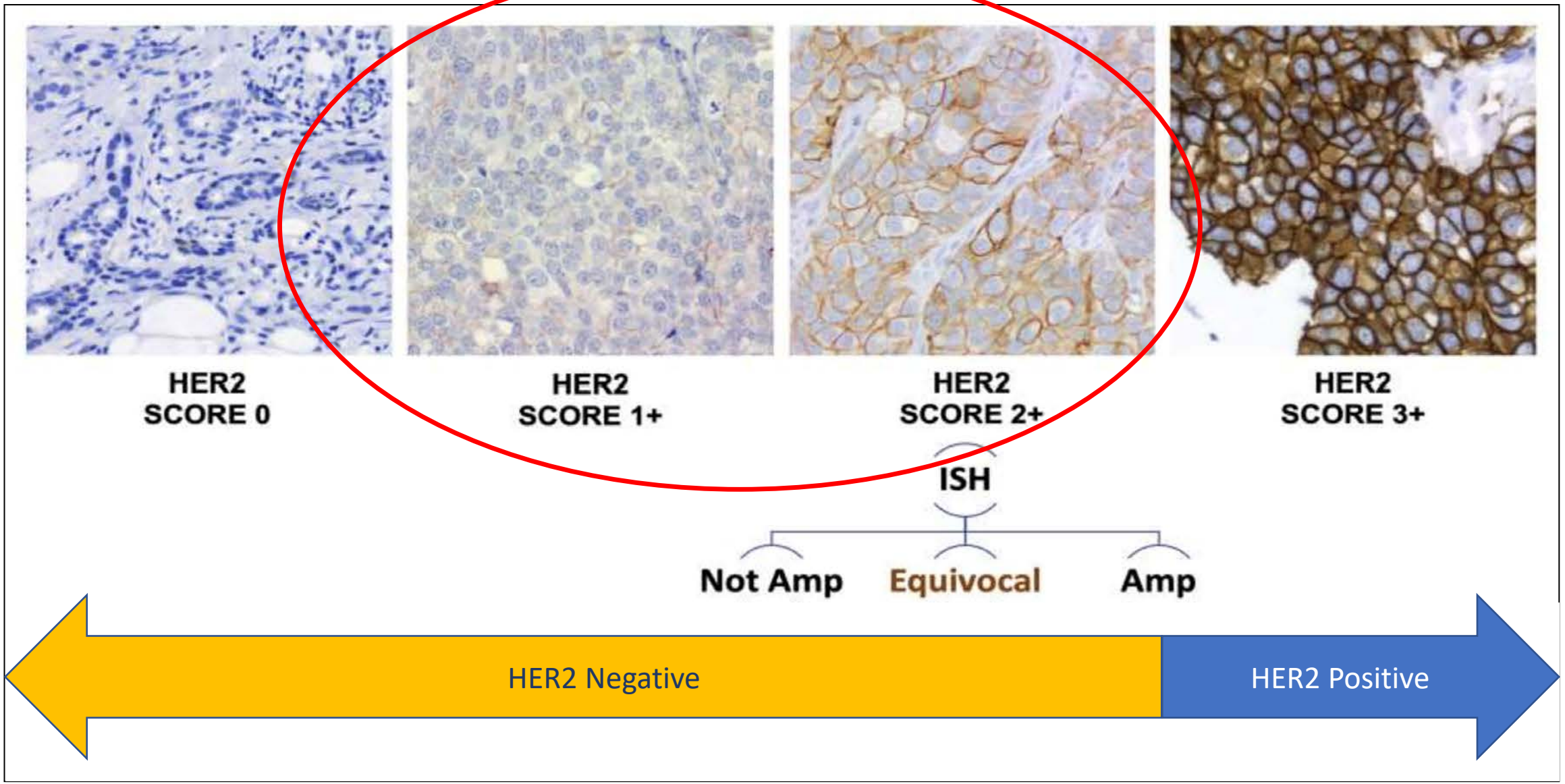
Dr Joanna Metzner-Sadurski (Greenwood, South Carolina)

RTP RESEARCH TO PRACTICE

From HER2-Positive to HER2-Low Breast Cancer

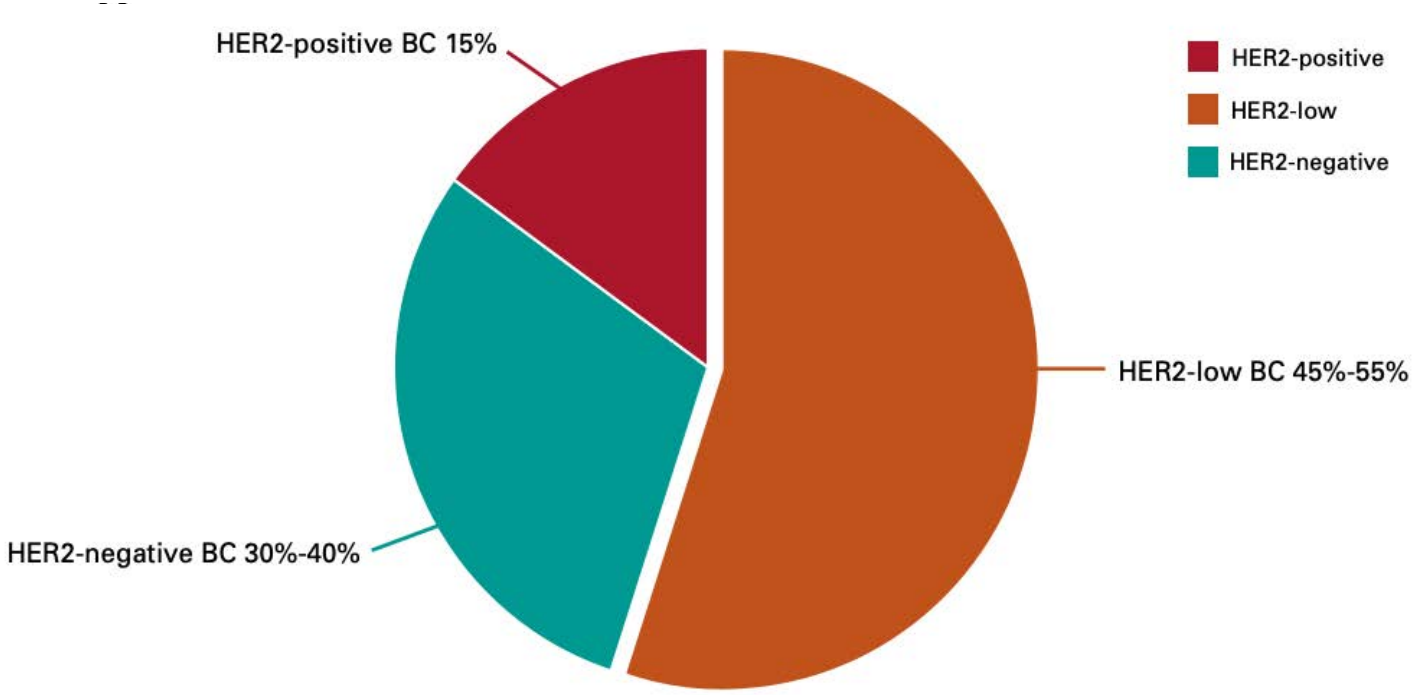
Shanu Modi, MD
Attending, Breast Medicine Service
Memorial Sloan Kettering Cancer Center
New York, New York

Current Binary Classification of HER2 in Breast Cancer



Modified from Marcio C, et al – Seminars in Cancer Biology 2021

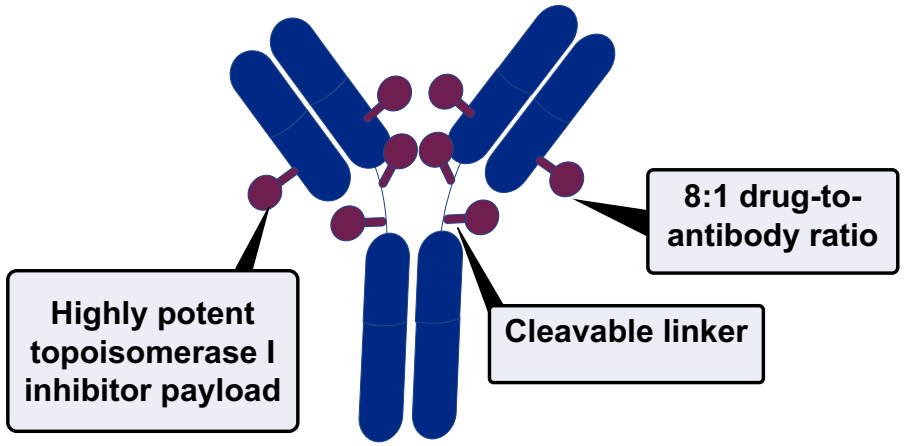
HER2-low Breast Cancer (IHC 1+ or 2+/ISH negative)



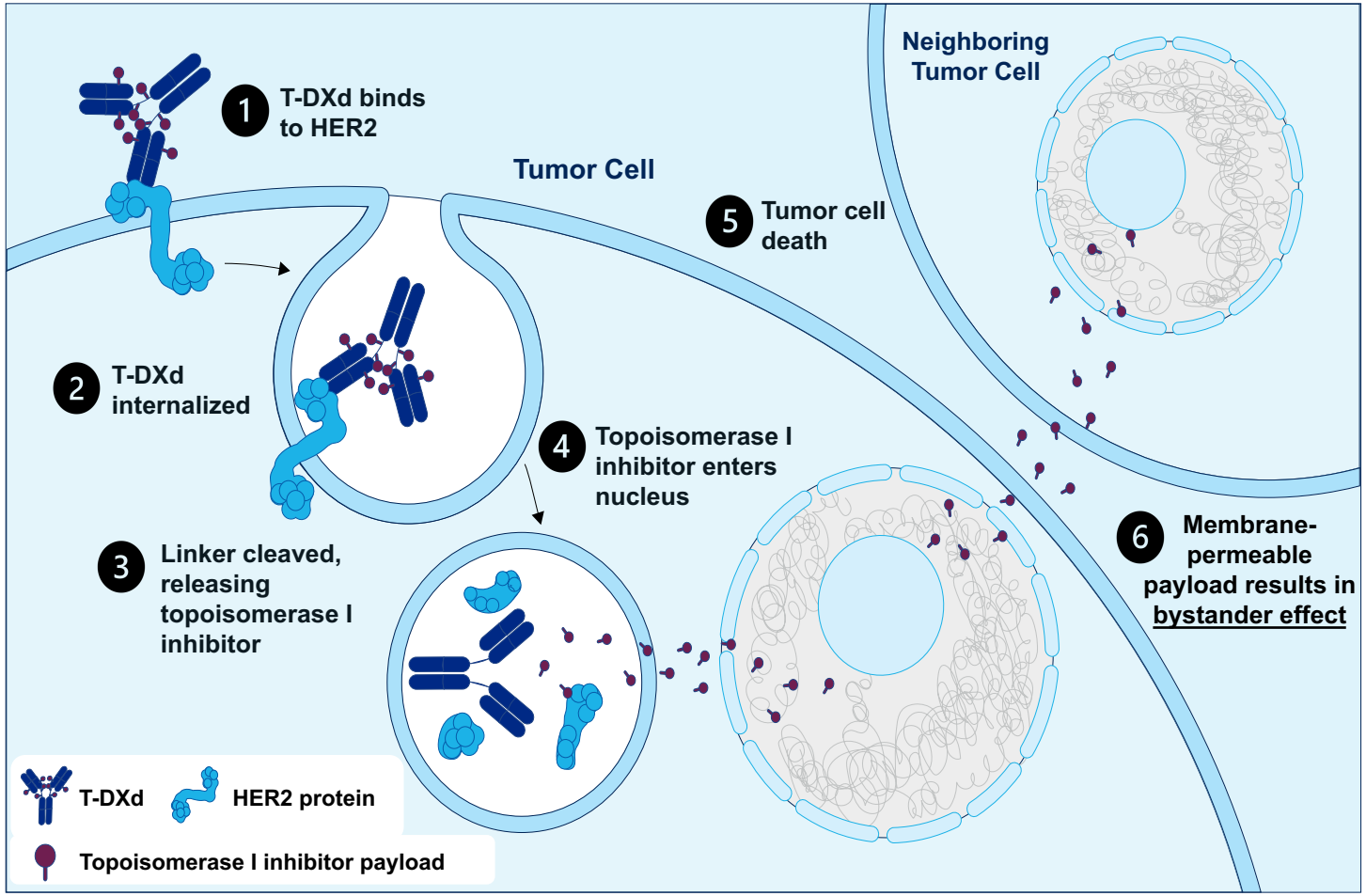
- Predominantly HR+
- Prognostically and biologically indistinct from HER2 IHC 0 BC
- Not a unique subtype
- Targetable by new generation antibody drug conjugates

Tarantino, et al. J Clin Oncol. 2020.

Trastuzumab Deruxtecan (T-DXd): MOA, Bystander Effect, and Rationale for Targeting HER2-low MBC



Internalization of T-DXd leads to release of the DXd payload and subsequent cell death in the target tumor cell and neighboring tumor cells through the bystander effect



Adapted with permission from Modi S, et al. *J Clin Oncol* 2020;38:1887-96. CC BY ND 4.0.

HER2, human epidermal growth factor receptor 2; MOA, mechanism of action; mBC, metastatic breast cancer; mPFS, median progression-free survival; ORR, objective response rate; T-DXd, trastuzumab deruxtecan.

1. Nakada T, et al. *Chem Pharm Bull*. 2019;67:173-85. 2. Ogitani Y, et al. *Clin Cancer Res.* 2016;22:5097-108. 3. Modi S, et al. *J Clin Oncol* 2020;38:1887-96.

DESTINY-Breast04: First Randomized Phase 3 Study of T-DXd versus Treatment of Physicians Choice for HER2-low mBC

An open-label, multicenter study (NCT03734029)

Patients[a]
- HER2-low (IHC 1+ vs IHC 2+/ISH−), unresectable, and/or mBC treated with 1-2 prior lines of chemotherapy in the metastatic setting
- HR+ disease considered endocrine refractory

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 373)

HR+ ≈ 480
HR− ≈ 60

TPC
Capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel[c]
(n = 184)

Primary endpoint
- PFS by BICR (HR+)

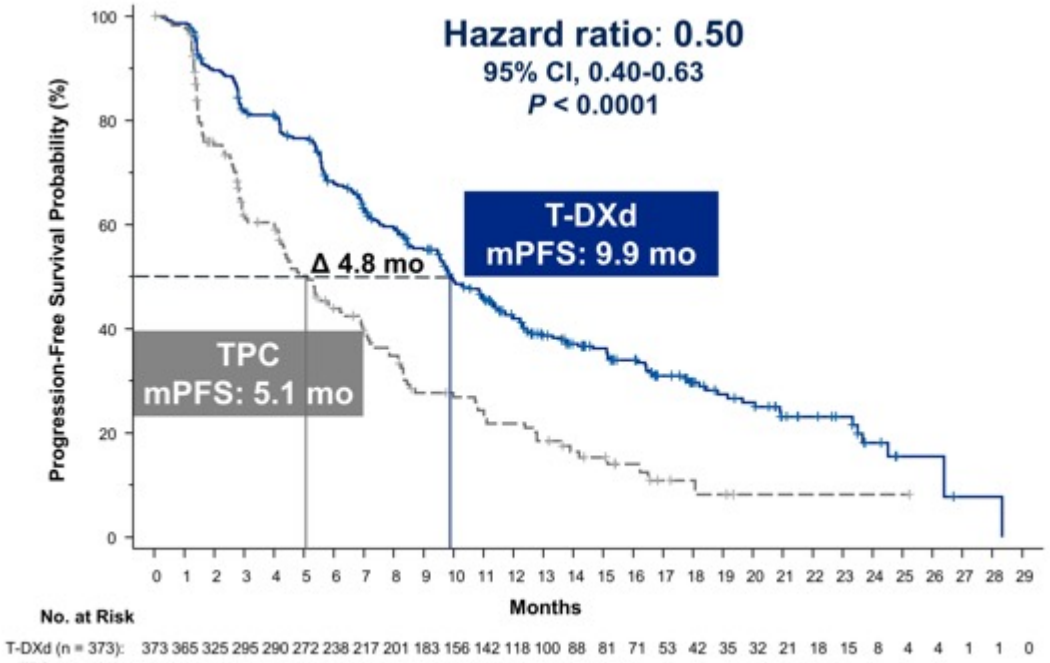
Key secondary endpoints[d]
- PFS by BICR (all patients)
- OS (HR+ and all patients)

Stratification factors
- Centrally assessed HER2 status[b] (IHC 1+ vs IHC 2+/ISH−)
- 1 vs 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) vs HR−

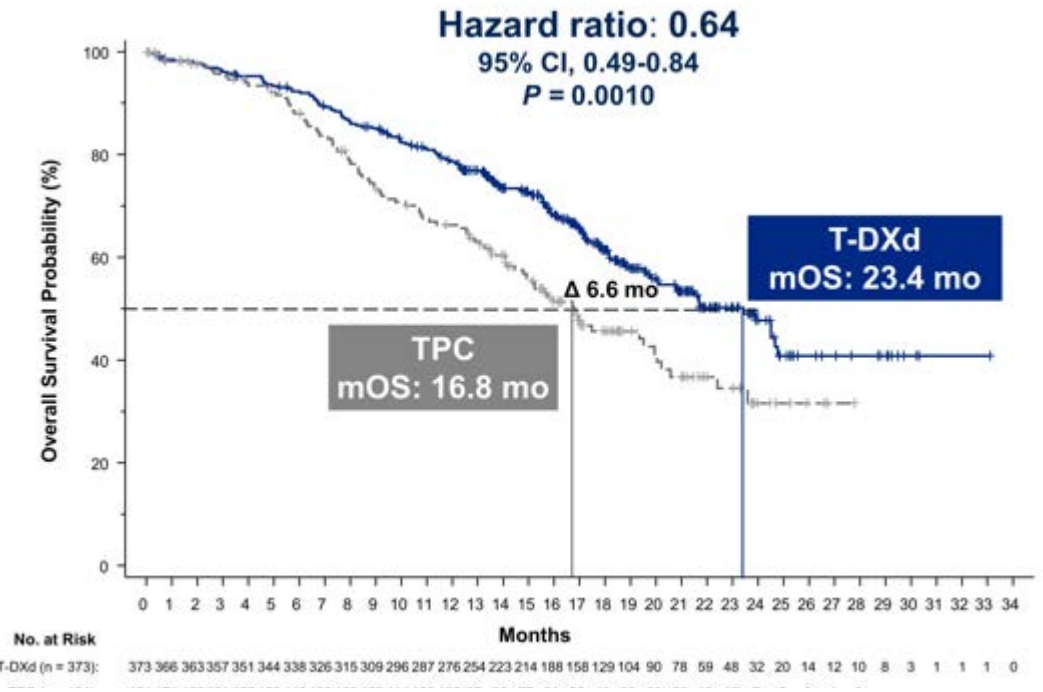
BICR, blinded independent central review; CDK, cyclin-dependent kinase; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; Q3W, every three weeks; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational use only [IUO] Assay system. [c]TPC was administered accordingly to the label. [d]Other secondary endpoints included ORR (BICR and investigator), DOR (BICR), PFS (investigator), and safety; efficacy in the HR− cohort was an exploratory endpoint.

DESTINY-Breast04: Results

PFS in all patients



OS in all patients



2022 FDA Approved T-DXd as the new SOC For HER2 Low (1+ or 2+/ISH-) MBC

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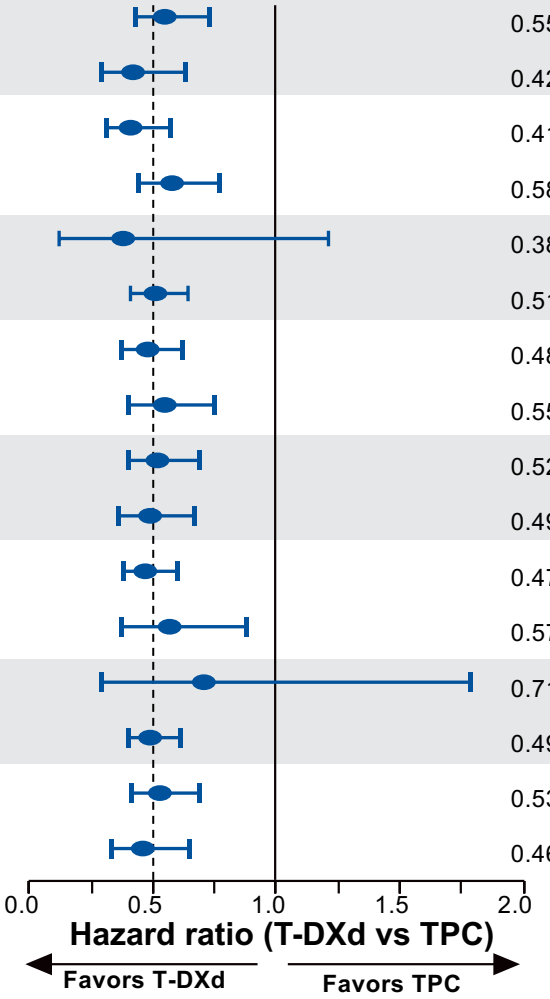
Modi S, et al. Presented at: ASCO 2022 Annual Meeting; June 3-June 7, 2022; Chicago, IL; Modi S et al, NEJM 2022.

DESTINY-Breast04: Updated Subgroup Analyses

Progression-free survival[a] (all patients)

		No. of Events/No. of Patients		Median PFS (mo, 95% CI)[a]		Hazard Ratio (95% CI)[b]
		T-DXd	TPC	T-DXd	TPC	
Prior CDK4/6i use (HR+ cohort)	Yes (n = 348)	149/233	74/115	10.0 (8.3-11.4)	5.4 (4.0-7.8)	0.55 (0.42-0.74)
	No (n = 143)	60/96	35/47	11.7 (9.5-17.7)	5.9 (4.3-8.2)	0.42 (0.28-0.64)
Disease burden[c]	Low (n = 235)	88/150	60/85	11.4 (9.8-16.2)	5.1 (3.1-7.3)	0.41 (0.30-0.58)
	High (n = 322)	155/223	67/99	9.5 (7.5-10.1)	4.8 (2.9-6.9)	0.58 (0.43-0.78)
Rapid progression[d]	Yes (n = 22)	9/14	6/8	8.2 (1.4-NE)	2.2 (0.6-NE)	0.38 (0.12-1.21)
	No (n = 535)	234/359	121/176	9.9 (9.0-11.3)	5.3 (4.2-6.9)	0.51 (0.41-0.64)
HER2 IHC status	IHC 1+ (n = 321)	134/214	75/107	10.0 (8.6-12.3)	4.8 (3.0-7.0)	0.48 (0.36-0.63)
	IHC 2+/ISH− (n = 236)	109/159	52/77	9.9 (8.0-11.5)	5.1 (2.9-7.1)	0.55 (0.39-0.76)
Prior lines of chemotherapy	1 (n = 321)	141/221	68/100	10.1 (8.4-12.2)	6.4 (4.3-7.8)	0.52 (0.39-0.70)
	2 (n = 234)	101/151	59/83	9.7 (8.1-11.4)	4.2 (3.0-5.4)	0.49 (0.35-0.68)
Age	<65 years (n = 426)	191/290	93/136	9.8 (8.4-11.1)	4.6 (2.9-5.9)	0.47 (0.37-0.61)
	≥65 years (n = 131)	52/83	34/48	11.4 (8.3-13.3)	6.2 (4.3-10.8)	0.57 (0.36-0.89)
Baseline CNS metastases	Yes (n = 32)	18/24	6/8	8.1 (4.0-11.3)	4.8 (0.6-11.0)	0.71 (0.28-1.80)
	No (n = 525)	225/349	121/176	10.1 (9.5-11.5)	5.1 (4.2-6.8)	0.49 (0.39-0.62)
Prior anthracycline treatment[e]	Yes (n = 342)	155/239	81/113	9.8 (8.5-11.7)	5.3 (3.0-7.9	0.53 (0.40-0.70)
	No (n = 205)	88/134	46/71	10.0 (7.2-12.5)	4.6 (3.0-6.8)	0.46 (0.32-0.66)

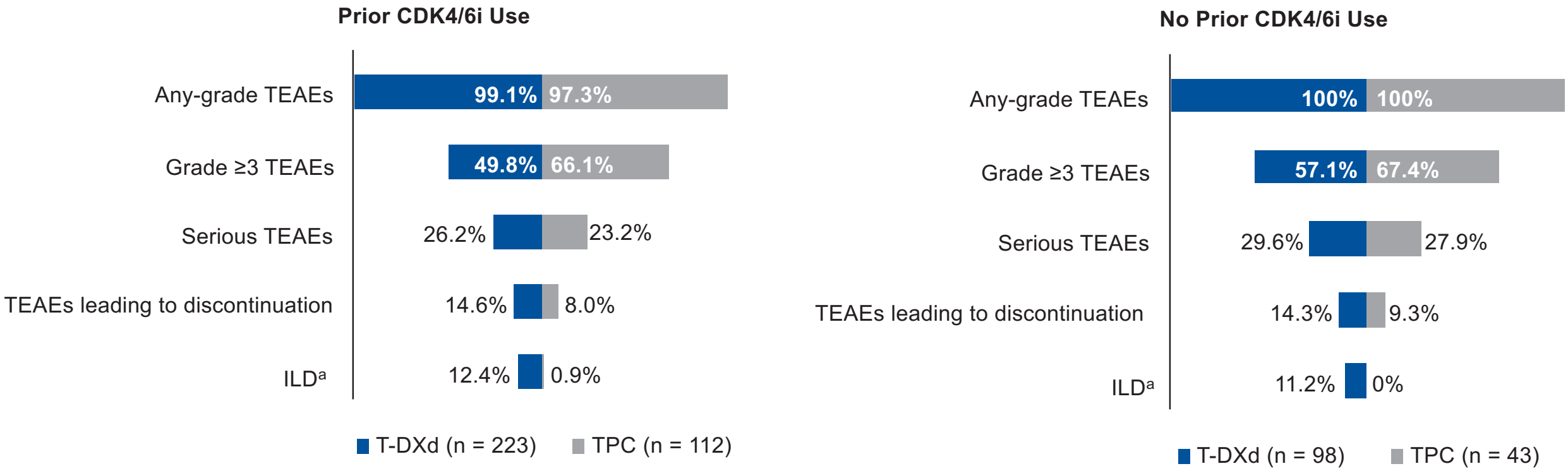


Dashed line at 0.50 represents median PFS for all patients (Modi S et al. *N Engl J Med*. 2022;387(1):9-20).

[a]Median PFS is from Kaplan-Meier analysis. CI for median was computed using the Brookmeyer-Crowley method. [b]Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. [c]Disease burden was defined by the number of metastatic disease sites at baseline (low = 0-2; high = 3+). At baseline, 69.8% of patients had liver metastases. [d]Rapid progressor status was defined as disease progression within 6 months of concluding a prior course of chemotherapy in early breast cancer.

Harbeck N et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster P1-11-0.

DB04: Safety by CDK4/6i use (all patients)

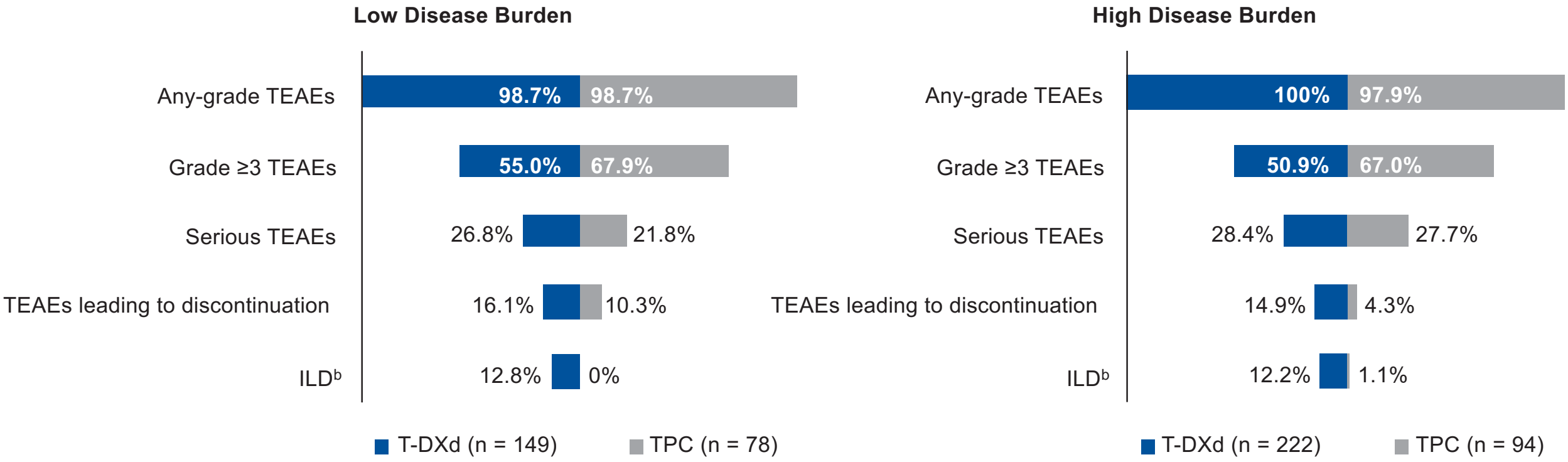


CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.

[a]Adjudicated ILD events per the ILD Adjudication Committee.

Harbeck N et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster P1-11-0.

DB04: Safety by disease burden[a] (all patients)



HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.
[a]Disease burden was defined by the number of metastatic disease sites at baseline (low = 0-2; high = 3+). At baseline, 69.8% of patients had liver metastases.
[b]Adjudicated ILD events per the ILD Adjudication Committee.
Harbeck N et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster P1-11-0.

DESTINY-Breast04: Determination of HER2 Low Status

N=1340
samples submitted

↓

N=1060
HER2 Low locally &
Centrally testable

↓

N=823
Centrally confirmed HER2 Low

↓

N=557
Eligible for Trial

Concordance Between Historical and Central HER2 IHC Results[a]

HER2 Status by Central Testing, n	HER2 Status by Historical Result, n				Total
	IHC 0	IHC 1+	IHC 2+/ISH−	IHC 2+/ISH+	
IHC 0	18	157	51	2	228
IHC 1+	18	**344**	**126**	3	491
IHC 2+/ISH−	5	**122**	**231**	0	358
IHC 2+/ISH+	0	9	11	1	21
IHC 3+	1	2	7	0	10
Total	42	634	426	6	1108

- central testing using the PATHWAY HER2 4B5 assay (and INFORM HER2 Dual ISH DNA Probe Cocktail when applicable)

- 78% (823/1060) of samples centrally confirmed HER2 low
- Among discordant samples: 208/237 (88%) were centrally scored IHC 0, and 29/237 (12%) were scored IHC 2+/ISH+ or IHC 3+

Prat A et al, SABCS 2022

Factors Associated With Scoring Agreement

Feature	Patients With Historical and Valid Central HER2 Results (n = 1108), n (%)	Overall Percentage Agreement (95% CI)
Region of origin		
North America	252 (22.7)	0.85 (0.81-0.90)
Europe and Israel	461 (41.6)	0.70 (0.66-0.74)
Asia, excluding China	287 (25.9)	0.82 (0.77-0.86)
China	108 (9.7)	0.68 (0.59-0.76)
Specimen collection time (relative to study screening)		
2013 or earlier	94 (8.5)	0.64 (0.54-0.74)
2014-2018	421 (38.0)	0.75 (0.71-0.79)
2019 or later	555 (50.1)	0.79 (0.75-0.82)
Missing	38 (3.4)	0.89 (0.80-0.99)

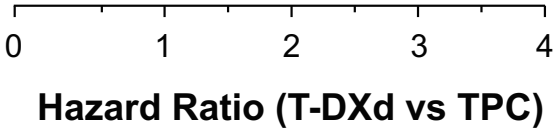
- Scoring agreement of HER2 tumor samples varied by region and collection date

HER2, human epidermal growth factor receptor 2.

Prat A et al. San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster HER2-18.

Median PFS by Tumor Sample Characteristics Among Patients Enrolled in DESTINY-Breast04

	Number of Events		Median PFS, Months (95% CI)		
Subgroup	**T-DXd**	**TPC**	**T-DXd**	**TPC**	**Hazard Ratio (95% CI)**
Tumor location					
Primary (n = 196)	96/136	43/60	9.6 (7.1-11.3)	4.2 (1.6-6.4)	0.47 (0.32-0.70)
Metastases (n = 359)	145/235	84/124	10.9 (9.5-12.3)	5.4 (4.3-7.1)	0.50 (0.38-0.66)
Specimen type					
Biopsy (n = 448)	189/299	103/149	10.9 (9.6-12.0)	5.3 (4.2-6.9)	0.46 (0.35-0.59)
Excision/resection (n = 108)	53/73	24/35	7.5 (5.7-9.9)	3.0 (1.4-11.0)	0.57 (0.33-1.0)

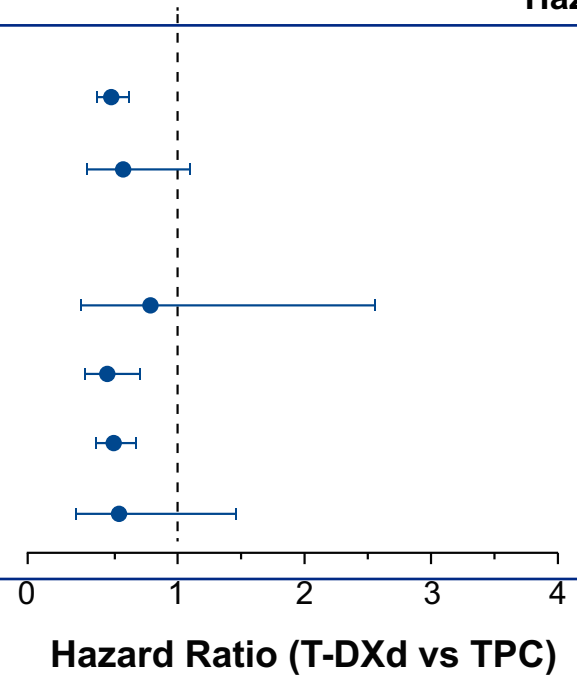


PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Prat A et al. San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster HER2-18.

Median PFS by Tumor Sample Characteristics Among Patients Enrolled in DESTINY-Breast04 (continued)

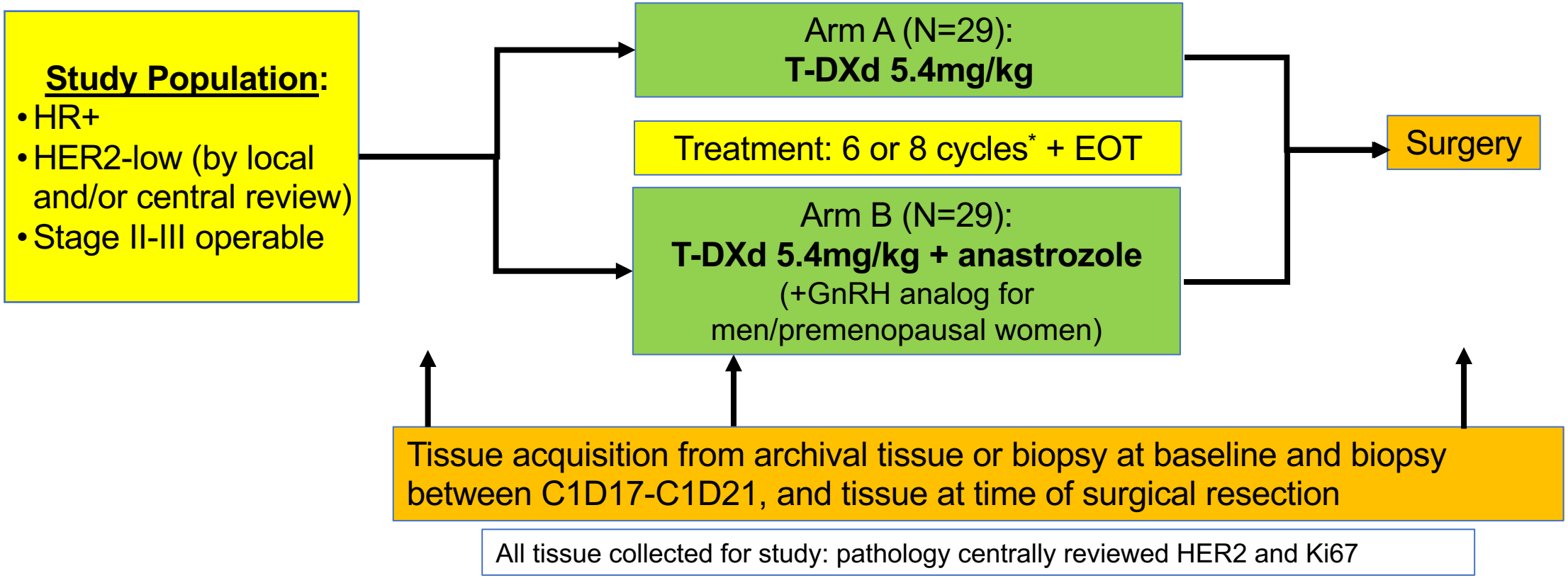
	Number of Events		Median PFS, Months (95% CI)		
Subgroup	**T-DXd**	**TPC**	**T-DXd**	**TPC**	**Hazard Ratio (95% CI)**
Collection type					
Archival tissue (n = 482)	203/324	109/158	10.3 (8.6-12.0)	5.3 (4.2-7.0)	0.48 (0.37-0.61)
Newly obtained tissue (n = 75)	40/49	18/26	9.7 (5.6-10.9)	4.8 (2.8-6.9)	0.57 (0.30-1.1)
Tumor specimen collection date					
2013 and earlier (n = 29)	11/19	9/10	7.0 (2.8-NE)	6.8 (1.4-11.1)	0.78 (0.24-2.54)
2014-2018 (n = 175)	76/126	33/49	11.4 (9.5-15.1)	4.3 (1.6-7.0)	0.44 (0.28-0.70)
2019 or later (n = 310)	137/203	75/107	9.8 (8.4-11.3)	5.1 (4.1-7.1)	0.49 (0.37-0.66)
Missing (n = 43)	19/25	10/18	6.6 (2.8-10.8)	2.8 (1.2-8.3)	0.54 (0.20-1.4)



- For patients enrolled in DESTINY-Breast04, efficacy of T-DXd compared with TPC was consistent regardless of tumor sample characteristics

PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Prat A et al. San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster HER2-18.

TRIO-US B-12 (TALENT): Neoadjuvant HER2 Low Trial



* Originally, 6 cycles of treatment were given but in 02/2022, an amendment increased the number of treatment cycles from 6 to 8 for newly enrolled participants, or those who had not yet had surgery.

Presented by Bardia A, Hurvitz S; SABCS 2022

RCB Results by Arm, Number of Cycles and Stage

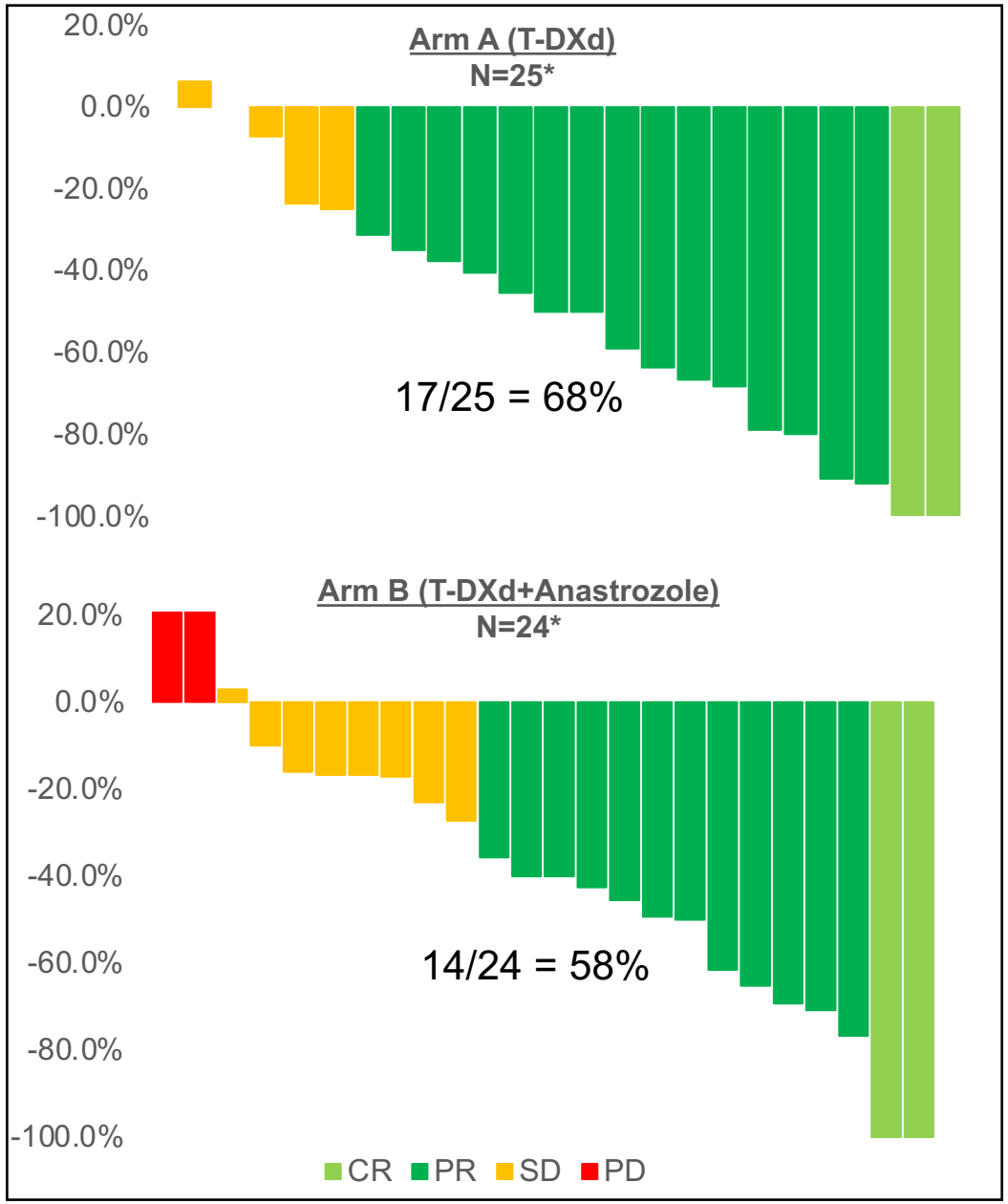
Cycles	Stage at Baseline	Arm A (T-DXd) N=22*				Arm B (T-DXd+Anastrozole) N=20**			
		RCB-0	RCB-I	RCB-II	RCB-III	RCB-0	RCB-I	RCB-II	RCB-III
6 Cycles	Stage IIA	0	1 (5%)	2 (9%)	0	0	1 (5%)	6 (30%)	0
	Stage IIB	0	1 (5%)	4 (18%)	2 (9%)	0	0	3 (15%)	1 (5%)
	Stage IIIA	0	0	1 (5%)	2 (9%)	0	0	1 (5%)	1 (5%)
	Stage IIIB	0	0	1 (5%)	0	0	0	0	0
8 Cycles	Stage IIA	0	0	2 (9%)	0	0	1 (5%)	1 (5%)	0
	Stage IIB	0	0	1 (5%)	1 (5%)	0	0	2 (10%)	0
	Stage IIIA	1 (5%)	0	0	0	0	1 (5%)	0	0
	Stage IIIB	0	0	0	0	0	0	0	0

RCBi = Residual cancer burden index; RCB 0 = pCR

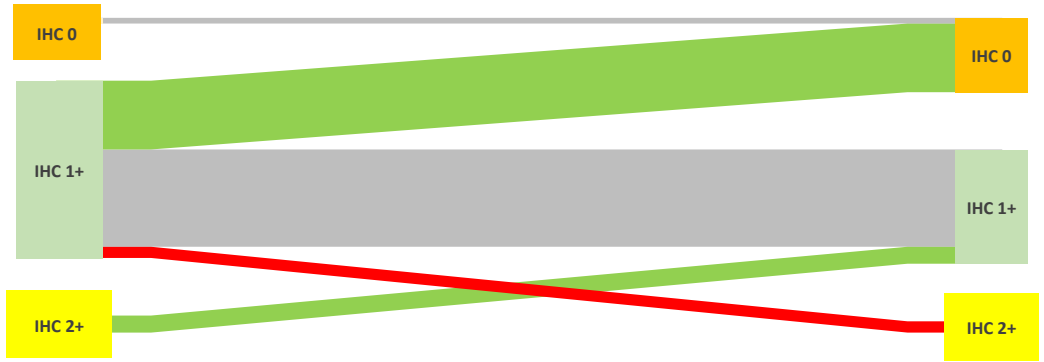
- As of data cutoff 11/25/2022, denominator excludes pts currently awaiting surgery or actively on treatment (3 pts in Arm A and 4 pts in Arm B pending surgical data, 4 active pts in Arm A and 5 active pts in Arm B).
- *4 pts discontinued early **3 pts discontinued early
- IHC Status did not appear to be associated with RCB

Presented by Bardia A, Hurvitz S; SABCS 2022

Objective Response Rate (based on local imaging)

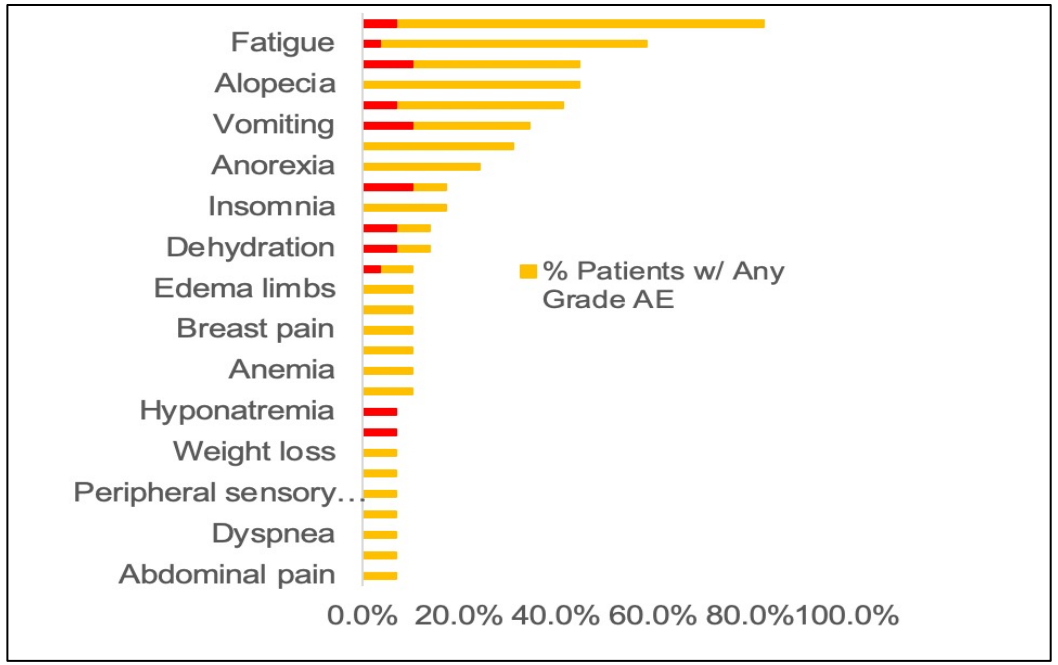


HER2 Change from Baseline to Surgery (by Central Review)



- 48.6% (17/35) had change in HER2 IHC
- Of those, majority (88.2%) had decrease in HER2

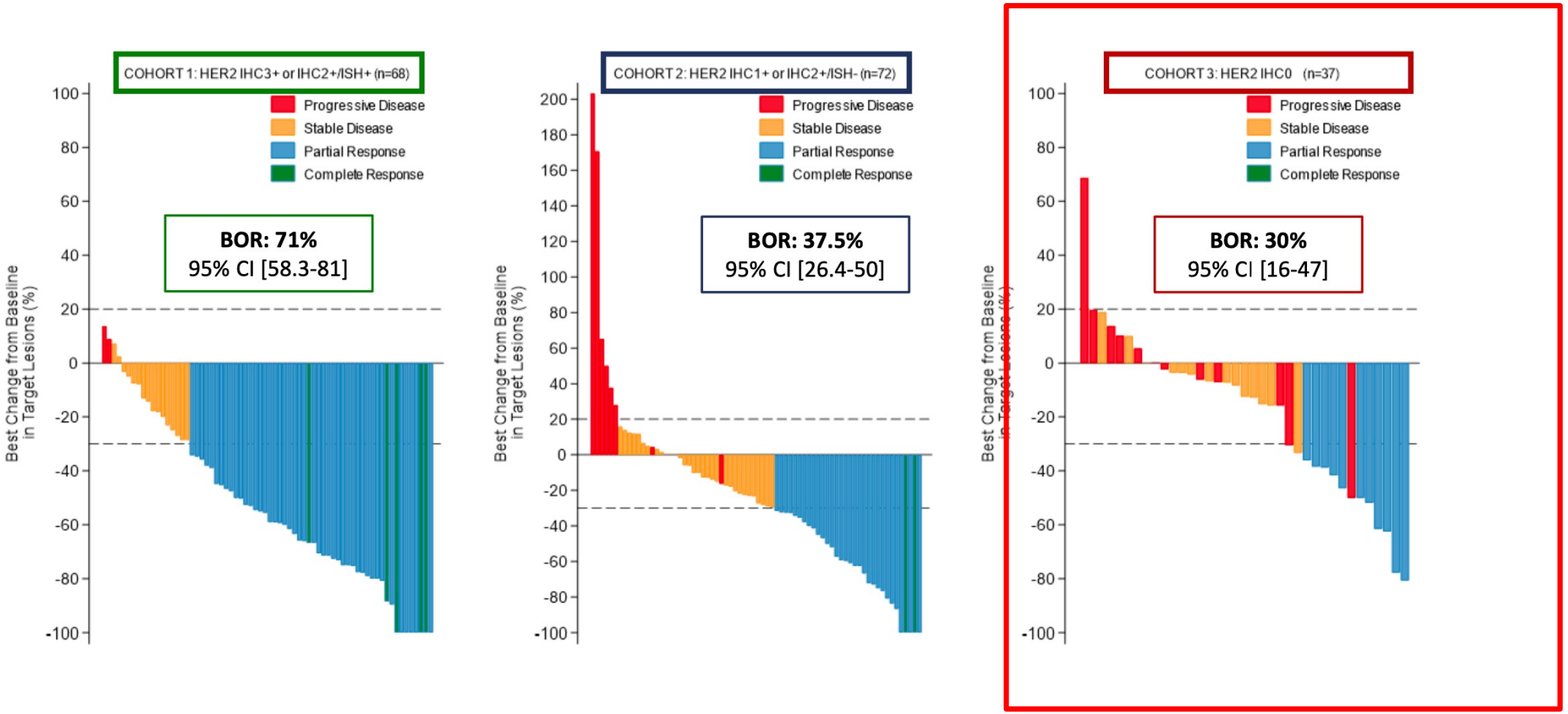
Arm A T-DXd Related AEs (N=29)



HER2 LOW: Challenges

What is the Threshold Level of HER2 Expression to activate T-DXd?

DAISY, Phase 2 Trial of T-DXd: Activity seen in HER2 IHC 0 Cohort

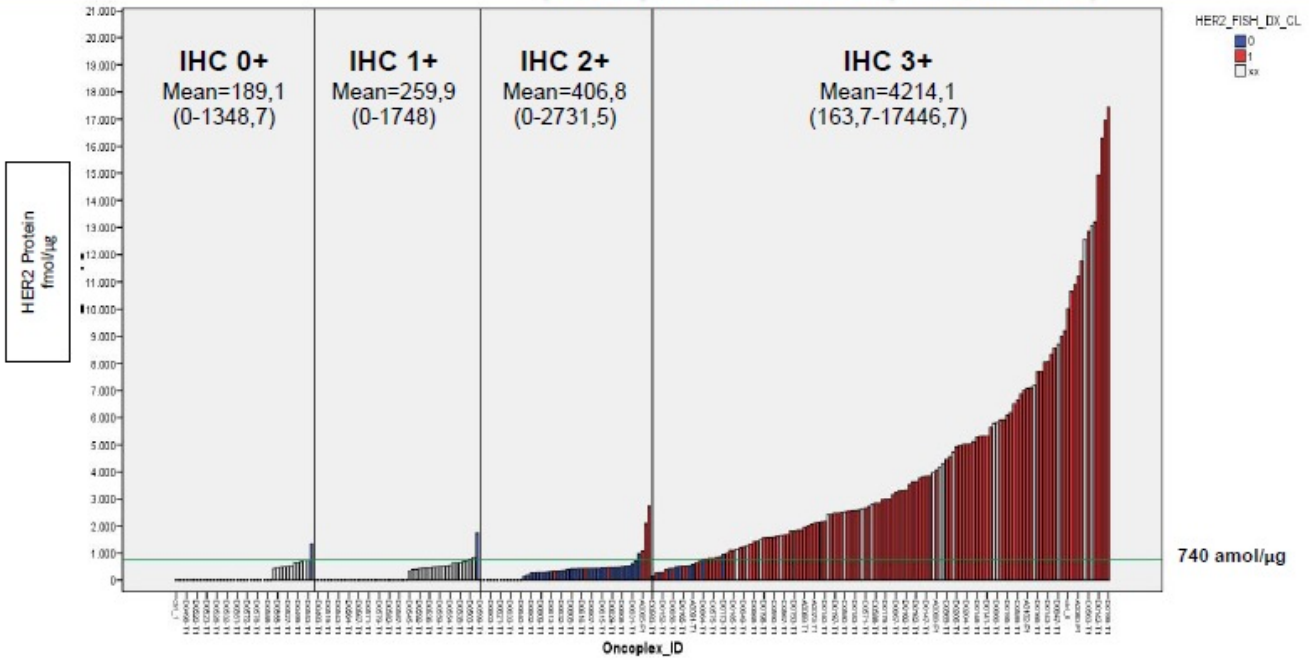


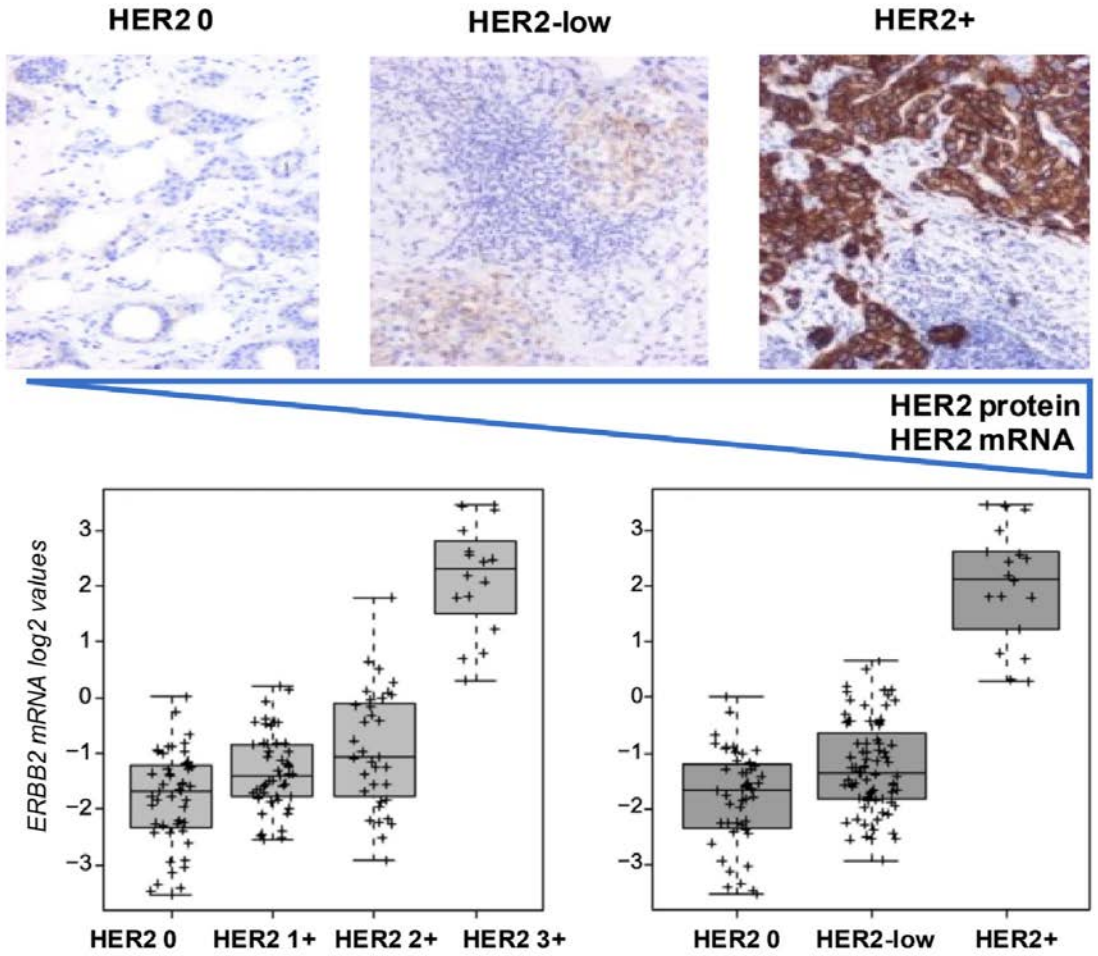
IHC 0 Cohort med DoR: 6.8mo (CI: 2.8; NR) ; med PFS: 4.2mo (CI: 2.0; 5.7)

Dieras, V et a; SABCS 2021

Are There Alternate Methods of Measuring HER2 Expression?

Quantitative Measurement of HER2 levels by Multiplexed Mass Spectrometry from FFPE tissue

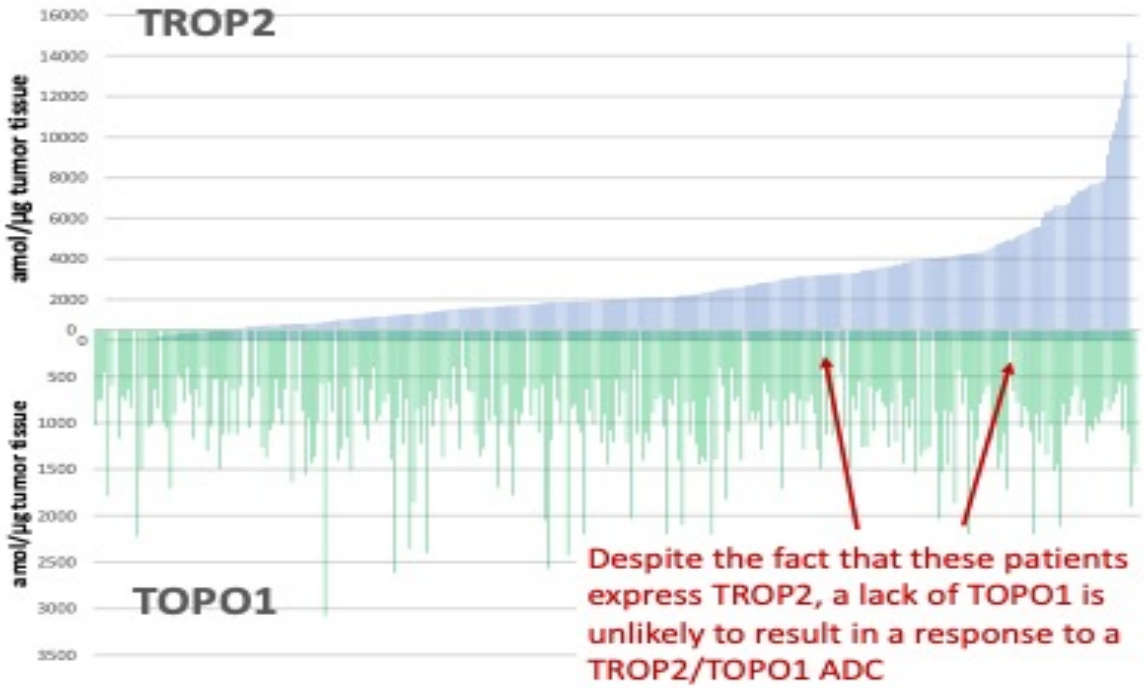




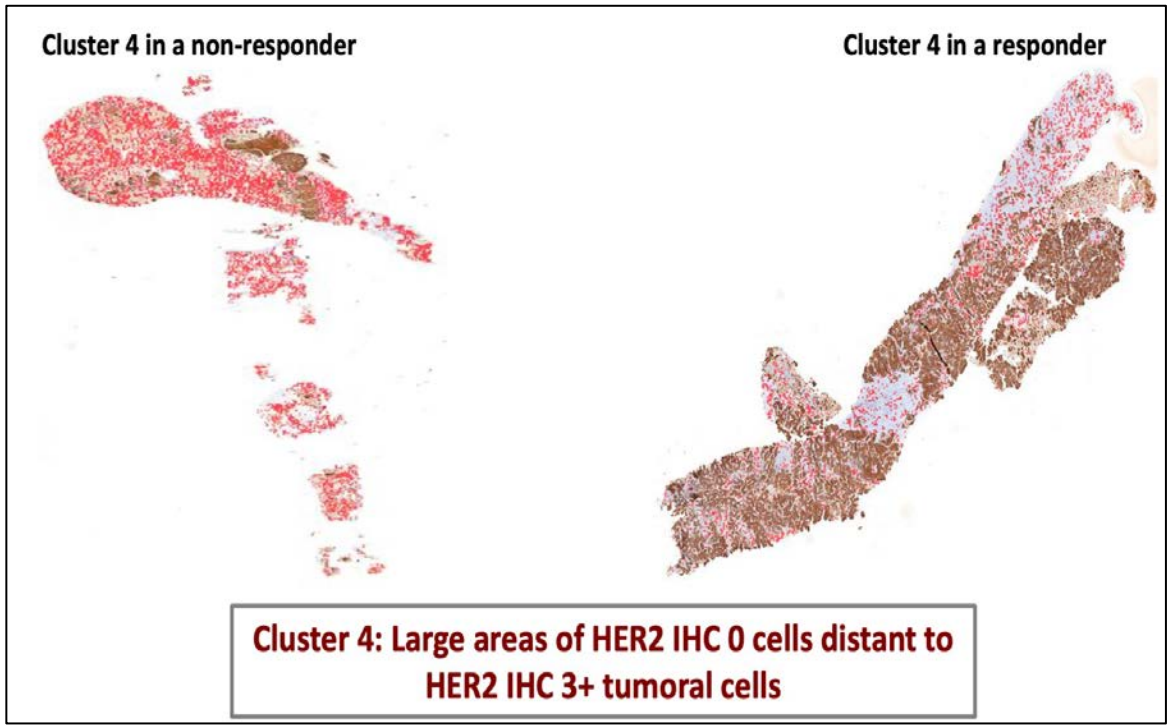
Nuciforo P et al, Mol Oncol 2016; Schettini P et al, The Breast 2021

Novel Biomarkers of Response: Payload Markers and Spatial Heterogeneity

Clinical Survey of TROP2 antibody-drug conjugate target and payload biomarkers in multiple cancer indications using multiplex mass spectrometry



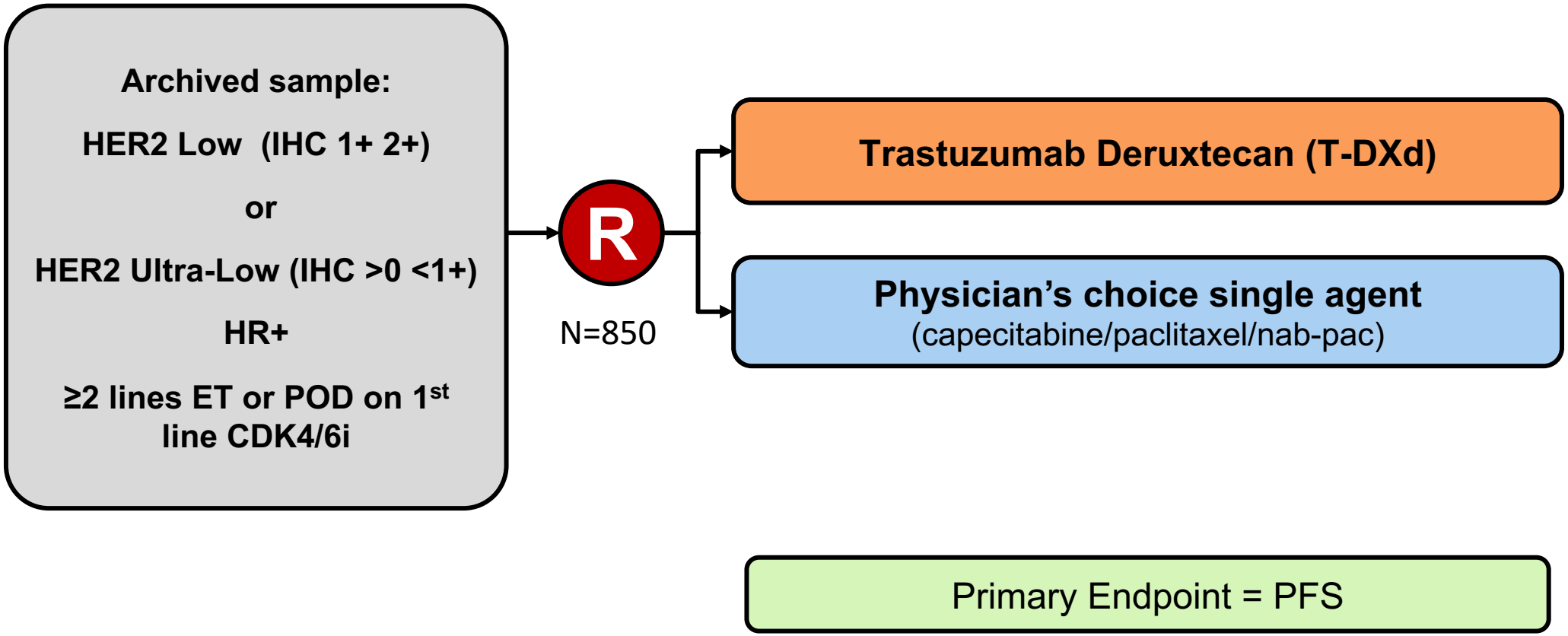
Spatial heterogeneity of target antigen as a predictor of response to T-DXd in HER2+ MBC



Biomarkers of Toxicity?

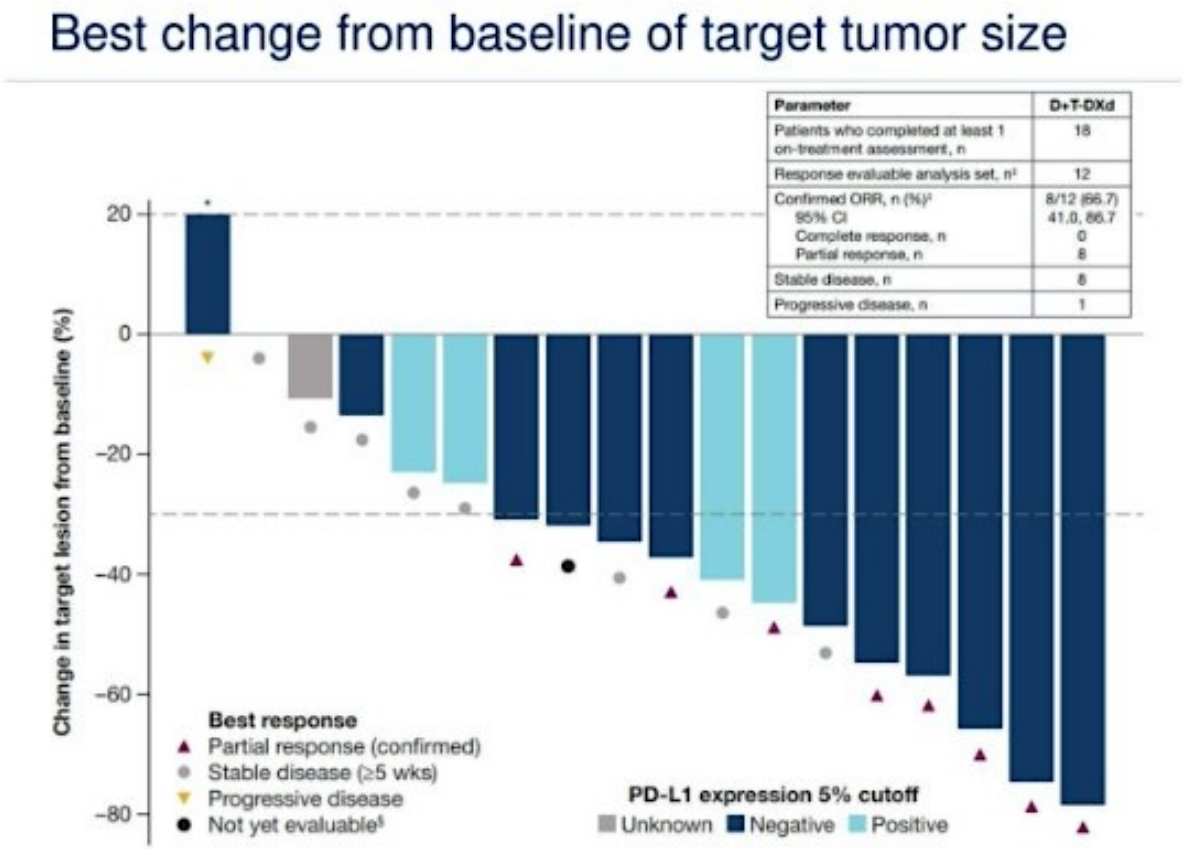
Thyparambil S et al, AACR 2022; Dieras, V et al, SABCS 2021

DESTINY Breast-06: Chemotherapy-naïve, HR+, HER2 LOW or HER2 Ultra-Low MBC



ClinicalTrials.gov Identifier: NCT04494425

HER2 LOW TNBC:
BEGONIA Phase 1b/2 Platform Study of durvalumab (D) combinations in TNBC
Preliminary Results for Arm 6: D+T-DXd in HR- HER2 LOW MBC (TNBC)



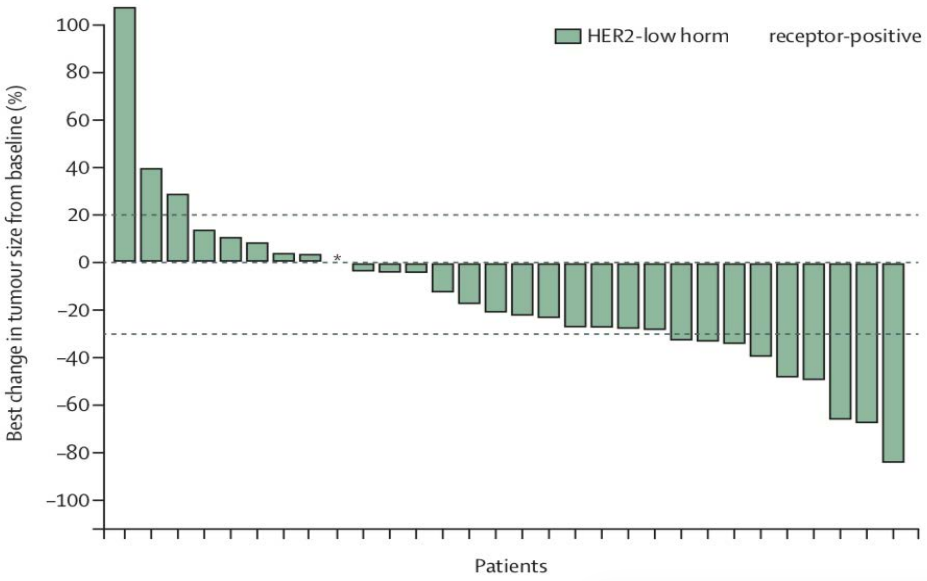
Local testing of HER2 expression successfully identified patients with HER2 IHC1+ and HER2 IHC2+/ISH– tumors, who benefit from this treatment combination.

In this small group of patients, responses were observed in both PD-L1–positive (confirmed ORR 1/1 [100%]) and –negative (confirmed ORR 7/10 [70.0%]) groups (5% cutoff).

Schmid P et al ASCO 2021

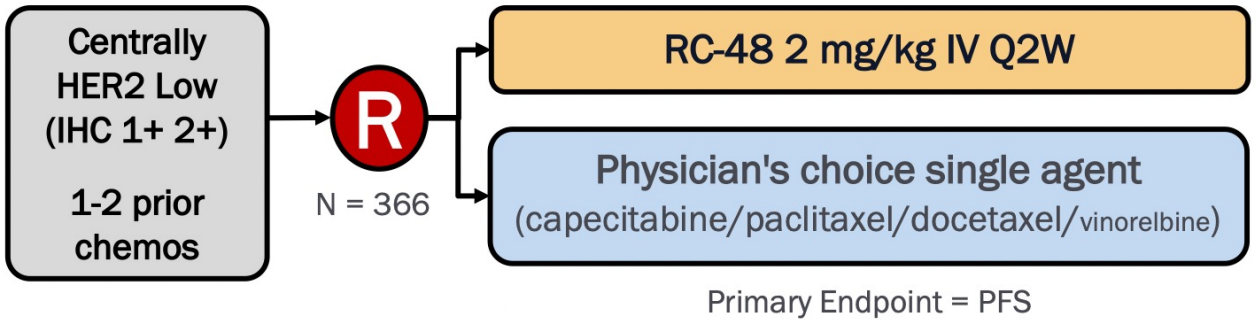
Novel ADCs for HER2-low in Development

Trastuzumab duocarmazine (SYD985)[1]



49 HER2-low mBC patients: ORR 32%, mPFS 4 mo

Randomized Phase 3 Study: RC48-ADC vs TPC for HER2-Low MBC



- Banerji U, et al. *Lancet Oncol.* 2019;20(8):1124–1135; Wang J, et al. Presented at ASCO 2021.

Can we Maximize the potential of T-DXd via Combinations?

DESTINY Breast 08: Study Schema

Part 1: Dose Finding

Patient population

- HR+ or HR−, HER2-low (IHC 1+ or IHC 2+/ISH−) metastatic breast cancer
  - HR+ patients: ≥1 prior line of ET and ≥1 prior line of CTX for metastatic disease
  - HR− patients: ≥1 prior line of CTX for metastatic disease

Centrally assigned

- Module 1: T-DXd + capecitabine (HR+ or HR−)
- Module 2: T-DXd + durvalumab + paclitaxel (HR+ or HR-)
- Module 3: T-DXd + capivasertib (HR+ or HR-)
- Module 4: T-DXd + anastrozole (HR+ patients only)
- Module 5: T-DXd + fulvestrant (HR+ patients only)

CTX, chemotherapy; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; T-DXd, trastuzumab deruxtecan.

Part 2: Dose Expansion Based on RP2D From Part 1

Patient population

- **Module 1** (HR+ or HR−)
  - HR+: only 1 prior line of ET but no prior CTX for mBC
  - HR−: only 1 prior line of CTX for mBC
- **Module 2** (HR−): no prior CTX for mBC[a]
- **Module 3** (HR−): only 1 prior line of CTX for mBC
- **Modules 4 and 5** (HR+): only 1 prior line of ET but no prior CTX for mBC

Allocation to open modules (dependent on available RP2D)

A

- Module 1: T-DXd + capecitabine (HR+ or HR−) (n=20)
- Module 2: T-DXd + durvalumab + paclitaxel (HR−)
- Module 3: T-DXd + capivasertib (HR−) (n=40)[c]
- Module 4: T-DXd + anastrozole (HR+)
- Module 5: T-DXd + fulvestrant (HR+)

[a] Patients who have received CTX in the neoadjuvant or adjuvant setting are eligible, as long as they have had a disease-free interval of >12 months.
[b] Molecularly defined subgroup of special interest, PD-L1(+).
[c] Molecularly defined subgroup of special interest, AKT/PTEN/PIK3CA altered

Clinicaltrials.gov Identifier: NCT04556773

DESTINY-Breast09 Phase III Trial Design

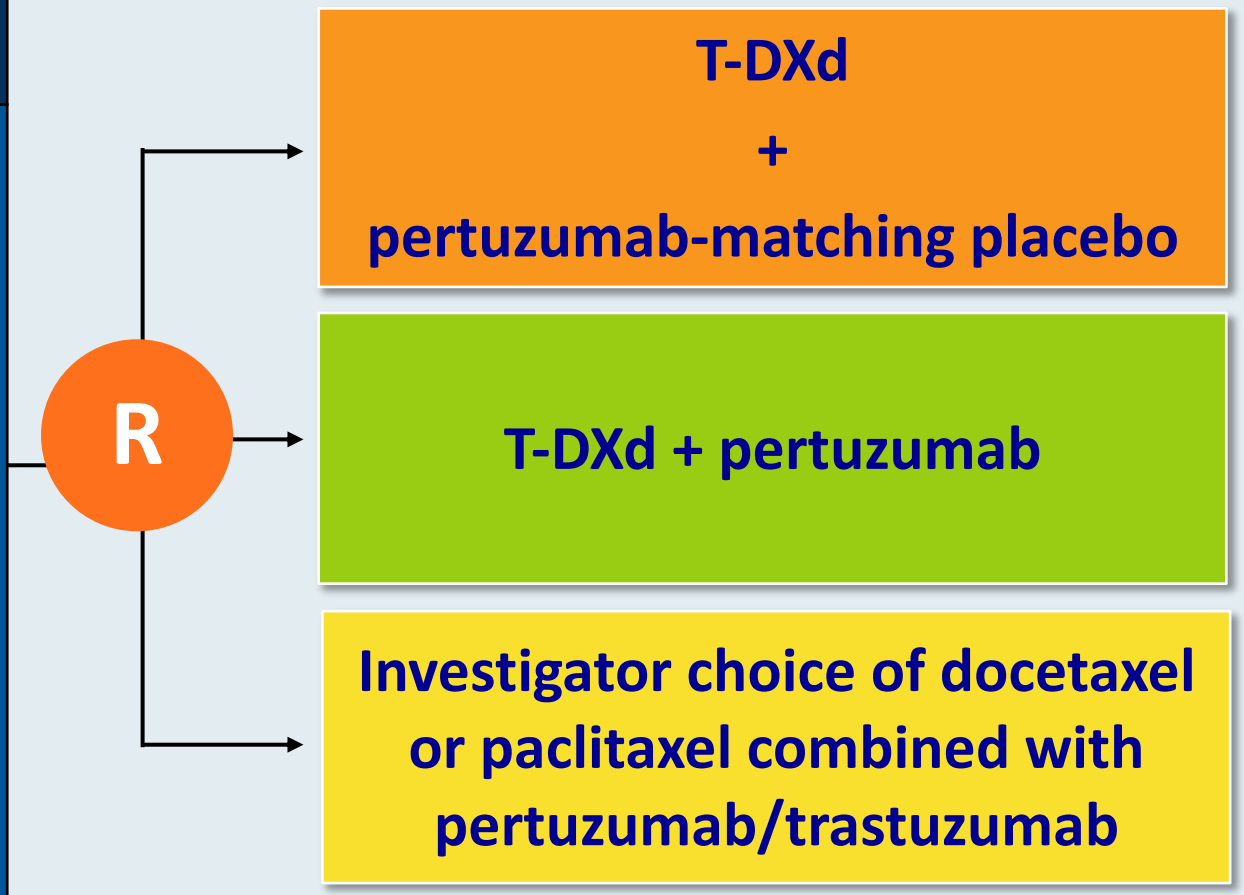
Estimated enrollment: N = 1,134

Pathologically documented breast cancer:

- Advanced or metastatic
- Locally assessed and prospectively centrally confirmed as IHC 3+ or ISH+
- Documented by local testing as HR-positive or negative in the metastatic setting

No prior chemotherapy or HER2-targeted therapy for advanced or metastatic disease or only 1 previous line of ET in the metastatic setting

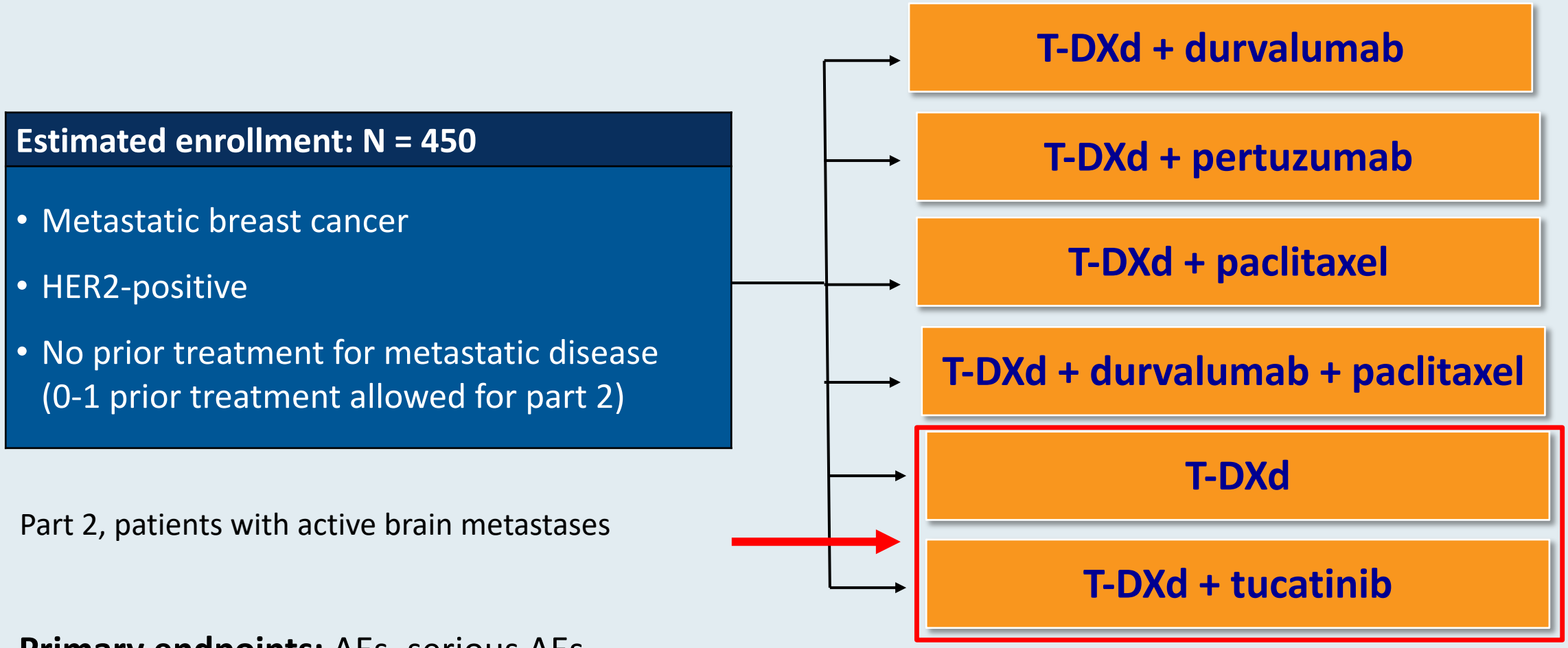
Prior (neo)adjuvant chemotherapy or HER2-targeted therapy allowed if >6 months from treatment to diagnosis of metastasis



Primary endpoint: Progression-free survival

www.clinicaltrials.gov. NCT04784715. Accessed December 2022.

DESTINY-Breast07 Phase I/II Trial Design



Part 2, patients with active brain metastases

Primary endpoints: AEs, serious AEs

Secondary endpoints include objective response rate, PFS, PFS2, duration of response, overall survival

www.clinicaltrials.gov. NCT04538742. Accessed December 2022.

Select Ongoing Trials Evaluating Tucatinib for HER2-Positive Metastatic Breast Cancer

Trial identifier	Phase (N)	Setting	Regimens	Estimated completion date
HER2CLIMB-02 (NCT03975647)	III (N = 565)	Unresectable, locally advanced or metastatic disease Prior treatment with a taxane and trastuzumab in any setting	• T-DM1 + placebo • T-DM1 + tucatinib	2024
HER2CLIMB-05 (NCT05132582)	III (N = 650)	Unresectable, locally advanced or metastatic disease No evidence of PD after 1L taxane and HP for advanced disease	*As maintenance after 1L therapy* • HP + placebo • HP + tucatinib	2027
HER2CLIMB-04 (NCT04539938)	II (N = 70)	Unresectable, locally advanced or metastatic disease Prior treatment with a taxane and trastuzumab	• Tucatinib + trastuzumab deruxtecan	2025

HP = trastuzumab and pertuzumab

www.clinicaltrials.gov. Accessed December 2022.

RTP RESEARCH TO PRACTICE

Summary: Beyond HER2+ BC

- Next generation ADCs with advanced pharmaceutical properties have not only improved outcomes in HER2+ BC and have allowed us to move into new populations
- HER2 Low breast cancer is today a targetable new subgroup
  - T-DXd is the first approved HER2 targeted therapy for this population
  - But this is still a new and evolving space and we may need better quantitative biomarker assays to optimize patient selection for these new HER2 ADC therapies
  - And we remain excited about the potential to have other agents in the future for this pop of pts
- Clearly Understanding Mechanisms of Resistance, identifying novel biomarkers and Sequencing studies will be key to optimizing and personalizing ADC therapy in the future

MODULE 5: Incidence and Management of Adverse Events Associated with HER2-Targeted Therapy — Dr Hurvitz

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Case Presentation: 62-year-old woman with recurrent triple-positive mBC whose disease converts to HER2-negative, PIK3CA-positive at the time of progression

Dr Dhatri Kodali (Houston, Texas)

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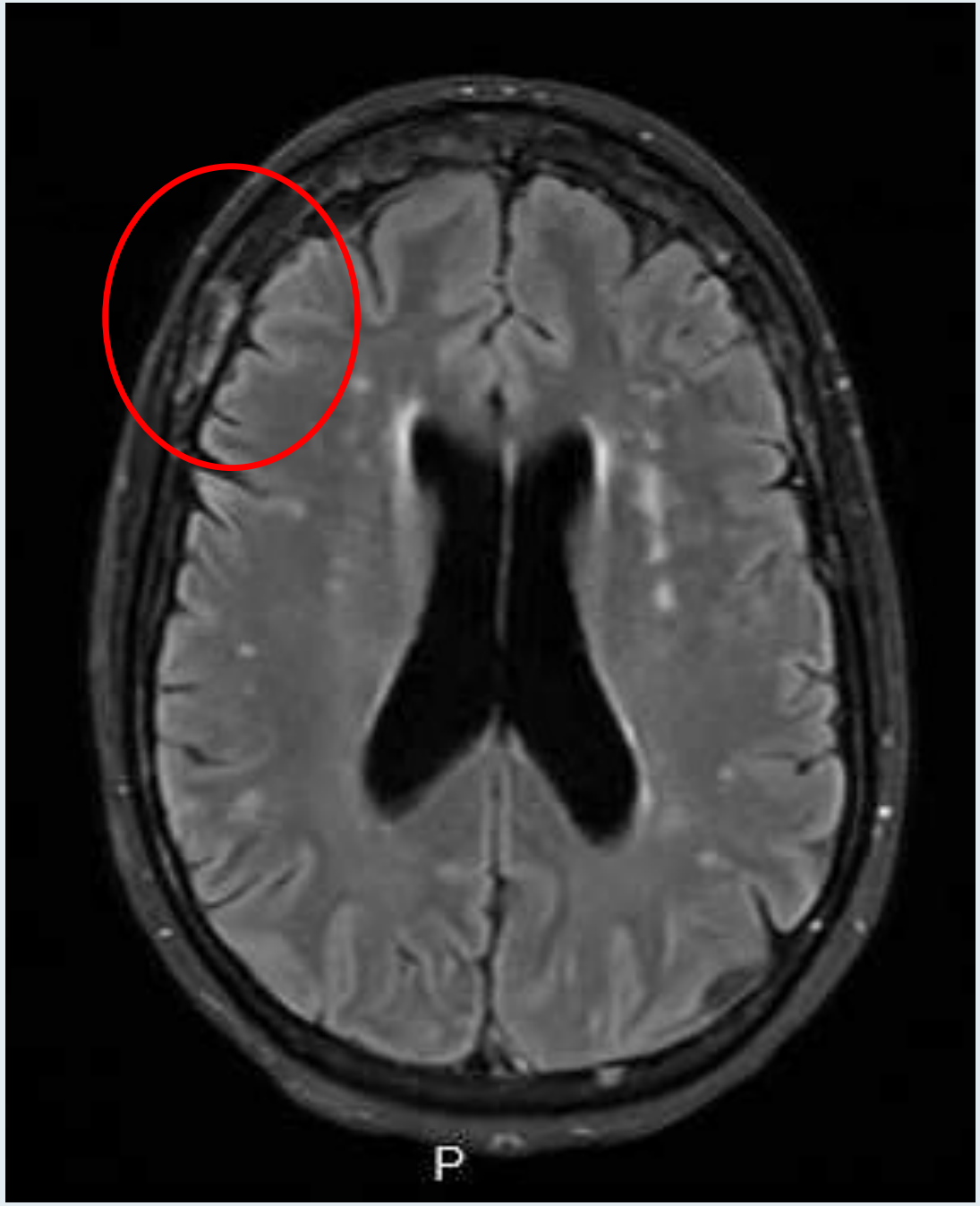
Case Presentation: 52-year-old woman with triple-positive mBC, s/p THP and letrozole, now with dural metastasis

Dr Kimberly Ku (Bloomington, Illinois)

RTP
RESEARCH
TO PRACTICE



Incidence and Management of Adverse Events Associated with HER2-Targeted Therapy

Sara A. Hurvitz, MD

Professor of Medicine

Director, Breast Oncology Program

University of California, Los Angeles

Neratinib

NALA Study: Safety and Tolerability

Treatment-Emergent AEs Occurring in ≥10% of Patients in the Safe Population

Adverse event	N + C (n = 303)		L + C (n = 311)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Diarrhea	252 (83.2)	74 (24.4)	206 (66.2)	39 (12.5)
Nausea	161 (93.1)	13 (4.3)	132 (42.4)	9 (2.9)
PPE syndrome	139 (45.9)	29 (9.6)	179 (96.3)	39 (11.3)
Vomiting	138 (49.9)	12 (4.0)	97 (31.2)	6 (1.9)
Decreased appetite	107 (35.3)	8 (2.6)	67 (21.5)	7 (2.3)
Fatigue	104 (34.3)	9 (3.0)	97 (31.2)	10 (3.2)
Constipation	94 (31.0)	4 (1.3)	41 (13.2)	1 (0.3)
Stomatitis	62 (20.5)	6 (2.0)	83 (26.7)	8 (2.6)
Weight decreased	60 (19.8)	1 (0.3)	41 (13.2)	2 (0.6)
Rash	30 (9.9)	0	69 (22.2)	2 (0.6)
Anemia	45 (14.9)	6 (2.0)	3! (16.4)	11 (3.5)
Dizziness	43 (14.2)	1 (0.3)	31 (10.0)	2 (0.6)
Cough	37 (12.2)	0	34 (10.9)	0
Abdominal pain	36 (11.9)	3 (1.0)	45 (14.5)	6 (1.9)
Asthenia	36 (11.9)	8 (2.6)	36 (11.6)	9 (1.6)
Hypokalemia	39 (11.6)	14 (4.6)	44 (141)	20 (6.4)
Paronychia	35 (11.6)	2 (0.7)	49 (15.8)	3 (1.0)
Pyrexia	33 (10.9)	0	32 (10.3)	1 (0.3)
Headache	32 (10.6)	1 (0.3)	o1 (16.4)	3 (1.0)

Saura C, et al. *J Clin Oncol*. 2020;38(27):3138-3149.

**Neratinib + capecitabine is off-label in HER2+ mBC.*

Diarrhea Grades

Gastrointestinal disorders					
CTCEA term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 to 6 stools per day over baseline; moderate increase in ostomy output compared to baseline: limiting instrumental activities of daily living (ADLs)	Increase of ≥7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADLs	Life-threatening consequences; urgent intervention indicated	Death

CONTROL: Incidence of Treatment-Emergent Diarrhea By Worst Grade

- **All preventive strategies reduced incidence of grade ≥3 diarrhea compared with historical control of 40%, without grade 4 diarrhea**
- **Dose escalation: Neratinib at a daily dose of 120 mg for week 1, followed by a daily dose of 160 mg for week 2, and a 240-mg daily dose for week 3 and thereafter for the duration of treatment**

Treatment-Emergent Diarrhea Incidence, n (%)	Loperamide (n = 137)	Budesonide + Loperamide (n = 64)	Colestipol + Loperamide (n = 136)	Colestipol + Loperamide PRN (n = 104)	Neratinib Dose Escalation (n = 60)
No diarrhea	28 (20)	9 (14)	23 (17)	5 (5)	1 (2)
Grade 1	33 (24)	16 (25)	38 (28)	34 (33)	25 (42)
Grade 2	34 (25)	21 (33)	47 (35)	32 (31)	25 (42)
Grade 3	42 (31)	18 (28)	28 (21)	33 (32)	9 (15)
Grade 4	0	0	0	0	0

Barcenas. Ann Oncol. 2020;31:1223. Chan. Lancet Oncol. 2016;17:367. Neratinib (full prescribing information) 2021.

AE Management with Neratinib

Consider & Discuss with Patients:	Prevention & Management of AEs

• May cause severe diarrhea including dehydration, hypotension, renal failure, and death
• In combination with capecitabine and without prophylaxis:
  • Median time to first onset of grade ≥3 diarrhea: 11 days
  • Median duration of grade ≥3 diarrhea: 3 days
• May cause severe hepatotoxicity
	• Antidiarrheal prophylaxis should be given to all patients and should be initiated with the first dose of neratinib
	  • If diarrhea occurs despite prophylaxis, patients should receive additional antidiarrheals, fluids, and electrolytes as clinically indicated
	  • Permanently discontinue neratinib in patients experiencing grade 4 diarrhea or grade ≥2 diarrhea that occurs after maximal dose reduction
	• Alternate: **use 2-week dose-escalation schedule to initiate treatment**
	• Monitor liver function tests for the first 3 months of treatment and then every 3 months while on treatment and as clinically indicated
	  • Permanently discontinue neratinib in patients with grade ≥4 liver abnormalities

Neratinib (full prescribing information) 2021.

Tucatinib

HER2CLIMB Study: Safety and Tolerability

Adverse events summary

TEAEs	Tucatinib combination (N = 404) n (%)	Placebo combination (N = 197) n (%)
Any TEAE	401 (99.3)	191 (97.0)
Grade ≥3 TEAE	245 (60.6)	101 (51.3)
Any serious TEAE	123 (30.4)	58 (29.4)
Death due to TEAE	6 (1.5)	5 (2.5)
Discontinued any study treatment due to TEAE	52 (12.9)	23 (11.7)
Discontinued tucatinib/ placebo due to TEAE	24 (5.9)	8 (4.1)
Discontinued capecitabine due to TEAE	47 (11.6)	22 (11.2)
Discontinued trastuzumab due to TEAE	17 (4.2)	7 (3.6)

Adverse events reported in ≥20% of patients in the tucatinib arm

Adverse event	Tucatinib combination (N = 404) n (%)		Placebo combination (N = 197) n (%)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any adverse event	401 (99.3)	245 (60.6)	191 (97.0)	101 (51.3)
Diarrhea	331 (81.9)	**53 (13.1)**	106 (53.8)	**17 (8.6)**
Palmar-plantar erythrodysesthesia syndrome	264 (65.3)	**57 (14.1)**	105 (53.3)	**18 (9.1)**
Nausea	243 (60.1)	16 (4.0)	88 (44.7)	7 (3.6)
Fatigue	193 (47.8)	22 (5.4)	87 (44.2)	8 (4.1)
Vomiting	152 (37.6)	13 (3.2)	51 (25.9)	8 (4.1)
Decreased appetite	105 (26.0)	3 (0.7)	41 (20.8)	0
Stomatitis	105 (26.0)	10 (2.5)	28 (14.2)	1 (0.5)
Headache	96 (23.8)	3 (0.7)	40 (20.3)	3 (1.5)
Aspartate aminotransferase increased	89 (22.0)	19 (4.7)	22 (11.2)	1 (0.5)
Anemia	88 (21.8)	17 (4.2)	24 (12.2)	5 (2.5)
Alanine aminotransferase increased	85 (21.0)	23 (5.7)	13 (6.6)	1 (0.5)
Blood bilirubin increased	81 (20.0)	4 (1.0)	21 (10.7)	5 (2.5)

Curigliano G, et al. *Ann Oncol.* 2022;33:321-329.

AE Management of Tucatinib

Be Aware:	Management of AEs
• May cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death • Can cause severe hepatotoxicity	• If diarrhea occurs, administer antidiarrheal treatment as clinically indicated – Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea – Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue • Monitor ALT, AST, and bilirubin prior to starting tucatinib, every 3 weeks during treatment, and as clinically indicated • Management of AEs may require temporary interruption, dose reduction, or discontinuation

T-DXd

ILD Grading

Grade	
1	Asymptomatic, radiographic findings only
2	Symptomatic, not interfering with activities of daily living
3	Symptomatic, interfering with activities of daily living or oxygen indicated
4	Life-threatening or ventilator support required
5	Fatal

Skeoch S, et al. *J Clin Med*. 2018;7(10):356.

DESTINY-Breast01 Adverse Events of Special Interest: Interstitial Lung Disease

	Patients who received T-DXd 5.4 mg/kg (N = 184)					
Preferred term, n (%)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Any grade/ total**
Interstitial lung disease	20 (10.9%)		1 (0.5)	0	4 (2.2)	**25 (13.6)**

All events 15.8% and grade 5 in 5 (2.7%) at update (ESMO 2021)

Among the 25 total events

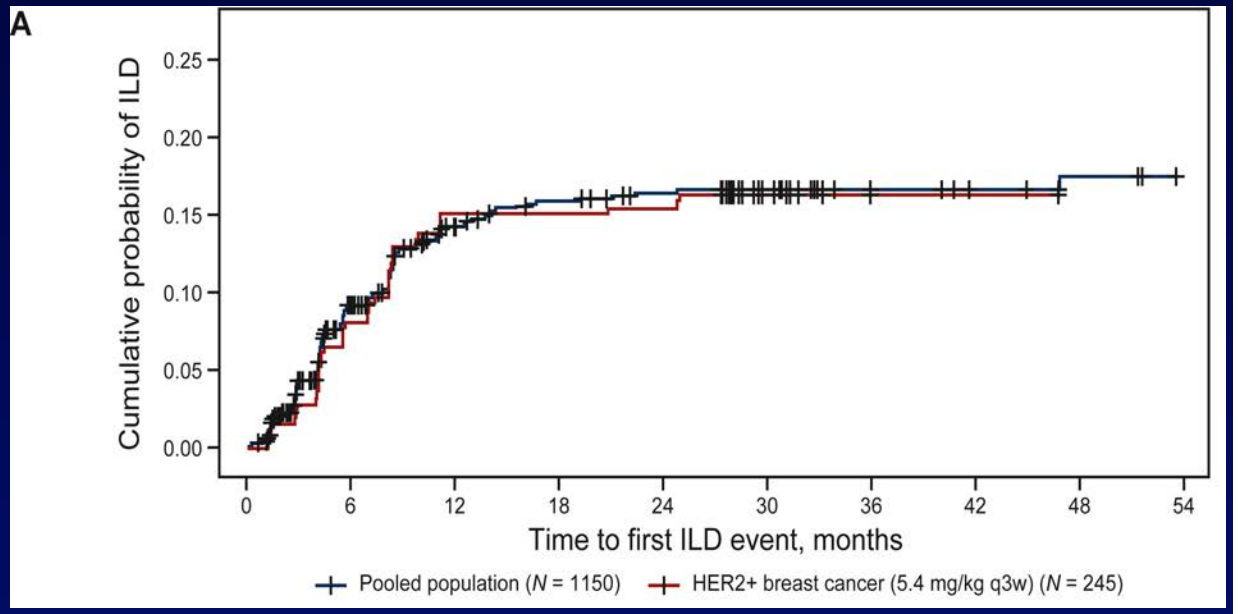
- Median time to investigator-reported onset was 193 days (range, 42-535 days)
- Of the 4 fatal cases, onset was from 63 to 148 days, 3 patients received steroids as part of treatment, and death occurred 9 to 60 days after diagnosis

Recommendations: Monitor for symptoms. Hold T-DXd, and start steroids as soon as ILD is suspected.

Krop IE, et al. SABCS 2019; Abstract GS1-03. Modi S, et al. *N Engl J Med.* 2020;382:610-621.

Pooled analysis of drug-related interstitial lung disease and/or pneumonitis in nine trastuzumab deruxtecan monotherapy studies

A



B

Potential risk factor	Patients, *n* (*N* = 1150)	Hazard ratio[a] (95% CI)
Age group		
<65 years	754	1.56 (1.02-2.38)
≥65 years	396	Ref
Country		
Japan	506	2.08 (1.45-2.98)
Non-Japan	644	Ref
Lung comorbidities[b]		
Yes	81	1.75 (1.03-2.98)
No	1069	Ref
Baseline renal function[c,d]		
Normal	470	Ref
Mild decrease	458	1.24 (0.83-1.84)
Moderate/severe decrease	196	2.73 (1.65-4.52)
Time since disease diagnosis[c]		
0 to ≤4 years	624	Ref
>4 years	403	1.82 (1.20-2.75)
Dose		
5.4 mg/kg q3w	315	Ref
6.4 mg/kg q3w	808	1.30 (0.85-1.99)
>6.4 mg/kg q3w	27	2.92 (1.32-6.42)
Baseline SpO_2[c]		
≥95%	1080	Ref
<95%	57	2.14 (1.11-4.13)

Time to first adjudicated drug-related ILD/pneumonitis event. Among 177 patients who had ILD, 154 (87.0%) had a first ILD/pneumonitis event within 12 months of starting treatment. Median time onset: 5.4 months (range, <0.1-46.8 months).

Powell CA et al. *ESMO Open* 2022 7DOI: (10.1016/j.esmoop.2022.100554)

DESTINY-Breast03: Drug Related AEs and ILD/Pneumonitis

Table 2. Most Common Drug-Related Adverse Events and Adjudicated Drug-Related Interstitial Lung Disease or Pneumonitis.

Event	Trastuzumab Deruxtecan (N=257)		Trastuzumab Emtansine (N=261)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Most common drug-related adverse events				
Blood and lymphatic system disorders				
Neutropenia*	110 (42.8)	49 (19.1)	29 (11.1)	8 (3.1)
Anemia†	78 (30.4)	15 (5.8)	37 (14.2)	11 (4.2)
Leukopenia‡	77 (30.0)	17 (6.6)	20 (7.7)	1 (0.4)
Thrombocytopenia§	64 (24.9)	18 (7.0)	135 (51.7)	65 (24.9)
Gastrointestinal disorders				
Nausea	187 (72.8)	17 (6.6)	72 (27.6)	1 (0.4)
Vomiting	113 (44.0)	4 (1.6)	15 (5.7)	1 (0.4)
Diarrhea	61 (23.7)	1 (0.4)	10 (3.8)	1 (0.4)
Constipation	58 (22.6)	0	25 (9.6)	0
General disorders				
Fatigue¶	115 (44.7)	13 (5.1)	77 (29.5)	2 (0.8)
Investigations				
Aspartate aminotransferase increased	60 (23.3)	2 (0.8)	97 (37.2)	13 (5.0)
Alanine aminotransferase increased	50 (19.5)	4 (1.6)	71 (27.2)	12 (4.6)
Metabolism and nutrition disorders				
Decreased appetite	67 (26.1)	3 (1.2)	33 (12.6)	0
Skin and subcutaneous tissue disorders				
Alopecia‖	93 (36.2)	1 (0.4)	6 (2.3)	0
Adjudicated drug-related interstitial lung disease or pneumonitis**	27 (10.5)	2 (0.8)	5 (1.9)	0

Nausea most common event!
>70%

Grade 3/4 neutropenia 19%

All grade ILD 10.5%
No grade 4 or 5 ILD events

Cortes J…Hurvitz S, et al. *N Engl J Med.* 2022;386.

DESTINY-Breast04 Adverse Events

Table 3. Most Common Drug-Related Adverse Events (in ≥20% of Patients) in the Safety Analysis Set.*

Event	Trastuzumab Deruxtecan (N=371)		Physician's Choice of Chemotherapy (N=172)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Blood and lymphatic system disorders				
Neutropenia†	123 (33.2)	51 (13.7)	88 (51.2)	70 (40.7)
Anemia‡	123 (33.2)	30 (8.1)	39 (22.7)	8 (4.7)
Thrombocytopenia§	88 (23.7)	19 (5.1)	16 (9.3)	1 (0.6)
Leukopenia¶	86 (23.2)	24 (6.5)	54 (31.4)	33 (19.2)
Gastrointestinal disorders				
Nausea	271 (73.0)	17 (4.6)	41 (23.8)	0
Vomiting	126 (34.0)	5 (1.3)	17 (9.9)	0
Diarrhea	83 (22.4)	4 (1.1)	31 (18.0)	3 (1.7)
Constipation	79 (21.3)	0	22 (12.8)	0
Investigations: increased aminotransferase levels‖	87 (23.5)	12 (3.2)	39 (22.7)	14 (8.1)
General disorders: fatigue**	177 (47.7)	28 (7.5)	73 (42.4)	8 (4.7)
Metabolism and nutrition disorders: decreased appetite	106 (28.6)	9 (2.4)	28 (16.3)	2 (1.2)
Skin and subcutaneous tissue disorders: alopecia	140 (37.7)	0	56 (32.6)	0

Nausea most common event! >70%

Grade 3/4 neutropenia ~14%

All grade ILD 12.1%
Grade 5 ILD events in 3 patients (0.8%)

Modi S, et al. *N Engl J Med.* 2022;387

Strategies to Manage ILD Associated With *HER2*-Directed ADCs

Monitor

Suspected ILD

Urge patients to immediately report cough, dyspnea, fever, and/or new or worsening pulmonary symptoms

- Monitor patients for signs/symptoms of ILD
- Promptly investigate evidence of ILD
- Evaluate patients with suspected ILD by radiographic imaging and assess as follows

Confirm

Assessments should include

- High-resolution CT
- Pulmonologist consult
- Blood culture and CBC; other blood tests as needed
- Consider bronchoscopy and bronchoalveolar lavage (BAL) if indicated and feasible
- Pulmonary function tests (PFTs) and pulse oximetry
- Arterial blood gases, if indicated
- As soon as ILD suspected, collect 1 blood sample for pharmacokinetics (PK) assessment, if feasible
- Rule out other causes of ILD (eg, progression, infection, other drugs, radiotherapy)
- All ILD events should be followed until resolution and after drug discontinuation

Manage

- **Grade 1 T-DXd:** Hold until resolved to Grade 0; consider corticosteroids (0.5 mg/kg/day prednisolone), then
  - *If resolved ≤28 days from onset:* Maintain dose
  - *If resolved >28 days after onset:* Reduce dose by 1 level
- **Grade 1 T-DM1:** Permanently discontinue
- **Grades 2-4:** Permanently discontinue treatment and promptly initiate systemic corticosteroid treatment (eg, ≥1 mg/kg/day prednisolone or equivalent for ≥14 days followed by taper for ≥4 weeks)

Ado-trastuzumab emtansine PI 2022 (https://www.gene.com/download/pdf/kadcyla_prescribing.pdf). Fam-trastuzumab deruxtecan-nxki PI 2022 (https://daiichisankyo.us/prescribing-information-portlet/getPIContent?productName=Enhertu&inline=true). URLs accessed 9.2.2022. Tarantino P, et al. *JAMA Oncol*. 2021;7(12):1873-1881.

T-DXd Related Nausea

	BEFORE T-DXd	Days 2-4	Days 5-21	Dose delays/ modifications
First cycle	5-HT3 receptor antagonist (RA) (**palonosetron**) + DEX	DEX ± 5-HT3 RA **OR** metoclopramide	**Olanzapine** or metoclopramide ± DEX	
Subsequent cycles, *if treatment in Cycle 1 not adequate*	NK1 receptor antagonist **(aprepitant)** ± 5-HT3 RA + DEX ± olanzapine	NK1 RA + 5-HT3 RA ± DEX **OR** DEX ± metoclopramide ± olanzapine	Same as above	Grade 3: delay dose until resolved to grade ≤1 If >7 days until resolution, reduce dose by 1 level

DEX = dexamethasone.

Rugo, Bianchini et al, 2022., slide courtesy of Julie LaBarbera, NP

What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of ER-Positive Breast Cancer

Part 2 of a 2-Part CME Satellite Symposium Series Held in Conjunction with the 2022 San Antonio Breast Cancer Symposium®

Thursday, December 8, 2022

7:15 PM – 9:15 PM CT (8:15 PM – 10:15 PM ET)

Faculty

Aditya Bardia, MD, MPH

Matthew P Goetz, MD

Virginia Kaklamani, MD, DSc

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